A Modular Synthesis of Ketones and Gem-diborylalkanes by Catalytic Carbon Insertion with Non-stabilized Diazoalkanes

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Boston College

Graduate School of Arts and Sciences

Department of Chemistry

A MODULAR SYNTHESIS OF KETONES AND *GEM*-DIBORYLALKANES BY CATALYTIC CARBON INSERTION WITH NON-STABILIZED DIAZOALKANES

A dissertation

by

ANDREW JOSEPH WOMMACK

submitted in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy
August 2011

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2011

Acknowledgements

I feel that my time at Boston College has been a unique graduate experience. I am fortunate to have observed many different styles of professorship through my interactions and conversations with different faculty members and with my fellow students. I entered graduate school with high hopes of being led and taught by great chemists, great leaders. I leave graduate school with the important lesson that no one professor is the perfect boss, but it is the continuing effort to become better leaders that makes them great. I will take these lessons, both the good and the bad, with me as I encounter whatever opportunities may come.

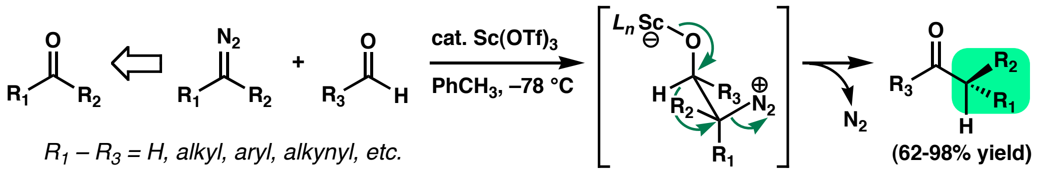
At BC there is an open atmosphere for discussion between most inter-group members, and this has been a benefit to the development in my thinking about chemical problems, from an organic chemist's point of view. I hope to bring this "lens" to ideas and problems in my future training and profession.

It was my Father who taught me that after you look back on a period of accomplishments, the only thing that really matters is the relationships you have built. My time at Boston College has been one of great development for me. A fellow student at BC once said that graduate school can turn you into your worst self if you let it. I whole-heartedly agree that, without people to support your emotional health, you can let yourself become a base version of your true potential. When you start to solely commit yourself to just one task, you can feel complete and completely miserable, simultaneously. This is obviously not limited to the graduate experience, it is a human condition, but I have been fortunate to extract this lesson from my time here at BC.

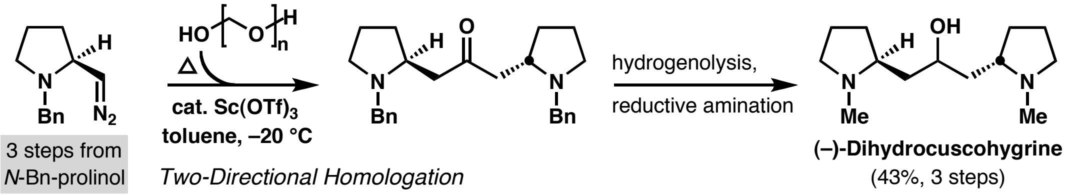
The philosophy that originally drew me to organic chemistry is the notion that the only limitation to what can be achieved in this chemical discipline is your imagination. Through the initial encouragement in my undergraduate experience, I found an outlet for my desire to become both artist and philosopher. I still hold to that belief that if you have the vision, there is a method. Throughout graduate school I have held to this exciting possibility, and because of the limitless human imagination I will always love the art of organic chemistry.

One of the best decisions I made during my time in Boston was building and continually pursuing a relationship with Tara. In her, I have found my best friend and companion. Graduate school certainly exerts stress on any relationship, but because of her patience and understanding, the journey through these past five years has been enriched.

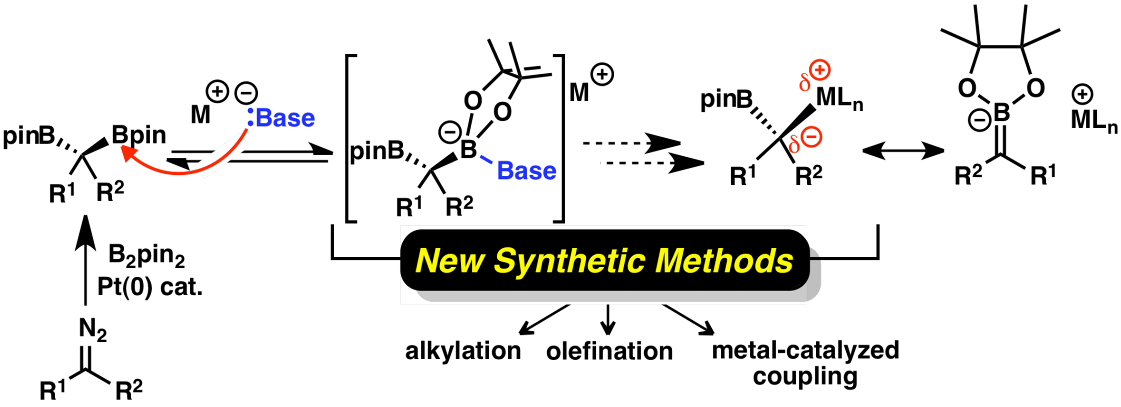
Chapter 1: The reaction of diazomethane with simple aldehydes to deliver methyl ketones has a long studied history in the art of organic synthesis. Formyl electrophiles have also been homologated with trimethylsilyldiazomethane, diazoacetates, and aryl-diazomethanes that very rarely proceed with catalytic activation. Due to the stigma of handling non-stabilized diazoalkanes this history is limited to examples utilizing α–diazoesters and entirely missing are examples of tertiary α–substituted ketone synthesis beginning with disubstituted (internal) diazoalkanes. This work describes a general catalytic procedure for convergent ketone production using non-stabilized, mono- and disubstituted diazomethanes. The method involves mild reaction conditions, produces molecular nitrogen as the only byproduct, and includes six examples of chiral ketone synthesis from various aryl, heteroaryl, or aliphatic aldehydes. The latter feature, together with new evidence that the catalytic reaction mechanism invokes a stereospecific, intramolecular C–H migration, sets the stage for an enantioselective synthesis of acyclic ketones by asymmetric carbon insertion. The remarkable tolerance of this transformation to steric crowding in either reaction partner is showcased in a simple, five-step construction of the complete carbon framework in achyrofuran, a complex dibenzofuranoid.



Chapter 2: Paraformaldehyde is an inexpensive and readily available source of carbon (~30 USD/kg). Upon heating, the polymer thermally depolymerizes to yield gaseous formaldehyde that can be bubbled through reactions or stored in solution at low temperature. In this work, a new and general strategy for complex ketone synthesis is described based on Sc-catalyzed, double diazoalkyl C–H insertion reactions with formaldehyde as a 1-C source. The method forms di-, tri-, and even tetrasubstituted acetones efficiently, and it has streamlined a synthesis of the *Erythroxylon* alkaloid (–)-dihydrocuscohygrine in which absolute stereochemistry in a proline-based starting material is preserved.


H
N
Bn
N_2
3 steps from
N-Bn-prolinol
HO
O
n
H
Δ
cat. Sc(OTf)$_3$
toluene, –20 °C
Two-Directional Homologation
H
O
N
Bn
N
Bn
hydrogenolysis,
reductive amination
H
OH
N
Me
N
Me
(–)-Dihydrocuscohygrine
(43%, 3 steps)

Chapter 3: Use of geminally-substituted diorganometallics often gives new forms of reactivity that are unavailable to their monosubstituted counterparts. With the expanding use of boronic acids in many areas of synthetic organic methodology, an underappreciated research area has been full development of disubstitited *gem*-diboronic ester derivatives for use in tandem reactions, olefination methods, metal-catalyzed coupling reactions, and transmetallations to mixed *gem*-diorganometallics. The nature of molecular boron is routinely engaged through its Lewis acidic vacant *p*-orbital, and, after metalation, this orbital interaction is enlisted to stabilize α-carbanion or α-carbanion-like species to allow dependable reactivity in various applications. The platinum-catalyzed geminal diboration of diazoalkanes provides reliable and efficient access to a full range of disubstitited *gem*-diboronic esters enabling the exploration of novel methodologies.


pinB
Bpin
R1
R2
M
Base
pinB
O
O
B
Base
R1
R2
M
pinB
ML_n
δ+
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R1
R2
O
O
B
R2
R1
ML_n
B2pin2
Pt(0) cat.
N2
R1
R2
New Synthetic Methods
alkylation
olefination
metal-catalyzed coupling

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Chapter 1. A General Synthesis of Ketones by Catalytic Carbon Insertion of Diazoalkanes into the Formyl C-H Bond.[1]

1.1 *Introduction and Background*

Ketones are typically prepared by the addition of an organometallic reagent to the carbonyl group followed by a reoxidation event. Indeed, formation of a C–C σ-bond via nucleophilic addition of an organometallic reagent to an aldehyde substrate represents one of the most elementary transformations in organic synthesis. The start of organometallic chemistry dates to 1849 with Frankland's early work with organozinc compounds.[2] By the turn of the 20th century, the use of organozinc reagents in organic synthesis was largely supplanted by main-group organometallics due to the rapid growth of Grignard chemistry and the development of practical routes to organolithium compounds.[3] Following isolation of an alcohol

---

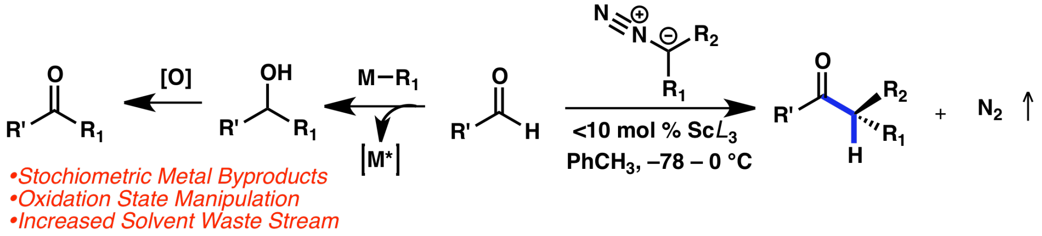
(1) " A General Synthesis of Ketones by Catalytic Carbon Insertion into the Formyl C-H Bond. Concise Access to the Presumed Biosynthetic Progenitor of Achyrofuran," Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11*, 3202–3205.

(2) (a) "Ueber die Isolirung der organischen Radicale," E. Frankland, *Ann. Chem. Pharm.* **1849**, *71,* 171–213. (b) "XXVII-On the Isolation of the Organic Radicals," E. Frankland, *J. Chem. Soc.* **1850**, *2*, 263–296. (c) "Zinc Alkyls, Edward Frankland, and the Beginnings of Main-Group Organometallic Chemistry," D. Seyferth, *Organometallics* **2001**, *20*, 2940–2955. For a review on asymmetric organozinc addition to carbonyls, see: " "Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds," Pu, L.; Yu, H. -B. *Chem. Rev.* **2001**, *101,* 757–824.

(3) (a) "Sur Quelques Nouvelles Combinais Organométalliques du Magnésium et leur Application à des Synthèses D'alcools et D'hydrocarbures," V. Grignard, *C. R. Hebd. Seances. Acad. Sci* **1900**, *130,* 1322–1324. (b) "Über die Einfachsten Metallorganischen Alkaliverbindungen," W. Schlenk and J. Holtz, *Chem. Ber.* **1917**, *50*, 262–274. (c) "Untersuchungen Über Alkali-Organische Verbindungen. V. Eine Bequeme Synthese Einfacher Lithiumalkyle," K. Ziegler and H. Colonius, *J. Liebigs Ann. Chem.* **1930**, *479* 135–149. (d) "Metalation as a Side Reaction in the Preparation of Organolithium Compounds," H. Gilman, W. Langham and A.L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106–109. (e) For a review on asymmetric organomagnesium and organolithium addition to

product, a readjustment in oxidation state is required to obtain the ketone. Unattractive features of these traditional two-step approaches include the need for stoichiometric amounts of the metal and oxidant as well as increased solvent and waste streams. A portion of my doctoral work has focused on the development of an efficient strategy for the synthesis of acyclic ketones, encompassing the preparation of metal-free carbon nucleophiles, catalytic activation of the electrophile, and the consolidation of two reaction steps into one, (Scheme 1).

Scheme 1: Synthetic Options for Ketone Formation


[O]
M−R1
[M*]
<10 mol % ScL3
PhCH3, −78 – 0 °C
+ N2 ↑
•Stochiometric Metal Byproducts
•Oxidation State Manipulation
•Increased Solvent Waste Stream

1.1.a *Literature Precedent for Homologation of Aldehydes with Diazoalkanes*

Investigations into the use of diazomethane (Scheme 2; R_1, R_2 = H) as a nucleophile for formal insertion into the aldehydic C-H bond began at the turn of the 20th century (path a, Scheme 2).[4] Schlotterbeck is often credited as the discoverer of this aldehyde chain elongation reaction, since he extensively studied reactions of diazomethane with both aryl and

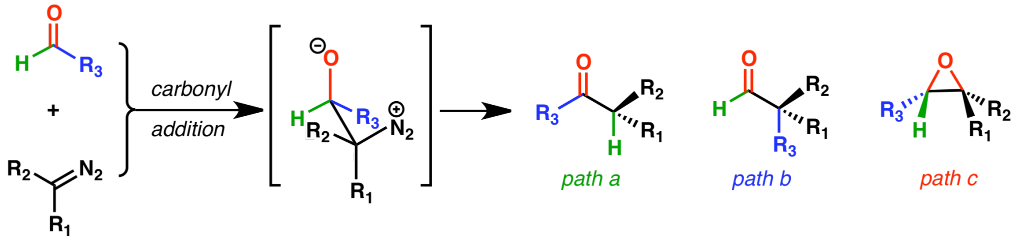
---

carbonyls, see: "Asymmetric Addition of Achiral Organomagnesium Reagents or Organolithiums to Achiral Aldehydes or Ketones: a Review," Lunderer, M. R.; Bailey, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.; Sommer, M. B. *Tetrahedron: Asymmetry* **2009**, *20*, 981–998.

(4) "The Reaction of Diazomethane and Its Derivatives with Aldehydes and Ketones," Gutche, C. D. *Org. React.* **1954**, *8*, 364–429.

aliphatic aldehydes.[5] However, the same transformation was reported by Büchner and Curtius, von Pechmann, and Meyer earlier wherein the aldehyde was exposed to diazomethane in ether or a methanol solution of the carbonyl was treated with strong base in the presence of the nitrosoalkylurethane.[6] As shown below in Scheme 2, the reaction to afford a ketone product involves diazoalkyl addition to the carbonyl group to give a diazonium betaine intermediate; subsequent 1,2-shift of the aldehydic C-H bond gives the chain elongated product with evolution of dinitrogen as the only stoichiometric byproduct (path a).[4] Also illustrated in Scheme 2 is the fact that alternative modes of 1,2 rearrangement can provide two other products (paths b and c). Early empirical datum suggest that increasing the steric bulk in an aliphatic aldehyde promotes path a.[4]

Scheme 2



If one considers the effect of electronic differences in aromatic aldehydes, the results are conflicting, since both electron-rich and electron-poor electrophiles afford similar regioisomeric product distributions.[7] Solvent effects can also exert a role. For example, the use of methanol as a promoter in ethereal solutions increases the amount of oxirane formed from path c. This level of regiochemical understanding can be summarized as, "reactions of aldehydes with diazomethane in dry ether give predominantly methyl ketones, whereas increasing homologation of the aldehyde occurs as alcohols are added to the solvent."[8]

---

[5] "Umwandlung von Aldhyden in Ketone durch Diazomethan," Schlotterbeck, F. *Ber*. **1907**, *40*, 479–488.

[6] (a) "Synthese von Ketonsäureäthern aus Aldehyden und Diazoessigäther," Buchner, E.; Curtius, T. *Ber.*, **1885**, *18*, 2373. (b) "Ueber Diazomethan," v. Pechmann, H. *Ber.* **1898**, *28*, 855–861. (c) "Über die Einwirkung von Diazomethan auf Aldehydsäuren und Aldehyde," Meyer, H. *Monatsh.* **1905**, *26*, 1295–1301.

Research towards expanding the scope and efficiency of the aldehyde homologation process has been recently renewed, but catalysis with non-stabilized diazoalkanes remained elusive until our work.[9] There are currently five major types of aldehyde homologation methods that rely on diazo compounds and provide ketone products (path a, Scheme 2). The first protocol involves in situ generation of the nucleophile via the Bamford-Stevens reaction, which is a base promoted decomposition of aryl tosyl hydrazones.[10] Such reaction parameters have been extended as a means to circumvent the potential dangers typically associated with the

---

(7) "Über die Einwirkung von Diazo-methan auf Piperonal III," Mosettig, E.; Czadek, K. *Monatsh*. **1931**, *57*, 291.

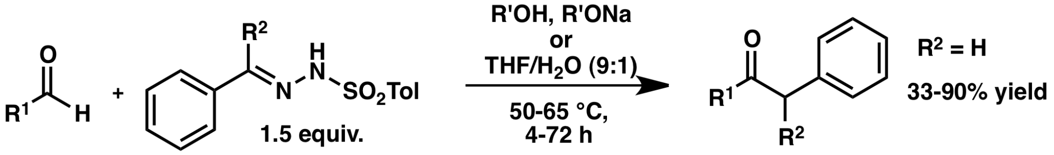
(8) "Developments in the use of diazo-alkanes," Cowell, G. W.; Ledwith, A. *Q. Rev. Chem. Soc.*, **1970**, *24*, 119–167.

(9) (a) "Preparation of 4-Oxo-L-norvaline via Diazomethane Homologation of β-Aspartyl Semialdehyde," Werner, R. M.; Shokek, O.; Davis, J. T. *J. Org. Chem.* **1997**, *62*, 8243–8246. (b) For a review, see: Gutsche, C. D. *Org. React.* **1954**, 8, 364–429.

(10) (a) "A Simple Method for the Synthesis of Substituted Benzylic Ketones: Homologation of Aldehydes via the in Situ Generation of Aryldiazomethanes from Aromatic Aldehydes," Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **2000**, *65*, 6458–6461. (b) "A Simple, User-Friendly Process for the Homologation of Aldehydes Using Tosylhydrazone Salts," Aggarwal, V. K.; de Vicente, J.; Pelotier, B.; Holmes, I. P.; Bonnert, R. V. *Tetrahedron Lett.* **2000**, *41*, 10327–10331. (c) "The Use of Tosylhydrazone Salts as a Safe Alternative for Handling Diazo Compounds and Their Applications in Organic Synthesis," Fulton, R. J.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem*. **2005**, *8*, 1479–1492.

purification of diazoalkanes. Unfortunately methods based on Bamford-Stevens chemistry inevitably come with limitations on scope and functional group tolerance due to the strongly basic reaction conditions required.[10b,c]

Scheme 3



In particular, extension of this method for the generation of enantiopure α–chiral ketones is prohibited by facile racemization.

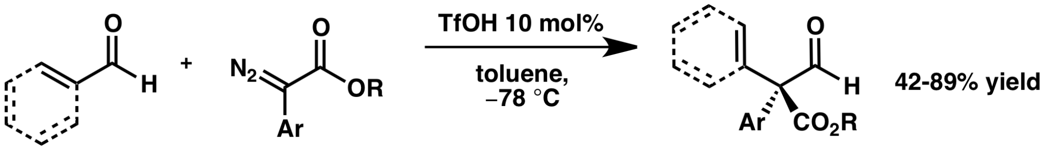
A second useful method for the insertion of diazonucleophiles into the aldehydic C-H bond requires the use of carbonyl-stabilized diazo compounds. These less reactive reagents are more easily handled and amenable to purification, and this facilitated their development earlier in the timeline of the aldehyde homologation reaction.[11] The attenuated reactivity of these nucleophiles mandates the need for activation of the carbonyl electrophile. It had been noted that addition of methanol as a Brønsted acid promoter not only diverts the regiochemical outcome of the reaction, but it also increases the reactivity of the process.[8] A more modern study using H-bonding as a means of Lewis activation has shown that insertion into the aldehydic C-C bond can be an efficient, albeit

---

(11) For reviews of methods for the synthesis of α–diazo ketones, see: a) Regitz, M.; Maas, G. *Diazo Compounds, Properties and Synthesis;* Academic Press: New York, **1986.** (b) Regitz, M. In *The Chemistry of Diazonium and Diazo Groups;* Patai, *S.,* Ed.; Wiley: New York, **1978;** Chapter 17. (c) "Detonation Properties of Ethyl Diazoacetate," Clark, J. D.; Shah, A. S.; Peterson, J. C.; Patelis, L.; Kersten, R. J. A.; Heemskerk, A. H.; *Thermochim. Acta* **2002**, *386*, 73–79. (d) "New Syntheses of Diazo Compounds," Maas, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 8186–8195.

limited, method (Scheme 4).[12] Modest stereoselectivity has been achieved via this strategy if a (–)-menthyl ester is incorporated into the diazocarbonyl compound.[12]

Scheme 4



A third class of aldehyde homologations is based on stabilized diazocarbonyl compounds in a reaction with a metal-based Lewis acid. This method was developed by Roskamp employing $SnCl_2$ as the Lewis acid activator for a variety of aldehyde electrophiles (Scheme 5).[13] Following his seminal report, a diversity of Lewis acids has been applied to the methodology including a chiral system based on Sc(II)-N,N-dioxide complexes.[14] Nonetheless, the limitation of using only carbonyl-stabilized diazoalkanes for accessing only β-keto esters has remained a common theme.[13,14,15]

---

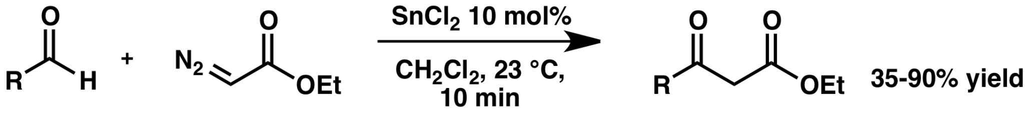
(12) "Brønsted Acid-Catalyzed Insertion of Aryldiazoacetates to sp^2 Carbon–CHO Bond: Facile Construction of Chiral All-Carbon Quaternary Center," Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 2434–2435.

(13) "A Selective Method for Diazoacetate Catalyzed the Direct Conversion of Aldehydes into b-Keto Esters with Ethyl by Tin(II) Chloride," Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258–3260.

(14) "Catalytic Asymmetric Roskamp Reaction of α-Alkyl-α-diazoesters with Aromatic Aldehydes: Highly Enantioselective Synthesis of α-alkyl-β-keto esters," Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc*. **2010**, *132*, 8532–8533.

(15) (a) "Tin(II) Chloride Catalyzed Addition of Diazo Sulfones, Diazo Phosphine Oxides, and Diazo Phosphonates to Aldehydes," Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131–1134. (b) "Synthesis of 1,3-Diketones using α–Diazo Ketones and Aldehydes in the Presence of Tin(II) Chloride," Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297–5299. (c) "Synthesis of γ-Unsubstituted α–Acyl-β-tetronic Acids from Aldehydes," Nomura, K.; Iida, T.; Hori, K.; Yoshii, E. *J. Org. Chem.* **1994**, *59*, 488–490. (d) "Total Synthesis of (+)-Galbulimima Alkaloid 13 and (+)-Himgaline," Evans, D. A.; Adams, D. J. *J. Am. Chem. Soc.* **2007**, *129,* 1048–1049. (e)

Scheme 5



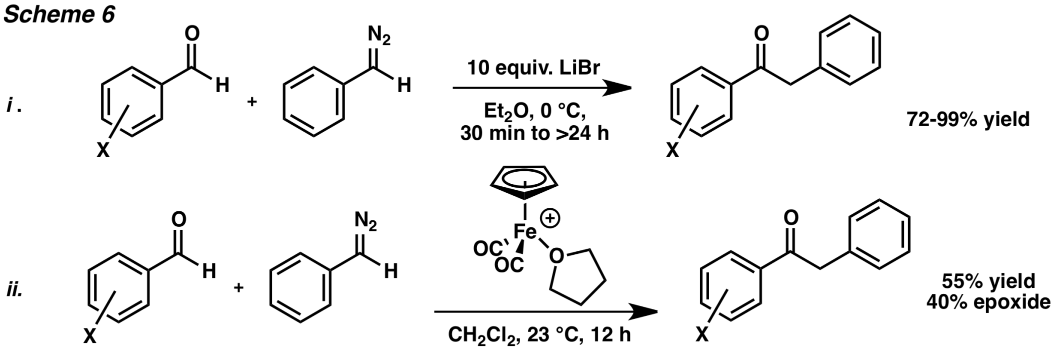
The use of non-stabilized diazoalkanes has been restricted to the use of diazomethane and trimethylsilyldiazomethane (TMSD) principally due to the more involved procedures associated with access to higher homologues of these nucleophiles. Nevertheless, studies have been undertaken to establish the reactivity and scope of aldehyde homologation with either/both diazomethane and TMSD.[16]

"Dramatic Solvent Effect on the Diastereoselectivity of Michael Addition: Study toward the Synthesis of the ABC Ring System of Hexacyclinic Acid," Toueg, J.; Prunet, J. *Org. Lett.* **2008**, *10*, 45-48. (f) "Selective Synthesis of α-Substituted β-Keto Esters From Aldehydes and Diazoesters on Mesoporous Silica Catalysts," Murata, H.; Ishitani, H.; Iwamoto, M. *Tetrahedron Lett.* **2008**, *49*, 4788. (g) "Some New Spiro Penicillins," Sheehan, J. C; Chacko, E.; Lo, Y. S.; Ponzi, D. R.; Sato, E. *J. Org. Chem.* **1978**, *43*, 4856-4859. (h) "Reactions of β, β, β-Trichloroethyl 6-Diazopenicillanate with Aldehydes and Schiff Bases," Sheehan, J. C.; Nakajima, K.; Chacko, E. *Heterocycles* **1979**, *13*, 227-234. (i) "Stereospecific Conversion of Penicillin to Thienamycin," Karady, S.; Amanto, J. S.; Reamer, R. A.; Weinstock, L. M.; *J. Am. Chem. Soc.* **1981**, *103*, 6765-6767. (j) "Reactions of 2,2,2-Trichloroethyl 6-Diazopenicillanate with Aromatic Aldehydes. *X*-Ray Crystal Structures of (3*S*,8α*S*)-2,2,2-Trichloroethyl 2,3-dihydro-6-(4-methoxyphenyl)-2,2-dimethyl-5-oxo-5*H*,8a*H*-thiazolo[2,3-*b*][1,3]oxazine-3-carboxylate and (2*S*,5*S*)-2,2,2-Trichloroethyl-4-formyl-2-(4-methoxyphenyl)-6,6-dimethyl-3-oxotetrahydro-1,4-thiazine-5-carboxylate," Jephcote, V. J.; Jowett, I. C.; John, D. I.; Edwards, P. D.; Luk, K.; Slawin, A. M.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2187-2194. (k) "Some Lewis Acid-Catalysed Reactions between 2,2,2-Trichloroethyl 6-Diazopenicillanate and Ketones," Jephcote, V. J.; John, D. I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2203-2205. (l) "Stereoselective Synthesis of α-Alkyl-β-keto Imides via Asymmetric Redox C−C Bond Formation between α-Alkyl-α-diazocarbonyl Compounds and Aldehydes," Hashimoto, T.; Miyamoto, H.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.*, **2009**, *131,* 11280–11281. (m) "Synthesis of β-Keto Esters In-Flow and Rapid Access to Substituted Pyrimidines," Bartrum, H. E.; Blakemore, D. C.; Moody, C. J.; Hayes, C. J. *J. Org. Chem.*, **2010**, *75*, 8674–8676. (n) "Lewis Acid-Catalyzed Reactions of Ethyl Diazoacetate with Aldehydes. Synthesis of α-Formyl Esters by a Sequence of Aldol Reaction and 1,2-Nucleophilic Rearrangement," Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5055–5058.

(16) (a) "New Methods and Reagents in Organic Synthesis. Ch. 8. Trimethylsilyldiazomethane. A New, Stable, and Safe Reagent For the Classical Arndt-Eistert Synthesis," Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1986**, *27*, 2005–2006. (b) "New Methods and Reagents in Organic Synthesis; 73. Trimethylsilyldiazomethane: A Convenient Reagent for the Conversion of Aliphatic Aldehydes to the Homologous Methyl Ketones," Aoyama, T.; Shioiri, T. *Synthesis* **1988**, 228–229.

The development of aldehyde homologation protocols that reliably afford regioselective results with the higher homologues of non-stabilzed diazonucleophiles has met with more limited success. As shown in Scheme 6, the reaction of phenyldiazomethane with various aromatic aldehydes has been accomplished with either (1) superstoichiometric amounts of LiBr, or (2) by the use of catalytic amounts of a cationic iron source by Anselme and Hossain, respectively.[17] These two methods illustrate how Lewis acid catalysis dramatically increases the efficiency of the process, but in the case of catalysis, selectivity issues remain unaddressed (eq. *ii.,* 40% epoxide byproduct). Moreover, the fact that only phenyldiazomethane was studied as a reactant means that considerable room for improvement is needed before the method could be seen as broadly synthetically viable.

Scheme 6



A series of detailed experiments was provided in reports from the Yamamoto group involving very bulky and oxaphilic organoaluminum promotors. Results show that reactions are more regioselective as the size of the substituent on aluminum is increased (Scheme 7, Me_3Al → MAD (methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)).[18] This is also a rare example in the literature that employs a more diverse selection of non-stabilized diazoalkanes. Regardless, an important consideration taken away from this work is that, in spite of extensive effort, organoaluminum-based Lewis acids fail to provide catalytic activity.

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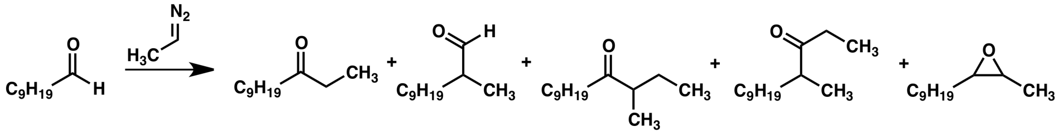
[17] (a) "Lithium Bromide Catalyzed Homologation of Aldehydes with Aryldiazomethanes," Loeschorn, C. A.; Nakajima, M.; McCloskey, P. J.; Anselme, J-P. *J. Org. Chem.* **1983**, *48*, 4407-4410. (b) "Iron Lewis acid catalyzed reactions of phenyldiazomethane with aromatic aldehydes," *Tetrahedron* **1998**, *54*, 349-358.

Scheme 7



Promotor / Solvent	(°C, h)	Combined % (GC yield)	(ratio)
MeOH / ether	0, 1.5	69%	(80 : 2 : 16 : 1 : 1)
Me_3Al / CH_2Cl_2	−78, 1	80%	(59 : 24 : 10 : 5 : 2)
1.0 equiv MAD / CH_2Cl_2	−78, 1	77%	(90 : 1 : 7 : 0 : 2)
0.5 equiv MAD / CH_2Cl_2	−78, 1	47%	(76 : 8 : 13 : 0 : 3)

Since true catalysis was lacking in the transformation of aldehydes to the homologous ketones with non-stabilized diazoalkanes, we were drawn to the challenge of developing a powerful and broadly applicable synthetic method – one based on a catalytic activator of the electrophile that could be easily outfitted with chiral ligands for eventual studies in enantioselective carbon insertion. In order to accomplish these two main goals, we first set out to safely synthesize non-stablized diazoalkanes in a

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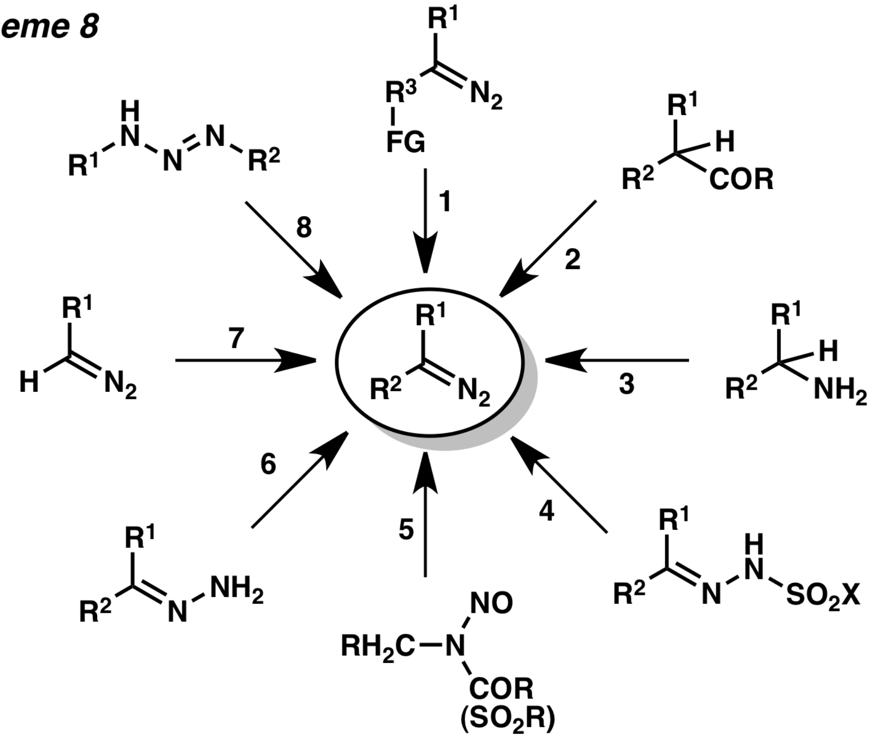
(18) (a) "Selective Homologation of Ketones and Aldehydes with Diazoalkanes Promoted by Organoaluminum Reagents," Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis*, **1994**, *12*, 1283–1290. (b) "Organoaluminum-Promoted Direct Conversion of Aldehydes to the Homologous Ketones or Oxiranes with Diazoalkanes," Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synlett*, **1994**, *7*, 521–523. (c) "Organoaluminum-Promoted Homologation of Ketones with Diazoalkanes," Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725–4726. (d) *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H.; Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, **2008.** (e) "Selective Homologation of Ketones and Aldehydes with Diazoalkanes Promoted by Organoaluminum Reagents," Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *ChemInform*, **1995**, *26*, 15.

practical and user-friendly manner.

1.1.4 *Literature Precedent for Diazoalkane Synthesis*

An exhaustive search of the literature illustrates the multiple and creative ways that chemists have sought to harness the unique reactivity of the diazo functional group. As summarized in Scheme 8, major routes for the synthesis of diazo compounds include: (1) substituent modification of an existing diazo compound, (2) diazo-group transfer onto activated methylene or methine compounds, (3) diazotization of α-acceptor-substituted primary aliphatic amines, (4) base-induced decomposition of sulfonylhydrazones, (5) alkaline cleavage of *N*-alkyl-*N*-nitroso sulfonamides, carboxamides, ureas, and urethanes, (6) dehydrogenation of hydrazones, (7) electrophilic substitution at diazomethyl compounds, and (8) triazene fragmentation (rare).[11a,b,d] We sought to create a method applicable to complex synthetic settings and viewed carbonyl compounds themselves as viable diazoalkane precursors. As such, we have focused our efforts on streamlining approaches based on hydrazone oxidation, ensuring that they are both mild and functional group-tolerant.

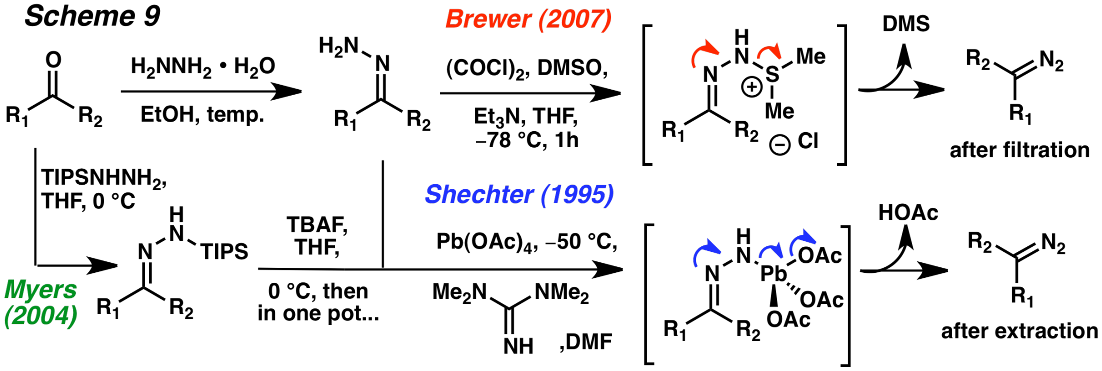
Scheme 8


R¹
R³
N₂
FG
H
R¹
N
N
N
R²
R¹
H
R²
COR
1
8
2
R¹
H
N₂
7
R¹
R²
N₂
3
R¹
H
R²
NH₂
6
5
4
R¹
R²
N
NH₂
NO
RH₂C
N
COR
(SO₂R)
R¹
H
R²
N
N
SO₂X

1.1.c *Optimization of Non-Stablized Diazoalkane Synthesis.*

Early on, our lab identified that the dehydrogenation of hydrazones can reliably afford access to both aryl- and alkyl-based non-stabilized diazo compounds by a modification of previously reported methods. A report from Brewer and coworkers offered a new extension of the Swern reagent to dehydrogenate aryl hydrazones to the corresponding aryl-substituted diazomethane reagent in good to excellent yields (Scheme 9). Initially, our efforts to extend this Swern-type method to alkyl-substituted diazomethanes met with highly variable results, perhaps due to the reagents' inherent instability at the required reaction temperatures and/or exposure to the protic byproduct, Et_3N•HCl, which is in agreement with observations made by the original authors.[19]

Scheme 9



Brewer (2007)
$H_2NNH_2 \cdot H_2O$
EtOH, temp.
$(COCl)_2$, DMSO,
Et_3N, THF, –78 °C, 1h
DMS
after filtration
$TIPSNHNH_2$, THF, 0 °C
Myers (2004)
TBAF, THF,
0 °C, then in one pot...
Shechter (1995)
$Pb(OAc)_4$, –50 °C,
,DMF
HOAc
after extraction

In order to efficiently and reliably access alkyl-based diazo compounds, we needed a more potent oxidation strategy that could be performed at low temperature. This requirement was met by the previous efforts of Shechter and coworkers (Scheme 9).[20] They found that employing Lead(IV) tetracetate in the presence of an organic amine base, one could attain moderate to excellent yields of non-stabilized diazoalkanes. More important was their choice of solvent, by performing the oxidantion in DMF, a simpler hydrocarbon extraction using pentane or hexanes was all that was needed to obtain the desired product in pure form in solution. In brief tests, we also established that hypervalent iodine oxidants[21] could produce the desired diazoalkane, but iodobenzene was a consistent contaminant in final diazoalkane stock solutions using the Schechter purification method (vida infra). To more thoroughly expand

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(19) "Diazo Preparation via Dehydrogenation of Hydrazones with "Activated" DMSO," Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789–1792.

(20) "Advantageous Syntheses of Diazo Compounds by Oxidation of Hydrazones with Lead Tetraacetate in Basic Environments," Holton, T. L.; Shechter, H. *J. Org. Chem.* **1995**, *60*, 4725–4729.

(21) For excellent reviews of hypervalent iodine in modern organic chemistry, see: (a) "Recent Developments in the Chemistry of Polyvalent Iodine Compound," Zhdankin, V. V.; Stang, P. J. *Chem. Rev.*, **2002**, *102*, 2523–2584. (b) "Chemistry of Polyvalent Iodine," Zhdankin, V. V.; Stang, P. J. *Chem. Rev.*, **2008**, *108*, 5299–5358.

functional group tolerance within the target diazoalkane, a protecting group strategy was needed to prevent azine formation during hydrazone synthesis (or heterocycle formation in the case of α,β–unsaturation). The Myers group had reported a diazoalkane synthesis incorporating *N*-silyl protection in the intermediate hydrazone (Scheme 9).[22] We modified this method after deducing that a monosilyl hydrazine reagent would be the most atom economical choice for hydrazone synthesis. A report by Soderquist et al. applied TIPS-hydrazine to the preparation of unsymmetrical azines, and a procedure for its generation from TIPSCl and hydrazine was available on gram scale.[23] The silyl-based protecting group was installed to sterically prohibit the terminal nitrogen of the hydrazone to act in an undesired nucleophilic capacity.

Notably, our hybrid methods do not require isolation or even warming of the potentially unstable and toxic diazo compounds. Each of the necessary manipulations is carried out in solution at low temperature, and the titer for a given nucleophile is obtained by quenching a stock solution aliquot with a benzoic acid derivative, followed by quantitative analysis. These syntheses can be carried out on gram scale, and the diazoalkane solutions can be stored at –78 ºC for months without degradation. Access to these reagents facilitated our investigation into the

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(22) "A General Procedure for the Esterification of Carboxylic Acids with Diazoalkanes Generated in Situ by the Oxidation of *N*-tert-Butyldimethylsilylhydrazones with (Difluoroiodo)benzene," Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc*. **2004**, *126*, 12222–12223.

(23) "Unsymmetrical azines via triisopropylsilylhydrazine," Pomar, J. C. J.; Soderquist, J. A. *Tet. Lett.* **2000**, *41*, 3285-3290.

regioselective conversion of aldehydes to homologous ketones without the need for unnecessary, stabilizing, electron-withdrawing functional groups within the diazoalkane. Over the course of five years utilizing our procedures, no uncontrolled, destructive decompositions of the diazoalkanes have been observed.

My coworker, David C. Moebius, and I spent considerable time optimizing the modern methods for hydrazone oxidation and applying them to the synthesis of numerous mono- and disubstituted aryl- and alkyldiazomethanes. With Dave's discovery that simple Sc(III) salts are uniquely effective catalysts for diazoalkyl insertion with cycloalkanone electrophiles, my attention turned to the study of catalytically activating formyl electrophiles for the synthesis of acyclic α–substituted carbonyls.[1,24]

1.2 *Sc-catalyzed Homologation of Aldehydes to the Corresponding Ketones with Diazoalkanes.*

Previous studies to accomplish the one carbon homologation of cyclic ketones with substituted diazomethanes uncovered commercially available scandium (III) salts as potent effective catalysts.[22] This method, developed within our laboratory, has proven the unique role of Sc^{3+} as a Lewis acid tolerable of the diazoalkane – itself a strong Lewis base.

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(24) (a) "Catalytic Homologation of Cycloalkanones with Substituted Diazomethanes. Mild and Efficient Single-Step Access to α-Tertiary and α-Quaternary Carbonyl Compounds," Moebius, D. C.; Kingsbury, J. S. *J. Am. Chem. Soc*. **2009**, *131*, 878–879. (b) "Catalytic and Regioselective Ring Expansion of Arylcyclobutanones with Trimethylsilyldiazomethane. Ligand-Dependent Entry to β-Ketosilane or Enolsilane Adducts," Dabrowski, J. A.; Moebius, D. C.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. *Org. Lett.* **2010**, *12*, 3598–3601.

Scandium is typically afforded inclusion in the lanthanide series due to its outer valence shell being isoelectronic with the rare-earth metals, but its natural abundance in the earth's crust would not earn the element the title of extreme scarcity. Scandium, being found in a diverse array of natural mineral deposits, is as abundant as the element cobalt.[25] Cobalt, like the element Iron, is often thought of as a non-precious element and is currently being developed in organic synthesis as both a source of new organometallic reagents and a potential replacement to the more expensive catalysts of the "platinum group" metals.[26] The typical starting point for the synthesis of scandium (III) salts is Sc_2O_3, which is a byproduct of the extractive processes for uranium, iron, nickel, cobalt, tungsten, and the lanthanide rare-earth elements.[27] Scandium(III) has a Lewis acidity profile that places its salts in between the extreme electron acceptor aluminum and the other lanthanides.[27c] $Sc(OTf)_3$ is well known to possess high, chemoselective oxophilicity when employed in reactions containing multiple other strong Lewis bases.[27b] In addition to the electronic nature of the metal, scandium has the smallest ionic radius (0.754 Å) of all the lanthanides.[27c]

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(25) Lide, D. R. In *CRC Handbook of Chemistry and Physics*. CRC Press: Boca Raton, 2004; p 4–28.

(26) "Cobalt-Catalyzed Cross-Coupling Reactions," Cahiez, G.; Moyeux, A. *Chem. Rev.*, **2010**, *110,* 1435–1462.

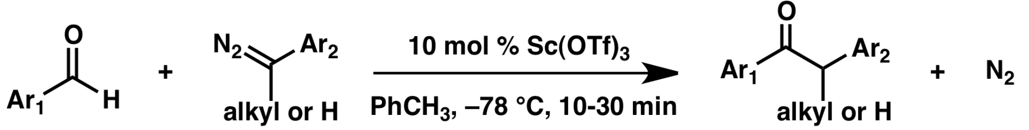
(27) (a) "Scandium Mineralization Associated with Hydrothermal Lazurite-Quartz Veins in the Lower Austroalpie Grobgneis Complex, East Alps, Austria," Bernhard, F. In *Mineral Deposits in the Beginning of the 21st Century*. Balkema: Lisse, 2001. (b) "Rare-Earth Metal Triflates in Organic Synthesis," Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227–2302. (c) "'Asymmetric' Catalysis by Lanthanide Complexes," Mikami, K.; Terada, M.; Matsuzawa, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3554-3572.

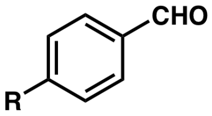
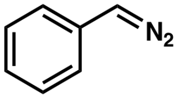
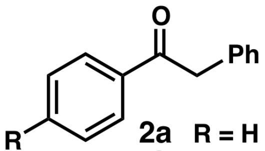
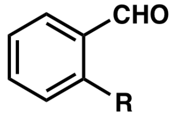
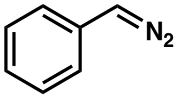
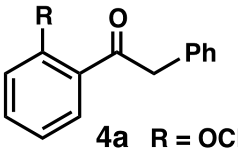
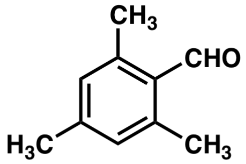
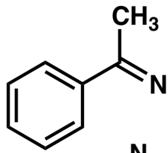
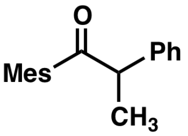
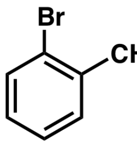
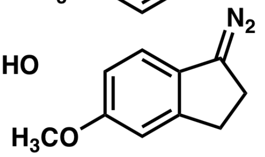
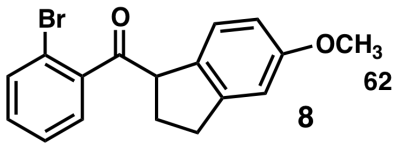
With our starting Lewis acid, we initiated experimentation by employing phenyldiazomethane as the nucleophile in a reaction with benzaldehyde in toluene at –78 ºC. Visual confirmation of the rapid consumption of phenyldiazomethane was noted as a loss of red color and vigorous evolution of nitrogen. Once gas production had decreased to a gentle bubbling and the intensity of the diazoalkane's color had dissipated (10 min), the reaction was warmed to ambient temperature (23 ºC) and worked up immediately by the addition of saturated ammonium chloride solution. The biphasic reaction mixture was then poured into a separatory funnel and the product extracted with diethyl ether. After further purification by silica gel chromatography, 1,2-diphenylethanone was isolated in 98% yield. This illustrates the highly selective nature of 1,2-rearrangement under Sc-catalysis. This initial result was one of great promise, and its planning was devised only after careful reaction optimization on our group's previous method for the selective homologation of cyclic ketones. To confirm the necessity of the $Sc(OTf)_3$, a control experiment was performed wherein the reaction was executed in the absence of the catalyst. After monitoring the reaction progress for over 12 h, no productive union between diazonucleophile and benzaldehyde was observed. After these first results confirmed that $Sc(OTf)_3$ is the optimal catalyst with what appeared to be optimal conditions in hand, we began to probe the scope of the catalytic aldehyde C-H bond modification.

1.3 *Aryl Aldehyde Homologation Reactions.*

As shown in Table 1, the synthesis of desoxybenzoins from aryldiazomethanes and various aryl aldehydes is quite general. At first, maintaining the diazonucleophile as the easily accessible phenyldiazomethane, the sterics and electronics of the electrophile were systematically varied. Insertion reactions involving selected electron-donating (OCH_3 or $N(CH_3)_3$, entries 2 and 3) or electron-withdrawing (NO_2 or CF_3, entries 4, 5) groups situated *para* to the formyl *ipso* carbon all proceed smoothly in >90% yield. Entry 3 is of particular note since the Lewis basic functionality of the *N,N*-dimethylaniline moiety could potentially attenuate catalyst efficacy. Such substituents can also be positioned *ortho* (96% yield for *o*-OCH_3, entry 6), and entries 7 and 8 confirm that halogens are easily tolerated in this more sterically demanding position.

Table 1 Diverse Aryl-Benzyl Alkanones by Catalytic Carbon Insertion.[a]



entry	electrophile	nucleophile	equiv of nucleophile	insertion product	yield (%)[b]
1	 **1a** R = H		1.1	 **2a** R = H	98(93)
2	**b** R = OCH_3		1.1	**b** R = OCH_3	97
3	**c** R = $N(CH_3)_2$		1.1	**c** R = $N(CH_3)_2$	98(89)
4	**d** R = NO_2		1.1	**d** R = NO_2	91
5	**e** R = CF_3		1.1	**e** R = CF_3	97(81)
6	 **3a** R = OCH_3		1.1	 **4a** R = OCH_3	96
7	**b** R = Cl		1.1	**b** R = Cl	95
8	**c** R = F		1.1	**c** R = F	89(88)
9		 **5**	2.0	 **6**	63[c]
10		 **7**	1.1	 **8**	62

[a]Conditions: 10 mol % $Sc(OTf)_3$, –78 °C, 0.2 M in $PhCH_3$; Isolated yields after chromatography. [b]Yield in parentheses with 2 mol % $Sc(OTf)_3$. [c]Run at –45 °C to prevent precipitation of substrate.

We then proceeded to modulated the properties of the diazonucleophile. Results convincingly show that steric crowding in the aldehyde is not a prohibitive constraint either, as seen by the moderately efficient coupling of mesitaldehyde with the internal diazonucleophile methyl phenyl diazomethane (2 equiv, entry 9). A noted modification associated with entry 9 is the cryogenic demands of the electrophile. With a melting point of approximately 12 ºC in its pure form, the extremely hindered benzaldehyde derivative was observed to solidify and precipitate out of the reaction solution at temperatures below –45 ºC. With this single pot operation, the sterically congested aryl ketone **6** is produced that bypasses the probable optimization that would be encountered if a reoxidation event were required following a standard organometallic addition to the mesitaldehyde. Entry 10 shows that cyclic disubstituted (internal) diazomethanes can also be employed. In one-step, the complex acyl indane **8** is formed in 62% isolated yield. Observations that this particular diazoalkane was relatively less stable upon prolonged storage and also during the course of the reaction can be attributed to the electron-rich nature of the diazonucleophile. The decomposition of the diazonucleophile was on the order of weeks when stored under inert atmosphere at –78 ºC, but when in the presence of $Sc(OTf)_3$ the destructive pathways were increased to the order of seconds, as confirmed by ReactIR visualization studies.[28] Fortunately for our purposes, the rate of productive union of the aldehyde electrophile with the non-stabilized diazoalkane was faster than this noted decomposition pathway, as determined by empirical observations of the reaction's efficiency.

Given the efficiency and short reaction times associated with our method, attempts were made to lower the loading of the scandium

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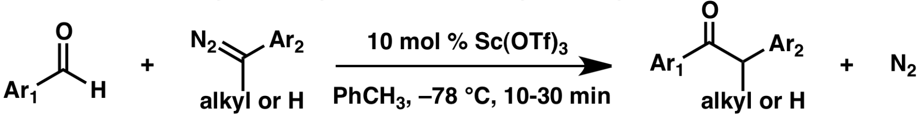
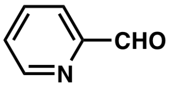
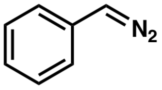
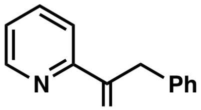
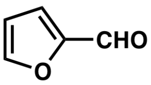
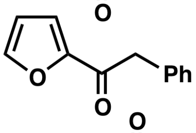
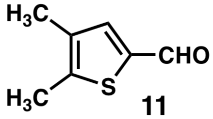
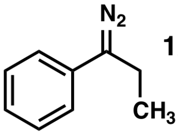
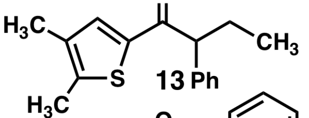
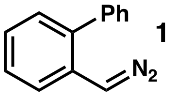
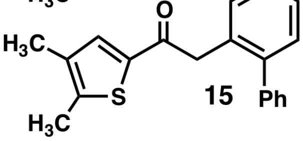
(28) The most prevalent decomposition product for diazoalkane with Sc^{3+} salts was azine mixtures.

catalyst. Thus, reactions were carried out using only 2 mol % $Sc(OTf)_3$ with a total reaction time of 30 min for entries 1, 3, 5, and 8, and the corresponding yields for pure products are 93, 89, 81, and 88%, respectively. These results bode well for the future development of the aldehyde homologation process in a catalytic enantioselective setting.

As seen in Table 2, the homologation procedure is also effective for the selected heteroaromatic carbaldehydes pyridine-2-carboxaldehyde (84% of **9**, entry 1) and furfural (90% **10**, entry 2), which confirms the tolerance of these potential Lewis basic functionality within the heterocycles. Application of carbon insertion to the synthesis of more elaborate ketones that possess chirality is feasible. Entry 10 of Table 1 is one example, and 4,5-dimethylthiophene-2-carbaldehyde **11** engages both the internal diazo compound **12** to form **13** in 82% yield. Finally, it deserves mention that *ortho* substitution is viable in the diazoalkane as well (74% for **15**, entry 4).

Table 2 Heteroaryl-Benzyl Alkanones by Catalytic Carbon Insertion.[a]



entry	electrophile	nucleophile	equiv of nucleophile	insertion product	yield (%)
1			1.1	 **9**	84
2			1.1	 **10**	90
3	 **11**	 **12**	1.1	 **13**	82
4		 **14**	1.1	 **15**	74

[a]Conditions: 10 mol % Sc(OTf)$_3$, –78 °C, 0.2 M in PhCH$_3$; Isolated yields after chromatography. [b]Run at –45 °C to prevent precipitation of substrate.

1.4 *Alkyl Aldehyde Homologation Reactions*

Next it was of interest to explore the access to mixed aryl-alkyl and alkyl-alkyl ketone syntheses through the appropriate combination of aldehyde and diazoalkane (Table 3). Reaction of 2-bromobenzaldehyde with the potentially labile[29] cyclopropyl methyl diazomethane (**16**) affords a chiral aryl-alkyl product in 74% yield (**17**, entry 1, Table 2) with no observable byproducts due to strain release.[30]

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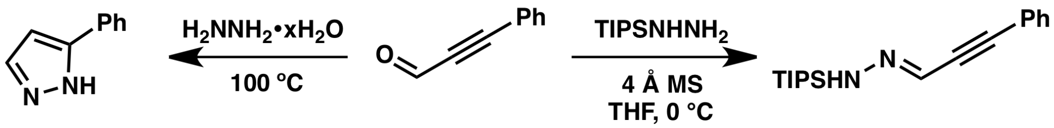
[29] "Synthesis of Cyclobutenes by Highly Selective Transition-Metal-Catalyzed Ring Expansion of Cyclopropane," Xu, H.; Zhang, W.; Shu, D.; Werness, J. B.; Tang, W. *Angew. Chem. Int. Ed.* **2008**, *47*, 8933-8936.

[30] The mixture of *E* and *Z* azine was isolated as the major byproduct accounting for mass recovery.

Entry 2 confirms that alkyl-alkyl ketone synthesis is viable for dialkyl diazomethanes and aliphatic electrophiles that are β–branched (78% of **19**). Even the very hindered electrophile pivaldehyde reacts in a coupling process that is further noteworthy since neither *trans→cis* isomerization of the geranial-derived diazo compound **20** nor bond migration of the β,γ–unsaturated enone **21** into conjugation with the ketone is observed (entry 3). Alkyne-substituted diazoalkanes are also suitable reactants (77% homopropargylic ketone **23**, entry 4) and this particular entry highlights the importance of the monosilyl-based protection strategy that was developed for sensitive unsaturated functionality within the planned diazoalkane.

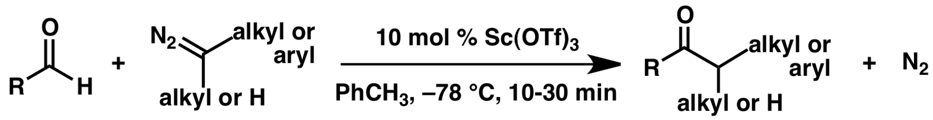
To further illustrate the problematic production of the major heterocyclic byproducts known as either pyrazolines or pyrazoles (based on the level on unsaturation within the heterocycle), we initiated the synthesis of the free, unprotected hydrazone under our standard protocol to obtain aryl-substituted diazomethanes.

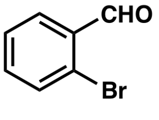
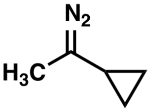
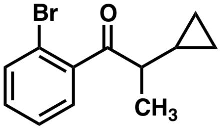
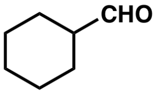
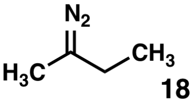
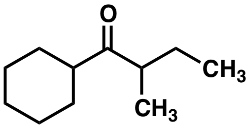
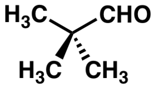
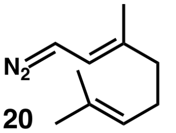
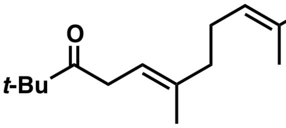
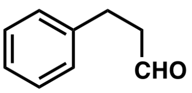
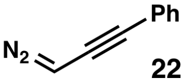
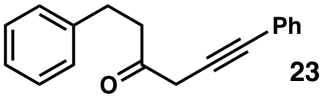
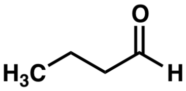
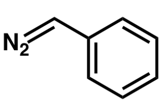
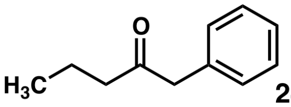
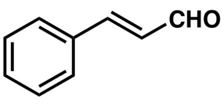
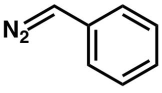
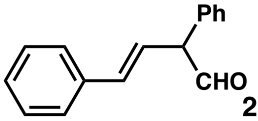
Scheme 10



As shown in Scheme 10, after adding the starting carbonyl compound, 3-phenylpropiolaldehyde, to a flask containing hydrazine hydrate with stirring the flask was sealed and heated to 100 ºC for 10 h. Following the standard extractive workup procedure, the heterocycle 5-phenyl-1*H*-pyrazole was isolated in an unoptimized 72% yield. The alternative monosilyl-hydrazone was produced in quantitative yield, which was subsequently deprotected at low temperature (–78 °C) with tetra-*n*-butylammonium fluoride in THF and immediately oxidized under the Shechter procedure.[20] Although the oxidation to this sensitive alkynyl diazomethane suffered moderate irreproducibility in our hands, upon successful isolation of the diazoalkane solution, the aldehyde homologation reaction was quite efficient.

Table 3 Diverse Alkanones by Catalytic Carbon Insertion.[a]



entry	electrophile	nucleophile	equiv of nucleophile	insertion product	yield (%)
1		 **16**	1.1	 **17**	74
2		 **18**	1.1	 **19**	78
3		**20** 	1.1	 **21**	88
4		 **22**	1.1	 **23**	77
5			1.1	 **24**	87
6			1.1	 **25**	25[b]

[a]Conditions: 10 mol % Sc(OTf)$_3$, –78 °C, 0.2 M in PhCH$_3$, Isolated yields after chromatrography. [b]55% of cinnamyl benzyl ketone was also isolated.

The smooth and complete consumption of phenyldiazomethane in entries 5 and 6 further illustrate the high reactivity of scandium-catalyzed aldehyde activation, but the latter result with cinnamaldehyde is a revealing contrast to that in entry 5: its reaction with phenyldiazomethane gives, along with the expected ketone, 25% of α–aryl aldehyde **25**.[12] Currently, this is the only substrate for which competitive C–C (vs. C–H) insertion has been detected. Empirical studies to clarify the significance of the vinyl group could in principle enable access to such equally useful, α–substituted carbonyls.[31]

1.5 *Isotopic Labeling Experiments*

Given that a vinylic 1,2-C–C bond shift precedes the formation of **25,** an analogous C–H bond migration in the Sc-complexed diazonium betaine could account for the predominance of ketone products (Scheme 11, path a). A pathway involving S_N2 closure to the epoxide (Scheme 2, path c) and subsequent rearrangement has been ruled out by the following control experiments: exposure of either *cis* or *trans*-stilbene oxide to 10 mol % $Sc(OTf)_3$ in toluene at –78 °C cleanly gives diphenylacetaldehyde upon warming. These data are consistent with the results of previous studies on Lewis acid-catalyzed Meinwald

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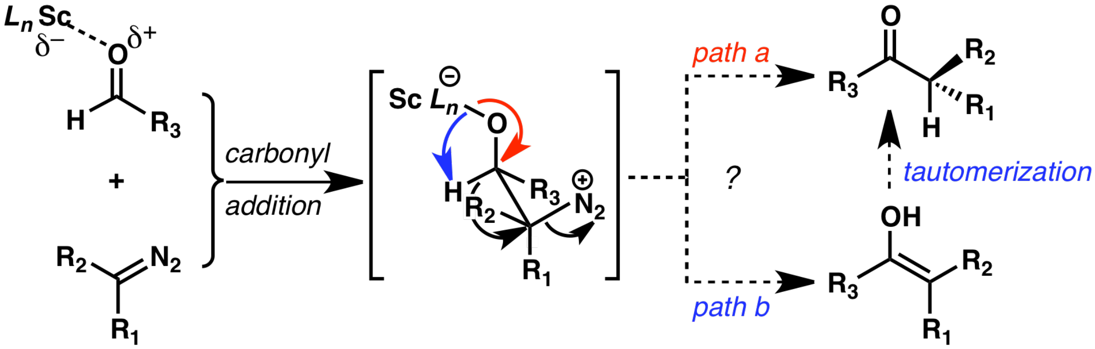
(31) For an example of vinyl migration in the HBF_4 promoted homologation of α,β-unsaturated ketones with diazomethane, see: "A New Reaction of Diazomethane with α,β-Unsaturated Ketones," Johnson, W. S.; Neeman, M.; Birkeland, S. P. *Tetrahedron Lett.* **1960**, *1*, 1-5.

rearrangement studies in several laboratories.[32] Nonetheless, a third plausible mechanism would involve intermolecular E2 elimination of N_2 to give an enol intermediate followed by tautomerization (Scheme 11, path b). Due to previous studies, an intramolecular tautomerization is ruled out due to the prohibitively high energy barrier associated with the 1,3 shift.[33]

Scheme 11



To distinguish between these two possibilities, the double isotopic labeling experiment illustrated in Scheme 12 was performed. Scandium-catalyzed homologation of a 1:1 mixture of perdeuteriobenzaldehyde and benzaldehyde with 3-diazocyclohex-1-ene gives *only* the products of intramolecular C–H transfer (Scheme 11, path a) according to high-

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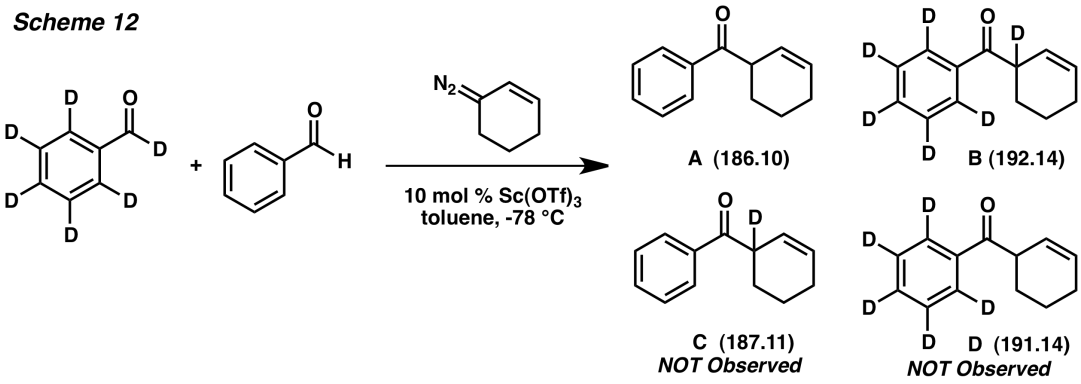
(32) (a) "Highly Regioselective Rearrangement of 2,3-Diaryloxiranes into 2,2-Diarylacetaldehydes Catalyzed by Ytterbium Porphyrin Complex, Yb(TPP)OTf," Takanami, T.; Nakajima, S.; Nakadai, S.; Hino, F.; Suda, K. *Heterocycles* **2009**, *77*, 365-374. (b) "Epoxide Ring-Opening and Meinwald Rearrangement Reactions of Epoxides Catalyzed by Mesoporous Aluminosilicates." Robinson, M. W. C.; Davies, A. M.; Buckle, R.; Mabbett, I.; Taylor, S. H.; Graham, A. E. *Org. Biomol. Chem.* **2009**, *7*, 2559-256. (c) "Efficient Rearrangement of Epoxides Catalyzed by a Mixed-Valent Iron Trifluoroacetate [$Fe_3O(O_2CCF_3)_6(H_2O)_3$]." Ertürk, E.; Göllü, M.; Demir, A. S. *Tetrahedron* **2010**, *66*, 2373-2377. (d) "Copper(II) Tetrafluoroborate-Promoted Meinwald Rearrangement Reactions of Epoxides." Robinson, M. W. C.; Pillinger, K. S.; Mabbett, I.; Timms, D. A.; Graham, A. E. *Tetrahedron* **2010**, *66*, 8377-8382.

(33) (a) "A Quantum Mechanical Study of the Mechanism of the Enol-Ketone Tautomerism," Klopman, G.; Andreozzi, P. *Bull. Soc. Chim. Belg.* **1979**, *88*, 875-882. (b) "Ab Initio Molecular Dynamics Study of the Keto–Enol Tautomerism of Acetone in Solution," Cucinotta, C. S.; Ruini, A.; Catellani, A.; Stirling, A. *ChemPhysChem* **2006**, *7*, 1229-1234.

resolution mass spectrometric analysis and none of the products **C** and **D**, which would result from isotopic scrambling during the tautomerization event.

Scheme 12



Using the relatively new instrumentation referred to as Direct Analysis in Real Time (DART™) that is coupled to the AccuTOF-LC™ atmospheric pressure ionization mass spectrometer, the minimally purified product mixture was observed at high-resolution with exact mass measurements for all components therein. This instrument was commercialized by Cody and Laramée for the JEOL company in 2005.[34]

DART is based on the atmospheric pressure interactions of long-lived electronic excited-state atoms or molecules with the sample and the surrounding atmospheric gases. A cut-away schematic of the DART ion source is shown in Figure 1.

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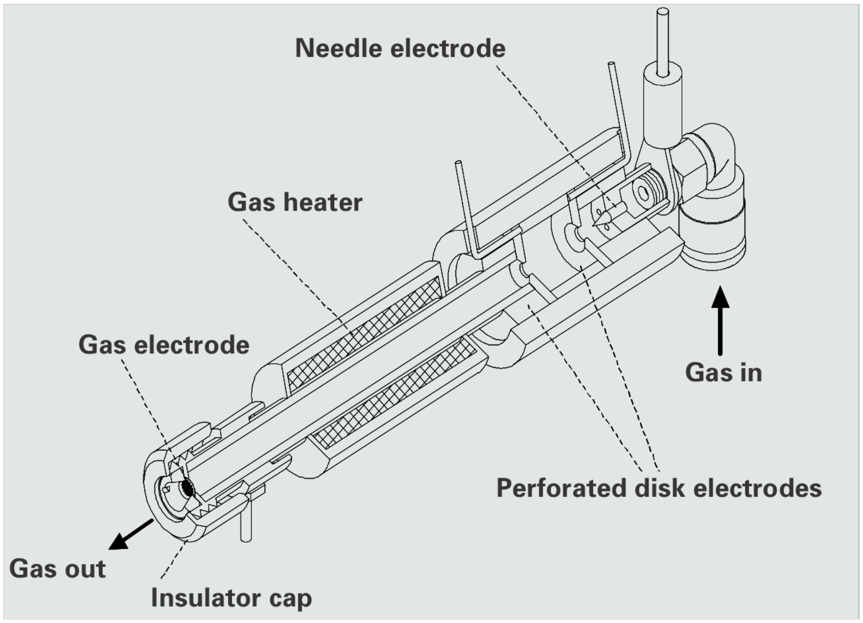
(34) (a) "Versatile New Ion Source for the Analysis of Materials in Open Air under Ambient Conditions," Cody, R. B.; Laramée, J. A.; Durst, H. D. *Anal. Chem.* **2005**, *77*, 2297–2302. (b) "Direct mass spectrometric analysis of flavors and fragrances in real applications using DART," Haefliger, O.P.; Jeckelmann, N. *Rapid Commun. Mass Spectrom.* **2007**, *21*, 1361–1366.

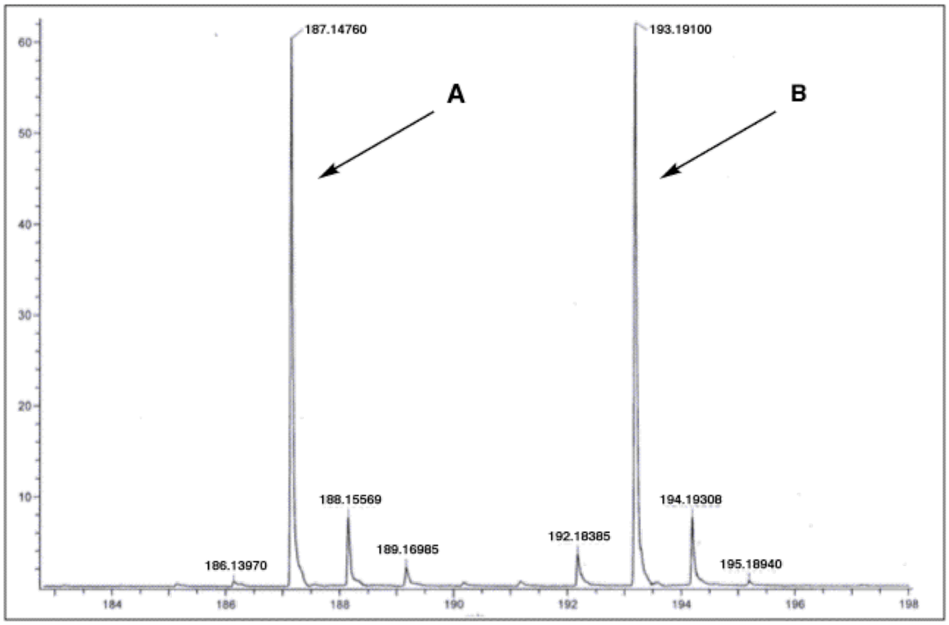
***Figure 1*:** Schematic Diagram of DART Ion Source



reproduced from ref. 33a

A gas (typically helium or nitrogen) flows through a chamber where an electrical discharge produces ions, electrons, and excited-state (metastable) atoms and molecules (He* or $H_2O^{\bullet+}$). Most of the charged particles are removed as the gas passes through perforated lenses or grids and only the neutral gas molecules, including metastable species, remain. A perforated grid at the exit of the DART provides several functions: (1) it prevents ion-ion and ion-electron recombination, (2) it acts as a source of electrons by surface Penning ionization, and (3) it serves as an electrode to promote ion drift toward the orifice of the mass spectrometer's atmospheric pressure interface via simple electrostatic interactions. This provides the opportunity for the Penning ionization to be in a “filtered ambient atmosphere” so that the metastable species ionize atmospheric oxygen and/or water, which in turn provides the necessary ionization energy to produce ionized species of the analyte.[33a] The unique technique provides the mass spectrometrist a method to analyze samples as the intermediates form in their most fleeting moments (in “Real Time”). For example, 2-propenesulfenic acid and its isomer propanethial *S*-oxide have been successfully detected prior to rearrangement to allicin upon the slicing of a garlic clove.[35] The method is particularly attractive to organic chemists[36] due to its capacity to identify analytes that are combined as a mixture with closely related compounds, as in our isotopic labeling experiment.[35]

***Figure 2*:** Mass Spectrum for Isotopic Labeling Experiment



The readout for our isotopic labeling experiment (Scheme 12) is shown in Figure 2 and reveals the complete transformation of starting materials to products **A** and **B**. There is clearly a predominance of peaks corresponding to $[M+H]^+$ for structures **A** and **B**. Although the peaks at 188.1557 and 192.1839 could in principle correspond to deuterium crossover structures **C** and **D**, analogous control experiments carried out with only benzaldehyde or d_6-benzaldehyde generate high-resolution mass spectra identical to the individual mass distributions seen in Figure 2. The presence of these signals is attributed to the natural abundance of ^{13}C and the starting level of enrichment in the commercial d_6-benzaldehyde. Overall, the fact that aldehyde homologation proceeds by stereospecific intramolecular C–H bond migration bodes well for the future development of a catalytic asymmetric carbon insertion reaction with formyl acceptors.

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[35] "Applications of Direct Analysis in Real Time–Mass Spectrometry (DART-MS) in *Allium* Chemistry. 2-Propenesulfenic and 2-Propenesulfinic Acids, Diallyl Trisulfane 'S'-Oxide and Other Reactive Sulfur Compounds from Crushed Garlic and Other Alliums,” Block, E.; Dane, A. J.; Thomas, S.; Cody, R. B. *J. Agric. Food Chem.* **2010**, *58*, 4617–4625.

[36] “HRMS Directly From TLC Slides. A Powerful Tool for Rapid Analysis of Organic Mixtures,” Smith, N. J.; Domin, M. A.; Scott, L. T. *Org. Lett.* **2008**, *10*, 3493–3496.

1.6 *Biological Relevance of Achyrofuran.*

As a test of the utility of catalytic carbon insertion with a complex aldehyde, we commenced a total synthesis of the naturally occurring antihyperglycemic agent achyrofuran.[37] Achyrofuran is isolated from the plant *Achyrocline satureioides* and is commonly known in Brazil as macela or marcela (see Figure 3). This molecule contains two differentially oxygenated prenyl groups on a dibenzofuran core and has a long history

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(37) "Achyrofuran, a New Antihyperglycemic Dibenzofuran from the South American Medicinal Plant *Achyrocline satureioides,"* Carney, J. R.; Krenisky, J. M.; Williamson, R. T.; Luo, J. *J. Nat. Prod.* **2002**, *65*, 203-205.

in traditional South American medicine[38] More specifically, it shows considerable promise as a competitive inhibitor of AMP at the allosteric regulatory site of fructose 1,6-bisphosphatase (FBPase), which is a key enzyme in the liver for the gluconeogenesis pathway.[39] This allosteric site is also the biological target of fructose-2,6-bisphosphate. When this small phosphorylated biomolecule is produced, as a function of high blood sugar levels, the enzymatic conversion of fructose-1,6-bisphosphate to fructose-6-phosphate is diminished. This step in the gluconeogenesis pathway is often described as the rate-limiting step in the production of glucose from smaller precursor biomolecules.

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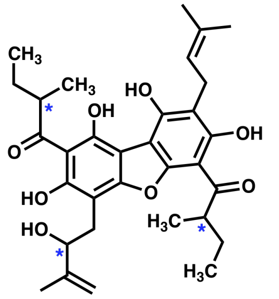
(38) (a) "Effects of Hydroalcoholic Extracts of *Portulaca pilosa* and *Achyrocline satureioides* on Urinary Sodium and Potassium Excretion," Rocha, M. J. A.; Fulgencio, S. F.; Rabetti, A. C.; Nicolau, M.; Simoes, C. M. O.; Ribeiro-do-Valle, R. M. *J. Ethnopharmacol*. **1994**, *43*, 179–183. (b) "Polyphenols from *Achyrocline satureioides,"* Ferraro, G. E.; Norbedo, C.; Coussio, J. D. *Phytochemistry* **1981**, *20*, 2053–2054. (c) "Flavonoids from Four Compositae Species," Mesquita, A. A. L.; Correa, D. B.; De Padua, A. P.; Guedes, M. L. O.; Gottlieb, O. R. *Phytochemistry* **1986**, *25*, 1255–1256. (d) "Isolation of a Kawa-pyrone from *Achyrocline satureioides,*" Kaloga, M.; Hänsel, R.; Cybulski, E.-M. *Plant Med.* **1983**, *48*, 103–104. (e) "Immunologically Active Metallic Ion-Containing Polysaccharides of *Achyrocline satureioides,"* Puhlmann, J.; Knaus, U.; Tubaro, L.; Schaefer, W.; Wager, H. *Phytochemistry* **1992**, *31*, 2617–2621.

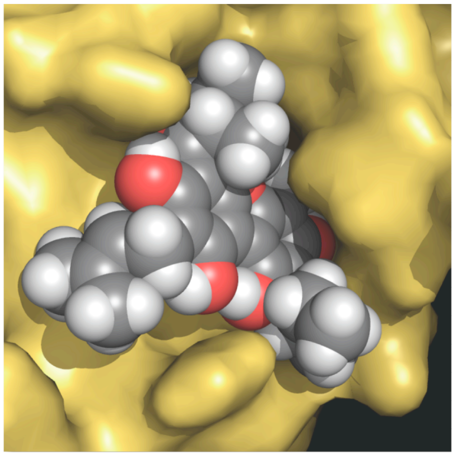
(39) (a) "Designing Inhibitors Against Fructose 1,6-bisphosphatase: Exploring Natural Products for Novel Inhibitor Scaffolds," Heng, S.; Harris, K. M.; Kantrowiz, E. R. *Eur. J. Med. Chem.* **2010**, *45*, 1478-1484. (b) Kobayashi, Y.; Yamaguchi, Y.; Takeda, N.; Kubota, S.; Miyata, O.; Naito, T.; Tagawa, N. Proceedings of the International Congress of Endocrinology, 13th, Rio de Janeiro, Brazil, Nov. 8-12, 2008, 349-352.

Figure 3: Achyrofuran, an Antihyperglycemic Dibenzofuran from the South American Medicinal Plant *Achyrocline satureioides*

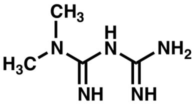


relative and absolute stereochemistry unknown

J. Nat. Prod. **2002**, *65*, 203-205



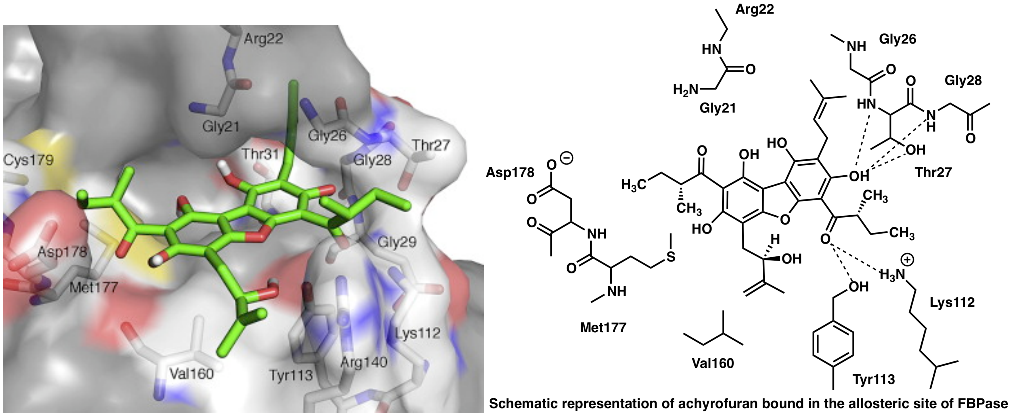
Docking simulation with achyrofuran bound in the allosteric regulatory site of FBPase.
reproduced from ref. 37a



Metformin (Glucophage^{TM})
(BMS, FDA approval in 1994)

Currently, the same allosteric site naturally occupied by fructose-2,6-bisphosphate is the site of therapeutic action by the biguanide pharamaceutical metformin, known as Glucophage™ by Bristol-Myers Squibb and Janumet™ by Merck (see Figure 3). As shown in Figure 4, the Kantrowitz group at Boston College has completed initial *in silico* docking studies whereby the natural product achyrofuran, as one potential diastereomer, was found to tightly dock in this allosteric site by way of five hydrogen-bonding interactions and nine hydrophobic interactions.[37c]

Figure 4: Docking Simulation


Arg22
Gly21
Gly26
Thr27
Cys179
Thr31
Gly28
Asp178
Gly29
Met177
Lys112
Val160
Tyr113
Arg140
Arg22
HN
O
H_2N
Gly21
NH
Gly26
O
Gly28
HN
N
H
O
OH
Thr27
Asp178
O
O
O
HO
OH
O
H_3C
CH_3
OH
CH_3
CH_3
HO
O
H
OH
O
H_3N
Lys112
OH
NH
S
NH
Met177
Val160
Tyr113

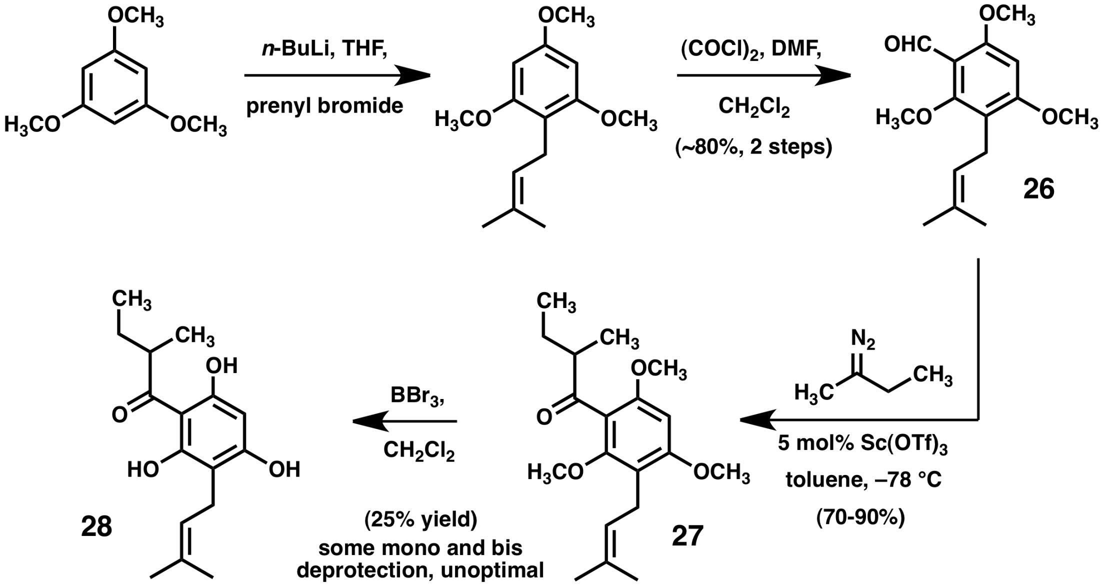
Schematic representation of achyrofuran bound in the allosteric site of FBPase

1.7 *Synthesis of Preachyrofuran.*

Initially, a synthetic strategy was chosen that alleviates the challenge associated with early installation of the stereodefined allylic alcohol in one of the two prenyl domains. This synthetic plan is attractive because it allows the complete carbon framework of the natural product to be prepared in approximately five steps by way of biomimetic oxidative dimerization.

The pathway of synthesis of the monomer needed for homodimerization is shown in Scheme 13. Starting from the 1,3,5-trimethoxybenzene, the prenyl group was installed using a standard aryl lithiation/alkylation event. The resulting tetrasubstituted arene is then formylated under Vilsmeier-Haack conditions. Reaction of 2-diazobutane with the complex benzaldehyde **26** gives the desired dialkylated trimethoxybenzene (**27**) in high yield. It was during attempted global demethylation that the synthetic efficiency initially suffered. Only a 25% isolated yield of the desired disubstituted triphenol can be obtained using the standard deprotecting agent boron tribromide under forcing conditions.[40] It was at this point that a thorough scan of the literature identified an equally reactive but potentially less acidic de-etherification protocol.

Scheme 13: Initial Forward Synthetic Progress to Triol Monomer



We suspected that tautomerization to the corresponding enol of ketone **27** can occur under the strongly Lewis acidic condition, possibly triggering decomposition pathways including Aldol reactions. Therefore, a

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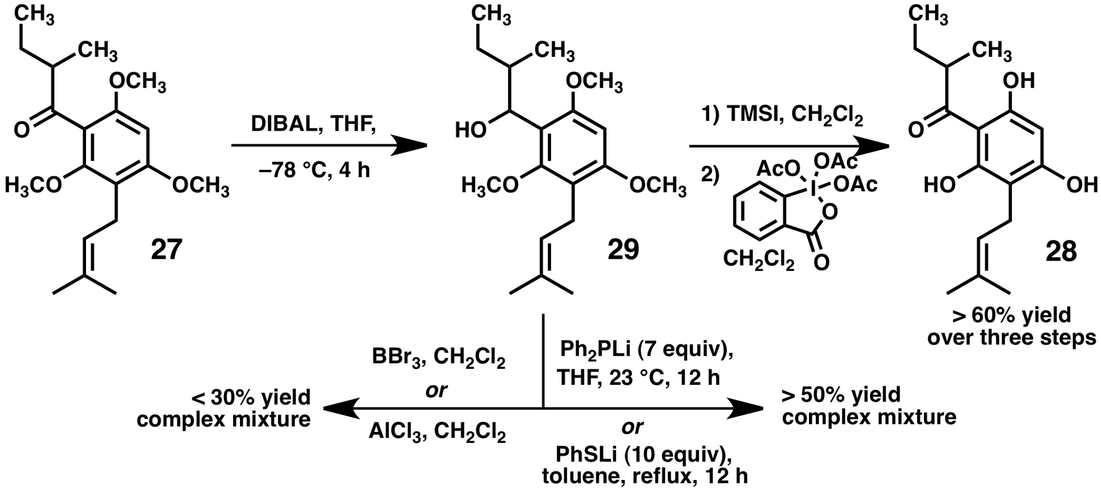
(40) For selected examples in synthesis, see: (a) "A Concise Total Synthesis of Triptolide," Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K.-W.; Zou, N.; Letcher, R. M. *J. Org. Chem.* **1998**, *63,* 6446–6447. (b) "A Rationally Designed Prototype of a Molecular Motor," Kelly, T. R.; Silva, R. A.; De Silva, H.; Jasmin, S.; Zhao, Y. *J. Am. Chem. Soc.* **2000**, *122*, 6935-6949. (c) "Syntheses and ^{1}H NMR Spectroscopy of Rigid, Cofacially Aligned, Porphyrin–Bridge–Quinone Systems in Which the Interplanar Separations between the Porphyrin, Aromatic Bridge, and Quinone Are Less than the Sum of Their Respective van der Waals Radi," Iovine, P. M.; Kellett, M. A.; Redmore, N. P.; Therien, M. J*J. Am. Chem. Soc.* **2000**, *122,* 8717-8727. (d) "Synthesis of Tetracyclic Heterocompounds as Selective Estrogen Receptor Modulators. Part 1. Process Development for Scale-up of 2,5,8-Substituted 5,11-Dihydrochromeno[4,3-*c*]chromene Derivatives," Li, X.; Reuman, M.; Russell, R. K.; Adams, R.; Ma, R.; Beish, S.; Branum, S.; Youells, S.; Roberts, J.; Jain, N.; Kanojia, R.; Sui, Z. *Org. Process Res. Dev.* **2007**, *11*, 414-421. (e) "Construction of Peptoids with All *Trans*-Amide Backbones and Peptoid Reverse Turns via the Tactical Incorporation of *N*-Aryl Side Chains Capable of Hydrogen Bonding," Stringer, J. R.; Crapster, J. A.; Guzei, I. A.; Blackwell, H. E. *J. Org. Chem.* **2010**, *75*, 6068-6078.

three-step sequence was envisioned to prohibit the formation of byproducts beginning with simple reduction of the carbonyl to the secondary alcohol (Scheme 13). Although application of the BBr_3 conditions was met with a slight increase in the yield of the triphenol corresponding to **29**, the search for an entirely different reagent was desirable in order to elevate the yield of the transformation to synthetically useful levels. The BBr_3 protocol was still delivering significant levels of byproducts that may be due to the hydrobromination of the trisubstituted alkene.[41] Briefly, trichloroalane was tested as a substitute in the reaction, but to no avail; the production of a complex and impure reaction mixture was obtained (Scheme 14). In turn this outcome prompted us to screen alternative deprotection reagents that would not generate such an acidic reaction medium.

Scheme 14: Overcoming the Global Demethyaltion Hurdle to Access the Triol Monomer



CH3
CH3
OCH3
O
H3CO
OCH3
27
DIBAL, THF,
–78 °C, 4 h
CH3
CH3
OCH3
HO
H3CO
OCH3
29
1) TMSI, CH2Cl2
2) AcO OAc I OAc O O
CH2Cl2
CH3
CH3
OH
O
HO
OH
28
> 60% yield over three steps
BBr3, CH2Cl2
or
AlCl3, CH2Cl2
< 30% yield complex mixture
Ph2PLi (7 equiv), THF, 23 °C, 12 h
or
PhSLi (10 equiv), toluene, reflux, 12 h
> 50% yield complex mixture

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[41] "Shortcut Syntheses of Naturally Occurring 5-Alkylresorcinols with DNA-Cleaving Properties," Fürstner, A.; Seidel, G. *J. Org. Chem.*, **1997**, *62*, 2332–2336.

The transformation was attempted with lithium dipheynylphosphide and the lithium anion of benzenethiol with hopes that a soft anion could offer a mechanism of nucleophilic deprotection under basic conditions.[42] It is known that these nucleophiles are effective due to the resonance stabilization of the phenolate anion that engenders the appropriate level of *O*-Me bond weakening. Yields exceeding 50% were recorded for both of these reagents, but each reaction also produced complex crude reaction mixtures (Scheme 14). The recognition of trimethylsilyl iodide as a highly active reagent in previous deprotection settings for phenolic methyl ethers encouraged us to try this reagent.[43] Following its careful purification, trimethoxy benzyl alcohol **29** was effectively deprotected. A nearly quantitative oxidation of the alcohol to the desired ketone **28** with Dess-Martin periodinane[44] provides a 60% isolated yield over three-steps that are highly reproducible (Scheme 14).

---

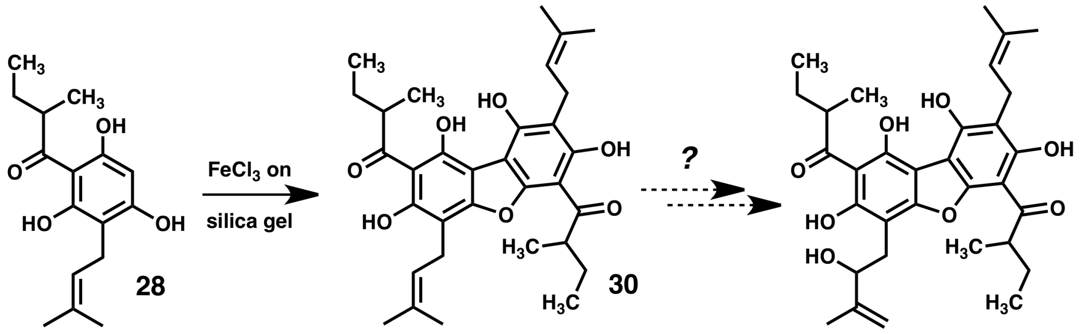
(42) Representative examples for the phosphide and sulfide demethylation reactions, respectively: (a) "Formal Total Synthesis of (+)-Diepoxin σ," Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319-6337. (b) "Total Synthesis of (−)-Macrocarpal C. Stereoselective Coupling Reaction with a Novel Hexasubstituted Benzene $Cr(CO)_3$ Complex as a Biomimetic Chiral Benzyl Cation Equivalent," Tanaka, T.; Mikamiama, H.; Maeda, K.; Iwata, C.; In, Y.; Ishida, T. *J. Org. Chem.* **1998**, *63*, 9782-9793.

(43) (a) "Selective *O*-Demethylation of Catechol Ethers. Comparison of Boron Tribromide and Iodotrimethylsilane," Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444–4446. For selected examples in various synthetic settings, see: (b) "Synthesis and Antitumor Activity of New Glycosides of Epipodophyllotoxin, Analogues of Etoposide, and NK 611," Daley, L.; Guminski, Y.; Demerseman, P.; Kruczynski, A.; Etiévant, C.; Imbert, T.; Hill, B. T.; Claude Monneret, C. *J. Med. Chem.* **1998**, *41*, 4475–4485. (c) "Synthesis and Characterization of a Blue Light Emitting Polymer Containing Both Hole and Electron Transporting Units," Lu, J.; Hlil, A. R.; Sun, Y.; Hay, A. S.; Maindron, T.; Dodelet, J.-P.; D'Iorio, M. *Chem. Mater.* **1999**, *11*, 2501-2507.

(44) (a) "A Useful 12-I-5 Triacetoxyperiodinane (The Dess-Martin Periodinane) for the Selective Oxidation of Primary or Secondary Alcohols and a Variety of Related 12-I-5 Species," Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. (b) "Acceleration of the Dess-Martin Oxidation by Water," Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.*, **1994**, *59*, 7549–7552.

After successful tri-demethylation, the triphenol **28** undergoes efficient regioselective oxidative dimerization and dehydrative furan ring closure to give “pre-achyrofuran” **30**, a structure that is likely the biosynthetic precursor of the natural product (Scheme 15). A minor byproduct produced was the homodimer of the triphenol, which could be resubjected to the oxidative conditions for ring closure.

Scheme 15: Biomimetic Oxidative Dimerization to Deliver "Pre-achyrofuran"



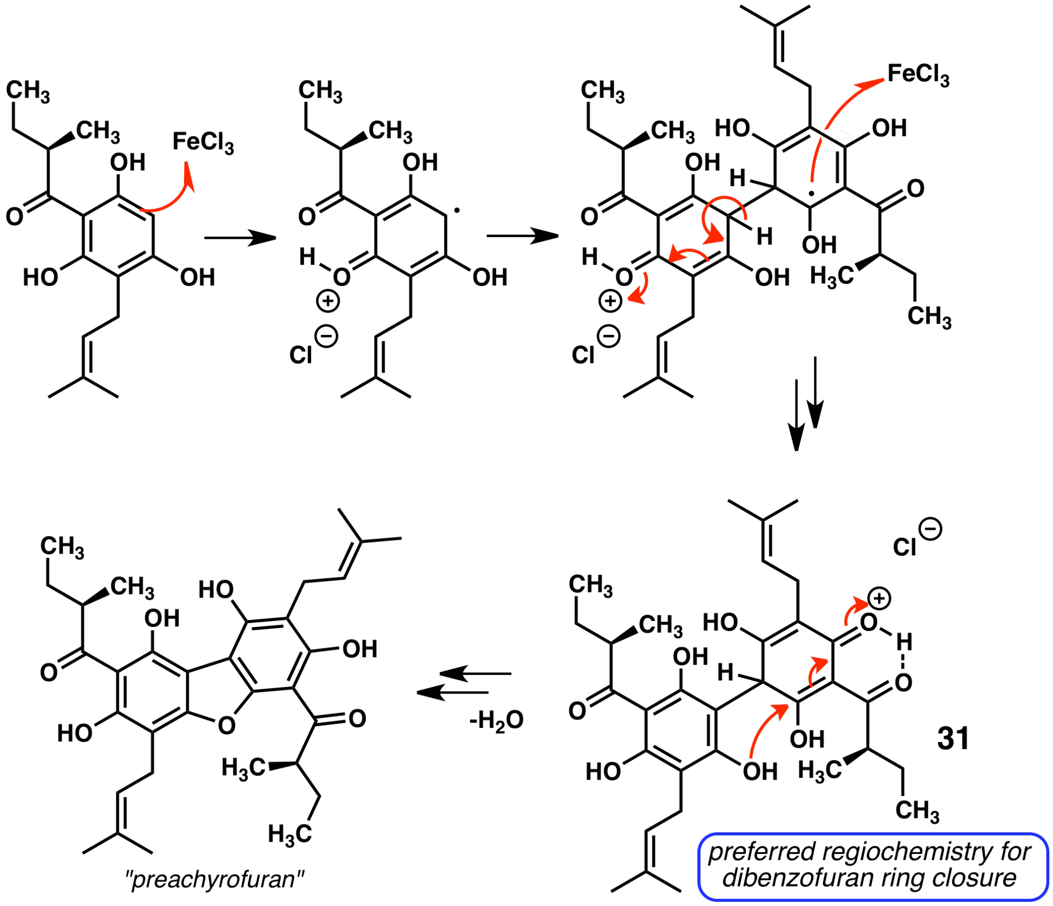
"pre-achyrofuran"
(40-50% along with uncyclized homodimer)

achyrofuran

Site-selective functionalization
and
separation of diastereomers
for
structural confirmation

At first glance the basis for a perfectly regioselective cyclization may not be obvious. However, upon analysis of the dimerized product **31**, the most nucleophilic phenolic oxygen and the site of highest electrophilicity can be easily rationalized (Scheme 16).

Scheme 16: Proposed Biomimetic Oxidative Dimerization Mechanism



"preachyrofuran"

preferred regiochemistry for dibenzofuran ring closure

To assess which phenolic hydroxyl group is more electron rich, and therefore a better nucleophile, we considered the dimerized cation intermediate **31** (Scheme 16). The oxygen that is *para* to the acyl substituent, or farther away from the electron-withdrawing group in an inductive sense, possesses a greater nucleophilicity than the other two phenolic oxygens situated *ortho* to the acyl group. Of the two potential sites for Michael addition to the cyclic dienone moiety, the indicated carbon in **31** is a more electrophilic β–carbon because it is doubly activated thanks to the proximal the acyl group. It deserves mention that the Fe(III)-catalyzed dimerization afford only uncyclized homodimer as the coproduct, and we are confident that further improvement by optimization is likely.

1.8 *Further Synthetic Studies to Confirm the Natural Diastereomer of Achyrofuran.*

The final step in Nature's synthesis of achyrofuran likely proceeds via enzyme-mediated oxidation of the prenyl group with allylic transposition.[45] Although the absolute and relative configuration of achyrofuran still remains unknown, synthetic studies toward the target remain ongoing in our group. Several approaches are currently being evaluated. First among these involve attempts to install differentially oxidized prenyl groups by palladium-catalyzed coupling and modification of the protection strategy for the phenolic alcohols.

Following a known procedure the two-step protection to incorporate benzyl ethers on the naturally occurring phloroglucinol starting material,[46,47] the 1,3,5-tris(benzyloxy)benzene is monobrominated quantitatively by modification of a previously reported method (Scheme

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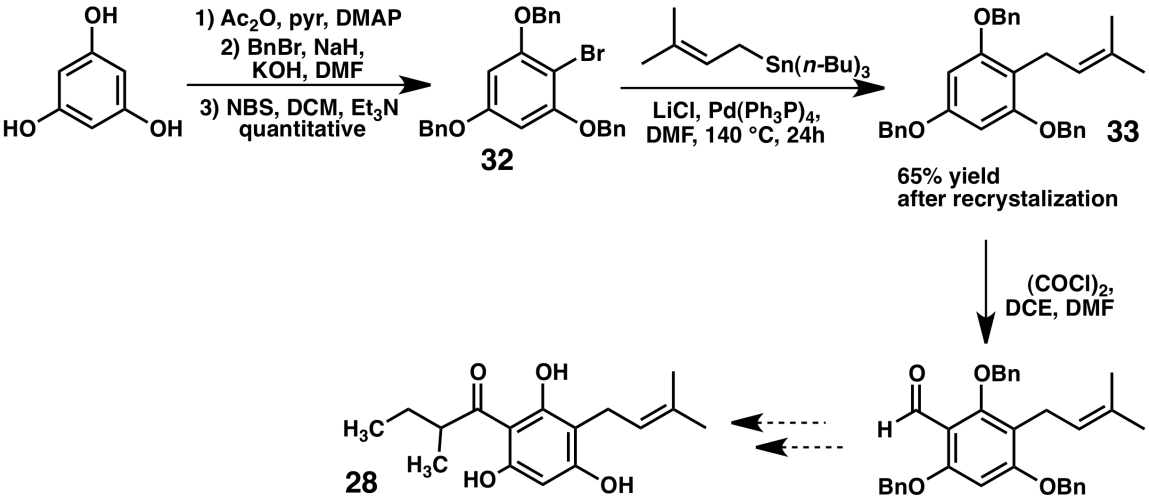
(45) (a) "A Novel Construction of Dibenzofuran-1,4-diones by Oxidative Cyclization of Quinone-arenols," Takeya, T.; Kondo, H.; Otsuka, T.; Tomita, K.; Okamoto, I.; Tamur, O. *Org. Lett.* **2007**, *9*, 2807–2810. (b) "A Biomimetic Strategy for the Synthesis of the Tricyclic Dibenzofuran-1,4-dione Core of Popolohuanone," Anderson, J. C.; Denton, R. M.; Wilson, C. *Org. Lett.* **2005**, *7*, 123–125.

(46) For recent examples, see: (a) "A New Phloroglucinol Derivative from the Brown Alga *Eisenia bicyclis*: Potential for the Effective Treatment of Diabetic Complication," Okada, Y.; Ishimaru, A.; Suzuki, R.; Okuyama, T. *J. Nat. Prod.* **2004**, *67*, 103–105. (b) "Phloroglucinol Derivatives from Three Australian Marine Algae of the Genus Zonaria," Blackman, A. J.; Rogers, G. I.; Volkman, J. K. *J. Nat. Prod.* **1988**, *51*, 158–160.

(47) "*O*-Benzylation of Phloroglucinol via Phloroglucinol Acetate," Haruo, K.; Fumiaki, N.; Murakami, K. *Synth. Comm*. **1996** , *26*, 531 – 534.

17).[48] The protected bromoarene **32** is then subjected to palladium catalyzed Stille coupling[49] with tributyl(3-methyl-2-butenyl)stannane[50] to afford prenyl-substituted arene **33** in 65% yield after recrystallization from hot methanol. Following the Vilsmeier formylation and aldehyde homologation as before (*vida supra*), the benzyl groups can be hydrogenatively deprotected to deliver the same monomer as previously synthesized (**28**).

Scheme 17: Continued Evolution of Synthetic Route


OH
HO
OH
1) Ac2O, pyr, DMAP
2) BnBr, NaH, KOH, DMF
3) NBS, DCM, Et3N
quantitative
OBn
Br
BnO
OBn
32
Sn(n-Bu)3
LiCl, Pd(Ph3P)4, DMF, 140 °C, 24h
OBn
BnO
OBn
33
65% yield
after recrystalization
(COCl)2, DCE, DMF
O
OBn
H
BnO
OBn
O
OH
H3C
H3C
HO
OH
28

One possible strategy is to homodimerize acylbromoarene **34** under oxidative conditions and then use well-timed Stille couplings to install the necessary prenyl domains (Scheme 18, eq *i*). If the acylbromoarene **34** fails to undergo efficient oxidative dimerization or the

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(48) "Synthesis and Structure Revision of Calyxin Natural Products," Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. of Org. Chem.* **2006** , *71*, 3176 – 318.

(49) For the role of inorganic salt addition to Stille coupling reactions, see: "Cuprous Chloride Accelerated Stille Reactions. A General and Effective Coupling System for Sterically Congested Substrates and for Enantioselective Synthesis," Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121,* 7600-7605.

(50) "Addition of Allylstannanes to an Oxy-Stabilized Carbenium Ion on a 1,7-Dioxaspiro[5.5]undecane Ring System," Brimble, M. A.; Fares A. F.; Turner, P. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 677-678.

Stille reaction cannot be performed with the oxygenated prenyl tin(IV) reagent, then "preachyrofuran" could be intercepted by a cycloaddition reaction with singlet oxygen, known as the Schenck ene reaction. This would be followed by a reduction of the intermediate peroxide to secure a separable mixture of diastereomers for structure determination purposes (Scheme 18, eq *ii*).[51] Literature precedent does show promise for the desired chemoselectivity of the Schenck ene reaction on the aromatic prenyl group with the empirical development of the "*cis* effect" and "geminal effect".[52] If the stoichiometry of the reactive oxygen species relative to the benzofuranoid substrate proves too untamed, then the Schenck reaction can be employed during the monomeric stage (Scheme 18, eq. *iii*). Following biomimetic oxidative dimerization with the unoxygenated counterpart (**28**), the statistical mixture of constitutional

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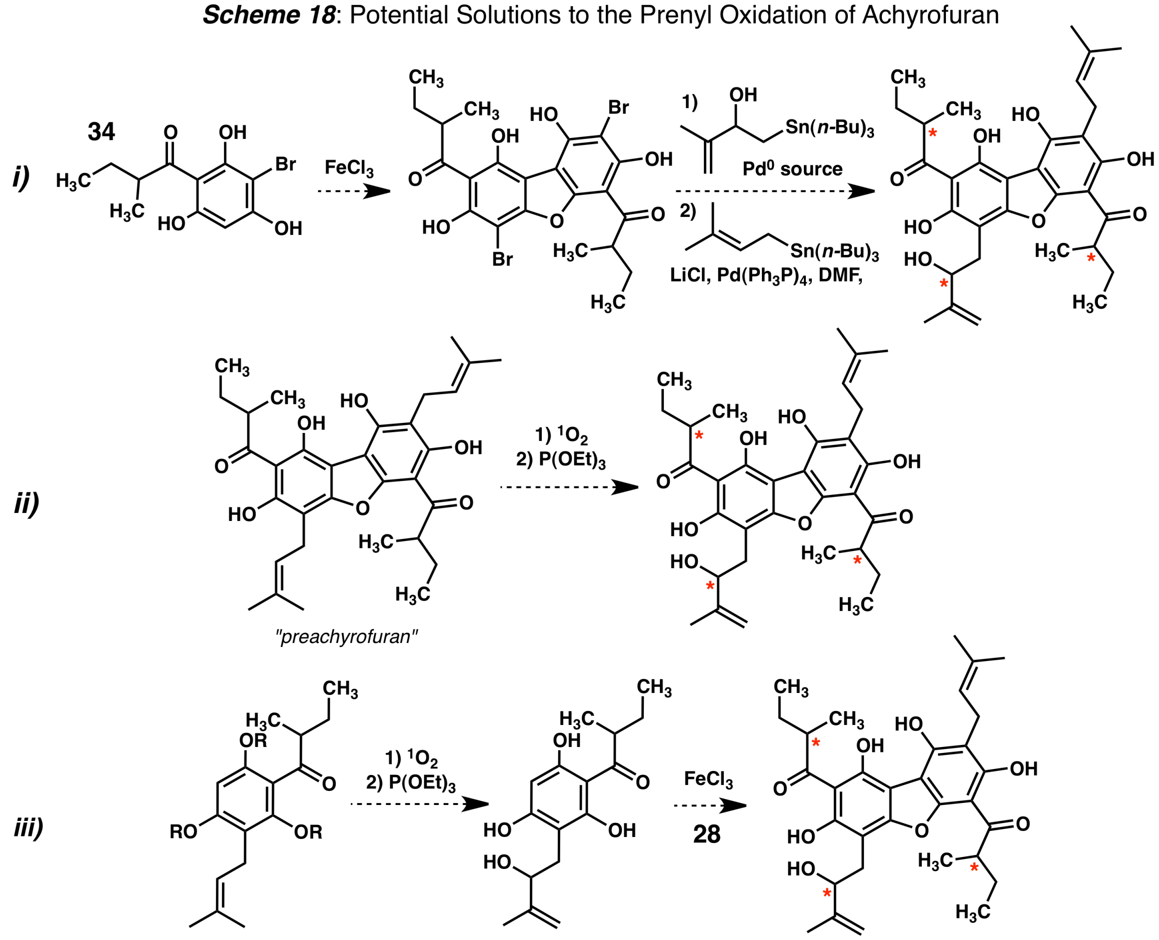
(51) For a review of singlet oxygen in organic synthesis, see: (a) "Singlet Oxygen in Organic Synthesis," Wasserman, H. H.; Ives, J. L. *Tetrahedron* **1981**, *37*, 1825-1852. For selected modern examples, see: (b) "Diastereoselective Singlet Oxygen Ene Reaction (Schenck Reaction) and Diastereoselective Epoxidations of Heteroatom-Substituted Acyclic Chiral Olefins: A Mechanistic Comparison," Adam, W.; Brünker, H.-G.; Kumar, A. S.; Peters, E.-M.; Peters, K.; Schneider, U.; von Schnering, H. G. *J. Am. Chem. Soc.* **1996**, *118*, 1899–1905. (c) "Ene Reaction of Singlet Oxygen, Triazolinedione, and Nitrosoarene with Chiral Deuterium-Labeled Allylic Alcohols: The Interdependence of Diastereoselectivity and Regioselectivity Discloses Mechanistic Insights into the Hydroxy-Group Directivity," Adam, W.; Bottke, N.; Krebs, O.; Lykakis, I.; Orfanopoulos, M.; Stratakis, M. *J. Am. Chem. Soc.* **2002**, *124*, 14403-14409. (d) "Kinetics of the Oxygenation of Unsaturated Organics with Singlet Oxygen Generated from H_2O_2 by a Heterogeneous Molybdenum Catalyst," Sels, B. F.; De Vos, D. E.; Jacobs, P. A. *J. Am. Chem. Soc.* **2007** *129*, 6916-6926.

(52) (a) "Geminal Selectivity of Singlet Oxygen Ene Reactions. The Nonbonding Large Group Effect," Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.*, **1990**, *112*, 6417–6419. (b) "Stereochemistry of the Singlet Oxygenation of Simple Alkenes: A Stereospecific Transformation," Alberti, M. N.; Vassilikogiannakis, G.; Orfanopoulos, M. *Org. Lett.*, **2008**, *10*, 3997–4000. (c) "The Stereochemistry of the Singlet Oxygen-Olefin Ene-Reaction." Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1980,** *102*, 1417–1418.

isomers and diastereomers could be separated for full structural confirmation.

Scheme 18: Potential Solutions to the Prenyl Oxidation of Achyrofuran



i)
34
FeCl$_3$
1)
Pd^0 source
2)
LiCl, Pd(Ph$_3$P)$_4$, DMF,
ii)
1) $^1O_2$
2) P(OEt)$_3$
"preachyrofuran"
iii)
1) $^1O_2$
2) P(OEt)$_3$
FeCl$_3$
28

The potential to rapidly assemble multiple derivatives of this dibenzofuranoid natural product by way of our modular synthesis pathways will facilitate in vitro studies with this small library of molecules.[37c]

1.9 *Conclusions.*

Research to expand the scope and generality of formal aldehyde C–H insertions with a diversity of nonstabilized diazoalkanes has been performed and communicated.[1] Our studies have been inspired by the traditional Roskamp reaction which affords only β-keto esters from carbonyl-stabilized diazo compounds. Engaging a hybrid oxidation protocol based on literature precedent has facilitated the use of previously inaccessible non-stabilized diazoalkanes in the homologation of aldehydes to homologous ketones. In addition to the studies on diversification of the coupling partners in this “modified Roskamp” method, support for a vital mechanistic prerequisite to the development of an enantioselective method has been established. Evidence for a C–H shift mechanism was observed in an isotopic labeling study and also by studying the synthesis and reactivity of other potential reaction intermediates. Application of the aldehyde homologation method to the synthesis of a complex aryl ketone in efforts towards the natural product achyrofuran has also been disclosed.

1.10 *Experimentals.*

General. Infrared spectra were recorded on a Mettler-Toledo ReactIR iC10 spectrophotometer, ν_{max} in cm^{-1}. Bands are reported as strong (s), medium (m), weak (w), and broad (br). ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26, $(CH_3)_2SO$: δ 2.50). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR were recorded on a Varian Gemini 2000 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.16, $(CD_3)_2SO$: δ 39.52). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry Facility.

Unless stated otherwise, all reactions were carried out in flame-dried glassware under an atmosphere of nitrogen in dry, degassed solvent with standard Schlenk or vacuum-line techniques. THF, Et_2O, toluene, CH_2Cl_2, DMF, pentane, and hexanes were dispensed from a Glass Contour solvent purification system custom manufactured by SG Waters LLC (Nashua, NH). Triisopropylsilylhydrazine was prepared as previously described.[22] Acetone was dried over calcium sulfate and distilled under nitrogen. Benzaldehyde (Aldrich), acetophenone (Aldrich), propiophenone (Aldrich), and 1,1,3,3-tetramethylguanidine (Acros) were vacuum distilled over calcium hydride. Dihydrocinnamaldehyde (Aldrich), 2-methoxybenzaldehyde (Aldrich), 4-methoxybenzaldehyde (Aldrich), 2-pyridinecarbox-aldehyde (Aldrich), furfural (Aldrich), pivalaldehyde (Aldrich), mesitaldehyde (Aldrich), and 4,5-dimethylthiophene-2-carboxaldehyde (Aldrich) were distilled under vacuum. 4-Trifluoromethylbenzaldehyde (Aldrich), 2-bromobenzaldehyde (Aldrich), 2-chlorobenzaldehyde (Aldrich), 2-butanone (Aldrich), cyclopropyl methyl ketone (Aldrich), and 2-fluorobenzaldehyde (Aldrich) were distilled under nitrogen atmosphere. Geranial was prepared from geraniol by careful oxidation according to a known method.[53] 4-Nitrobenzaldehyde (Aldrich) was recrystallized from water-isopropanol. $Pb(OAc)_4$ (Aldrich), after dissolution in minimal hot glacial acetic acid, deposited as bright white needles upon cooling. The crystals were washed in a fritted Schlenk filter with pentane, dried under vacuum, and then stored in a glovebox at –20 °C. Hydrazine hydrate (Aldrich), TBAF (Acros), 4-dimethylaminobenzaldehyde (Aldrich), 2-methoxy-1-indanone (Aldrich), 2-cyclohexen-1-one (Aldrich), 3-phenyl-2-propynal (Aldrich), powdered 4 Å molecular sieves (Aldrich), and $Sc(OTf)_3$ (Aldrich) were purchased and used as received. Unprotected hydrazones were prepared as described

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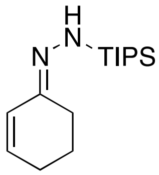
(53) “Oxidation of Nerol to Neral with Iodosobenzene and TEMPO, [(*Z*)-3,7-Dimethyl-2,6-octadienal],” Piancatelli, G.; Leonelli, F. *Org. Syn.* **2006**, *83*, 18-23.

previously.[54] Column chromatography was performed with EMD silica gel 60 (230-400 mesh) and driven with compressed air. Analytical TLC was carried out with EMD silica gel 60 F_{254} precoated plates (250 μm thickness) and a ceric ammonium molybdate or potassium permanganate stain for spot visualization.

Representative Procedure for Aliphatic Diazoalkane Synthesis and Handling:



2-Cyclohexen-1-one *N*-triisopropylsilylhydrazone. A 50 mL round bottom flask equipped with a Teflon-coated stir bar and a jointed vacuum adapter was charged with powdered 4 Å molecular sieves (4 g) and then flame-dried under vacuum. After backfilling with nitrogen, the vacuum adapter was swapped for a rubber septum, and 2-cyclohexen-1-one (1.06 g, 11.0 mmol, 1.0 equiv) and THF (22 mL) were added successively with stirring. The suspension was then cooled to 0 °C, and triisopropylsilylhydrazine (2.08 g, 11.0 mmol, measured by mass difference into a gas tight syringe) was slowly added dropwise using a syringe pump (2 h). After 30 min of additional stirring, the mixture was filtered through a pad of celite in a sintered glass Schlenk filter into a dry 100 mL round bottom flask cooled to 0 ºC. The original flask, molecular sieves, and celite were washed with two additional 10 mL portions of cold Et_2O. The resulting homogeneous filtrate was

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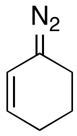
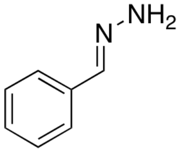
(54) "Oxidation of Hydrazones with Iodine in the Presence of Base," Pross, A.; Sternhill, S. *Aust. J. Chem.* **1970**, *23*, 989-1003.

concentrated on a rotovap equipped with an oil-free diaphragm pump (3-10 torr) to afford 2.90 g (11.0 mmol, >98%) of product as a colorless oil (~3:2 E:Z mixture, >98% pure by ^{1}H NMR analysis). If not used directly in the subsequent oxidation, this material was stored under nitrogen atmosphere at –20 °C.

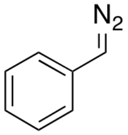


3-Diazocyclohex-1-ene. A flame-dried 50 mL round bottom flask equipped with an oversized Telflon-coated stir bar was charged with 2-cyclohexen-1-one *N*-triisopropylsilylhydrazone (402 mg, 1.51 mmol) and 10 mL of THF. After cooling the colorless solution to 0 ºC, 1.51 mL of TBAF (1.0 M in THF, 1.51 mmol, 1.0 equiv) was added by syringe, at which point a yellow-orange discoloration immediately occurred. The solution was stirred for 10 min and then concentrated under vacuum. Without purification and in the same vessel, the crude hydrazone was freed of residual solvent under vacuum, backfilled with nitrogen, and redissolved in 15 mL of DMF and 4.36 mL 1,1,3,3-tetramethylguanidine (34.7 mmol, 23 equiv). The resulting light pink solution was cooled to –45 °C (dry ice/1:1 ethanol:ethylene glycol) and $Pb(OAc)_4$, finely powdered and weighed into a large vial in a glovebox (736 mg, 1.66 mmol, 1.1 equiv), was added in three portions. After 45 min of stirring at –45 °C, 15 mL of precooled pentane was added and the mixture was stirred vigorously for 1 min. The violet pentane layer was removed with a syringe and transferred to a 100 mL pear-shaped flask cooled to –78 °C. The extraction step was repeated two to three more times (15 mL of pentane) until the extract was no longer colored. The combined pentane layers were washed once with 15 mL of 30% aqueous potassium hydroxide solution and twice with 15 mL portions of saturated aqueous ammonium chloride. In each case, prolonged (>30 sec) vigorous stirring was allowed, the aqueous layer was removed by syringe, and warming above the freezing point (–20 °C) was required for miscibility; these washes serve (respectively) to remove residual DMF and tetramethylguanidine from the organic extract – a prerequisite for efficient catalytic carbon insertion but not esterification. The diazoalkane solution was then transferred with rinsing (freezing the final aqueous wash at –78 °C is most convenient) to a 100 mL round bottom and concentrated under high vacuum at –45 °C to afford 3-diazocyclohex-1-ene as a violet solid. The NMR data that follow represent direct assay of this material without further purification. IR ($PhCH_3$): 2946 (m), 2867 (m), 2038 (s), 1247 (m), 885 (m). ^1H NMR (400 MHz, $CDCl_3$): d 6.01 (dt, *J* = 9.8, 2.0 Hz, 1H), 5.28 (dt, *J* = 9.8, 4.0 Hz, 1H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.08 (ddt, *J* = 6.0, 4.0, 2.0 Hz, 2H), 1.77 (dt, *J* = 6.4, 6.0, 2H). Typically, the solid is immediately redissolved in toluene and transferred (quantitatively, with rinsing) by cannula to a 1 mL volumetric flask. The active titer is determined by esterification with benzoic acid. Thus, 100 μL of the stock solution was diluted with 1 mL of THF in a 5 mL round bottom flask, cooled to –45 °C, and treated with benzoic acid dropwise by syringe (166 μL of 1.0 M in THF, 0.166 mmol, 1.1 equiv based on theoretical). Upon slow warming from –45 °C, the reaction mixture became colorless and nitrogen evolution was observed. This mixture was diluted with Et_2O (10 mL) and saturated sodium bicarbonate (10 mL) and transferred to a separatory funnel. After removal of the organic layer, the aqueous layer was washed with two additional 5 mL volumes of Et_2O. The pooled extract was dried over magnesium sulfate and concentrated to a light yellow oil. Purification by silica gel chromatography (TLC R_f = 0.28 in 97:3 hexanes:ethyl acetate) afforded 12.5 mg of the benzoate ester (41% yield, indicative of a 0.62 M stock solution of diazoalkane). Characterization follows for 2-cyclohexene-1-benzoate. IR (thin film): 2937 (w), 2867 (w), 1710 (s), 1451 (w), 1336 (w), 1314 (w), 1266 (s), 1175 (w), 1110 (m), 1069 (w), 1026 (w), 709 (s). ^1H NMR (400 MHz, $CDCl_3$): d 8.06 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.55 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 6.01 (ddt, *J* = 10.0, 3.2, 2.0 Hz, 1H), 5.51 (dt, *J* = 5.2, 1.6 Hz, 2H), 2.18-1.95 (m, 3H), 1.92-1.80 (m, 2H), 1.75-1.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): d 166.3, 132.9, 132.8, 130.9, 129.7, 128.4, 125.9, 68.8, 28.6, 25.3, 19.2. HRMS (ESI+) Calcd for $C_{13}H_{15}O_2^+$ $[M+H]^+$: 203.1072; Found: 203.1072.

Representative Procedure for Aryl Hydrazone Synthesis:

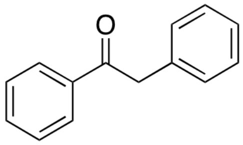


Benzaldehyde hydrazone. In a 2 dram vial equipped with a Teflon-coated stir bar, benzaldehyde (1.00 g, 9.43 mmol) was suspended in 2.0 mL of hydrazine hydrate. After sealing the vial with a Teflon-lined screw cap, the heterogeneous mixture was stirred rapidly with heating at 100 ºC. After 6 h, the mixture was cooled to 23 °C and the product was extracted with three 2 mL portions of CH_2Cl_2. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 1.10 g (9.16 mmol, 97%) of a colorless oil. This known compound was >98% pure and consisted of a >98:2 *E*:*Z* mixture according to ^{1}H NMR analysis.



Phenyldiazomethane. Prepared from benzaldehyde hydrazone according to the known procedure.[24a] IR ($PhCH_3$): 2975 (w), 2852 (w), 2062 (s), 1596 (m), 1499 (m), 1381 (m), 1184 (w), 1068 (m), 913 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, H), 4.96 (s, 1H).

Representative Procedure for Catalytic Homologation:



1,2-Diphenylethanone (2a). In a glovebox, a flame-dried 1 dram vial equipped with a Teflon-coated flea stir bar was charged with $Sc(OTf)_3$ (5.0 mg, 0.010 mmol, 0.10 equiv), sealed with a rubber septum, and removed from the glovebox. In a fume hood, toluene (0.50 mL, 0.2 M) was added by syringe, suspending but not dissolving the catalyst. After cooling the mixture to –78 °C, benzaldehyde (10.3 µL, 0.102 mmol, 1.0 equiv) and phenyldiazomethane (1.5 M in toluene, 74.5 µL, 0.112 mmol, 1.1 equiv, solution kept cold at –78 °C) were added in succession to the stirring reaction mixture by syringe. The reaction was stirred for 10 min at –78 °C, at which point the characteristic red color of the nucleophile had dissipated, leaving a turbid light yellow suspension. The reaction mixture was concentrated with a nitrogen purge and purified by flash chromatography (TLC R_f = 0.31 in 9:1 hexanes:ethyl acetate) affording 19.5 mg (0.0996 mmol, 98%) of **2a** as colorless oil. Characterization data for **2a** has been recorded previously.[55]

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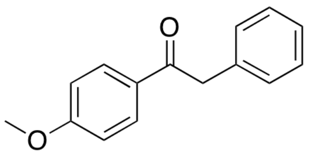
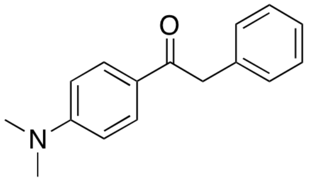
(55) "Et_2Zn-Mediated Rearrangement of Bromohydrin," Li, L.; Cai, P.; Guo, Q.; Xue, S. *J. Org. Chem*. **2008**, *73*, 3516-3522.



1-(4-Methoxyphenyl)-2-phenylethanone (2b). Prepared according to the general procedure on a scale of 0.061 mmol of *p*-methoxybenzaldehyde (7.4 μL), 0.067 mmol of phenyldiazomethane (42.4 μL of a 1.68 M solution in toluene, 1.1 equiv), and 0.0060 mmol of $Sc(OTf)_3$ (3.0 mg, 0.10 equiv) in 97% yield (0.0590 mmol, 13.4 mg) after chromatographic purification (TLC R_f = 0.26 in 95:5 hexanes:ethyl acetate. Characterization data for **2b** has been recorded previously.[56]



1-(4-Dimethylaminophenyl)-2-phenylethanone (2c). Prepared according to the general procedure on a scale of 0.102 mmol of *p*-(dimethylamino)benzaldehyde (15.2 mg, 1.0 equiv), 0.117 mmol of phenyldiazomethane (76.0 μL of a 1.45 M solution in toluene, 1.1 equiv), and 0.010 mmol of $Sc(OTf)_3$ (4.9 mg, 0.10 equiv) in 98% yield (0.0993 mmol, 23.7 mg) after chromatographic purification (TLC R_f = 0.25 in 90:10 hexanes:ethyl acetate). Characterization data for **2c** has been recorded previously.[57]

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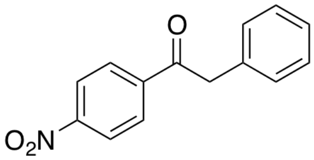
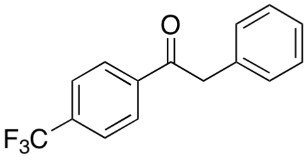
(56) "Direct Acylation of Aryl Bromides with Aldehydes by Palladium Catalysis," Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510-10511.

(57) "Nickel-Catalyzed Electrosynthesis of Ketones from Organic Halides and Iron Pentacarbonyl. Part 2. Unsymmetrical Ketones.," Dolhem, F.; Barhdadi, R.; Folest, J. C.; Nedelec, J. Y.; Troupel, M. *Tetrahedron* **2001**, *57*, 525-529.



1-(4-Nitrophenyl)-2-phenylethanone (2d). Prepared according to the general procedure on a scale of 0.102 mmol of *p*-nitrobenzaldehyde (15.3 mg), 0.117 mmol of phenyldiazomethane (76.0 μL of a 1.45 M solution in toluene, 1.1 equiv), and 0.010 mmol of $Sc(OTf)_3$ (4.9 mg, 0.10 equiv) in 91% yield (0.0924 mmol, 22.4 mg) after chromatographic purification (TLC R_f = 0.25 in 90:10 hexanes:ethyl acetate). **2d** has been synthesized previously, yet characterization data was not reported.[58] IR (thin film): 1694 (s), 1518 (m), 1351 (m), 746 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.34 (s, 2H), 7.28-7.41 (m, 5H), 8.18 (d, *J* = 8.8 Hz, 2H), 8.34 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.6, 120.1, 123.7, 126.3, 129.1, 129.6, 129.8, 139.1, 152.6, 196.4. HRMS (ESI+) Calcd for $C_{14}H_{12}NO_3^+$ $[M+1]^+$: 242.0772; Found: 242.1100.



1-(4-Trifluoromethylphenyl)-2-phenylethanone (2e). Prepared according to the general procedure on a scale of 0.0830 mmol of *p*-trifluoromethylbenzaldehyde (14.5 mg), 0.091 mmol of phenyldiazomethane (160 μL of a 0.57 M solution in toluene, 1.1 equiv), and 0.0080 mmol of $Sc(OTf)_3$ (4.1 mg, 0.10 equiv) in 97% yield (0.0805 mmol, 21.2 mg) after chromatographic purification (TLC R_f = 0.30 in 90:10

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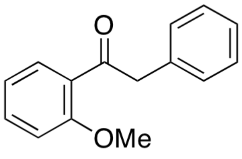
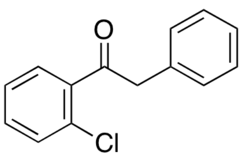
(58) "A simple, user-friendly process for the homologation of aldehydes using tosylhydrazone salts," Aggarwal, V. K.; de Vicente, J.; Pelotier, B.; Holmes, I. P.; Bonnert, R. V. *Tetrahedron Lett.* **2000**, *41*, 10327-10331.

hexanes:ethyl acetate). Characterization data for **2e** has been recorded previously.[59]



1-(2-Methoxyphenyl)-2-phenylethanone (4a). Prepared according to the general procedure on a scale of 0.104 mmol of *o*-anisaldehyde (15.5 mg), 0.114 mmol of phenyldiazomethane (200 μL of a 0.57 M solution in toluene, 1.1 equiv), and 0.010 mmol of $Sc(OTf)_3$ (4.9 mg, 0.10 equiv) in 96% yield (0.100 mmol, 22.6 mg) after chromatographic purification (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). Characterization data for **4a** has been recorded previously.[60]



1-(2-Chlorophenyl)-2-phenylethanone (4b). Prepared according to the general procedure on a scale of 0.0830 mmol of *o*-chlorobenzaldehyde (11.7 mg), 0.091 mmol of phenyldiazomethane (55 μL of a 1.66 M solution in toluene, 1.1 equiv), and 0.0080 mmol of $Sc(OTf)_3$ (4.1 mg, 0.10 equiv) in 95% yield (0.078 mmol, 18.2 mg) after chromatographic purification (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). IR (thin film): 2918 (w), 1699 (s), 1432 (m), 756 (m), 700 (m). ^1H NMR (400 MHz, $CDCl_3$): δ 4.26 (s, 2H),

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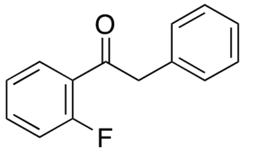
(59) "Palladium-Catalyzed Synthesis of Aryl Ketones by Coupling of Aryl Bromides with an Acyl Anion Equivalent," Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 14800-14801.

(60) "Microwave-Assisted Efficient Synthesis of 1,2-Diaryldiketones: a Novel Oxidation Reaction of Diarylalkynes with DMSO Promoted by $FeBr_3$," Le Bras, G.; Provot, O.; Peyrat, J.; Alami, M.; Brion, J. *Tetrahedron Lett.* **2006**, *47*, 5497-5501.

7.21-7.44 (m, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 43.8, 126.7, 127.5, 129.0, 129.2, 129.3, 129.5, 129.7, 131.0, 134.5, 135.6, 201.5. HRMS (ESI+) Calcd for $C_{14}H_{12}ClO^+$ [M+1]$^+$: 231.0532; Found: 231.1096.



1-(2-Fluorophenyl)-2-phenylethanone (4c). Prepared according to the general procedure on a scale of 0.100 mmol of *o*-fluorobenzaldehyde (10.5 μL), 0.110 mmol of phenyldiazomethane (66.3 μL of a 1.66 M solution in toluene, 1.1 equiv), and 0.010 mmol of Sc(OTf)$_3$ (5.0 mg, 0.10 equiv) in 89% yield (0.0890 mmol, 19.1 mg) after chromatographic purification (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). **4c** has been synthesized previously.[61] IR (thin film): 3028 (w), 1691 (s), 1109 (m), 907 (m), 732 (m). ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.31 (s, 2H), 7.21-7.44 (m, 5H), 7.71 (d, 2H, *J* = 8.6 Hz), 8.10 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 44.9, 115.2, 125.3, 127.0, 127.4, 127.5, 129.2, 129.3, 129.6, 134.5, 135.1, 201.4. HRMS (ESI+) Calcd for $C_{14}H_{12}FO^+$ [M+1]$^+$: 215.0827; Found: 215.1098.

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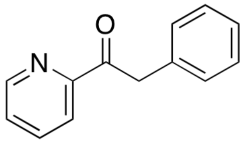
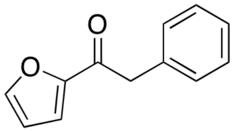
(61) "Synthese und Umsetzung Beidseitig Ungleich Substituierter neuer Monothiobenzile zu 1,3-Oxathiolen," Bak, C.; Praefcke, K. *J. Het. Chem.* **1980**, *17*, 1655-1657.



2-Phenylacetylpyridine (5). Prepared according to the general procedure on a scale of 0.083 mmol of pyridine-2-carboxaldehyde (8.9 mg), 0.0912 mmol of phenyldiazomethane (61.0 μL of a 1.50 M solution in toluene, 1.1 equiv), and 0.0080 mmol of $Sc(OTf)_3$ (4.1 mg, 0.10 equiv) in 84% yield (0.0698 mmol, 13.8 mg) after chromatographic purification (TLC R_f = 0.30 in 85:15 hexanes:ethyl acetate). Characterization data for **5** has been recorded previously.[62]



1-(2-Furyl)-2-phenylethanone (6). Prepared according to the general procedure on a scale of 0.10 mmol of furfural (8.3 μL), 0.110 mmol of phenyldiazomethane (66.3 μL of a 1.66 M solution in toluene, 1.1 equiv), and 0.010 mmol of $Sc(OTf)_3$ (4.9 mg, 0.10 equiv) in 90% yield (0.090 mmol, 16.8 mg) after chromatographic purification (TLC R_f = 0.30 in 90:10 hexanes:ethyl acetate). **6** has been synthesized previously, yet characterization data was not reported.[63] IR (thin film): 1669 (s), 1465 (m), 722 (m), 432 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.06 (s, 2H), 6.45 (dd, *J* = 3.5, 1.8 Hz, 1H),

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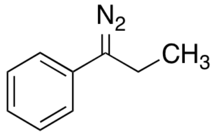
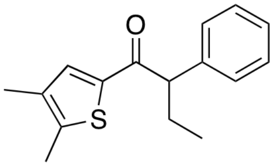
[62] "Synthesis, Structure–Activity Relationships, and Antitumor Studies of 2-Benzoxazolyl Hydrazones Derived from Alpha-(*N*)-acyl Heteroaromatics," Easmon, J.; Purstinger, G.; Thies, K.; Heinisch, G.; Hofmann, J. *J. Med. Chem.* **2006**, *49*, 6343-6350.

[63] "Aluminum Dodecatungstophosphate ($AlPW_{12}O_{40}$) as a Non-Hygroscopic Lewis Acid Catalyst for the Efficient Friedel-Crafts Acylation of Aromatic Compounds Under Solvent-Less Conditions," Firouzabdi, H.; Iranpoor, N.; Nowrouzi, F. *Tetrahedron* **2004**, *60*, 10843-10850.

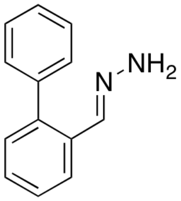
7.10 (dd, *J* = 3.5, 0.7 Hz, 1H), 7.15 (m, 5H), 7.58 (dd, *J* = 1.8, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 40.8, 112.6, 118.6, 127.5, 129.2, 129.7, 135.6, 147.1, 152.1, 185.0. HRMS (ESI+) Calcd for $C_{12}H_{11}O_2^+$ [M+1]$^+$: 187.0714; Found: 187.1147.



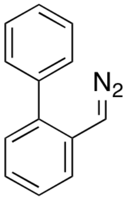
1-Diazo-1-phenylpropane (8). Prepared from propiophenone hydrazone according to the known procedure.[1a] IR (PhCH$_3$): 2044 (s), 1586 (w), 1496 (w). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36 (t, *J* = 8.5 Hz, 2H), 7.05 (t, *J* = 7.1 Hz, 1H), 6.92 (dd, *J* = 8.8, 1.2 Hz, 2H), 2.21 (q, *J* = 7.9 Hz, 2H), 1.14 (t, *J* = 8.5 Hz, 3H).



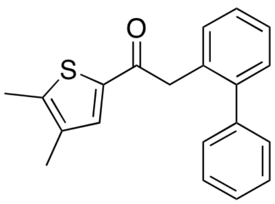
1-(4,5-Dimethylthiophen-2-yl)-2-phenylbutan-1-one (9). Prepared according to the general procedure on a scale of 0.0610 mmol of thiophene carboxaldehyde **7** (7.25 μL, 1.0 equiv), 0.067 mmol of 1-phenyl-1-diazopropane (250 μL of a 0.27 M solution in toluene, 1.1 equiv), and 0.0060 mmol of Sc(OTf)$_3$ (3.0 mg, 0.10 equiv) in 82% yield (0.0503 mmol, 13.1 mg) after chromatographic purification (TLC R$_f$ = 0.30 in 97.5:2.5 hexanes:ethyl acetate). IR (thin film): 2963 (w), 2927 (w), 1640 (s), 1440 (m), 1170 (m) 699 (m). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.87 (t, *J* = 7.7 Hz, 3H), 2.11 (s, 2H), 2.36 (s, 3H), 4.43 (t, *J* = 7.8 Hz, 1H), 7.18-7.33 (m, 5H), 7.39 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 12.4, 14.1, 14.3, 27.3, 56.8, 127.0, 127.9, 128.3, 129.0, 129.2, 135.6, 139.5, 140.1, 192.5. HRMS (ESI+) Calcd for $C_{16}H_{19}OS^+$ [M+1]$^+$: 259.1112; Found: 259.1457.



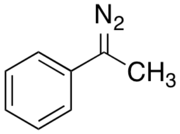
2-Phenylbenzaldehyde hydrazone. In a 2 dram vial equipped with a Teflon-coated stir bar, 2-phenylbenzaldehyde (0.120 g, 0.658 mmol) was dissolved in 0.35 mL (11 equiv) of hydrazine hydrate and 0.66 mL of ethanol. After sealing the vial with a Teflon-lined screw cap, the homogeneous mixture was stirred rapidly with heating at 100 ºC. After 10 h, the mixture was cooled to 23 °C, and the product was extracted with three 4 mL volumes of $CHCl_3$. The combined extracts were concentrated and then dried by azeotropic removal of water with benzene and concentrated under reduced pressure to afford 0.119 g (0.606 mmol, 92%) of a white solid. This material was converted directly to **10** without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44 (s, 2H), 7.37-7.46 (m, 8H), 7.70 (s, 1H), 7.96 (m, 1H). HRMS (ESI+) Calcd for $C_{13}H_{13}N_2^+$ [M+1]$^+$: 197.1034; Found: 197.1104.



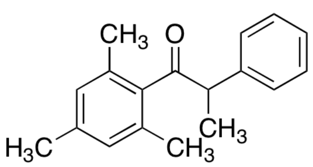
2-(Diazomethyl)biphenyl (10). Prepared from 2-phenylbenzaldehyde hydrazone according to the known procedure.[1a] IR ($PhCH_3$): 2050 (s), 1595 (m), 1381 (w), 1121 (w), 910 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (s, 1H), 7.41-7.51 (m, 8H), 8.35 (m, 1H).



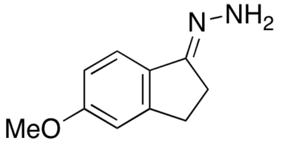
2-(Biphenyl-2-yl)-1-(4,5-dimethylthiophen-2-yl)ethanone (11). Prepared according to the general procedure on a scale of 0.061 mmol of thiophene carboxaldehyde **7** (7.3 μL), 0.0670 mmol of 2-(diazomethyl)biphenyl (213 μL of a 0.314 M solution in toluene, 1.1 equiv), and 0.0060 mmol of $Sc(OTf)_3$ (3.0 mg, 0.10 equiv) in 74% yield (0.0453 mmol, 11.1 mg) after chromatographic purification (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). IR (thin film): 2922 (w), 1659 (s), 1438 (w), 1187 (m), 719 (w), 704 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.34 (s, 3H), 4.09 (s, 2H), 7.01 (s, 1H), 7.28-7.44 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 14.2, 43.1, 127.0, 127.2, 128.2, 127.7, 128.3, 129.5, 130.2, 130.6, 134.8, 135.5, 138.7, 141.4, 142.3, 143.9, 190.5. HRMS (ESI+) Calcd for $C_{20}H_{19}OS^+$ $[M+1]^+$: 307.1112; Found: 307.1532.



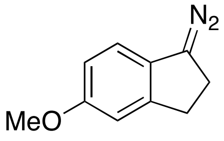
1-Diazo-1-phenylethane (12). Prepared from acetophenone hydrazone according to the known procedure.[1a] IR ($PhCH_3$): 2038 (s), 1596 (w), 1501 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (t, *J* = 8.4 Hz, 2H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.92 (dd, *J* = 8.8, 1.2 Hz, 2H), 2.17 (s, 3H).



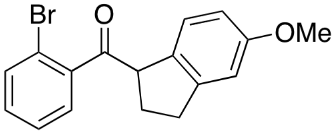
1-Mesityl-2-phenylpropan-1-one (13). Prepared according to the general procedure with adjustment of reaction temperature to –45 °C on a scale of 0.0812 mmol of mesitaldehyde (12.0 μL), 0.162 mmol of 1-diazo-1-phenylethane (144 μL of a 1.13 M solution in toluene, 2.0 equiv), and 0.016 mmol of $Sc(OTf)_3$ (8.0 mg, 0.10 equiv) in 63% yield (0.0512 mmol, 12.9 mg) after chromatographic purification (TLC R_f = 0.30 in 97.5:2.5 hexanes:ethyl acetate). IR (thin film): 2976 (w), 2930 (w), 1697 (s), 1453 (m), 698 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (d, *J* = 7.7 Hz, 3H), 1.88 (s, 6H), 2.24 (s, 3H), 4.17 (q, *J* = 7.8 Hz, 1H), 6.78 (s, 2H), 7.18-7.36 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 16.8, 19.3, 21.2, 54.3, 127.4, 128.5, 128.7, 128.8, 133.5, 138.5, 138.7, 139.2, 209.9. HRMS (ESI+) Calcd for $C_{18}H_{21}O^+$ $[M+1]^+$: 253.1548; Found: 253.1863.



5-Methoxy-indan-1-one hydrazone. In a 2 dram vial equipped with a Teflon-coated stir bar, 2-methoxy-1-indanone (0.20 g, 1.2 mmol) was dissolved in 2.5 mL of ethanol and added to 0.60 mL (10 equiv) of hydrazine hydrate. After sealing the vial with a Teflon-lined screw cap, the homogeneous mixture was stirred rapidly with heating at 100 ºC. After 10 h, the mixture was cooled to 23 °C and the product was extracted with three 8 mL portions of $CHCl_3$. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 0.193 g (1.10 mmol, 89%) of an ivory solid. This material was taken directly into the oxidation reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (t, *J* = 6.4 Hz, 2H), 3.08 (t, *J* = 6.4 Hz, 2H), 3.81 (s, 3H), 5.03 (br s, 2H), 6.81 (s, 1H), 6.83, (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H). HRMS (ESI+) Calcd for $C_{28}H_{31}O_3^+$ $[M+1]^+$: 415.2228; Found: 415.2264.

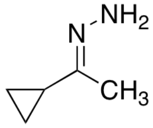


1-Diazo-5-methoxy-indane (14). Prepared from 5-methoxy-indan-1-one hydrazone according to the general procedure for aliphatic diazoalkane synthesis and handling. Used in homologation reactions immediately following the preparation of a concentrated solution in toluene.

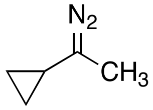


2-Bromophenyl(5-methoxy-indan-1-yl)methanone (15). Prepared according to the general procedure on a scale of 0.122 mmol of 2-bromobenzaldehyde (14.0 μL), 0.134 mmol of 1-diazo-5-methoxy-indane (200 μL of a 0.67 M solution in toluene, 1.1 equiv), and 0.012 mmol of $Sc(OTf)_3$ (6.0 mg, 0.10 equiv) in 62% yield (0.0756 mmol, 25.1 mg) after chromatographic purification (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). IR (thin film): 2939 (w), 1599 (s), 1489 (m), 1262 (m), 1028 (m), 758 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, *J* = 6.8 Hz, 2H), 3.48 (q, *J*

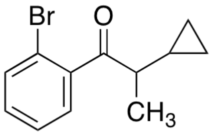
= 8.7 Hz, 2H), 3.79 (s, 3H), 3.84 (t, *J* = 6.9 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.80 (s, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 7.19-7.37 (m, 3H), 7.61 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.2, 32.2, 43.7, 47.0, 55.5, 55.6, 56.4, 71.9, 73.0, 87.3, 110.2, 112.6, 117.1, 119.1, 125.9, 127.4, 128.7, 131.3, 132.5, 133.5, 142.0, 146.5, 159.7, 204.7 HRMS (ESI+) Calcd for $C_{17}H_{16}BrO_2^+$ $[M+1]^+$: 332.0235; Found: 332.0382.



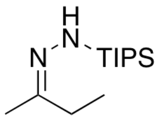
1-Cyclopropylethanone hydrazone. In a 2 dram vial equipped with a Teflon-coated stir bar, cyclopropyl methyl ketone (0.20 mL, 2.1 mmol) was suspended in 1.14 mL (10 equiv) of hydrazine hydrate. After sealing the vial with a Teflon-lined screw cap, the homogeneous mixture was stirred rapidly with heating at 100 ºC. After 10 h, the mixture was cooled to 23 °C and the product was extracted with three 8 mL portions of $CHCl_3$. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 0.200 g (2.04 mmol, 95%) of a clear oil. This material was taken directly into the oxidation reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.59-0.71 (m, 2H), 0.77-0.86 (m, 1H), 1.48-1.75 (m, 2H), 1.65 (s, 3H), 4.81 (br s, 2H). HRMS (ESI+) Calcd for $C_5H_{11}N_2^+$ $[M+1]^+$: 99.0878; Found: 99.0736.



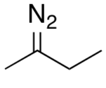
1-Cyclopropyl-1-diazoethane (16). Prepared from 1-cyclopropylethanone hydrazone according to the general procedure for aliphatic diazoalkane synthesis and handling (see compound **18** for isolation procedure). Used in homologation reactions immediately following the preparation of a concentrated solution in toluene.



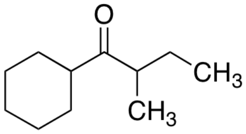
1-(2-Bromophenyl)-2-cyclopropylpropan-1-one (17). Prepared according to the general procedure on a scale of 0.061 mmol of 2-bromobenzaldehyde (8.8 μL,), 0.067 mmol of 1-cyclopropyl-1-diazoethane (60 μL of a 1.10 M solution in toluene, 1.1 equiv), and 0.0060 mmol of $Sc(OTf)_3$ (3.0 mg, 0.10 equiv) in 74% yield (0.0450 mmol, 11.4 mg) after chromatographic purification (TLC R_f = 0.30 in 90:10 hexanes:ethyl acetate). IR (thin film): 2972 (w), 1701 (s), 1429 (m), 1214 (m), 1022 (w), 968 (w), 757 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (m, 2H), 0.48 (m, 2H), 1.30 (d, *J* = 8.6 Hz, 3H), 2.57 (m, 1H), 7.23-7.38 (m, 3H), 7.59 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 3.8, 4.8, 14.7, 15.7, 50.6, 118.6, 127.3, 128.3, 131.0, 133.3, 143.1, 208.1. HRMS (ESI+) Calcd for $C_{12}H_{14}BrO^+$ $[M+1]^+$: 254.0129; Found: 255.0209.



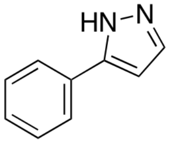
2-Butanone *N*-triisopropylsilylhydrazone. A 10 mL round bottom flask equipped with a Teflon-coated stir bar and a jointed vacuum adapter was charged with powdered 4 Å molecular sieves (4 g) and then flame-dried under vacuum. After backfilling with nitrogen, the vacuum adapter was swapped for a rubber septum and 2-butanone (0.27 mL, 3.0 mmol, 1.0 equiv) and THF (3 mL) were added successively with stirring. After cooling the suspension to 0 °C, triisopropylsilylhydrazine (0.50 g, 3.0 mmol, measured by mass difference into a gas tight syringe) was slowly added dropwise using a syringe pump (2 h). After 30 min of additional stirring, the mixture was filtered through a pad of celite in a sintered glass Schlenk filter into a dry 50 mL round bottom flask cooled to 0 ºC. The original flask, molecular sieves and celite were washed with two additional 5 mL portions of cold Et_2O. The resulting homogeneous filtrate was concentrated on a rotovap equipped with an oil-free diaphragm pump (3-10 torr) with a 0 ºC ice bath, affording 0.70 g (11 mmol, >98%) of product as a colorless oil. If not used directly in the subsequent oxidation, this material was stored under nitrogen at –20 °C.



2-Diazobutane (18). A flame-dried 50 mL round bottom flask with an oversized Telflon-coated stir bar was charged with 2-butanone *N*-triisopropylsilylhydrazone (700 mg, 2.95 mmol) and 10 mL of THF. After cooling the colorless solution to 0 ºC, 2.95 mL of TBAF (1.0 M in THF, 2.95 mmol, 1.0 equiv) was added by syringe, at which point a yellow-orange discoloration immediately occurred. The solution was stirred for 10 min and then concentrated with a nitrogen purge. Without purification and in the same vessel, the crude hydrazone was freed of residual solvent under vacuum at −20 ºC, purged with nitrogen, and redissolved in 15 mL of DMF and 5 mL of 1,1,3,3- tetramethylguanidine (59 mmol, 20 equiv). The solution was cooled to –45 °C (dry ice/acetonitrile bath) and $Pb(OAc)_4$, finely powdered and weighed into a large vial in a glovebox (1.40 g, 3.24 mmol, 1.1 equiv) was added in three portions. After 45 min of stirring at –45 °C, distillation glassware was affixed to the reaction flask and the system was placed under static high vacuum for 1.5 h with the reaction flask at 0 °C and a collection flask at −78 °C. Once all coloration had left the reaction flask, the distillation apparatus was swapped for a rubber septum in order to introduce 1 mL of toluene. The concentrated deep orange toluene layer was washed once with 5 mL of precooled 30% aqueous potassium hydroxide solution and twice with 5 mL portions of saturated aqueous ammonium chloride. In each case, prolonged (>30 sec) vigorous stirring was allowed, the aqueous layer was removed by syringe, and warming above the freezing point (–20 °C) was required for miscibility; these washes serve (respectively) to remove residual DMF and tetramethylguanidine from the distillate. The diazoalkane solution was then transferred quantitatively (freezing the final aqueous wash is most convenient) to a 2 mL volumetric flask for storage and use. The active titer was determined by esterification with benzoic acid. Thus, 100 μL of the stock solution was diluted with 1 mL of THF in a 5 mL round bottom flask, cooled to –45 °C, and treated with benzoic acid dropwise by syringe (295 μL of 1.0 M in THF, 0.295 mmol, 1.0 equiv based on theoretical). Upon slow warming from –45 °C, the reaction mixture became colorless and nitrogen evolution was observed. This mixture was diluted with Et_2O (10 mL) and saturated sodium bicarbonate (10 mL) and transferred to a separatory funnel. After removing the organic layer, the aqueous layer was washed with two additional 5 mL volumes of Et_2O. The pooled extract was dried over magnesium sulfate and concentrated to a light yellow oil. Purification by silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate) afforded 13.0 mg of sec-butyl benzoate (25% yield, indicative of a 0.73 M stock solution of diazoalkane **18**).



1-Cyclohexyl-2-methylbutan-1-one (19). Prepared according to the general procedure on a scale of 0.122 mmol of cyclohexane carboxaldehyde (14.7 μL), 0.13 mmol of 2-diazobutane (200 μL of a 0.67 M solution in toluene, 1.1 equiv), and 0.012 mmol of $Sc(OTf)_3$ (6.0 mg, 0.10 equiv) in 78% yield (0.0952 mmol, 16.1 mg) after chromatographic purification (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). **19** has been synthesized previously, yet characterization data was not reported.[64] IR (thin film): 2928 (w), 2854 (w), 1707 (s), 1450 (m), 1366 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.4 Hz, 3H), 1.13 (d, *J* = 8.5 Hz, 3H), 1.45-1.80 (m, 11H), 2.36 (m, 1H), 2.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 15.4, 25.3, 25.4, 25.9, 29.9, 40.5, 47.3, 211.8. HRMS (ESI+) Calcd for $C_{11}H_{21}O^+$ $[M+1]^+$: 169.1548; Found: 169.1573.



5-phenyl-1*H*-pyrazole.[65] In a 2 dram vial equipped with a Teflon-coated stir bar, 3-phenylpropiolaldehyde (0.10 mL, 0.819 mmol) was suspended in 0.438 mL (11.0 equiv) of hydrazine hydrate. After sealing the vial with a Teflon-lined screw cap, the homogeneous mixture was stirred rapidly with heating at 100 ºC. After 10 h, the mixture was cooled to 23 °C and extracted with three 8 mL portions of $CHCl_3$. The combined extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to afford 85.4 mg (0.594 mmol, 72%) of an clear oil after chromatographic purification (TLC Rf = 0.30 in 80:20 hexanes:ethyl acetate). IR (thin film): 2924, 2358, 2203, 1489, 756 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3): δ 2.76 (m, 4H), 3.58 (s, 2H), 7.18-7.32 (m, 10H). HRMS (ESI+) Calcd for C_9H_8N [M]+1: 145.0721 ; Found: 145.1096.

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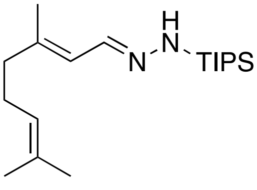
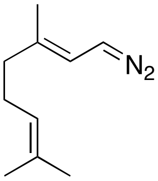
(64) "One-Pot Synthesis of Ketones Using *N*-Methoxy-*N*-Methyl-2-Pyridyl Urethane," Lee, N. R.; Lee, J. I. *Synth. Comm.* **1999**, *29*, 1249-1255.

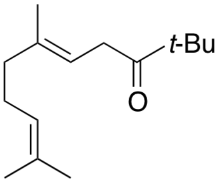
(65) "A Versatile Method for Suzuki Cross-Coupling Reactions of Nitrogen Heterocycle," Kudo, N.; Perseghini, M.; Fu, G. *Angew. Chem. Int. Ed. Eng.* **2006**, *45*, 1282-1284.



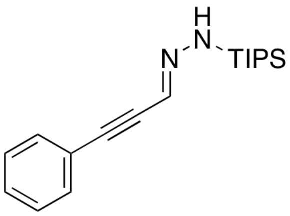
Geranial N-triisopropylhydrazone. Prepared according to the general procedure for diazoalkane synthesis and handling on a scale of 8.15 mmol of geranial (1.24 g), 8.15 mmol of triisopropylsilylhydrazine (1.53 g, 1.0 equiv), and 0.50 g of 4 Å molecular sieves in 10 ml of THF. Isolated a clear oil in 96% yield (2.52 g, 7.82 mmol) that was used directly in the subsequent oxidation without further purification.



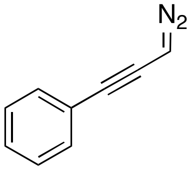
(*E*)-1-Diazo-3,7-dimethylocta-2,6-diene (20). Prepared according to the general procedure for diazoalkane synthesis and handling on a scale of 4.59 mmol geranial N-triisopropylhydrazone (1.48 g), 4.59 mmol TBAF (4.59 mL of a 1.0 M solution in THF), and 20 mL of THF. Then 46 mL of DMF, 13.2 mL of 1,1,3,3-tetramethylguanidine (106 mmol, 23.0 equiv), and 5.05 mmol of $Pb(OAc)_4$ (2.24 g, 1.1 equiv) were used in the oxidation. The diazoalkane was processed after extractive workup as a toluene solution for subsequent titration with benzoic acid and usage in homologation reactions.



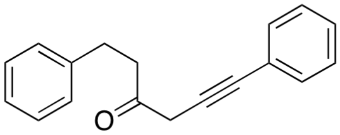
(E)-2,2,6,10-Tetramethylundeca-5,9-dien-3-one (21). Prepared according to the general procedure with adjustment of the reaction temperature to –20 °C on a scale of 0.100 mmol of pivaldehyde (11.4 μL), 0.110 mmol of (*E*)-1-diazo-3,7-dimethylocta-2,6-diene (133 μL of a 1.19 M solution in toluene, 1.1 equiv), and 0.010 mmol of Sc(OTf)$_3$ (4.9 mg, 0.10 equiv) in 88% yield (0.0881 mmol, 19.6 mg) after chromatographic purification (TLC R$_f$ = 0.30 in 95:5 hexanes:ethyl acetate). IR (thin film): 2967 (m), 2870 (m), 1708 (s), 1477 (w), 1450 (w), 1377 (w), 1365 (w), 1309 (w), 1094 (w), 1061 (w), 985 (w), 826 (w). ^{1}H NMR (400 MHz, CDCl$_3$): d 1.15 (s, 3H), 1.59 (s, 3H), 1.61 (d, *J* = 0.8 Hz, 3H), 1.67 (d, *J* = 0.8 Hz, 3H), 2.08-2.03 (m, 4H), 3.22 (dd, *J* = 6.8, 0.8 Hz, 2H), 5.10-5.06 (m, 1H), 5.34-5.30 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): d 16.7, 17.9, 25.9, 26.7, 26.8, 36.3, 39.8, 44.4, 116.9, 124.2, 131.6, 138.2, 214.3. HRMS (ESI+) $C_{15}H_{28}O^+$ [M+1]$^+$: Calcd for 223.2062; Found: 223.2054.



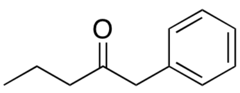
3-Phenylpropiolaldehyde triisopropylsilylhydrazone. A 10 mL round bottom flask equipped with a Teflon-coated stir bar and a jointed vacuum adapter was charged with powdered 4 Å molecular sieves (0.60 g) and then flame-dried under vacuum. After backfilling with nitrogen, the vacuum adapter was swapped for a rubber septum, and 3-phenylpropiolaldehyde (0.122 mL, 1.00 mmol) and THF (2 mL) were added successively with stirring. The suspension was then cooled to 0 °C, and triisopropylsilylhydrazine (188 mg, 1.00 mmol, measured by mass difference into a gas tight syringe) was slowly added dropwise using a syringe pump (2 h). After 30 min of additional stirring, the mixture was filtered through a pad of celite in a sintered glass Schlenk filter into a dry 50 mL round bottom flask cooled to 0 ºC. The original flask, molecular sieves, and celite were washed with two additional 5 mL portions of cold Et_2O. The resulting homogeneous filtrate was concentrated on a rotovap equipped with an oil-free diaphragm pump (3-10 torr), affording 0.29 g (0.97 mmol, 97%) of product as an oil. This material was used directly in the oxidation reaction without purification.



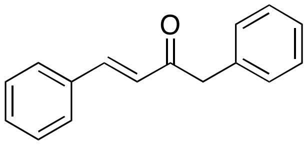
(3-Diazoprop-1-yn-1-yl)benzene (22). Prepared according to the general procedure for diazoalkane synthesis and handling on a scale of 0.890 mmol 3-phenylpropioaldehyde triisopropylsilylhydrazone (0.267 g), 0.89 mmol of TBAF (0.89 mL of a 1.0 M solution in THF, 1.0 equiv), and 5.0 mL of THF. After concentration of the organic solvent to leave a yellow oil, 9.0 mL of DMF, 2.3 mL of 1,1,3,3-tetramethylguanidine (17.8 mmol, 20 equiv), and 1.8 mmol of $Pb(OAc)_4$ (0.85 g, 2.0 equiv) were added in succession at –45 °C. The diazoalkane was processed after extractive workup as a toluene solution for subsequent titration with benzoic acid and usage in homologation reactions.



1,6-Diphenylhex-5-yn-3-one (23). Prepared according to the general procedure on a scale of 0.15 mmol of dihydrocinnamaldehyde (20 μL), 0.167 mmol of (3-diazoprop-1-ynyl)benzene (100 μL of a 1.56 M solution in toluene, 1.1 equiv), and 0.015 mmol of Sc(OTf)$_3$ (7.5 mg, 0.10 equiv) in 77% yield (0.118 mmol, 29.4 mg) after chromatographic purification (TLC Rf = 0.30 in 95:5 hexanes:ethyl acetate). IR (thin film): 2923 (w), 1684 (s), 1495 (m), 1453 (m), 734 (w). ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.98-3.00 (m, 2H), 3.04-3.06 (m, 2H), 3.49 (s, 2H), 7.21-7.24 (m, 3H), 7.29 (s, 1H), 7.31 (s, 1H), 7.32-7.34 (m, 3H), 7.43-7.45 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 29.9, 35.2, 43.2, 82.0, 85.0, 123.1, 126.5, 128.52, 128.54, 128.6, 128.8, 128.9, 140.9, 203.9. HRMS (ESI+) Calcd for $C_{18}H_{17}O^+$ $[M+1]^+$: 249.1235; Found: 249.1770.



1-phenylpentan-2-one (24). Prepared according to general procedure on a scale of 0.1016 mmol of 1-butanone (9.2 μL, 1.0 equiv), 0.112 mmol of phenyldiazomethane (67 μL of 1.66 M toluene solution, 1.1 equiv) and 0.01 mmol Sc(OTf)$_3$ (5 mg, 0.1 equiv) in 87% yield (0.0884 mmol, 14.4 mg) after chromatographic purification (TLC Rf = 0.3 in 95:5 hexanes:ethyl acetate), IR (thin film): 2962,1713, 1495, 1454, 741 cm^{-1}. NMR Characterization has been previously reported at lower field.[66] ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (t, *J* =7.2Hz, 3H), 1.50 (td, *J* =7.2Hz, 2H), 2.34 (t, *J* =7.2 Hz, 2H), 3.59 (s, 2H), 7.27-7.11 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 17.1, 43.8, 50.1, 126.8, 128.6, 129.3, 134.3, 208.3. HRMS (ESI+) Calcd for $C_{11}H_{15}O$+1 $[M+1]^+$: 163.1078; Found: 163.1199.



(*E*)-1,4-Diphenylbut-1-en-3-one. Prepared according to the general procedure on a scale of 0.122 mmol of cinnamaldehyde (15.3 μL, 1.0 equiv), 0.134 mmol of phenyldiazomethane (100 μL of a 1.45 M solution in toluene, 1.1 equiv), and 0.012 mmol of $Sc(OTf)_3$ (6.1 mg, 0.10 equiv) in 55% yield (0.067 mmol, 8.9 mg) after chromatographic purification (TLC Rf = 0.30 in 95:5 hexanes:ethyl acetate). IR (thin film): 3027 (w), 1661 (s), 1451 (w), 1172 (w), 980 (w), 734 (m), 688 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 2H), 6.79 (d, *J* = 8.7 Hz, 1H), 7.26-7.31 (m, 5H), 7.32-7.41 (m, 3H), 7.52 (m, 2H), 7.63 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) δ 197.28, 143.40, 143.39, 134.47, 134.46, 134.41, 134.41, 130.59, 129.52, 129.52, 128.94, 128.94, 128.80, 128.79, 128.40, 128.40, 127.02, 127.02, 125.22, 125.21, 48.39. HRMS (ESI+) Calcd for $C_{16}H_{15}O^+$ $[M+1]^+$: 223.1073; Found: 223.1068.

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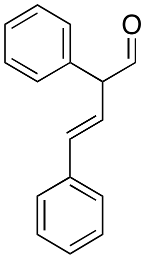
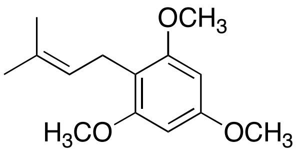
[66] "Palladium-Catalyzed Intermolecular Hydroamination of Alkynes: A Dramatic Rate-Enhancement Effect of *o*-Aminophenol," Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12670–12671.



(*E*)-2-Methyl-2,4-diphenylbut-3-enal (24). Prepared according to the general procedure on a scale of 0.122 mmol of cinnamaldehyde (15.3 μL), 0.134 mmol of methyl phenyl diazomethane **12** (400 μL of a 0.32 M solution in toluene, 1.1 equiv), and 0.012 mmol of $Sc(OTf)_3$ (6.1 mg, 0.10 equiv) in 25% yield (0.031 mmol, 6.1 mg) after chromatographic purification (TLC Rf = 0.35 in 95:5 hexanes:ethyl acetate). Characterization data for **2a** has been recorded previously.[67]



1-Prenyl-2,3,6-trimethoxybenzene. In a 200 mL round bottom flask equipped with a stir bar, 3.89 g (23.1 mmol) of 1,3,5-trimethoxybenzene was dissolved in 46 mL of cyclohexane. The resulting colorless solution was cooled to 0 °C and 20.0 mL of *n*-BuLi (1.62 M in hexanes, 32.4 mmol, 1.4 equiv) was added dropwise, turning the solution pale yellow in color. The reaction mixture was then heated to 65 °C for 30 min, at which point a fine, rust-colored precipitate had formed. After cooling the mixture to 23 °C, 4.0 mL (34.6 mmol, 1.5 equiv) of prenyl bromide was added dropwise from a syringe, and the mixture was again heated near the solvent boiling point for 2 h. Upon cooling to 23 °C, the reaction mixture was yellow in color but remained cloudy. The mixture was diluted with 100 mL of saturated sodium bicarbonate and transferred to a 250 mL separatory

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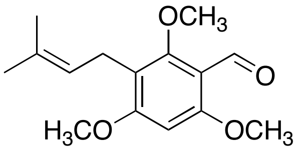
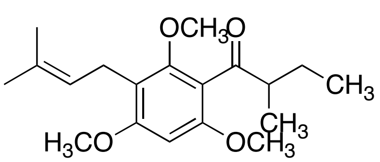
(67) "A Regiocontrolled Synthesis of Allylstannanes," Fleming, I.; Rowley, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2259.

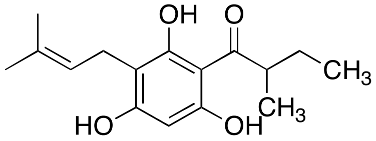
funnel with 50 mL of Et_2O. After agitation and removal of the organic layer, the aqueous layer was washed with two additional 50 mL volumes of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to an orange oil. Due to a minor impurity that co-elutes with the product, purification was best accomplished in two stages by separate chromatographies, first in 1.2:1 CH_2Cl_2:hexanes (TLC $R_f = 0.40$) and second in 15:1 hexanes:ethyl acetate (TLC $R_f = 0.30$). Concentration of pure fractions afforded 4.38 g (18.5 mmol, 80%) of a colorless oil that solidified when stored neat at –20 °C. IR (thin film): 2915 (w), 1592 (m), 1453 (m), 1202 (m), 1146 (m), 1114 (s), 809 (w). ^1H NMR (400 MHz, $CDCl_3$): δ 1.68 (s, 3H), 1.80 (s, 3H), 3.31 (d, J = 8.8 Hz, 2H), 3.82 (s, 9H), 5.23 (t, J = 6.8 Hz, 1H), 6.18 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 21.8, 25.9, 55.4, 55.9, 90.6, 110.8, 123.8, 130.5, 158.7, 159.4. HRMS (ESI+) Calcd for $C_{27}H_{35}O_4^+$ $[M+1]^+$: 423.2491; Found: 423.2491.



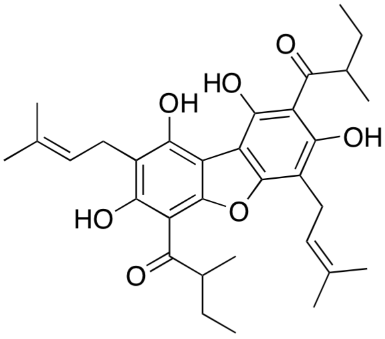
3-Prenyl-2,4,6-trimethoxybenzaldehyde (25). A 50 mL round bottom flask was charged with 322 μL (3.80 mmol, 1.2 equiv) of oxalyl chloride and 15 mL of CH_2Cl_2; the resulting homogeneous solution was cooled to 0 °C. At a rate conducive to the control of gas evolution, 295 μL (3.80 mmol, 1.2 equiv) of dimethylformamide was added by syringe. The reaction mixture was stirred for 30 min and warmed to 23 °C. A solution of 1-prenyl-2,3,6-trimethoxybenzene (750 mg, 3.17 mmol in 6 mL of cyclohexane) was then added through a cannula. The mixture was stirred for 4 h at 23 °C and then diluted with 50 mL of saturated sodium bicarbonate and 50 mL of ethyl acetate. After removal of the organic layer in a separatory funnel, the aqueous layer was washed with two additional 50 mL portions of ethyl acetate. Combined organic layers were dried over magnesium sulfate, filtered, and concentrated to a yellow oil. Purification by silica gel chromatography (TLC R_f = 0.30 in 1:1 hexanes:ethyl acetate) afforded 788 mg (2.98 mmol, 94%) of **25** as a pale yellow oil. IR (thin film): 2932 (w), 1673 (s), 1588 (m), 1224 (m), 1098 (s), 809 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (s, 3H), 1.75 (s, 3H), 3.24 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 3.88 (s, 6H), 5.11 (t, *J* = 6.8 Hz, 1H), 6.24 (s, 2H), 10.29 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 22.2, 26.0, 55.9, 56.1, 63.2, 91.1, 110.4, 116.6, 123.0, 131.8, 161.9, 162.4, 164.1, 188.1. HRMS (ESI+) Calcd for $C_{28}H_{35}O_5^+$ $[M+1]^+$: 451.2440; Found: 451.2450.



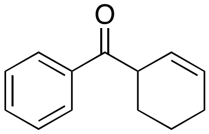
2-Methyl-1-(2,4,6-trimethoxy-3-(3-methylbut-2-enyl)phenyl)butan-1-one (26). Prepared according to the general procedure on a scale of 4.28 mmol of trimethoxybenzaldehyde (1.13 g), 4.7 mmol of 2-diazobutane (7.0 mL of a 0.67 M solution in toluene, 1.1 equiv), and 0.428 mmol of $Sc(OTf)_3$ (211 mg, 0.10 equiv) in 91% yield (3.89 mmol, 1.25 g) after chromatographic purification (TLC R_f = 0.30 in 90:10 hexanes:ethyl acetate). IR (thin film): 2938 (w), 2865 (w), 1694 (s), 1598 (m), 1460 (m), 1106 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.7 Hz, 3H), 1.11 (d, *J* = 8.8 Hz, 3H), 1.19 (m, 1H), 1.68 (s, 3H), 1.76 (s, 3H), 2.91 (m, 1H), 3.27 (d, *J* = 8.7 Hz, 2H), 3.69 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 5.16 (t, *J* = 6.7 Hz, 1H), 6.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0, 12.4, 15.2, 22.9, 25.4, 25.9, 49.1, 56.0, 56.1, 63.3, 92.0, 116.2, 123.5, 123.6, 131.7, 155.9, 156.4, 159.9, 208.6. HRMS (ESI+) Calcd for $C_{19}H_{29}O_4^+$ $[M+1]^+$: 321.2066; Found: 321.2075.



2-Methyl-1-(2,4,6-trihydroxy-3-(3-methylbut-2-enyl)phenyl)butan-1-one (27). To a CH_2Cl_2 solution (0.46 mL) of 0.047 mmol of **26** (15 mg) in a 1 dram vial was added 0.28 mmol of BBr_3 (27 μL, 6.0 equiv) at 23 °C. After sealing the vial with a Teflon-lined screw cap, the solution was heated at 35 °C for 12 h. The reaction mixture was then cooled to 23 °C and washed with an equivalent volume of saturated sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography (TLC R_f = 0.30 in 90:10 hexanes:ethyl acetate) delivered a clear oil in 15% yield (0.007 mmol, 2 mg). An alternative and much higher yielding deprotection strategy involves first reduction to the benzylic alcohol, then global demethylation with TMSI, and finally reoxidation with the Dess-Martin periodinane (65% overall, three steps). These details are not disclosed here because we are in the process of rerouting to phloroglucinol as a starting material and incorporating a more readily removable blocking group (benzyl) into the path of synthesis. IR (thin film): 3422 (br), 2972 (w), 2930 (w), 1626 (s) 1590 (m), 1422 (w), 1229 (m), 1158 (m), 1117 (m), 882 (w), 817 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.7 Hz, 3H), 1.18 (d, *J* = 8.8 Hz, 3H), 1.33 (s, 6H), 1.38 (m, 2H), 1.79 (t, *J* = 6.7 Hz, 1H), 2.59 (t, *J* = 6.7 Hz, 1H), 3.73 (m, 1H), 5.71 (s, 1H), 5.98 (br s, 3H). HRMS (ESI+) Calcd for $C_{16}H_{23}O_4^+$ $[M+1]^+$: 279.1795; Found: 279.1880.



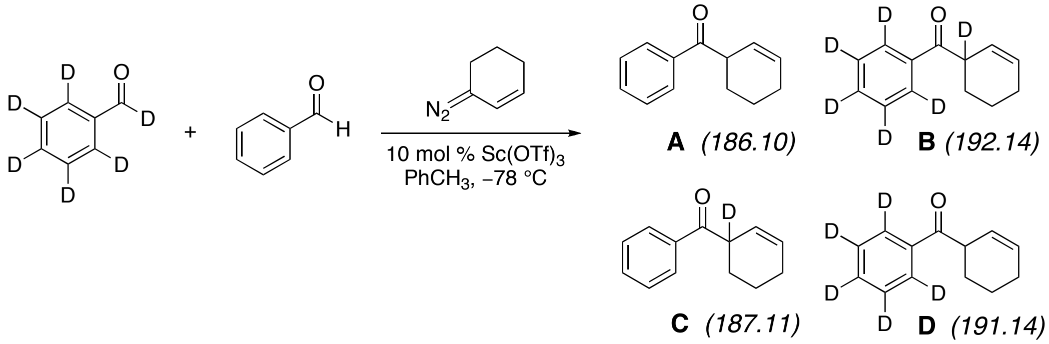
"Pre-achyrofuran" (28). To a slurry of 0.0576 mmol $FeCl_3$ on SiO_2 (0.144 g, 4.0 equiv) in CH_2Cl_2 (0.72 mL, 0.08 M) at 23 °C was added a 0.2 M solution of **27** (4.0 mg, 0.014 mmol) in CH_2Cl_2:CH_3CN (3:1). The faint yellow solution instantly turned dark brown, and after 5 min of rapid stirring the solution was filtered through a celite plug and concentrated to a brown oil. Purification by silica gel chromatography (TLC R_f of **28** = 0.30 in 95:5 hexanes:ethyl acetate) afforded 3.8 mg of the desired product (0.0071 mmol, 51%), 1.6 mg of the uncyclized homodimer (0.0029 mmol, 21%), and 0.9 mg of recovered starting material (0.0031 mmol, 21%). Characterization follows for the desired product dibenzofuran. IR (thin film): 3492 (b), 2927 (w), 1618 (s), 1420 (w), 1230 (w), 1159 (m), 1117 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.5 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.31 (s, 3H), 1.32 (s, 3H), 1.39 (m, 1H), 1.46 (m, 1H), 1.69 (s, 3H), 1.85 (s, 3H), 1.86-1.92 (m, 2H), 3.47 (m, 1H), 3.73 (m, 1H), 5.69 (br s, 2H), 5.99 (br s, 2H). HRMS (ESI+) Calcd for $C_{32}H_{41}O_7^+$ [M+1]$^+$: 537.1295; Found: 537.1259.



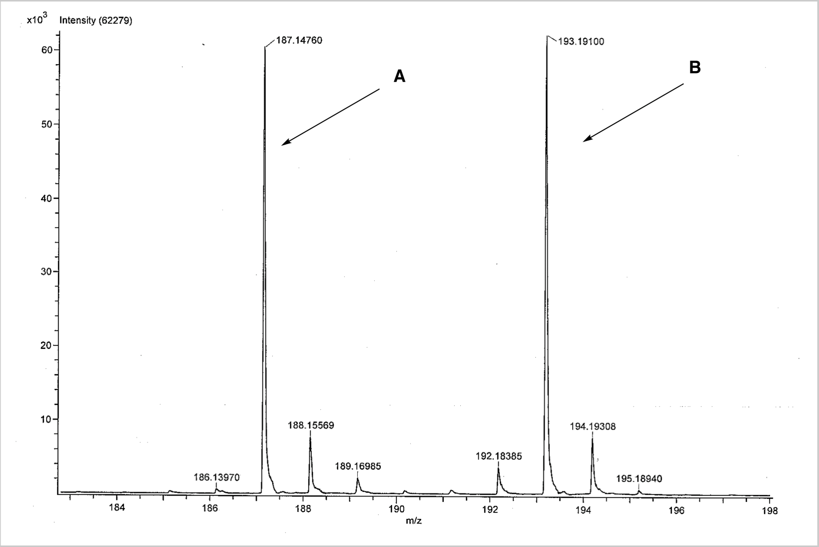
Cyclohex-2-enyl(phenyl)methanone. Prepared according to the general procedure on a scale of 0.162 mmol of benzaldehyde (16.4 μL), 0.179 mmol of 3-diazocyclohex-1-ene (488 μL of a 0.37 M solution in toluene, 1.1 equiv), and 0.016 mmol of $Sc(OTf)_3$ (8.0 mg, 0.10 equiv) in 87% yield (0.141 mmol, 26.4 mg) after chromatographic purification (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). IR (thin film): 2935 (w), 1680 (s), 1447 (m), 1209 (m), 960 (m), 695 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (m, 2H), 1.95 (m, 2H), 1.99 (m, 2H), 4.09 (m, 1H), 5.74 (m, 2H), 5.93 (m, 2H), 7.47 (t, *J* = 6.8 Hz, 2H), 7.54 (t, *J* = 6.8 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 25.2, 26.0, 42.0, 125.1, 128.2, 128.3, 130.4, 133.3, 136.4, 202.2. HRMS (ESI+) Calcd for $C_{13}H_{15}O^+$ [M+1]$^+$: 187.1078; Found: 187.1109.

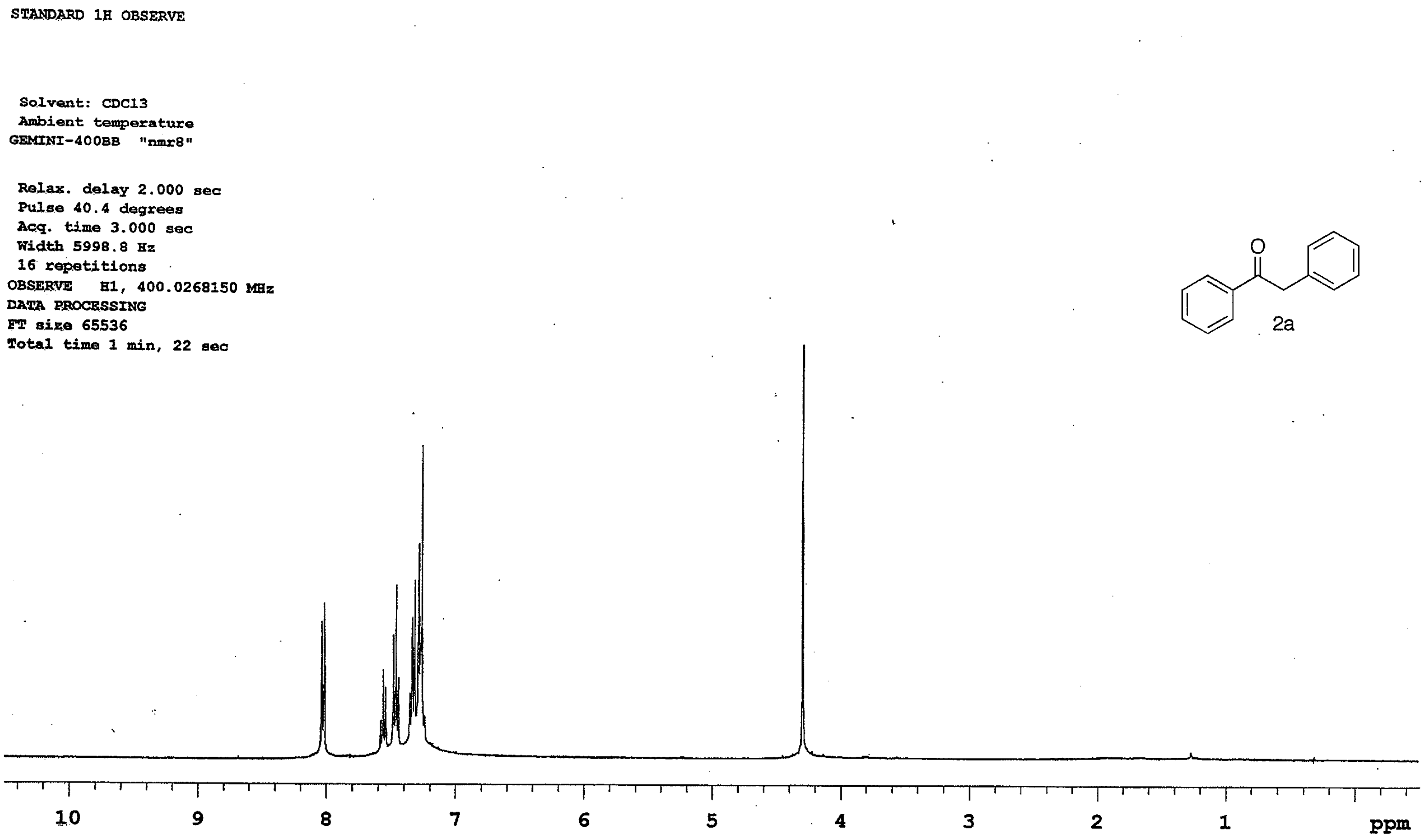
Deuterium Labeling Studies:

In order to distinguish between possible mechanistic pathways (see text of manuscript), the following experiment was undertaken: In a glovebox, a flame-dried 1 dram vial equipped with a Teflon-coated flea stir bar was charged with $Sc(OTf)_3$ (9.8 mg, 0.020 mmol, 0.10 equiv) and sealed with a rubber septum. In a fume hood, toluene (2.0 mL, 0.1 M) was added by syringe, suspending but not dissolving the catalyst. After cooling the mixture to –78 °C, 10.1 µL benzaldehyde (0.100 mmol, 0.50 equiv), 10.2 µL d_6-benzaldehyde (0.100 mmol, 0.50 equiv), and 470 µL 3-diazocyclohex-1-ene (0.470 M solution in toluene, 0.220 mmol, 1.1 equiv, solution kept cold at –78 °C) were added in succession to the stirring reaction mixture by syringe. The reaction was stirred for 10 min at –78 °C, at which point the characteristic purple color of the nucleophile had dissipated, leaving a turbid light yellow suspension. The reaction mixture was concentrated with a nitrogen purge and purified by flash chromatography (TLC R_f = 0.30 in 19:1 hexanes:ethyl acetate) affording 23.1 mg of a mixture of products **A** and **B**.



The high resolution mass spectrum of the mixture (see Figure) clearly shows a predominance of peaks corresponding to $[M+H]^+$ for structures **A** and **B**. Although the peaks at 188.1557 and 192.1839 could in principle correspond to deuterium crossover structures **C** and **D**, analogous control experiments carried out with just benzaldehyde or d_6-benzaldehyde generate high-resolution mass spectra identical to the individual mass distributions seen in the Figure. The presence of these ions is thus an artifact of the natural abundance of deuterium and the starting level of enrichment in the commercial d_6-benzaldehyde.





STANDARD 1H OBSERVE

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Relax. delay 2.000 sec
Pulse 40.4 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 400.0268150 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 22 sec

2a

```
STANDARD 1H OBSERVE

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     -300spot.fid   dm             nnn
   ACQUISITION      dmm              c
sfrq       400.029  dmf            200
tn              H1        PROCESSING
at           3.000  wtfile
np           35992  proc            ft
sw          5998.8  fn        not used
fb            3400
bs              16  werr
tpwr            63  wexp
pw             7.1  wbs
d1           2.000  wnt
tof              0
nt              16
ct              16
alock            n
gain      not used
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in               n
dp               y
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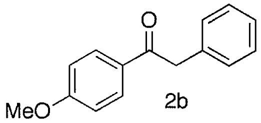
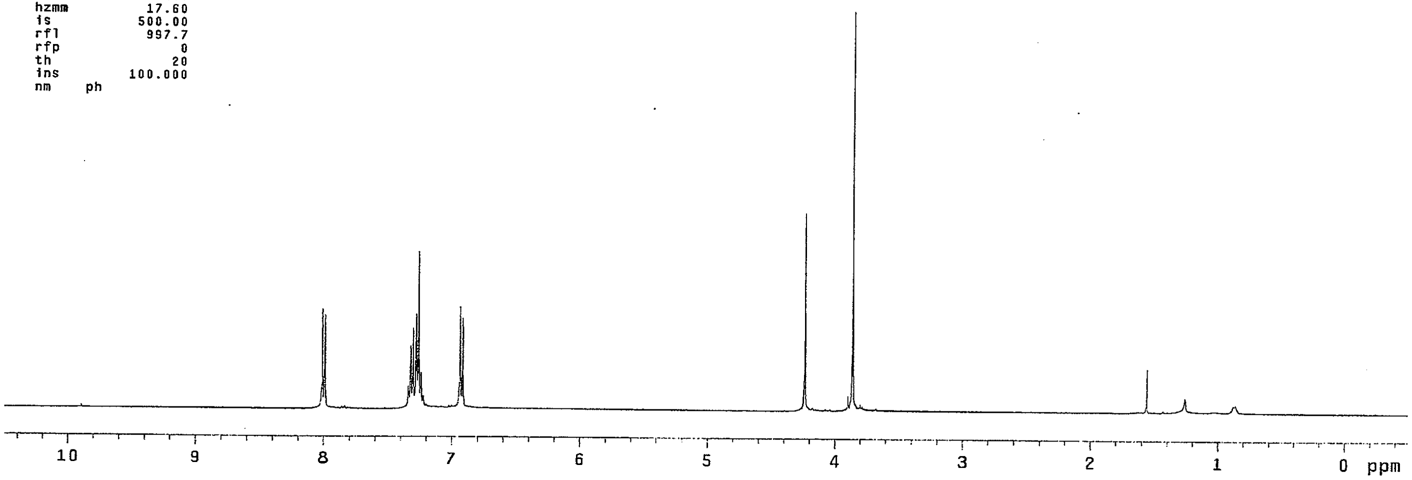


2b



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   ACQUISITION      dmm               c
sfrq       400.029  dmf             200
tn              H1       PROCESSING
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np           35992  proc             ft
sw          5998.8  fn         not used
fb            3400
bs              16  werr
tpwr            63  wexp
pw             7.1  wbs
d1           2.000  wnt
tof              0
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ct              12
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dp               y
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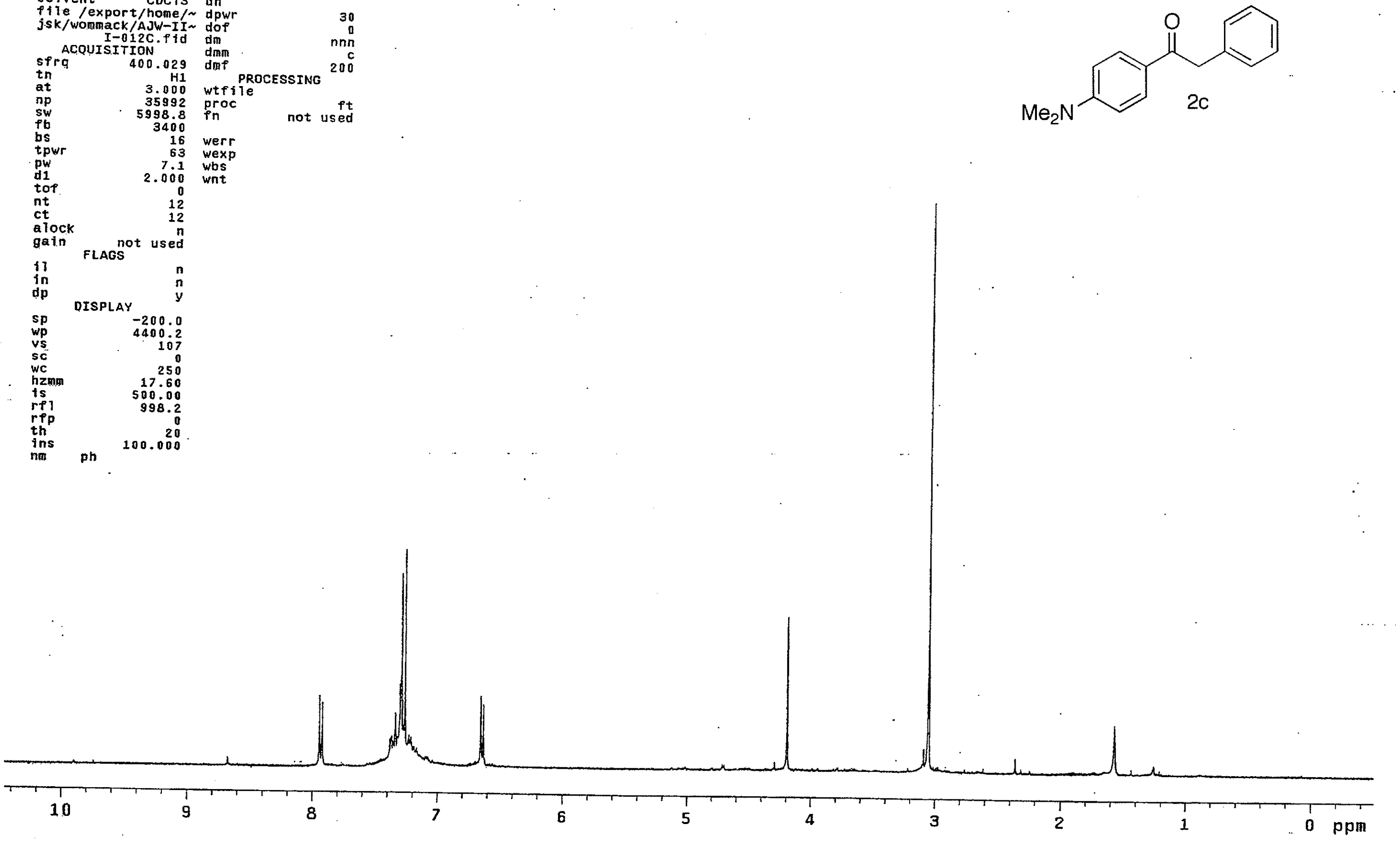

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STANDARD 1H OBSERVE

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   ACQUISITION      dmm             c
sfrq        400.029 dmf           200
tn               H1       PROCESSING
at            3.000 wtfile
np            35992 proc           ft
sw           5998.8 fn       not used
fb             3400
bs               16 werr
tpwr             63 wexp
pw              7.1 wbs
d1            2.000 wnt
tof               0
nt               16
ct               16
alock             n
gain       not used
       FLAGS
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dp                y
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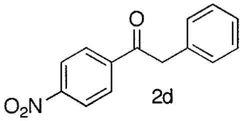
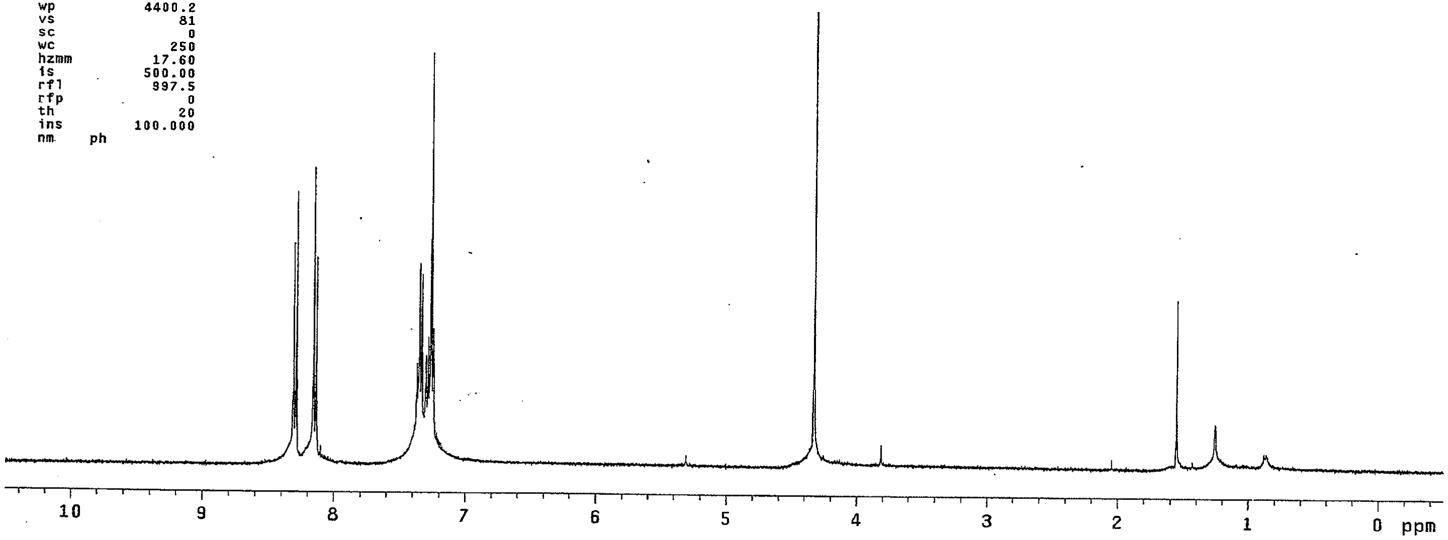


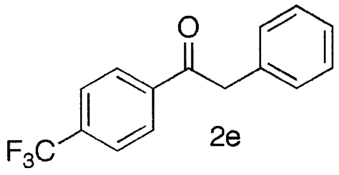
2d



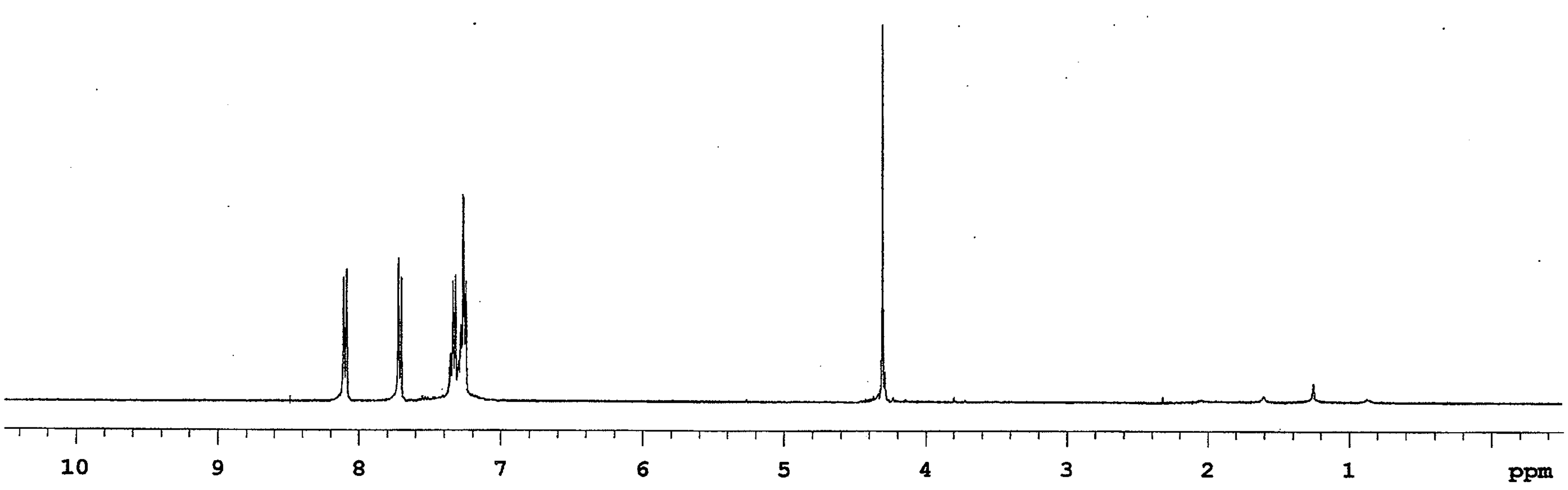
AJW-III-002prod

Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"

Relax. delay 2.000 sec
Pulse 40.4 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
12 repetitions
OBSERVE H1, 400.0268172 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 2 sec



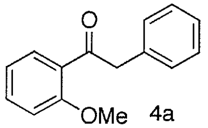
2e



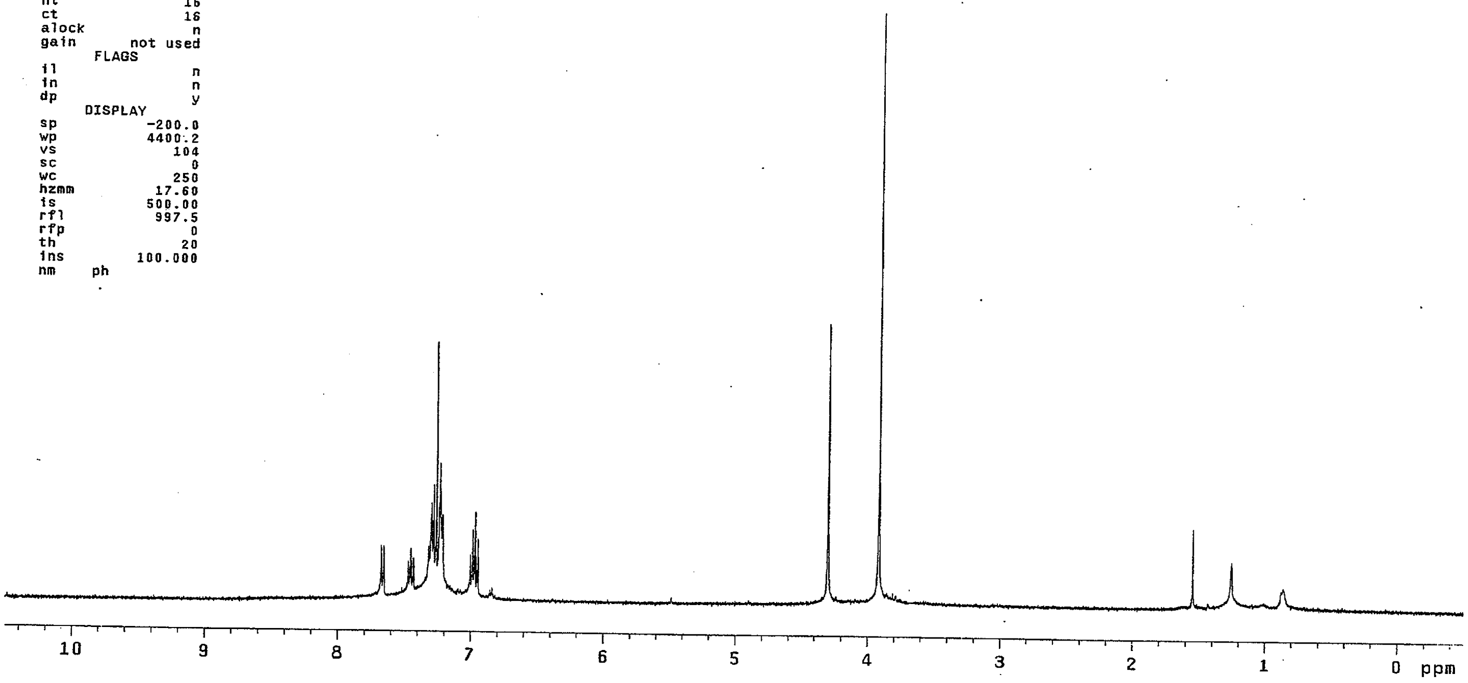
```
STANDARD 1H OBSERVE

exp1  std1h

       SAMPLE               DEC. & VT
date   Jul  9 2008  dfrq              0
solvent      CDCl3  dn
file /export/home/~ dpwr             30
jsk/wommack/AJW-II~ dof               0
    -299spot.fid    dm              nnn
    ACQUISITION     dmm               c
sfrq       400.029  dmf             200
tn              H1      PROCESSING
at           3.000  wtfile
np           35992  proc             ft
sw          5998.8  fn         not used
fb            3400
bs              16  werr
tpwr            63  wexp
pw             7.1  wbs
d1           2.000  wnt
tof              0
nt              16
ct              16
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
     DISPLAY
sp          -200.0
wp          4400.2
vs             104
sc               0
wc             250
hzmm         17.60
is          500.00
rfl          997.5
rfp              0
th              20
ins        100.000
nm     ph
```



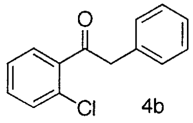
4a



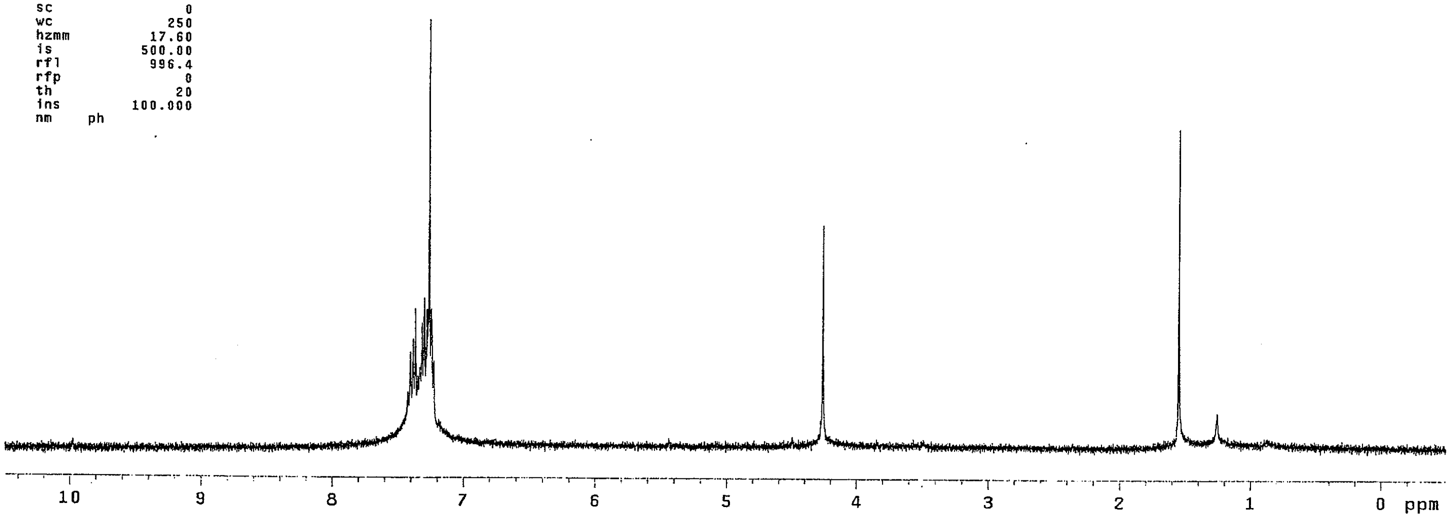
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                DEC. & VT
date   Jul 17 2008  dfrq              0
solvent      CDCl3  dn
file /export/home/~ dpwr             30
jsk/wommack/AJW-II~ dof               0
     -302spot.fid   dm              nnn
   ACQUISITION      dmm               c
sfrq       400.029  dmf             200
tn              H1      PROCESSING
at           3.000  wtfile
np           35992  proc             ft
sw          5998.8  fn         not used
fb            3400
bs              16  werr
tpwr            63  wexp
pw             7.1  wbs
d1           2.000  wnt
tof              0
nt              16
ct              16
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
     DISPLAY
sp          -200.0
wp          4400.2
vs              74
sc               0
wc             250
hzmm         17.60
is          500.00
rfl          996.4
rfp              0
th              20
ins        100.000
nm    ph
```



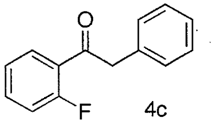
4b



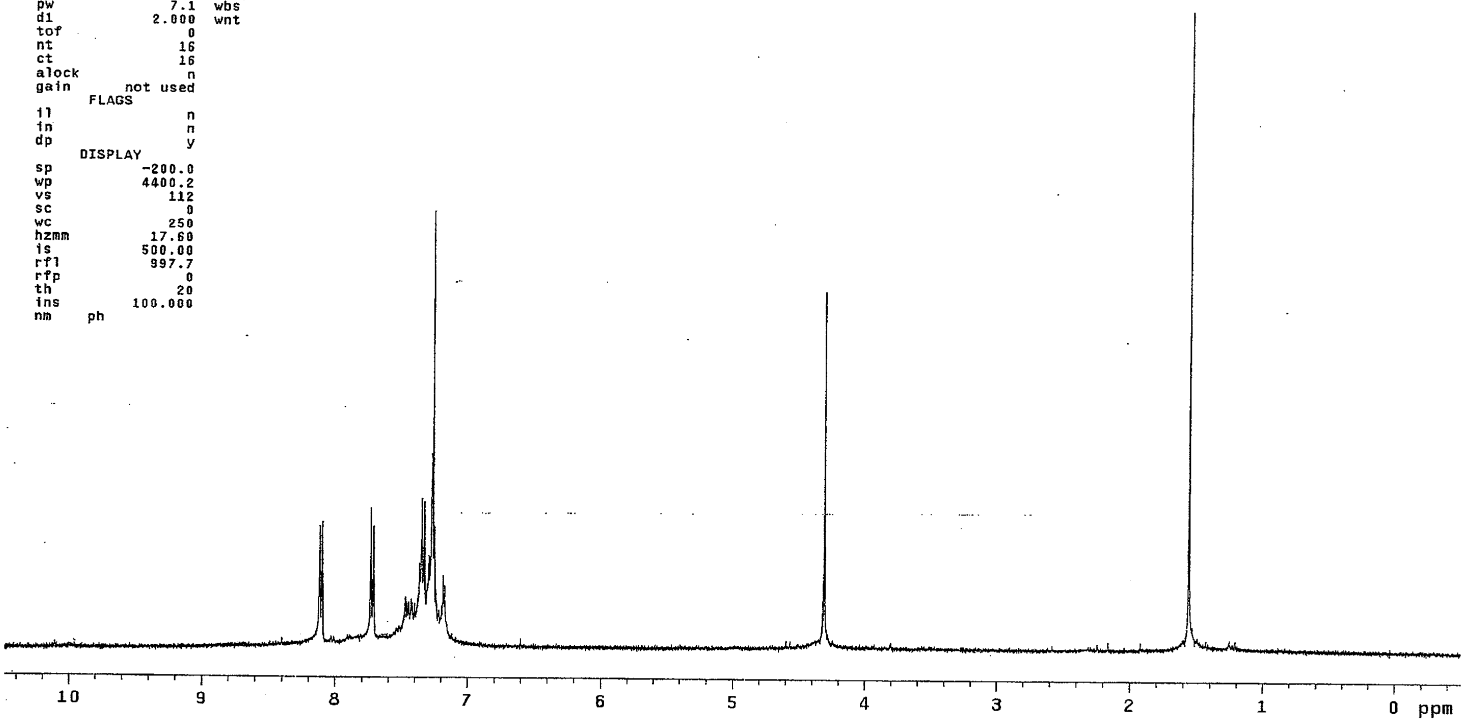
```
STANDARD 1H OBSERVE

exp1  std1h

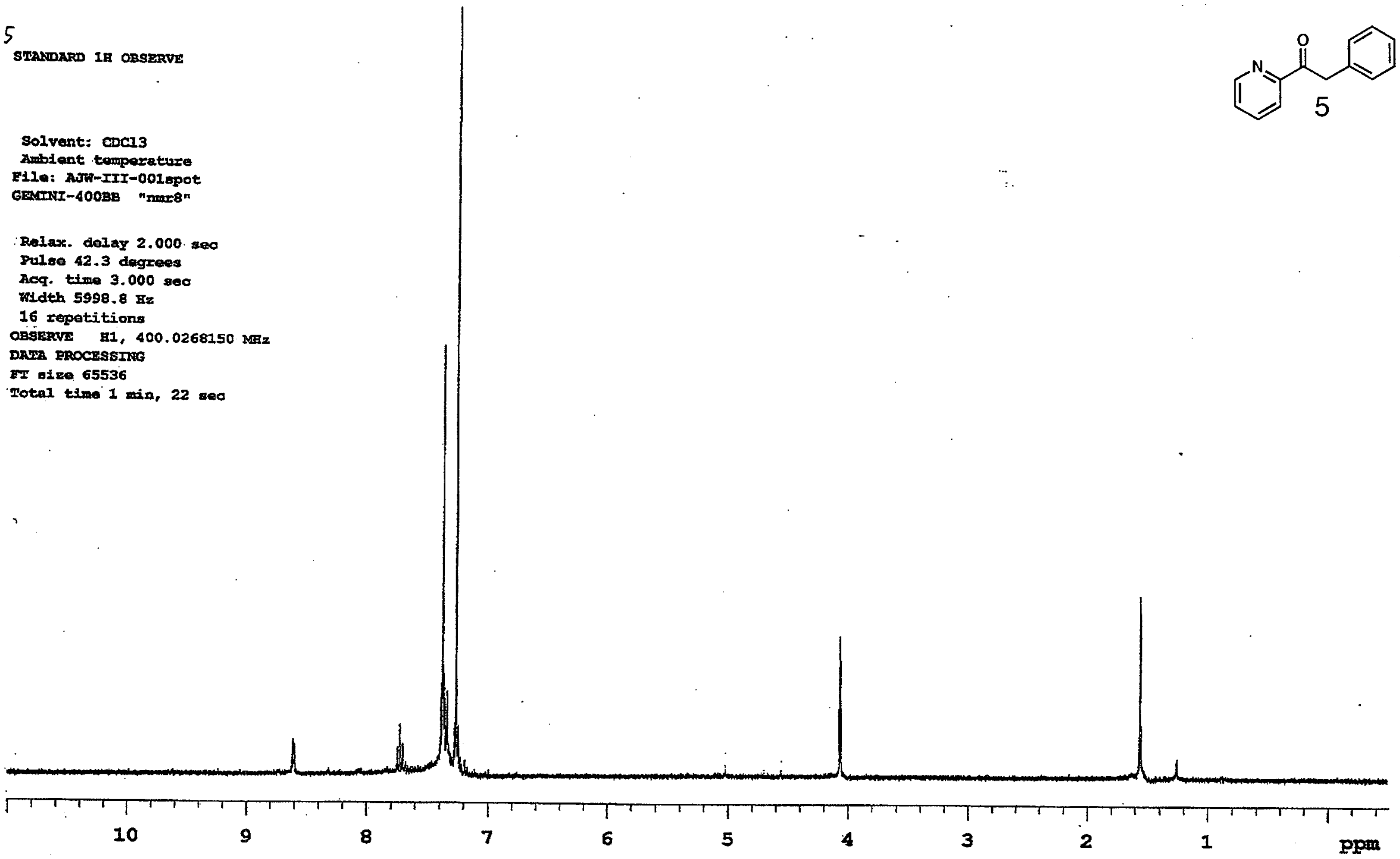
      SAMPLE              DEC. & VT
date   Aug  8 2008  dfrq             0
solvent       CDCl3  dn
file /export/home/~ dpwr            30
jsk/wommack/AJW-II~ dof              0
        I-037C.fid  dm             nnn
   ACQUISITION      dmm              c
sfrq        400.029  dmf            200
tn               H1      PROCESSING
at            3.000  wtfile
np            35992  proc            ft
sw           5998.8  fn        not used
fb             3400
bs               16  werr
tpwr             63  wexp
pw              7.1  wbs
d1            2.000  wnt
tof               0
nt               16
ct               16
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
     DISPLAY
sp           -200.0
wp           4400.2
vs              112
sc                0
wc              250
hzmm          17.60
is           500.00
rfl           997.7
rfp               0
th               20
ins         100.000
nm     ph
```



4c



5

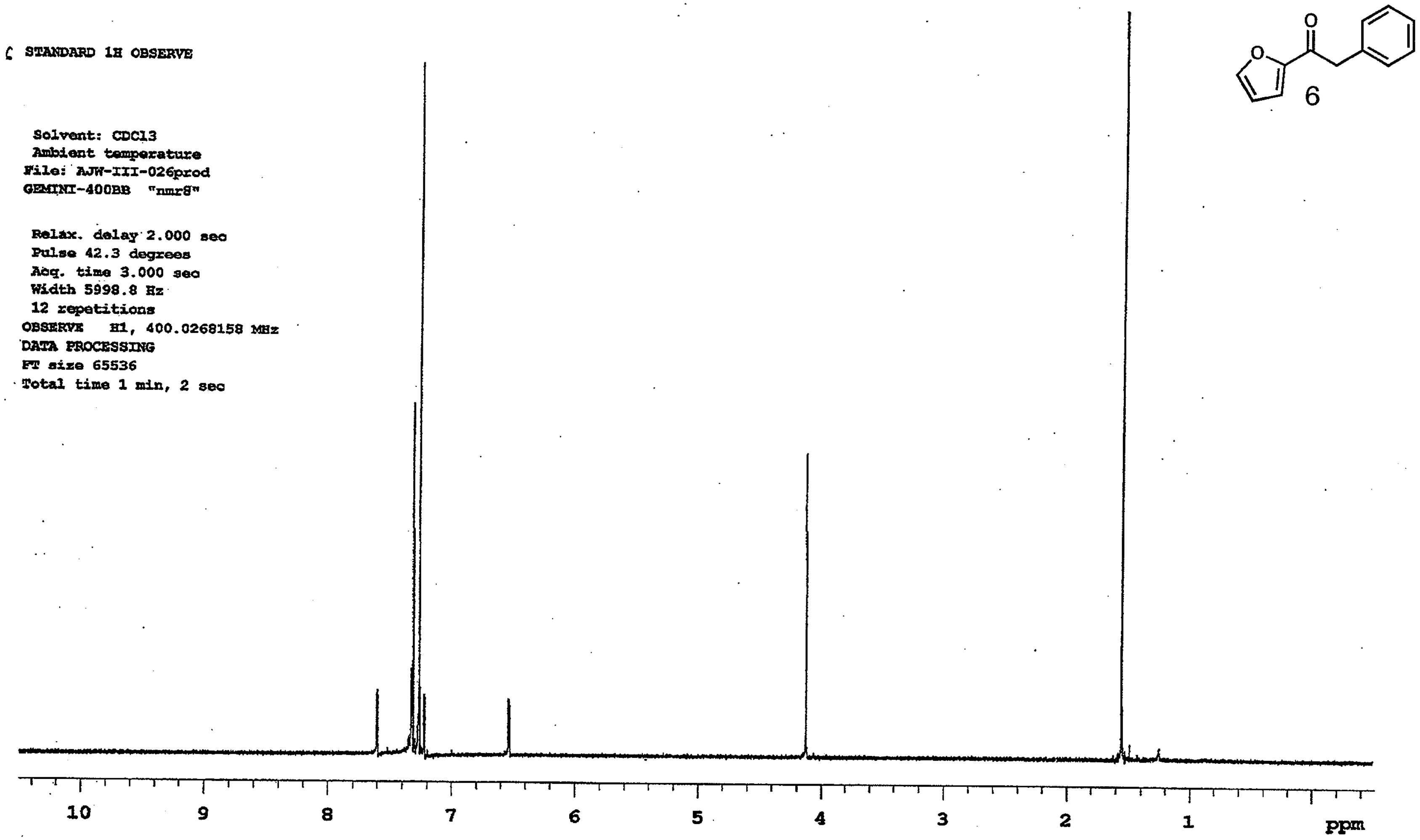


STANDARD 1H OBSERVE

Solvent: CDCl3
Ambient temperature
File: AJW-III-001spot
GEMINI-400BB "nmr8"

Relax. delay 2.000 sec
Pulse 42.3 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 400.0268150 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 22 sec

5



6

STANDARD 1H OBSERVE

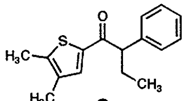
```
 Solvent: CDCl3
 Ambient temperature
File: AJW-III-026prod
GEMINI-400BB  "nmr8"

 Relax. delay 2.000 sec
 Pulse 42.3 degrees
 Acq. time 3.000 sec
 Width 5998.8 Hz
 12 repetitions
OBSERVE   H1, 400.0268158 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 2 sec
```

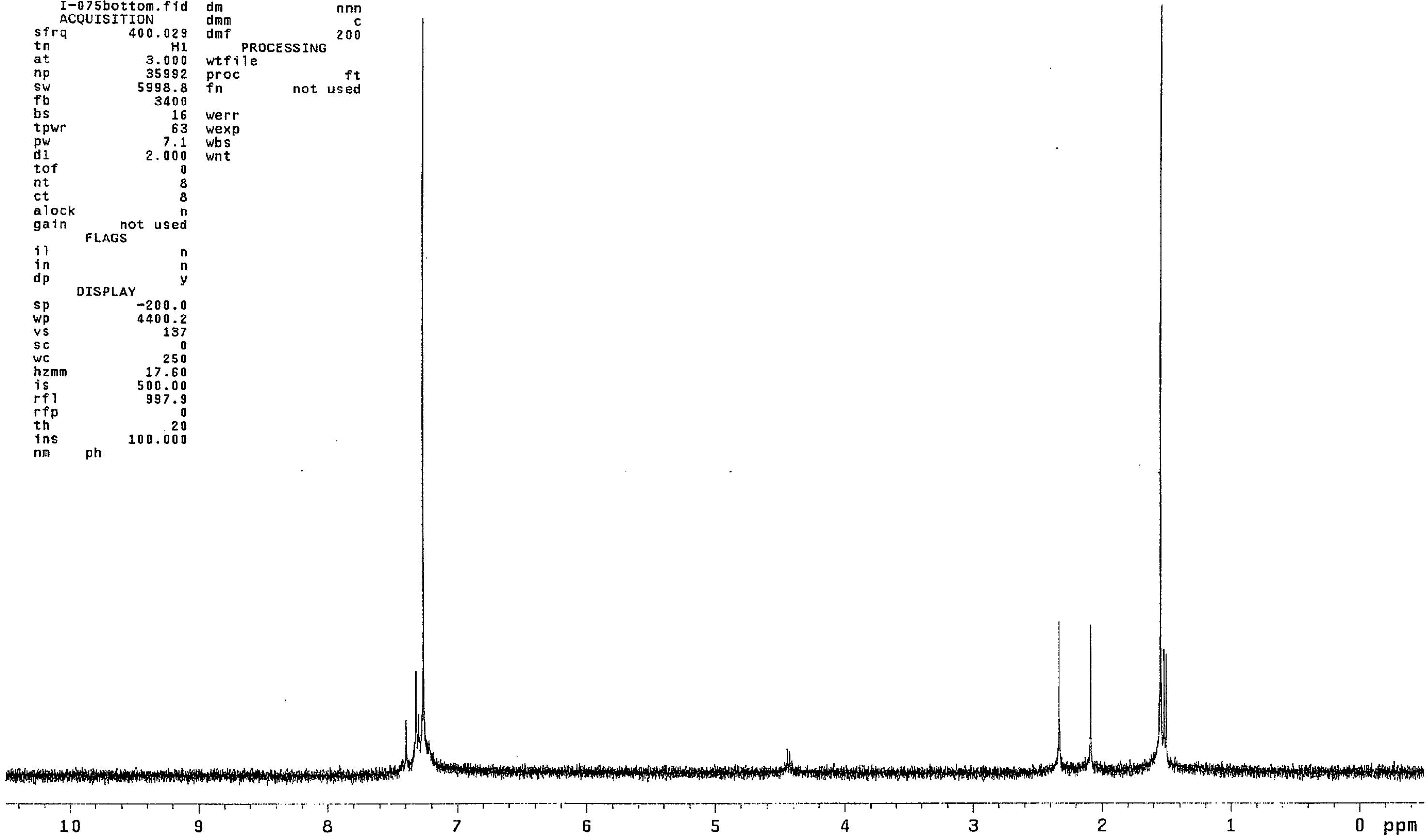
```
STANDARD 1H OBSERVE

exp1  std1h

     SAMPLE              DEC. & VT
date   Aug 29 2008  dfrq              0
solvent      CDCl3  dn
file /export/home/~ dpwr             30
jsk/wommack/AJW-II~ dof               0
   I-075bottom.fid  dm              nnn
   ACQUISITION      dmm               c
sfrq       400.029  dmf             200
tn              H1       PROCESSING
at           3.000  wtfile
np           35992  proc             ft
sw          5998.8  fn         not used
fb            3400
bs              16  werr
tpwr            63  wexp
pw             7.1  wbs
d1           2.000  wnt
tof              0
nt               8
ct               8
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
     DISPLAY
sp          -200.0
wp          4400.2
vs             137
sc               0
wc             250
hzmm         17.60
is          500.00
rfl          997.9
rfp              0
th              20
ins        100.000
nm    ph
```



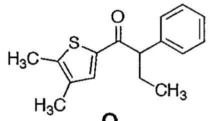
9



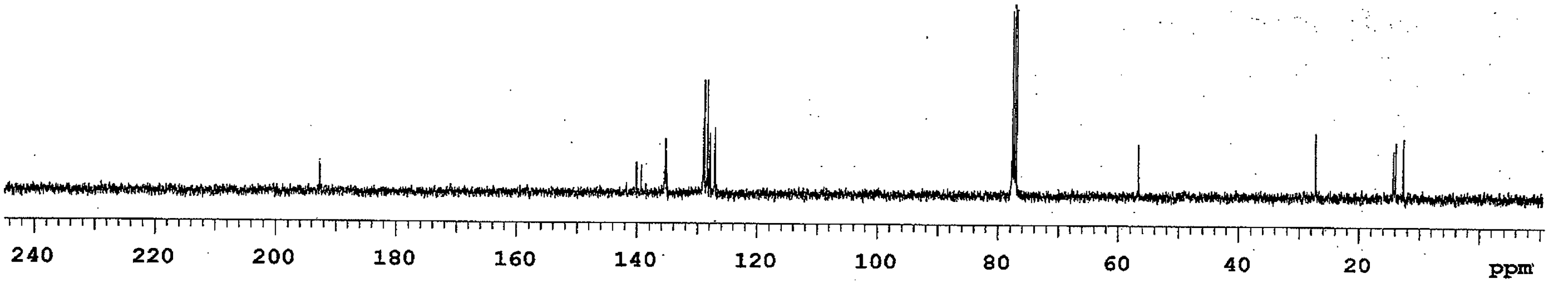
13C OBSERVE

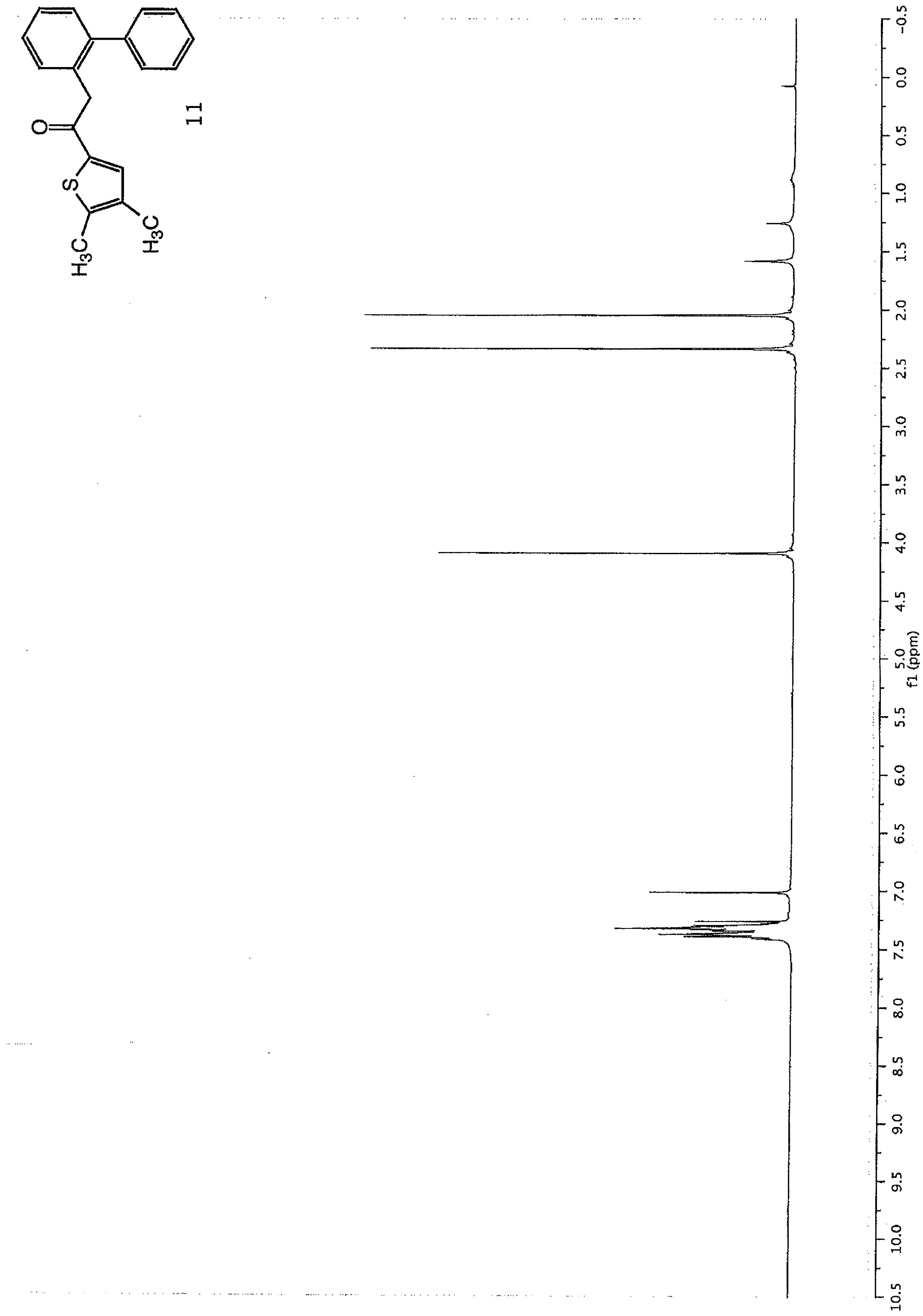
Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"

Relax. delay 4.000 sec
Pulse 64.8 degrees
Acq. time 0.640 sec
Width 25683.4 Hz
192 repetitions
OBSERVE C13, 100.5868063 MHz
DECOUPLE H1, 400.0288163 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 32 min, 3 sec

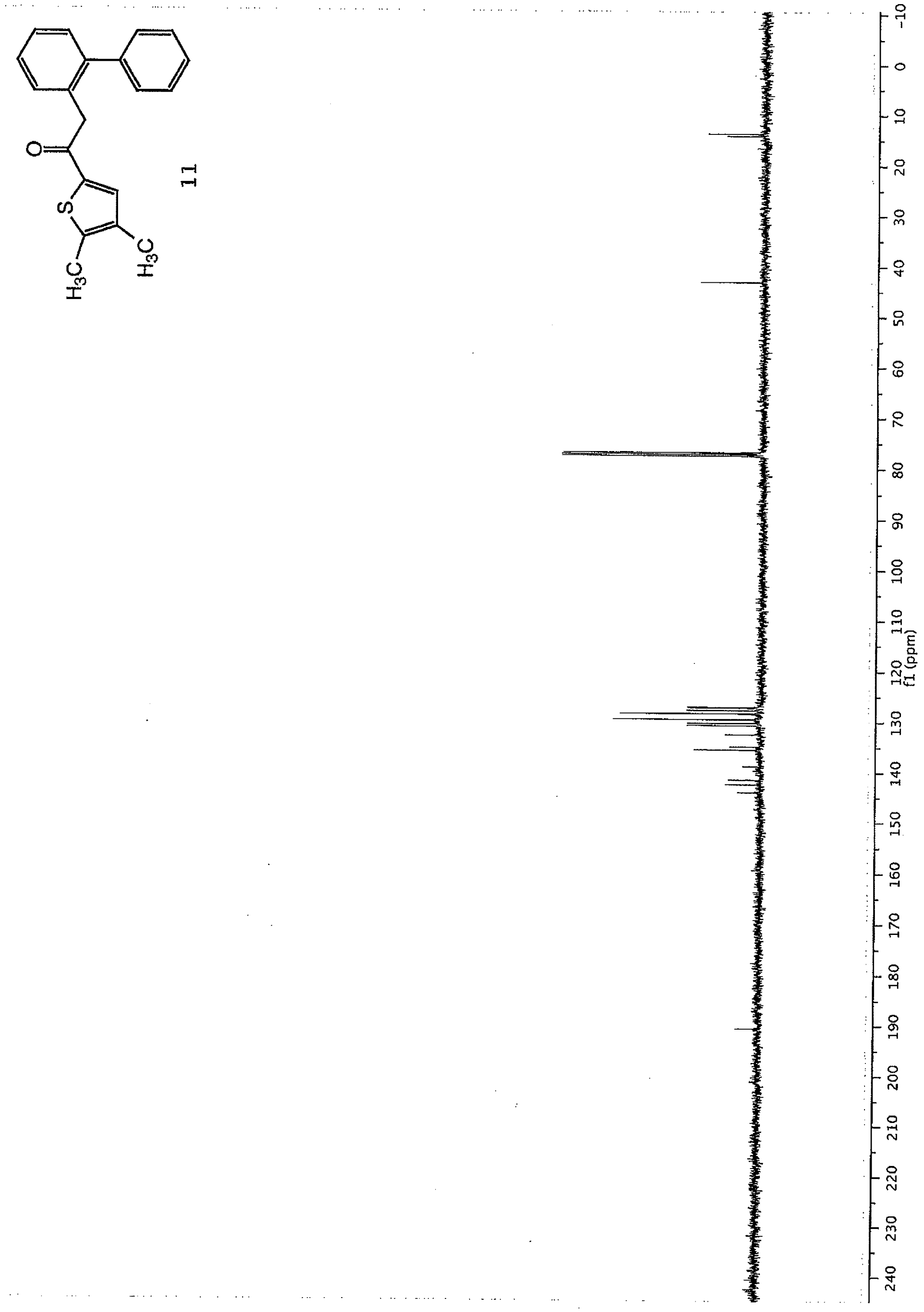


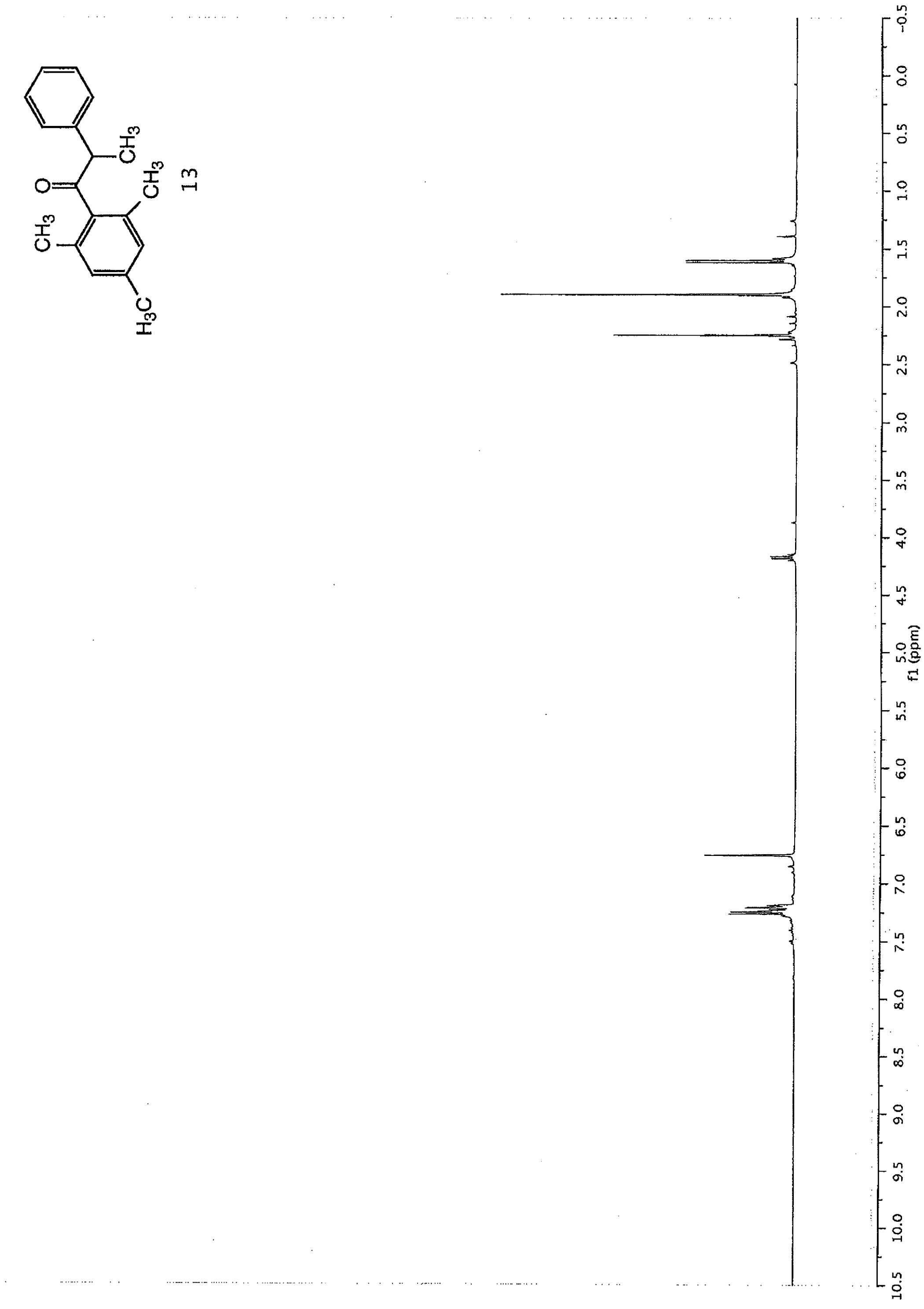
9



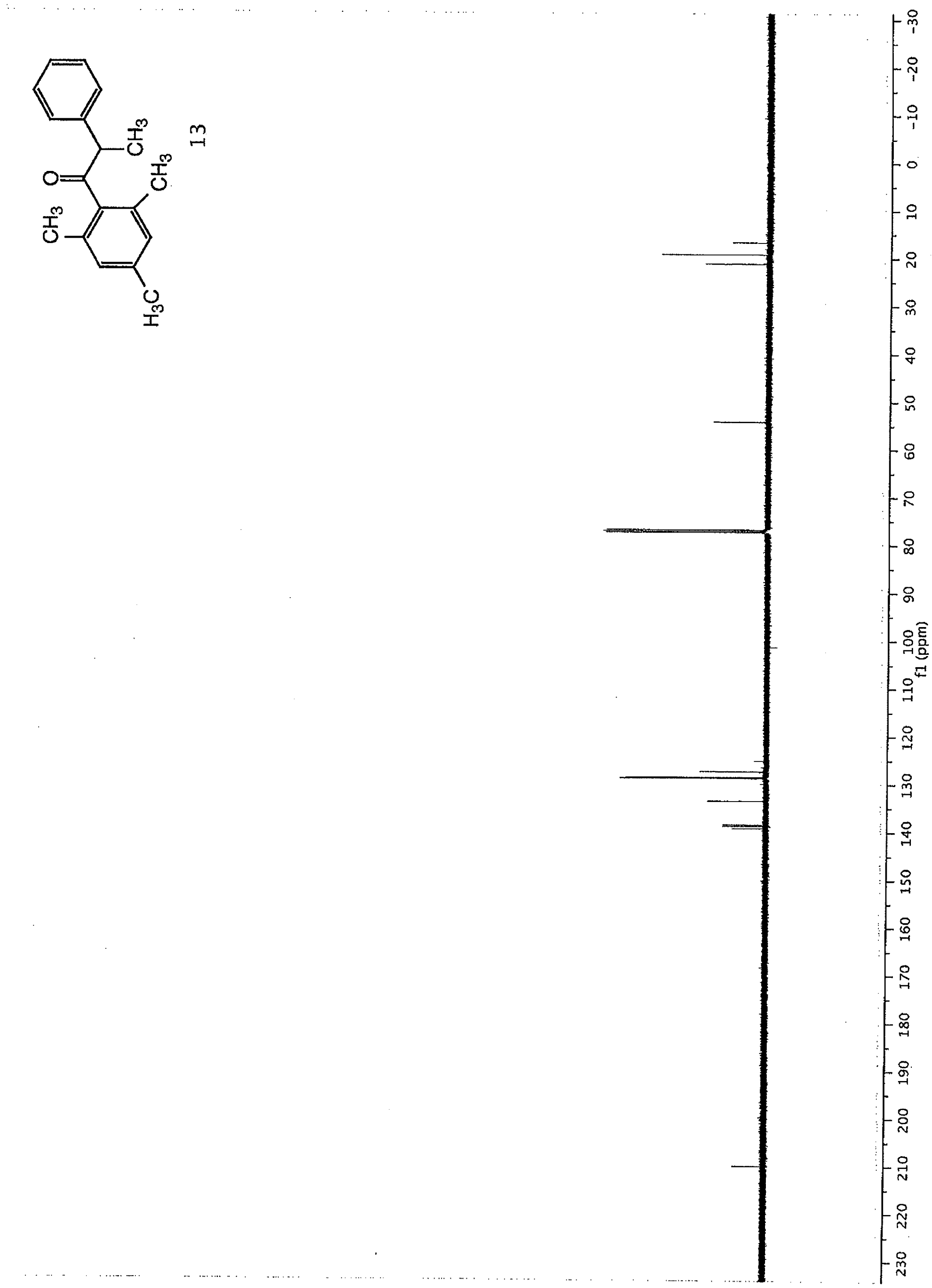

O
S
H3C
H3C
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
f1 (ppm)
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5

11

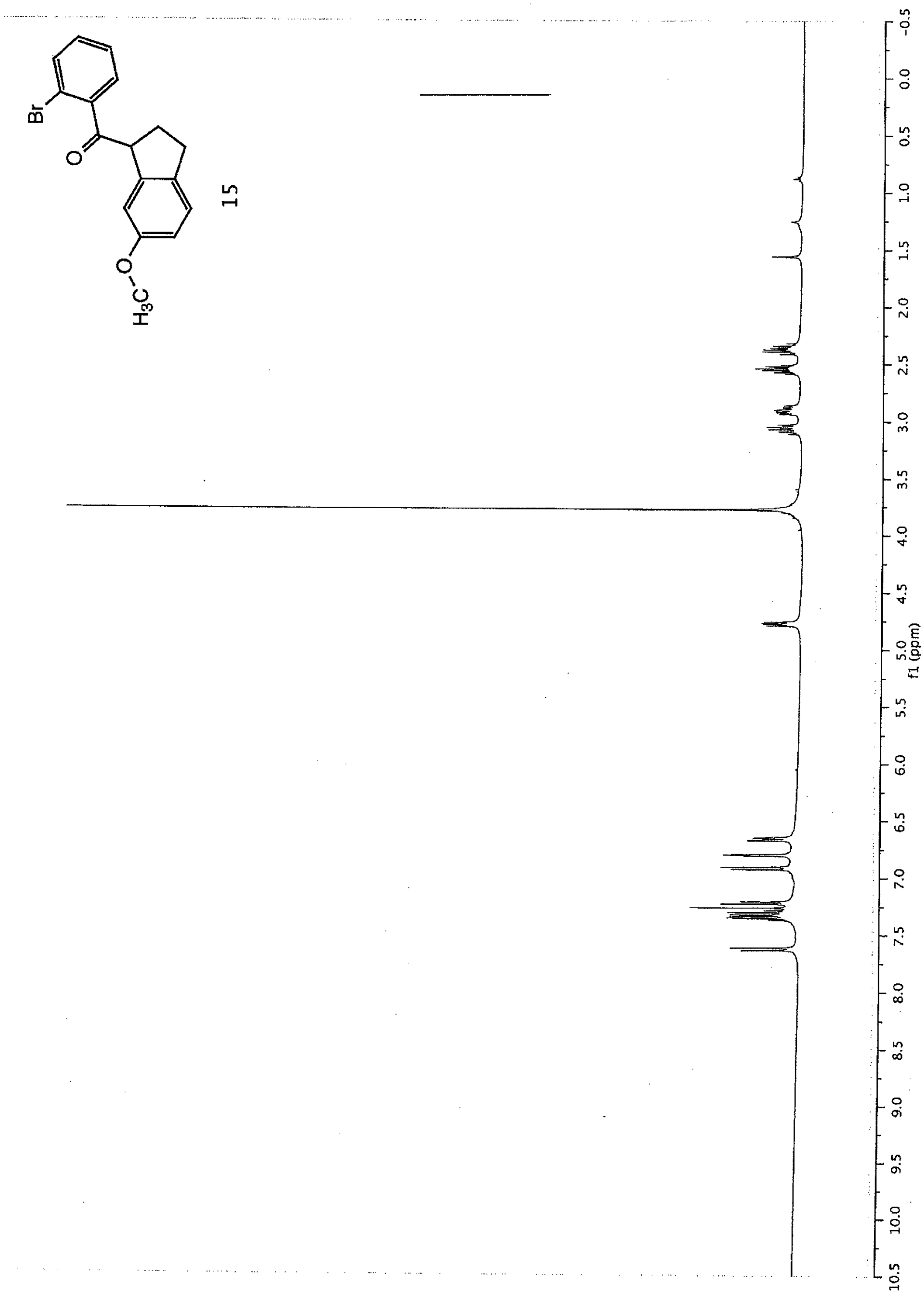

11
H3C
H3C
S
O
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


13

CH3
O
CH3
CH3
H3C
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

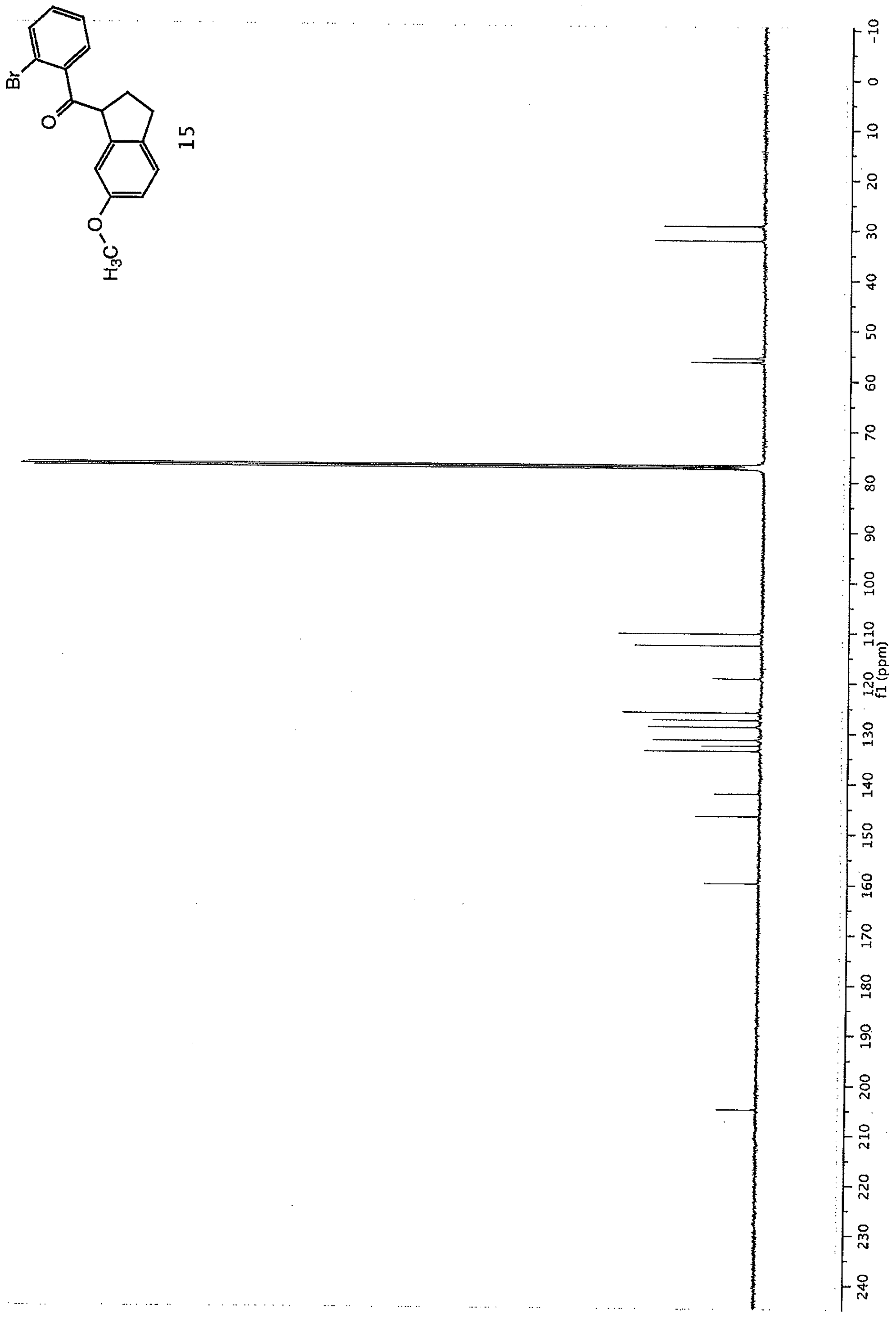

O
CH3
CH3
CH3
H3C
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)

13



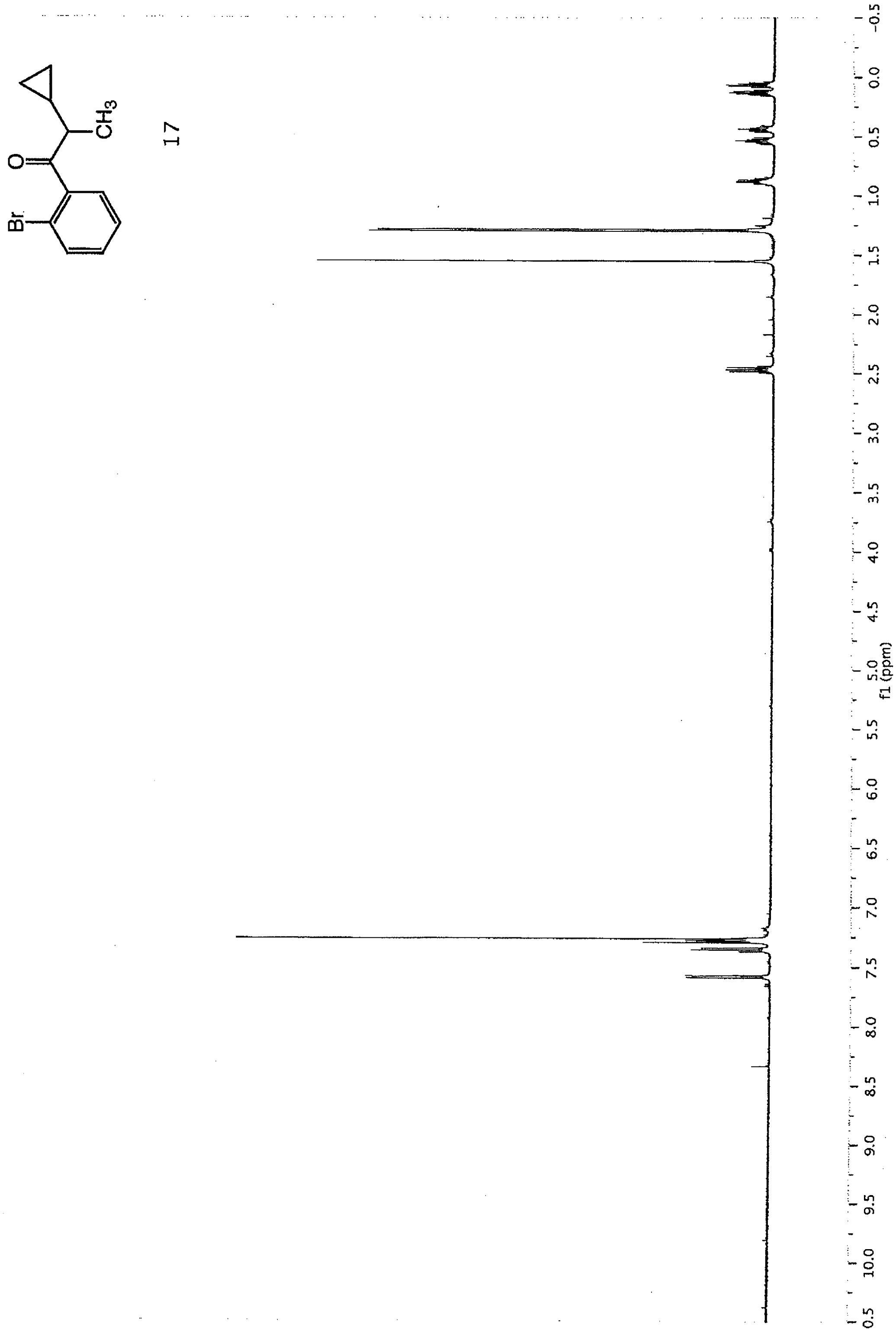
Br
O
H_3C
O
f1 (ppm)
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5

15

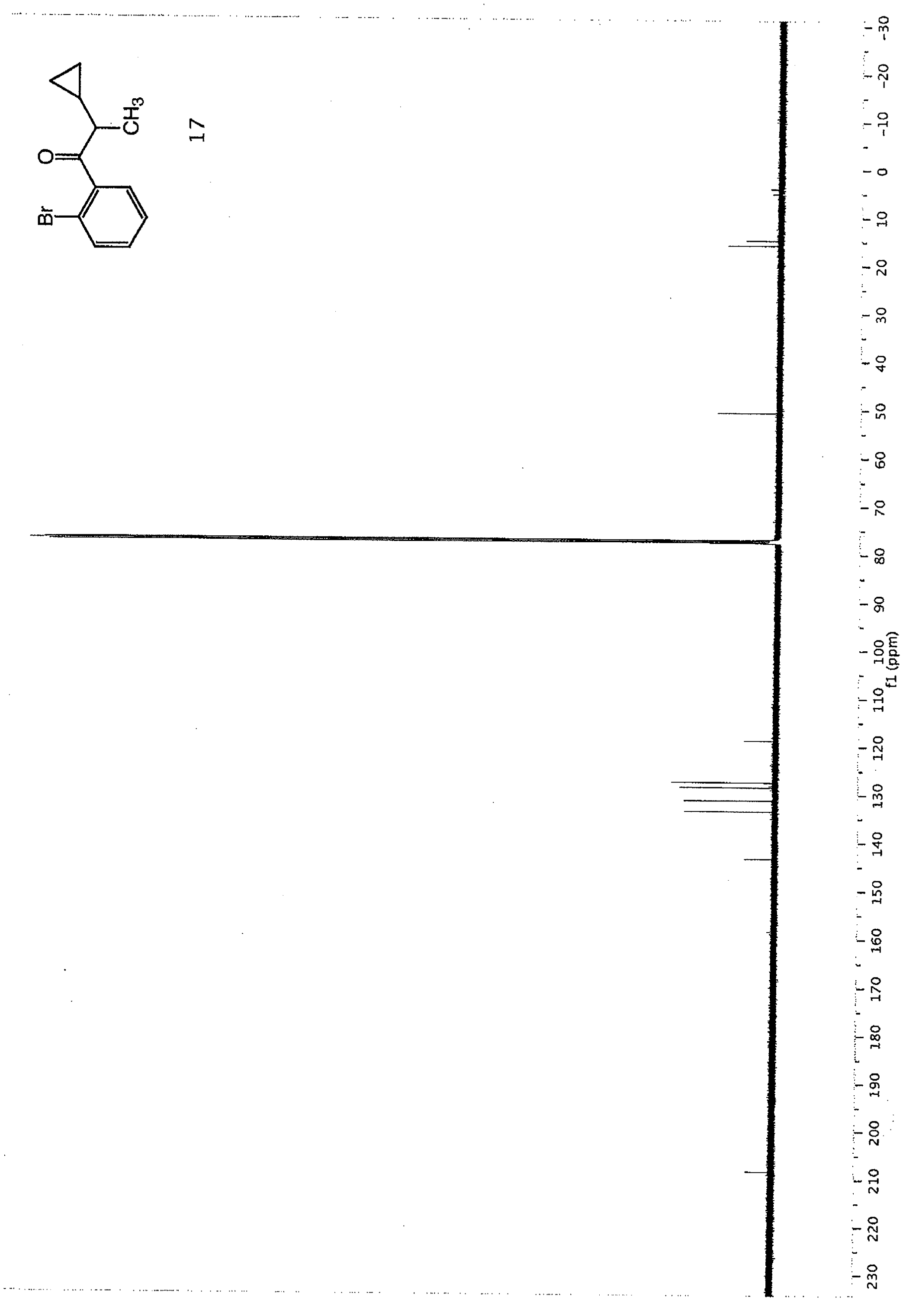


15

Br
O
O
H$_3$C
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
f1 (ppm)


17

Br
O
CH3
f1 (ppm)
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5



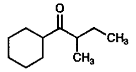
17

Br
O
CH3
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30

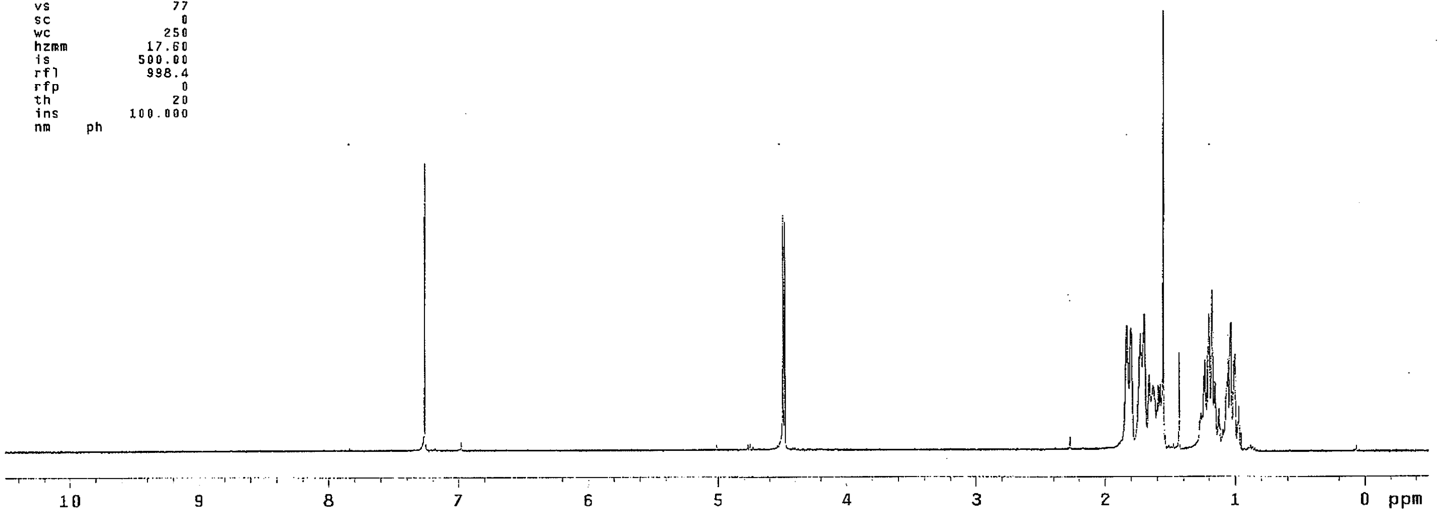
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE              DEC. & VT
date   Sep 11 2008  dfrq              0
solvent      CDCl3  dn
file /export/home/~ dpwr             30
jsk/wommack/AJW-II~ dof               0
     I-101spot.fid  dm              nnn
   ACQUISITION      dmm               c
sfrq       400.029  dmf             200
tn              H1        PROCESSING
at           3.000  wtfile
np           35992  proc             ft
sw          5998.8  fn         not used
fb            3400
bs              16  werr
tpwr            63  wexp
pw             7.1  wbs
d1           2.000  wnt
tof              0
nt              16
ct              16
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
     DISPLAY
sp          -200.0
wp          4400.2
vs              77
sc               0
wc             250
hzmm         17.60
is          500.00
rfl          998.4
rfp              0
th              20
ins        100.000
nm    ph
```



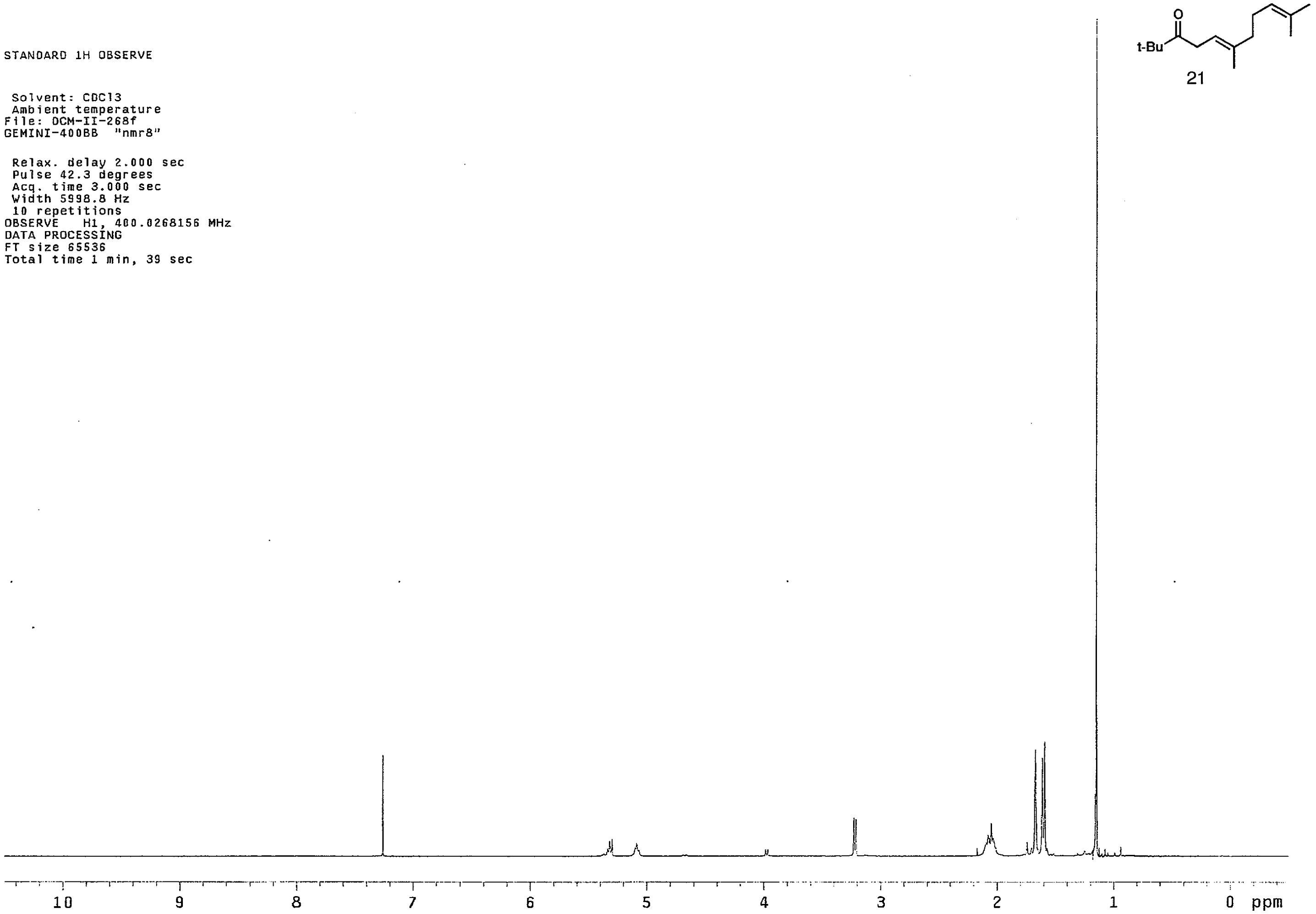
19

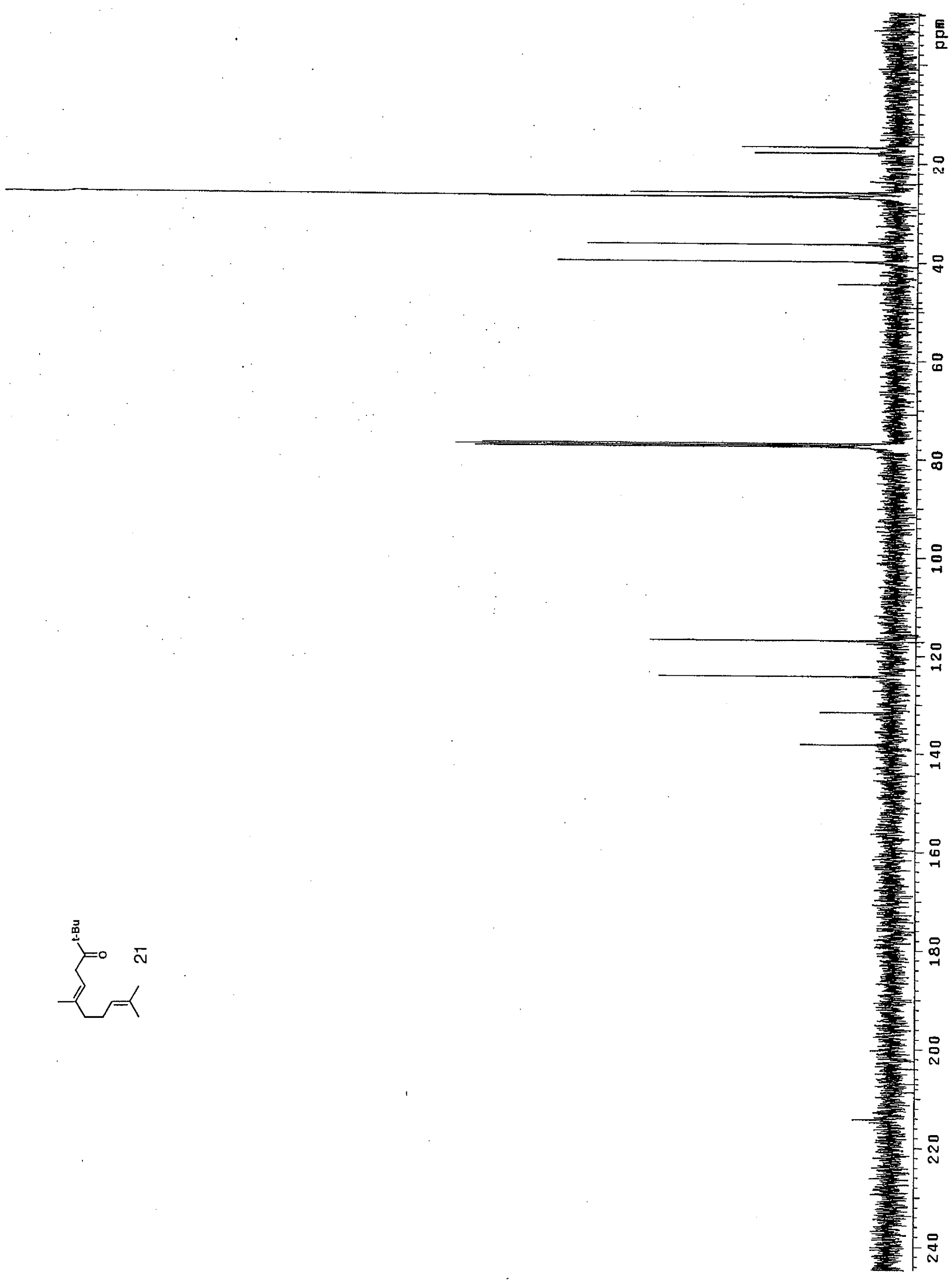


STANDARD 1H OBSERVE

Solvent: CDCl3
Ambient temperature
File: DCM-II-268f
GEMINI-400BB "nmr8"

Relax. delay 2.000 sec
Pulse 42.3 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
10 repetitions
OBSERVE H1, 400.0268156 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 39 sec



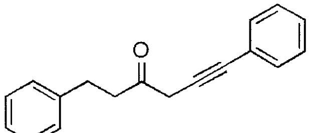


21

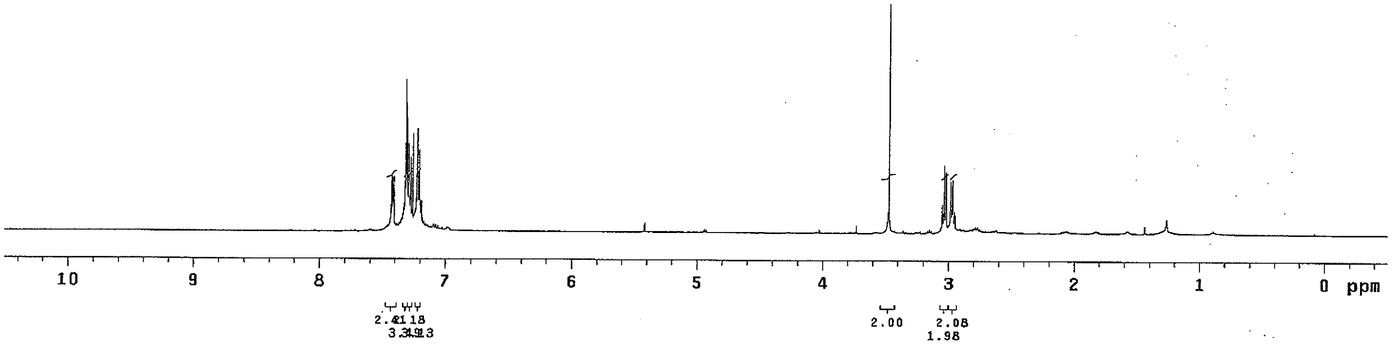
```
STANDARD PROTON PARAMETERS

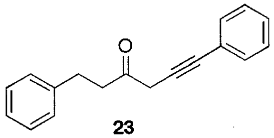
expl  s2pul

      SAMPLE               DEC. & VT
date   Jun 29 2009  dfrq         499.774
solvent      CDCl3  dn                H1
file /export/home/~ dpwr              30
jsk/AJW-IV-236prod~ dof                0
              .fid  dm               nnn
   ACQUISITION      dmm                c
sfrq       499.774  dmf              200
tn              H1  dseq
at           5.000  dres             1.0
np           70058  homo               n
sw          7005.9            DEC2
fb            4000  dfrq2              0
bs               4  dn2
tpwr            57  dpwr2              1
pw             4.6  dof2               0
d1               0  dm2                n
tof          497.0  dmm2               c
nt              48  dmf2             200
ct               0  dseq2
alock            n  dres2            1.0
gain      not used  homo2              n
      FLAGS               PROCESSING
il               n  wtfile
in               n  proc              ft
dp               y  fn          not used
hs              nn  math               f
     DISPLAY
sp          -249.9  werr
wp          5497.4  wexp
vs              42  wbs
sc               0  wnt              wft
wc             250
hzmm         21.99
is           33.57
rfl         4144.3
rfp         3628.3
th               7
ins          2.000
nm    ph
```



23



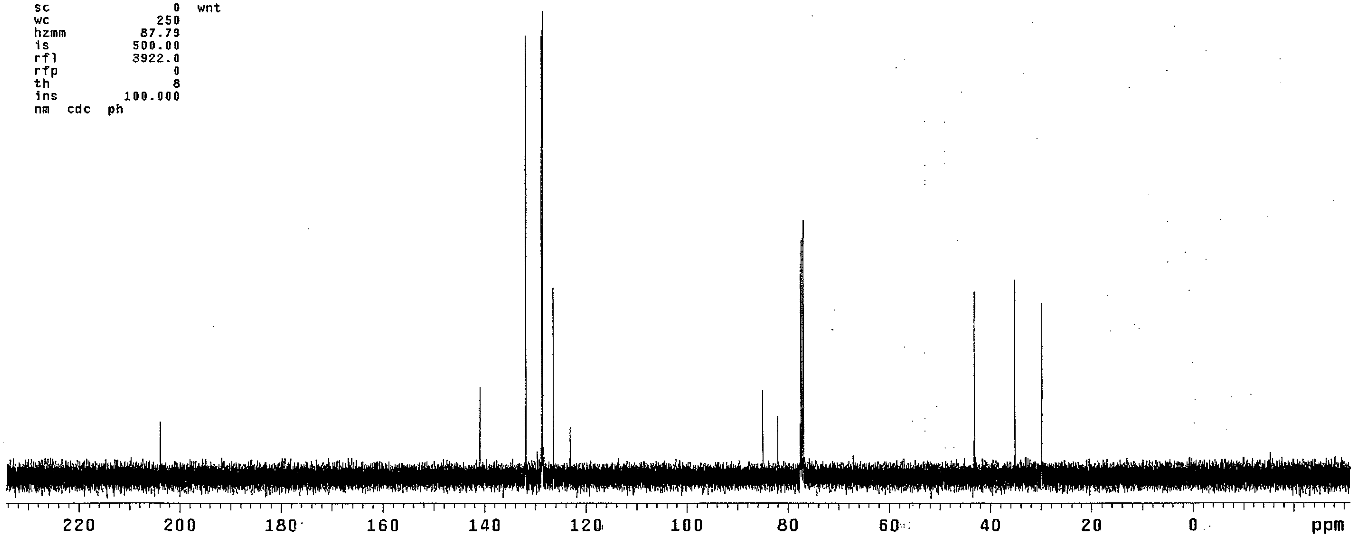


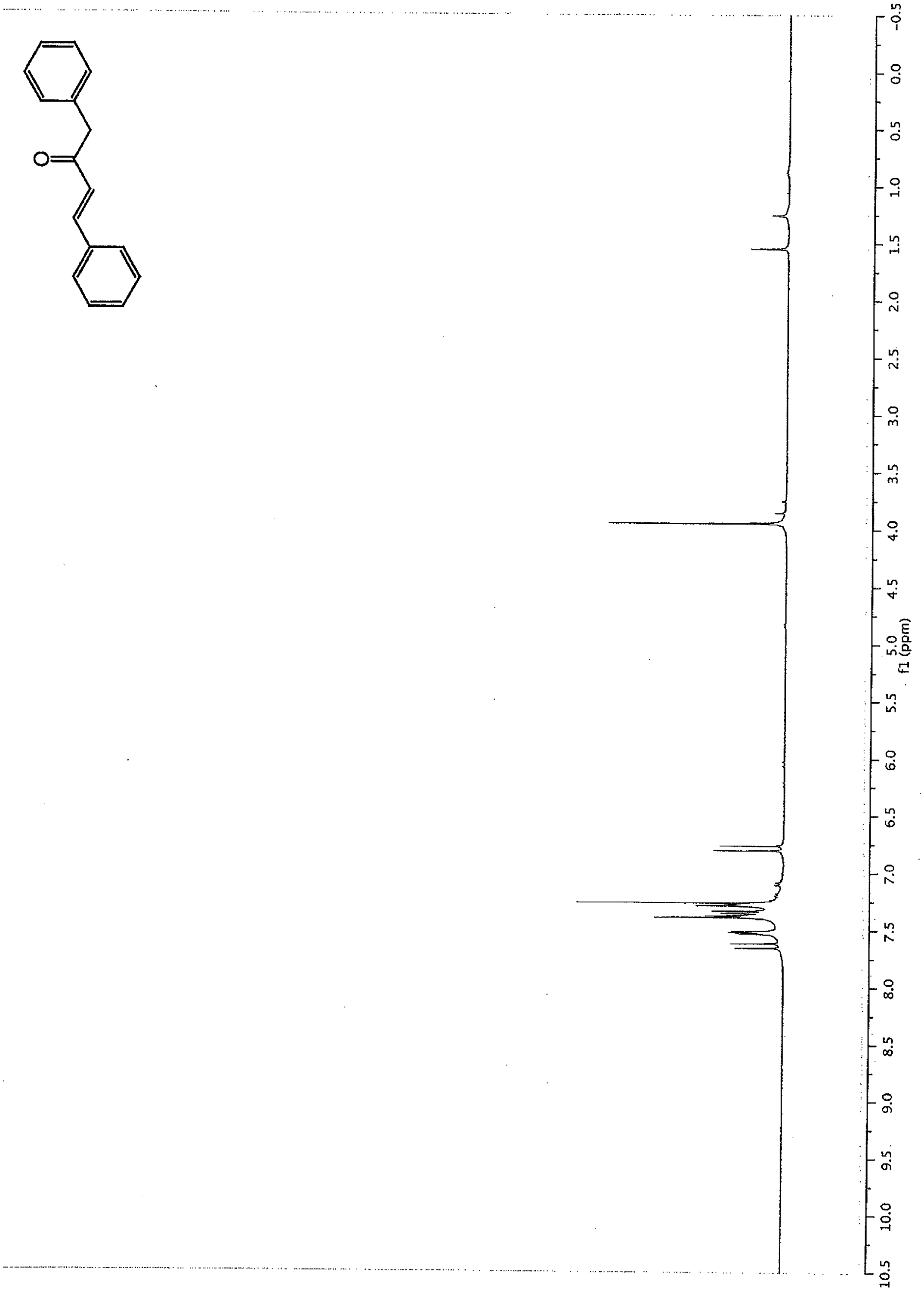
23

```
STANDARD CARBON PARAMETERS

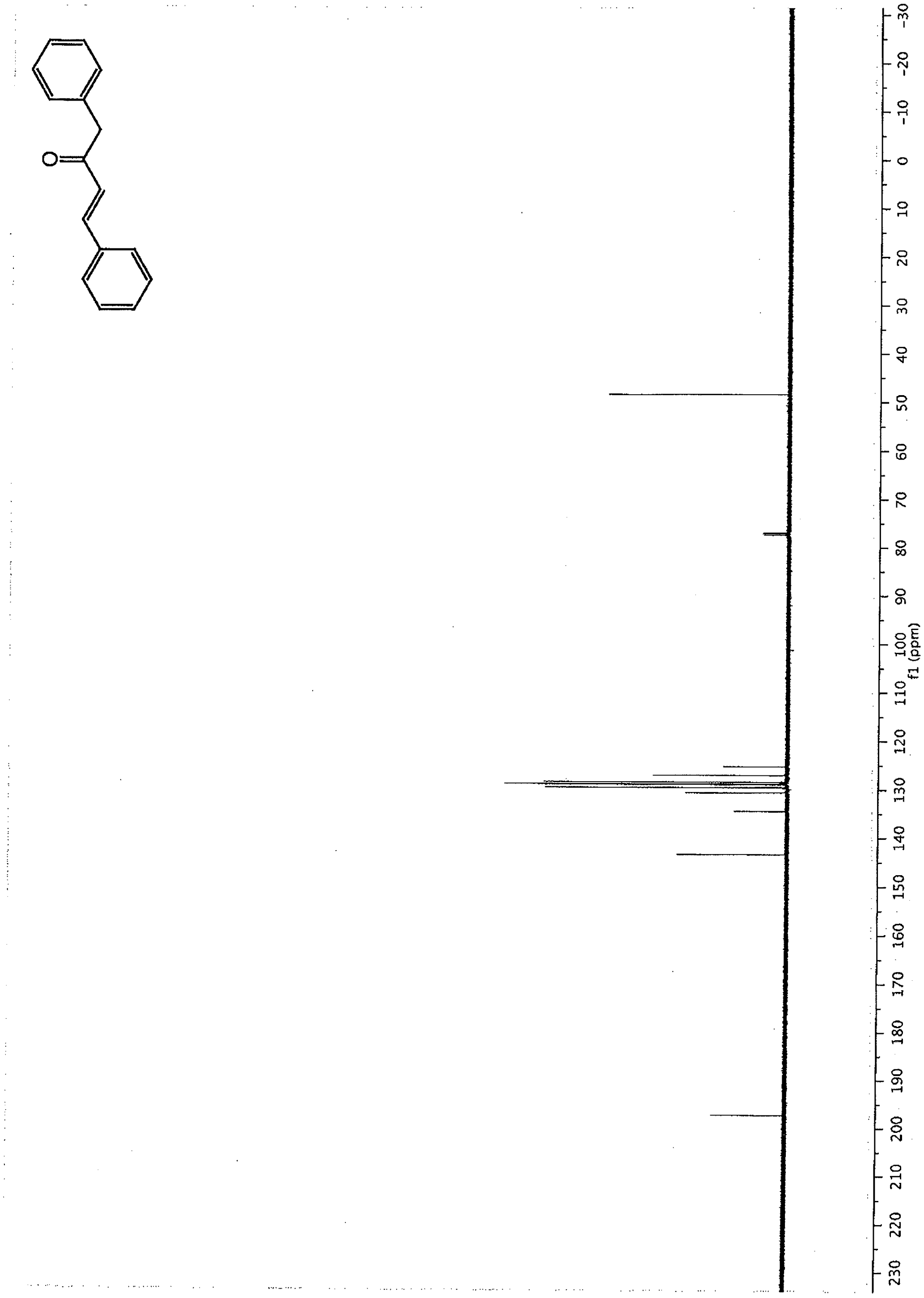
exp1  s2pul

      SAMPLE              DEC. & VT
date   Jun 29 2009  dfrq        499.774
solvent      CDCl3  dn               H1
file /export/home/~ dpwr             42
jsk/AJW-IV-236carb~ dof               0
          on1.fid   dm              yyy
   ACQUISITION      dmm               w
sfrq       125.680  dmf            7200
tn             C13  dseq
at           3.000  dres            1.0
np          200168  homo              n
sw         33361.1            DEC2
fb           18000  dfrq2             0
bs               4  dn2
tpwr            55  dpwr2             1
pw             7.0  dof2              0
d1           2.000  dm2               n
tof          818.6  dmm2              c
nt           12800  dmf2          10000
ct               0  dseq2
alock            n  dres2           1.0
gain      not used  homo2             n
      FLAGS               PROCESSING
il               n  wtfile
in               n  proc             ft
dp               y  fn         not used
hs              nn  math              f
     DISPLAY
sp         -3921.8  werr
wp         33360.9  wexp
vs              87  wbs             wft
sc               0  wnt
wc             250
hzmm         87.79
is          500.00
rfl         3922.0
rfp              0
th               8
ins        100.000
nm  cdc  ph
```

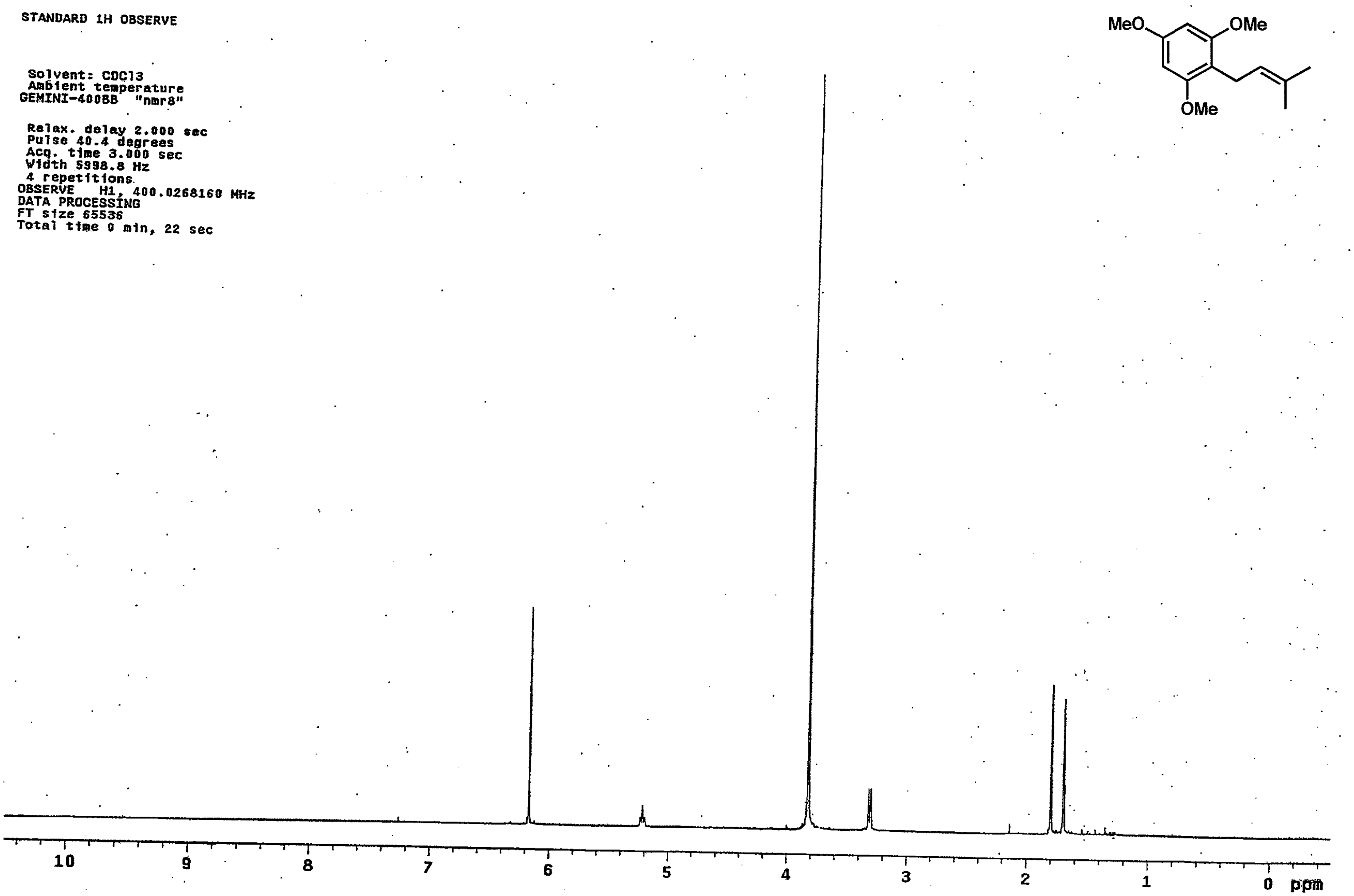




O
f1 (ppm)
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5



-30
-20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
f1 (ppm)
O



```
STANDARD 1H OBSERVE

 Solvent: CDCl3
 Ambient temperature
GEMINI-400BB  "nmr8"

 Relax. delay 2.000 sec
 Pulse 40.4 degrees
 Acq. time 3.000 sec
 Width 5998.8 Hz
 4 repetitions
OBSERVE   H1, 400.0268160 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 22 sec
```

```
13C OBSERVE


 Solvent: CDCl3
 Ambient temperature
GEMINI-400BB  "nmr8"

 Relax. delay 4.000 sec
 Pulse 64.8 degrees
 Acq. time 0.640 sec
 Width 25683.4 Hz
 224 repetitions
OBSERVE  C13, 100.5868180 MHz
DECOUPLE  H1, 400.0288163 MHz
 Power 45 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 65536
Total time 17 min, 57 sec
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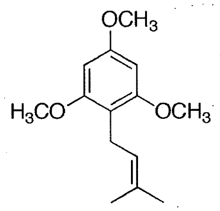

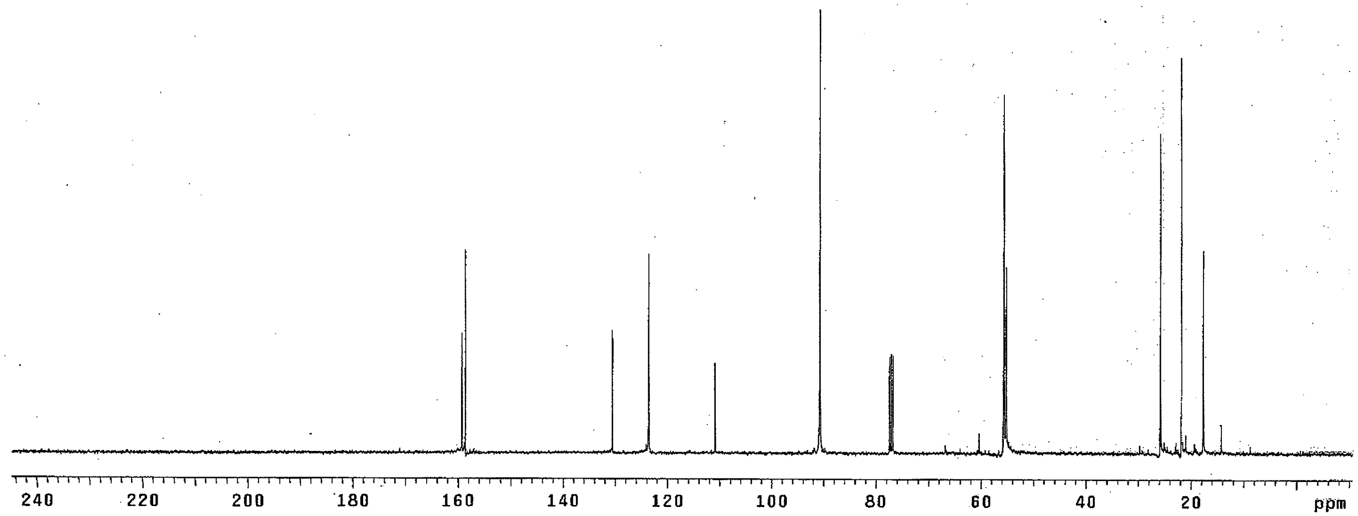

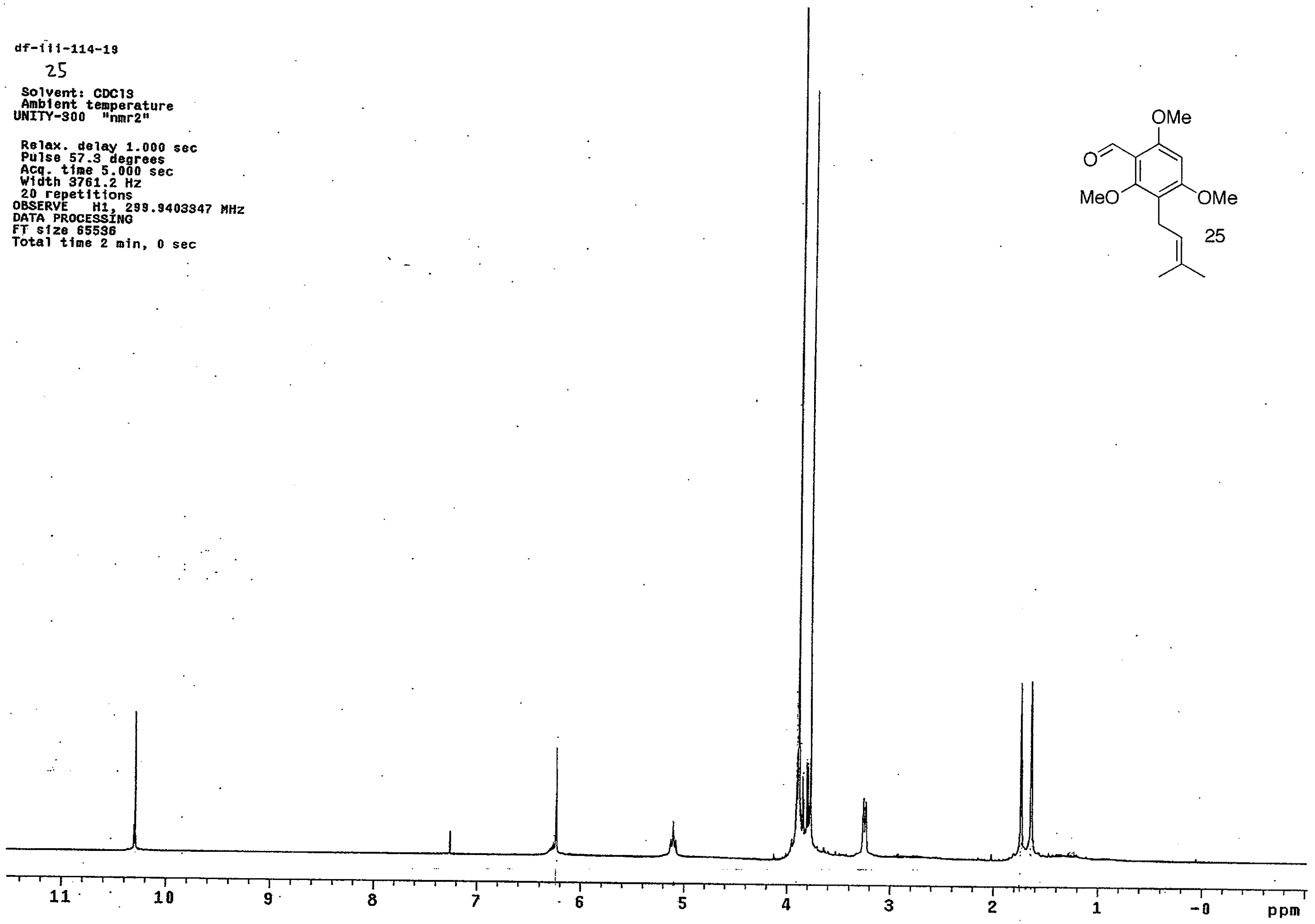

```
df-iii-114-19
   25
 Solvent: CDCl3
 Ambient temperature
UNITY-300  "nmr2"

 Relax. delay 1.000 sec
 Pulse 57.3 degrees
 Acq. time 5.000 sec
 Width 3761.2 Hz
 20 repetitions
OBSERVE   H1, 299.9403347 MHz
DATA PROCESSING
FT size 65536
Total time 2 min, 0 sec
```

```
13C OBSERVE

 Solvent: CDCl3
 Ambient temperature
File: AJW-aldecarbon
GEMINI-400BB  "nmr8"

 Relax. delay 4.000 sec
 Pulse 64.8 degrees
 Acq. time 0.640 sec
 Width 25683.4 Hz
 224 repetitions
OBSERVE  C13, 100.5868102 MHz
DECOUPLE  H1, 400.0288163 MHz
 Power 45 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 65536
Total time 19 min, 14 sec
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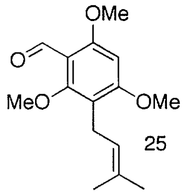

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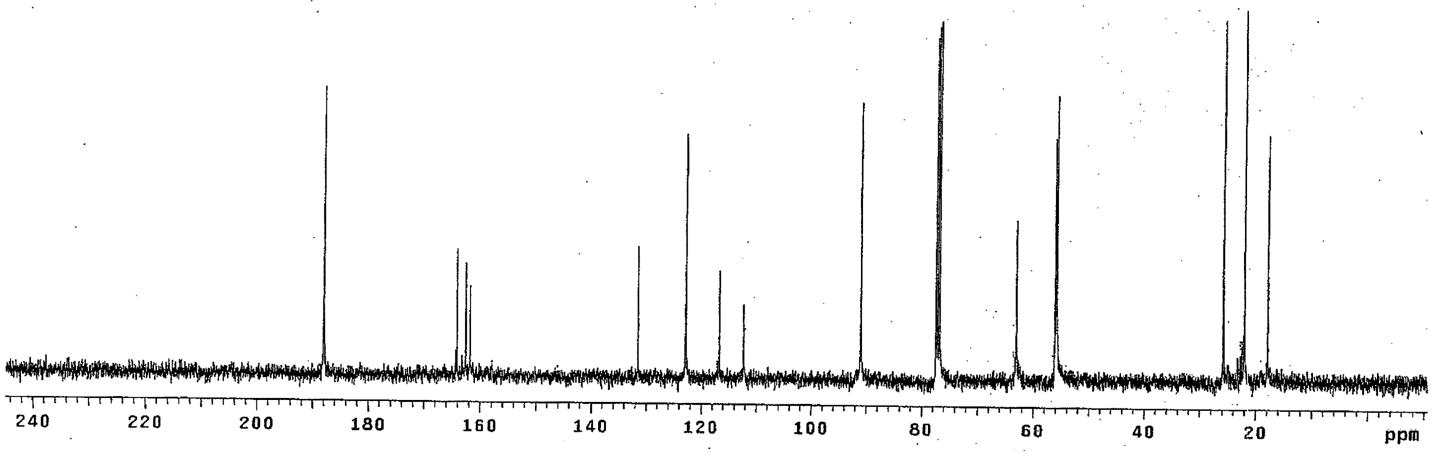
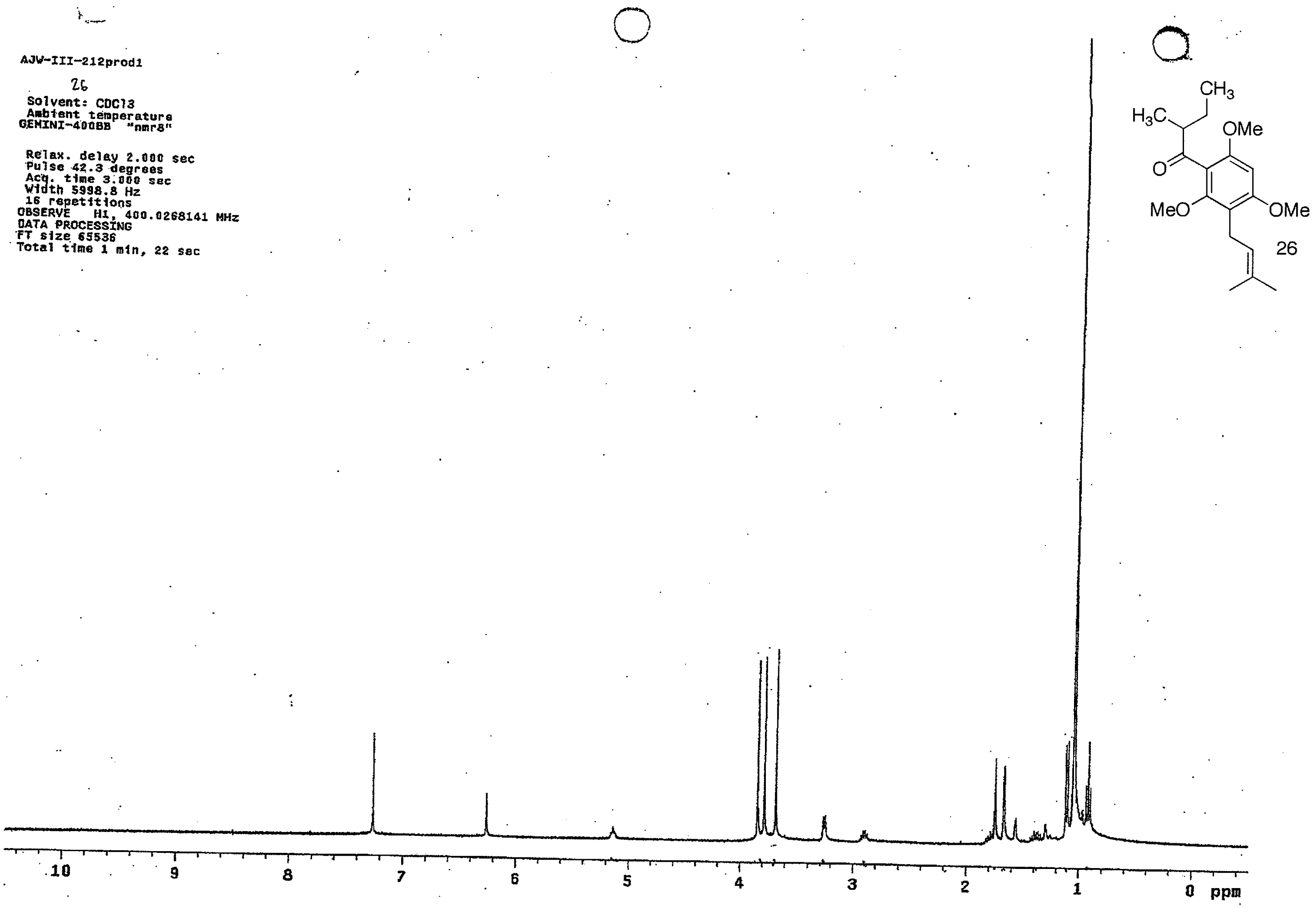


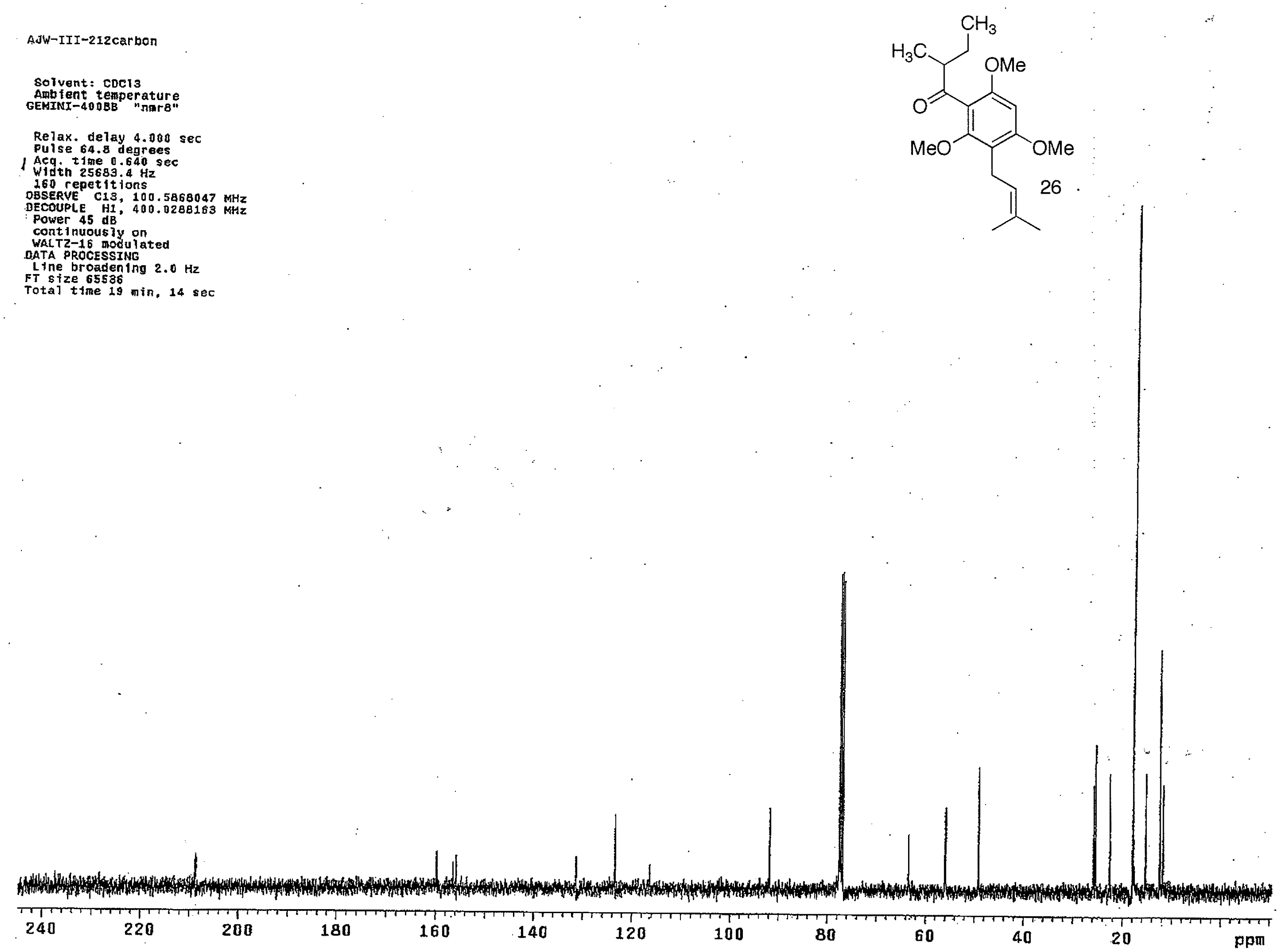


AJW-III-212prod1

26

Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"

Relax. delay 2.000 sec
Pulse 42.3 degrees
Acq. time 3.000 sec
Width 5998.8 Hz
16 repetitions
OBSERVE H1, 400.0268141 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 22 sec

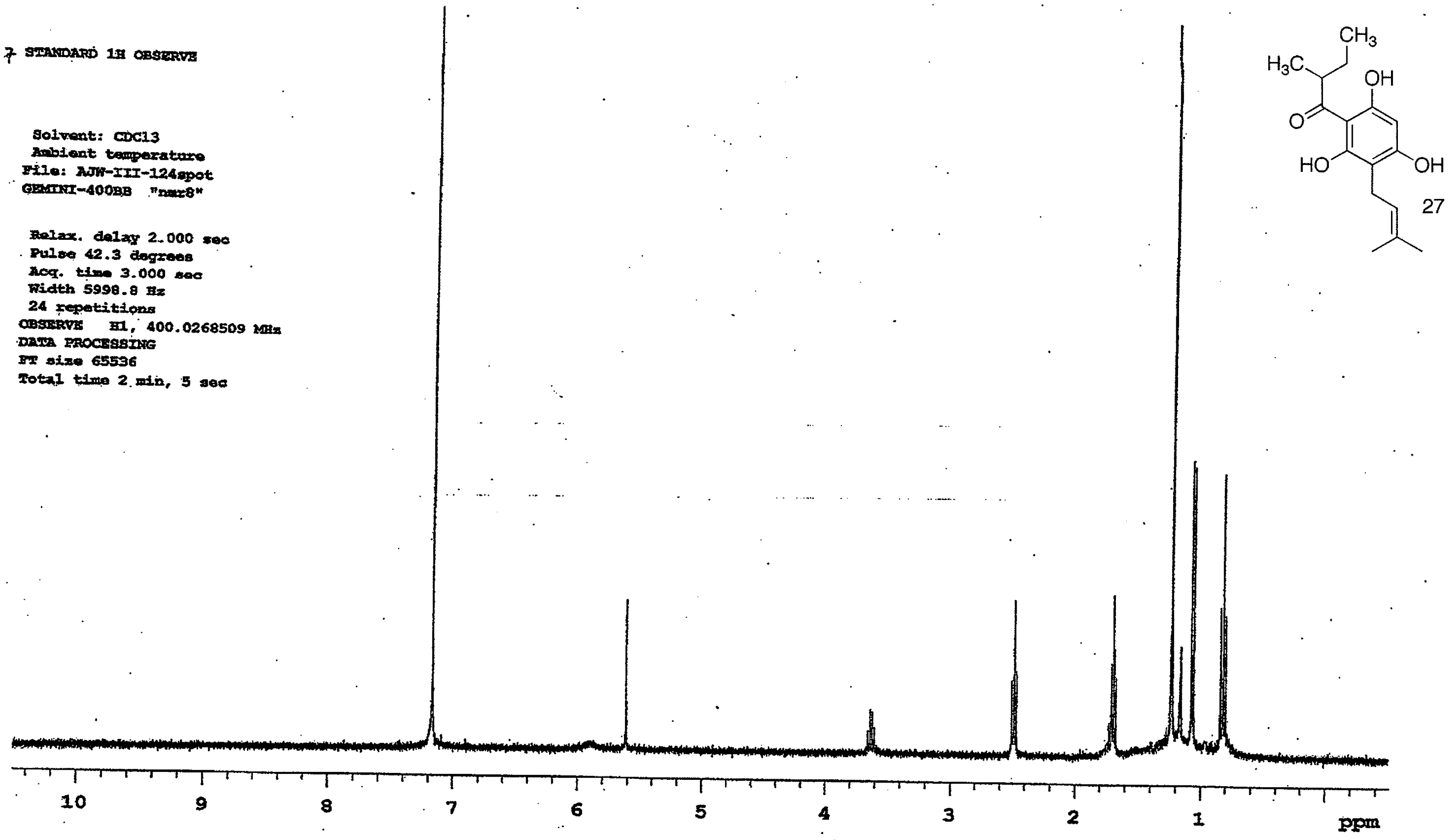


```
AJW-III-212carbon

 Solvent: CDCl3
 Ambient temperature
GEMINI-400BB  "nmr8"

 Relax. delay 4.000 sec
 Pulse 64.8 degrees
 Acq. time 0.640 sec
 Width 25683.4 Hz
 160 repetitions
OBSERVE  C13, 100.5868047 MHz
DECOUPLE  H1, 400.0288163 MHz
 Power 45 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 65536
Total time 19 min, 14 sec
```

26



27

```
7 STANDARD 1H OBSERVE

  Solvent: CDCl3
  Ambient temperature
 File: AJW-III-124spot
 GEMINI-400BB  "nmr8"

  Relax. delay 2.000 sec
  Pulse 42.3 degrees
  Acq. time 3.000 sec
  Width 5998.8 Hz
  24 repetitions
 OBSERVE   H1, 400.0268509 MHz
 DATA PROCESSING
 FT size 65536
 Total time 2 min, 5 sec
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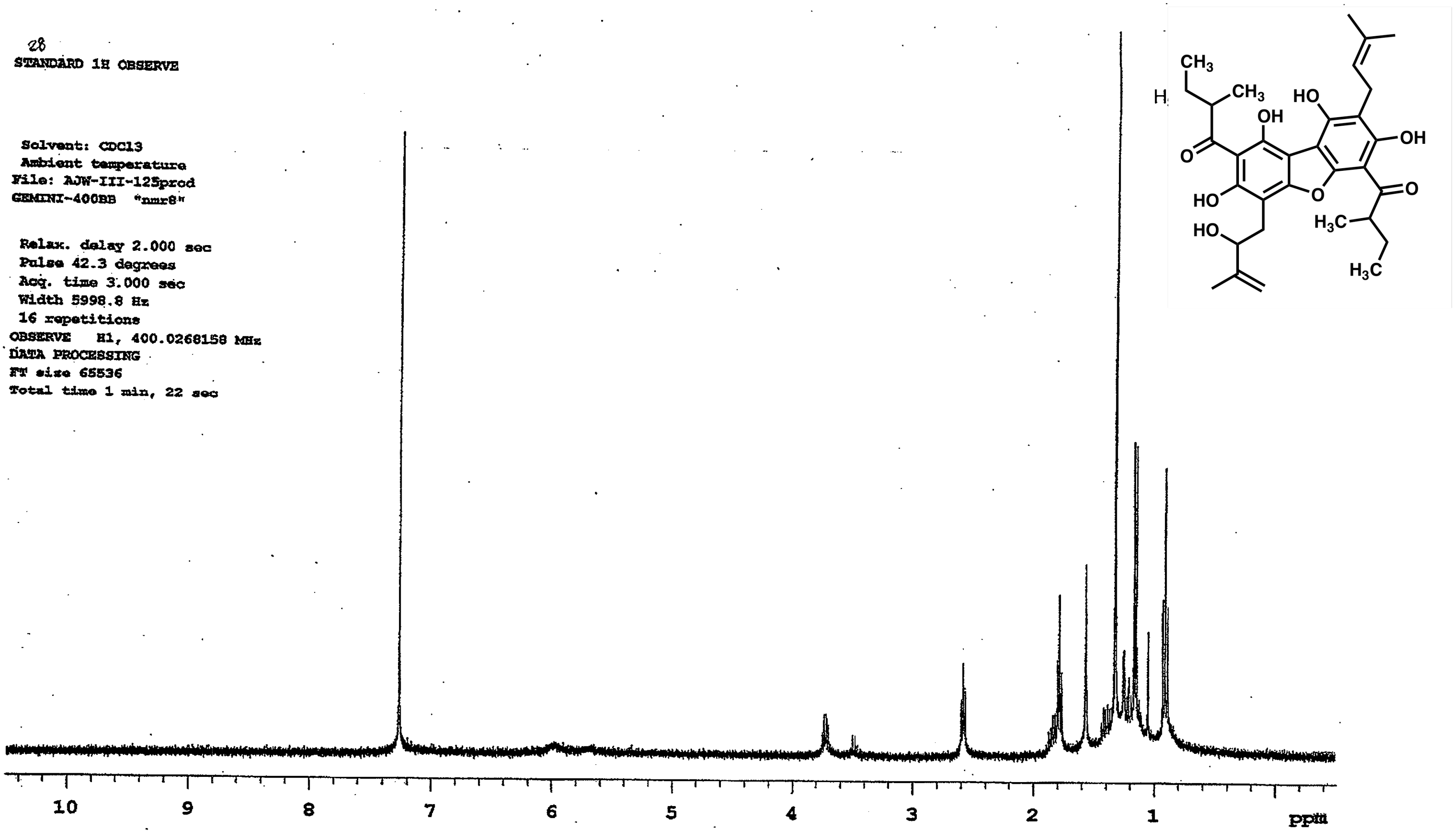
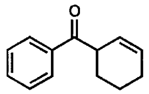
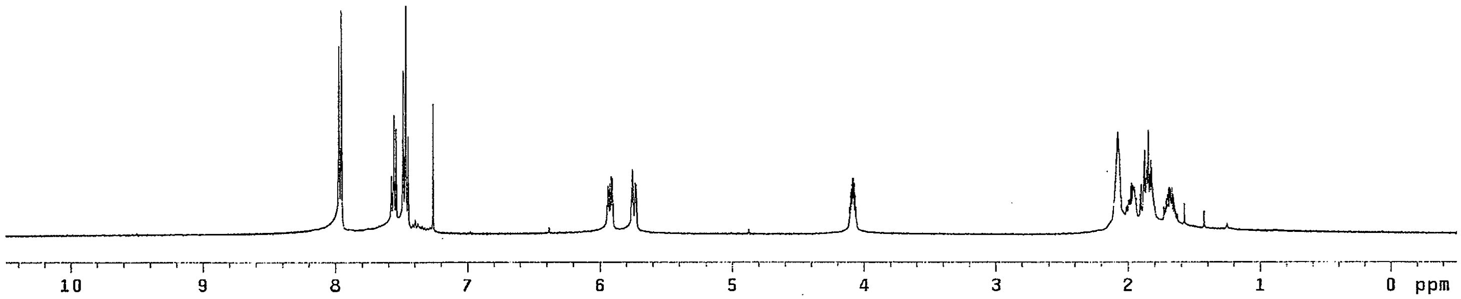


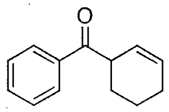
28

```
STANDARD 1H OBSERVE

 Solvent: CDCl3
 Ambient temperature
File: AJW-III-125prod
GEMINI-400BB  "nmr8"

 Relax. delay 2.000 sec
 Pulse 42.3 degrees
 Acq. time 3.000 sec
 Width 5998.8 Hz
 16 repetitions
OBSERVE   H1, 400.0268158 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 22 sec
```

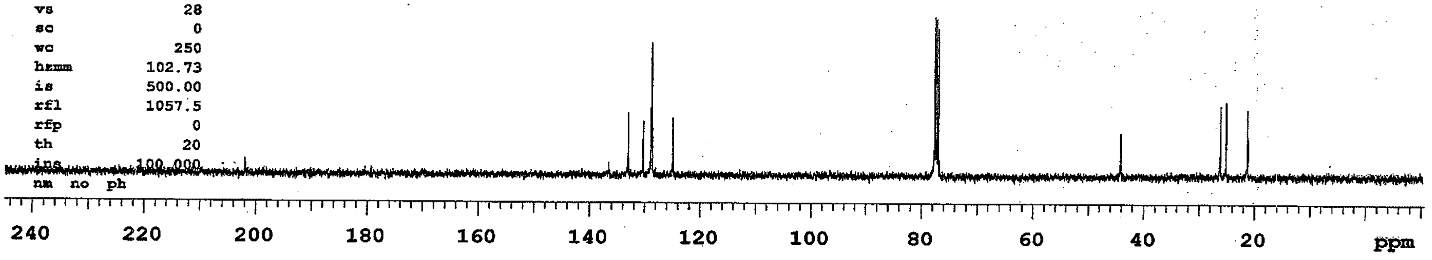
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                DEC. & VT
date   Dec  5 2008  dfrq                0
solvent      CDCl3  dn
file /export/home/~ dpwr               30
jsk/wommack/AJW-II~ dof                 0
      I-232s2.fid   dm                nnn
   ACQUISITION      dmm                 c
sfrq       400.029  dmf               200
tn              H1        PROCESSING
at           3.000  wtfile
np           35992  proc               ft
sw          5998.8  fn           not used
fb            3400
bs              16  werr
tpwr            63  wexp
pw             7.1  wbs
d1           2.000  wnt
tof              0
nt              16
ct              16
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
     DISPLAY
sp          -200.0
wp          4400.2
vs              39
sc               0
wc             250
hzmm         17.60
is          500.00
rfl          998.2
rfp              0
th              20
ins        100.000
nm    ph
```

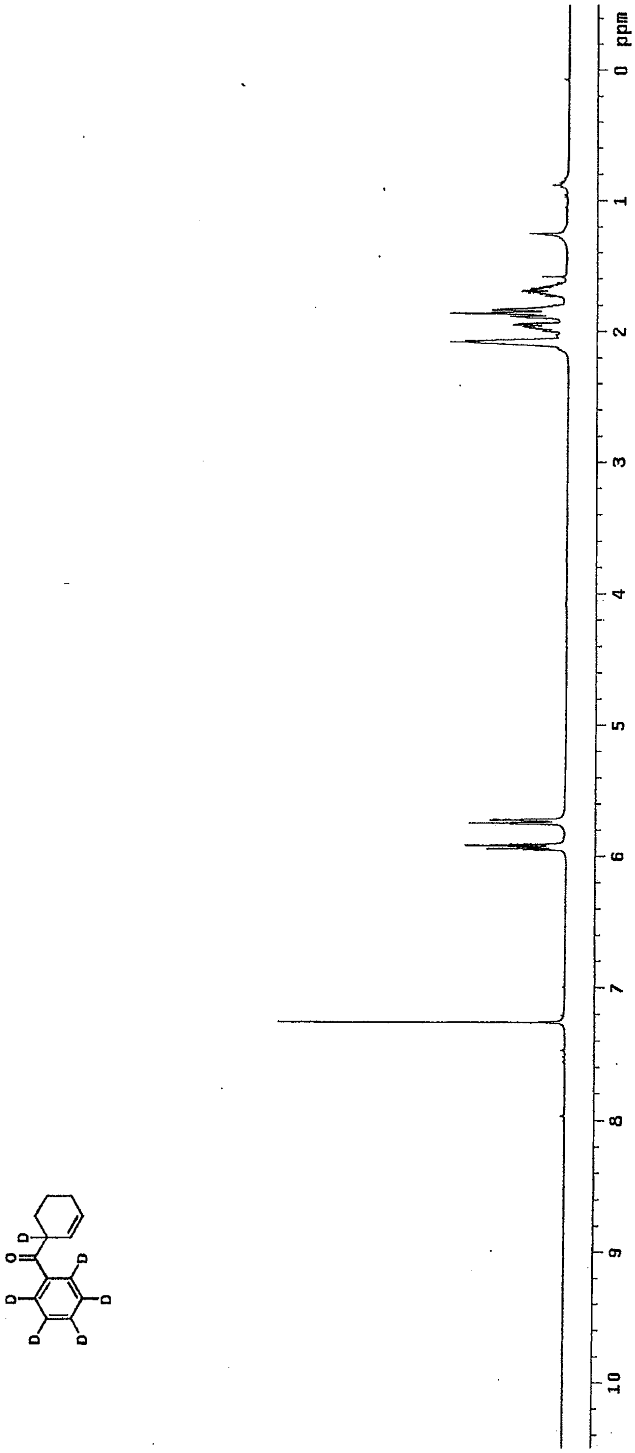






```
13C OBSERVE

exp1  std13c

      SAMPLE              DEC. & VT
date   Mar  3 2009  dfrq        400.029
solvent      CDCl3  dn               H1
file /export/home/~ dpwr             45
jsk/AJW-III-232car~ dof               0
          bon.fid   dm              yyy
   ACQUISITION      dmm               w
sfrq       100.599  dmf            9242
tn             C13      PROCESSING
at           0.640  lb             2.00
np           32876  wtfile
sw         25683.4  proc             ft
fb           14200  fn         not used
bs              16
tpwr            55  werr
pw             9.0  wexp
d1           4.000  wbs
tof         2271.7  wnt
nt             244
ct             244
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
     DISPLAY
sp         -1057.5
wp         25683.4
vs              28
sc               0
wc             250
hzmm        102.73
is          500.00
rfl         1057.5
rfp              0
th              20
ins        100.000
nm  no  ph
```




D
O
D
D
D
D
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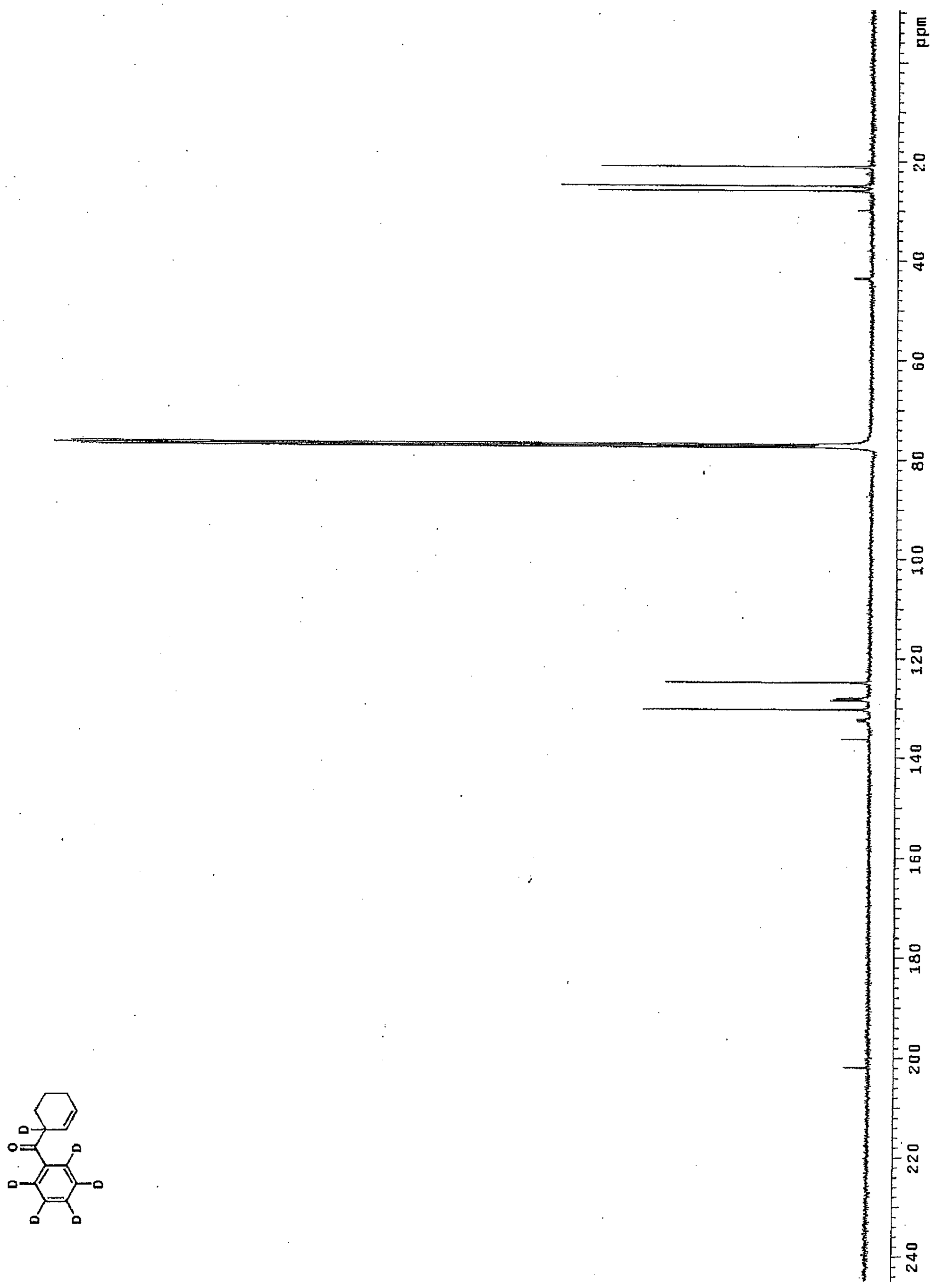
ppm
0
1
2
3
4
5
6
7
8
9
10


ppm
20
40
60
80
100
120
140
160
180
200
220
240
O
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tiChapter 2. A Bidirectional Synthesis of Ketones from Monomeric Formaldehyde by Catalytic C-H Insertion with Diazoalkanes.

2.1 *Introduction and Background*

It was near the completion of the project that studied the catalytic transformation of aldehydes to their homologous ketones with diazoalkanes that I noticed a report from Yamauchi *et al.* describing a successful total synthesis of a bis(pyrrolidine) natural product from the family of the *Erythroxylum* alkaloids.[68] As shown in Figure 1, this molecule, dihydrocuscohygrine (**1**), is the reduced form of another natural product from the same source – the symmetrical ketone known as cuscohygrine (**2**).[69] The structure and relative configuration of dihydrocuscohygrine was established by ^{1}H and ^{13}C NMR spectroscopies and mass spectrometry in comparison to synthetic material obtained by reduction of cuscohygrine.[69a]

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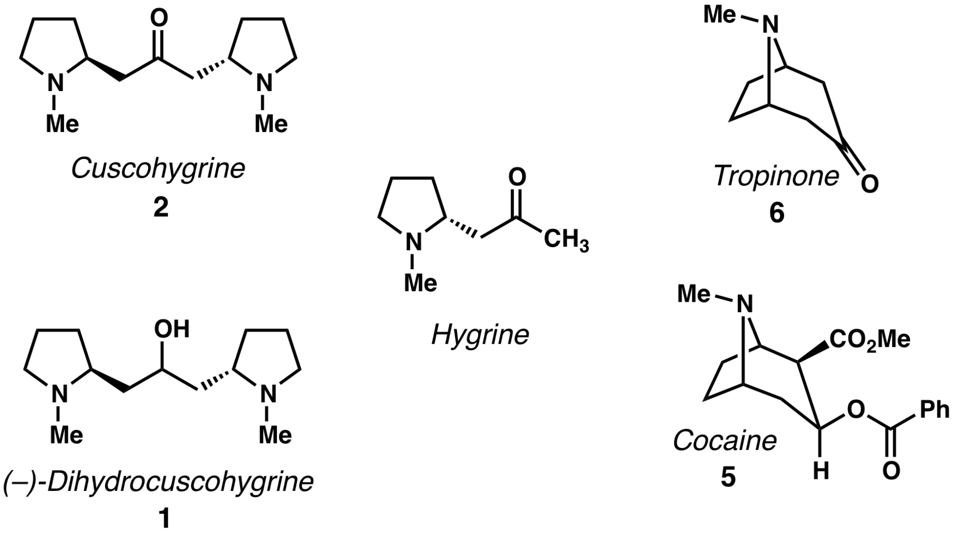
(68) "Concise Total Synthesis of (−)-Deoxocuscohygrine and (−)-Dihydrocuscohygrine," Yamauchi, T.; Hagiwara, S.; Higashiyama, K. *J. Org. Chem.* **2008**, *73*, 9784–9787.

(69) (a) "Isolation of Dihydrocuscohygrine from Peruvian Coca Leaves," Turner, C. E.; Elsohly, M. A.; Hanus, L.; Elsohly, H. N. *Phytochemistry* **1981,** *20*, 1403-1405. (b) "Studies on Erythroxylum coca Lam.," Hegnauer, R.; Finkenscher, L. H. *Pharm. Acta Helv.* **1960**, *35*, 43-64. (c) "Constituents of *Erythroxylon coca* II. Gas-Chromatographic Analysis of Cocaine and Other Alkaloids in Coca Leaves," Turner, C. E.; Ma, C. Y.; Elsohly, M. A. *J. Ethnopharma*. **1981**, *3*, 293-298.

Figure 1**:** Alkaloids from *Erythoxylon coca*



Cuscohygrine
2

Hygrine

Tropinone
6

(–)-Dihydrocuscohygrine
1

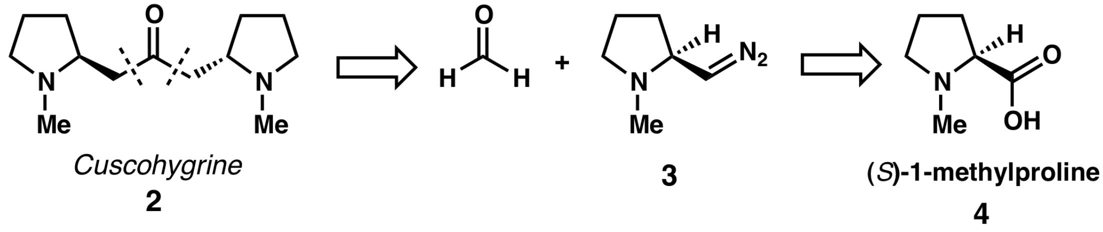
Cocaine
5

Viewing the latter product through a retrosynthetic lens, a remarkably direct approach was identified based on a disconnection guided by my recent research experience.

2.1.a ***Retrosynthetic Analysis Points to a New Methodological Development.***

As shown in Scheme 1, a bidirectional homologation transform applied to the target molecule identifies diazomethyl pyrrolidine (**3**) and monomeric formaldehyde as potential precursors. The diazoalkane, in turn, could be derived from the naturally occurring amino acid (*S*)-proline (see **4**). We were drawn to this idea because the elaboration of **3** from the corresponding *N*-methyl-pyrrolo aldehyde would challenge and test the mild and functional group tolerant hydrazone oxidation methods we were at this time quite familiar with.

Scheme 1: Initial Retrosynthetic Analysis to Amino Acid Starting Material



After this realization, a comprehensive consultation of the literature was performed to gain further background knowledge on these molecules. Cuscohygrine does possess biological activity, but its reduced analog (dihydrocuscohygrine) has not been reported to elicit any biological response of note.[66] It is a reasonable speculation to attribute this lack of study to a better-known bioactive metabolite of current and historical interest from the same coca plant (*Erythroxylon coca*) – cocaine (**5**). As seen in Figure 1, cocaine is a member of the tropane alkaloids, a class characterized by an easily distinguishable bicyclic *N*-alkyl-8-azabicyclo[3.2.1]octane core structure as in tropinone (**6**).

2.1.b *Divergence in the Biosynthesis of Pyrrolidine Alkaloids*

Although these two pairs of heterocyclic natural products may seem only moderately related, the number of reports by natural product chemists and botanists relating them are abundant. Multiple publications describe various methods to confirm in this plant species that both the cyclic and bridged bicyclic natural products originate from the same

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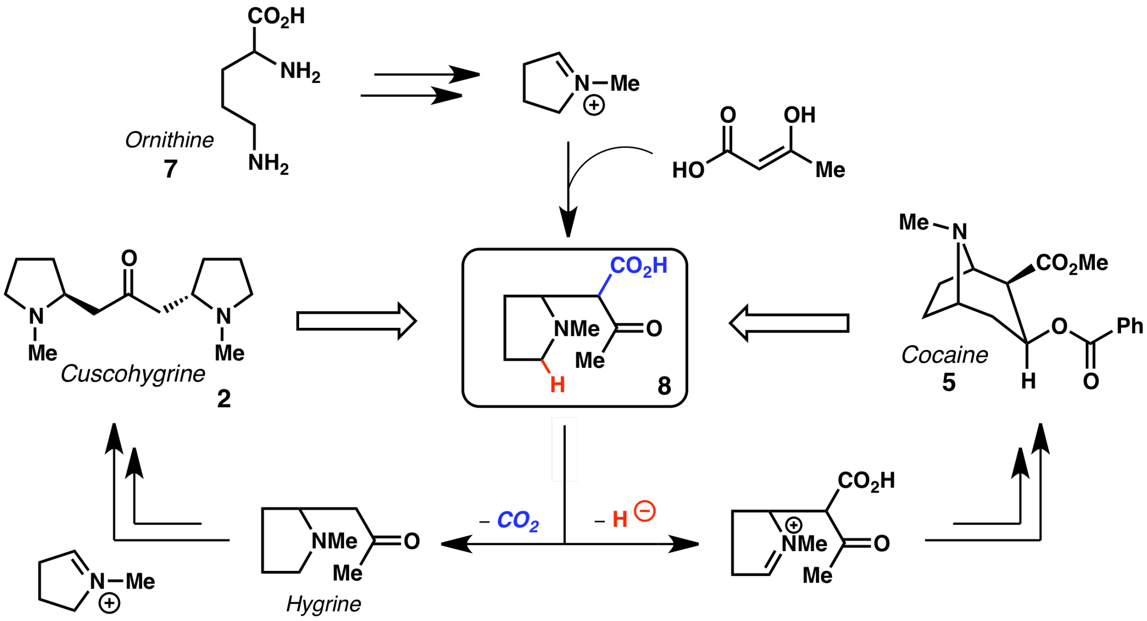
(66) (a) "Biological Activity of the Alkaloids of *Erythroxylum coca* and *Erythroxylum novogranatense,*" Novak, M.; Salemink, C. A.; Khan, I. *J. Ethnopharm.* **1984,** *10*, 261-274. (b) "Effects of the Administration of Coca Alkaloids on the Primary Immune Responses of Mice: Interaction with Δ9-Tetrahydrocannabinol and Ethanol," Watson, E. S.; Murphy, J. C.; Elsohly, H. N.; Elsohly, M. A.; Turner, C. E. *Toxicol. Appl. Pharmacol.* **1983,** *71*, 1-13.

carbon source.[70] Shown in Scheme 2 is the widely accepted biosynthetic pathway for this class of alkaloids. Ornithine (**7**) is established as the starting point based on multiple feeding studies[70] that were conducted with isotopically labeled (^{2}H, ^{3}H, ^{13}C and/or ^{14}C) materials.

Scheme 2: Biosynthetic Hypothesis of Cocaine and Cuscohygrine Divergence from a Common Intermediate.



Following the plant's bioconversion of ornithine (**7**) to 4-(methylamino)butanal (not shown) and a condensation to form the 1-methyl-3,4-dihydro-2*H*-pyrrol-1-ium ion, a Mannich reaction with the indicated tautomeric form of 3-oxobutanoic acid delivers the common

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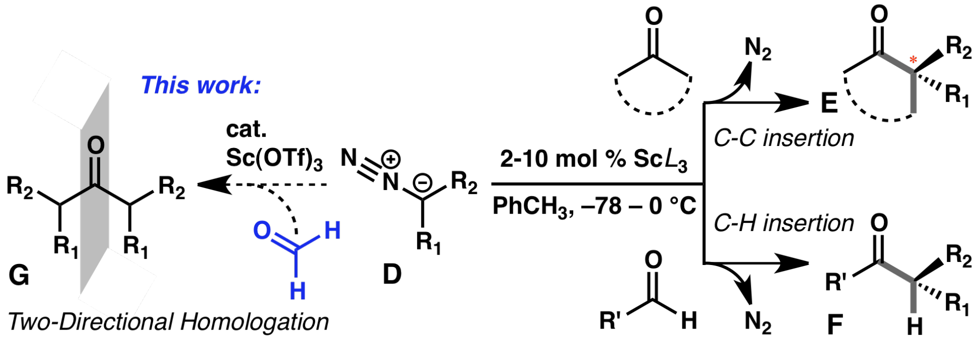
(70) (a) "Biosynthesis of the Pyrrolidine Rings of Cocaine and Cuscohygrine from [2-^{14}C]-Ornithine via a Symmetrical Intermediate," Leete, E. *J. Am. Chem. Soc.* **1982**, *104*, 1403–1408. (b) "A Revision of the Generally Accepted Hypothesis for the Biosynthesis of the Tropane Moiety of Cocaine," Leete, E.; Kim, S. H. *J. Am. Chem. Soc.* **1988**, *110*, 2976–2978. (c) "The Biosynthesis of Tropane Alkaloids in *Datura stramonium:* The Identity of the Intermediates between *N*-Methylpyrrolinium Salt and Tropinone," Robins, R. J.; Abraham, T. W.; Parr, A. J.; Eagles, J.; Walton, N. J. *J. Am. Chem. Soc.* **1997**, *119*, 10929–10934. (d) "Hygrine, Bona Fide Alkaloid or Artifact: Its Chemical Reduction, Novel Di-heptafluorobutyrylation and Sensitive Detection in South American Coca Leaves Using Capillary Gas Chromatography-Electron Capture Detection," Moore, J. M.; Casale, J. F.; Hays, P. A.; Klein, R. F. X.; Cooper, D. A. *J. Chromatogr., A*, **1995**, *704*, 483-494.

biosynthetic intermediate shown as structure **8**. The pyrrolidine ring in **8** (iminium ion formation by formal loss of hydride) and an intramolecular Mannich cyclization then forms the bicyclic core of the tropane alkaloids such as cocaine (**5**). Alternatively, the common intermediate **8** can undergo decarboxylation to deliver the natural product hygrine, which can then undergo intermolecular C–C bond formation with another equivalent of 1-methyl-3,4-dihydro-2*H*-pyrrol-1-ium ion, giving cuscohygrine (**2**). The cause of this biodivergence has not been elucidated. However, the previously mentioned feeding studies have included experiments with isotopically labeled hygrine. Data show that hygrine distributes its isotopic enrichment to cuscohygrine, presumably via the same Mannich type addition of the kinetic enolate of hygrine with the imminium ion.

2.1.c *Reliable Access to a Neutral Source of Monomeric Formaldehyde.*

The creative use of standard reagents to enhance synthetic efficiency, whether it is reducing waste and costs, increasing yield, or facilitating unusual bond connectivities, remains at the forefront of our science. With our group gaining expertise in the synthesis and application of non-stabilized diazo compounds as carbon nucleophiles in two new catalytic methods, we envisioned that the choice of the known one-carbon reagent formaldehyde as the electrophilic reaction partner would be a novel extension.

Scheme 3: Extension of Scandium(III) Catalysis to Symmetrical Ketone Products



Our work includes examples with the Sc^{3+}–catalyzed synthesis of α-chiral cyclic[23] and acyclic ketones[1] from cycloalkanone and aldehyde electrophiles, respectively (Scheme 3). More recently, our group optimized enantioselective routes to α-aryl medium ring ketones by ring expansion with aryldiazomethanes using simple bis(oxazoline) chiral ligands.[71] Knowing that scandium(III) provides reliable Lewis activation of myriad carbonyl groups (hindered, electron-rich, electron-poor, etc.), the use of the most simple carbonyl – formaldehyde – seemed to hold promise as a platform for rapid construction of symmetrical molecular complexity (**D** to **G**, Scheme 3). The fact that diazo compounds **D** are readily prepared from the corresponding carbonyl compounds with our blended hydrazone dehydrogenation method (*vida supra*) suggests that the potential iterative use of diazoalkane-carbonyl homologation can lead to even greater product diversity by a combination of our group's methods.[1,23,70]

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(71) "An Enantioselective Synthesis of 2-Aryl Cycloalkanones by Scandium-Catalyzed Carbon Insertion," Rendina, V. R.; Moebius, D. C.; Kingsbury, J. S. *Org. Lett.* **2011**, *13*, 2004–2007.

2.1.d *The Efficiency of Simultaneous Bidirectional Chain Elongation.*

When initially encountering a molecular target, the chemist performs the mental exercise of retrosynthetic analysis. This logic-based approach requires translation of a target molecule into ever more simple precursor structures. This practice is a repetitive one, until simple or readily available starting materials are reached. The method and terminology were formalized by Nobel laureate E. J. Corey and described in the book “The Logic of Chemical Synthesis”.[72] The deductive reasoning of retrosynthesis allows one to evaluate the stability and utility of various intermediates, and it can greatly sharpen the focus of our efforts in the laboratory. The most obvious but the least practical (both in terms of atom- and step-economy) method for synthetic planning involves a stepwise strategy wherein each substrate is modified at one position or functional group to give a new product. To improve on this linear procedure, a tactic for merging together two independent, complex intermediates exists and can reduce the total number of steps required (convergent strategy). For example, protection steps that may be necessary in a linear sequence may not be required if the two parts are divided (**A** chain and **B** chain in eq. 2, Figure 2). Another alternative builds off of a core structure and elongates and functionalizes in the appropriate directions. Most

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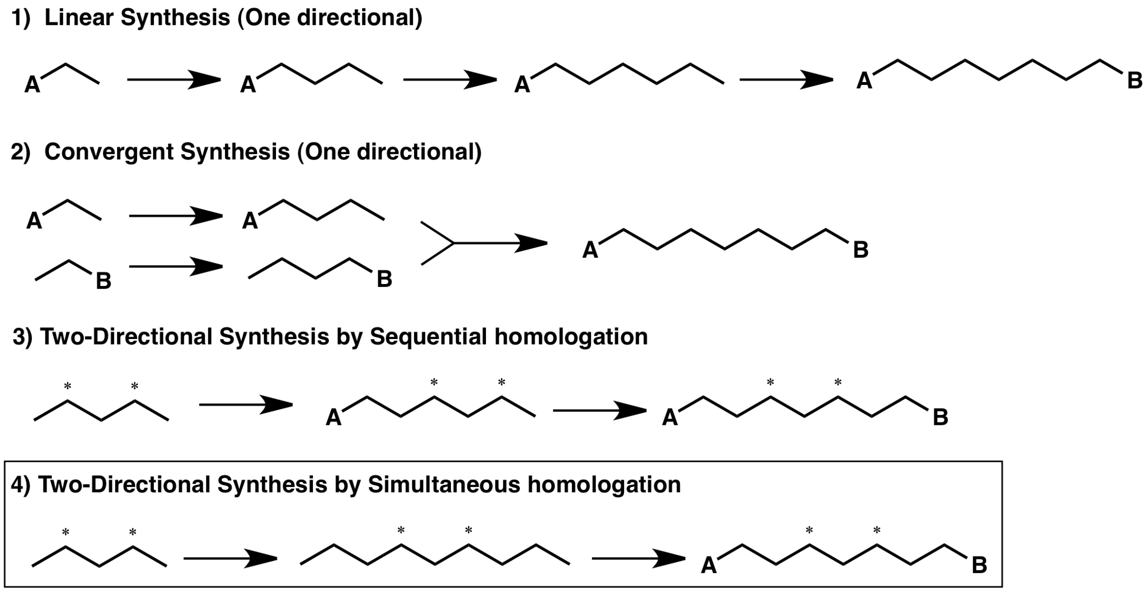
(72) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*. Wiley: New York, 1995.

applications of the two-directional strategy[73] require that the ends of the nascent chain be differentiated (eq 3, Figure 2). However, if the retrosynthetic plan has anticipated such a core structure that allows the same transformation to occur in a simultaneous fashion, then the effect is a bidirectional chain elongation strategy of the highest efficiency (eq 4. Figure 2).

Figure 2: Strategies for Chain Synthesis


1) Linear Synthesis (One directional)

2) Convergent Synthesis (One directional)

3) Two-Directional Synthesis by Sequential homologation

4) Two-Directional Synthesis by Simultaneous homologation

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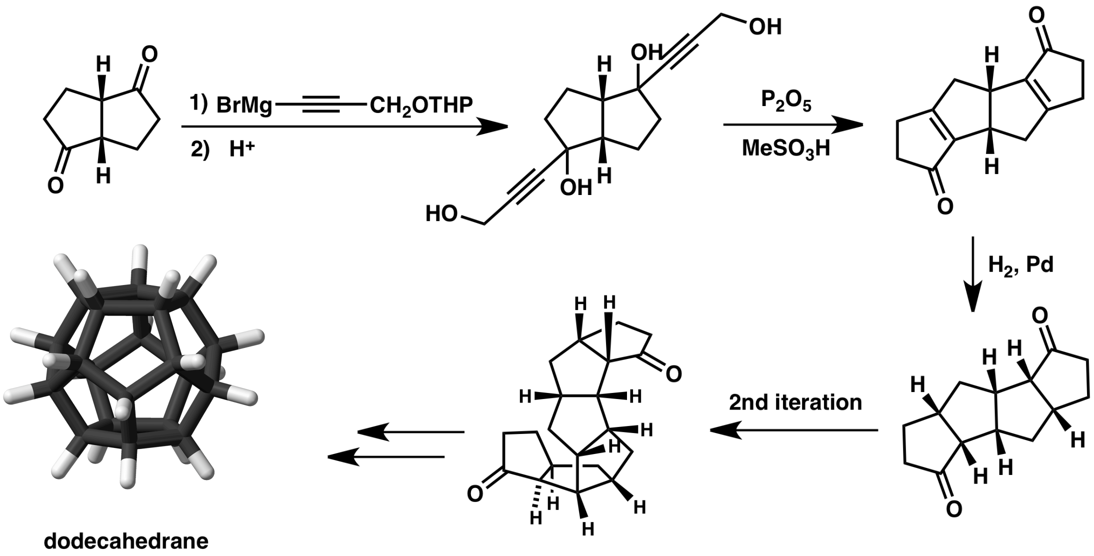
(73) For applications of two-directional strategies in natural product synthesis, see: (a) "Two-Directional Chain Synthesis and Terminus Differentiation," Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9-17. (b) "Synthesis of a C(22)-C(34) Halichondrin Precursor via a Double Dioxanone-to-Dihydropyran Rearrangement," Burke, S. D.; Buchanan, J. D.; Rovin, J. L. *Tetrahedron Lett.* **1991**, *32*, 3961-3964. (c) "Stereocontrolled Synthesis of 2,5-Linked Bistetrahydrofurans via the Triepoxide Cascade Reaction," Hoye, T. R. Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855-2862. (d) "Total Synthesis of Merrilactone A," Inoue, M.; Sato, T.; Hirama, M. *J. Am. Chem. Soc.* **2003**, *125*, 10772-10773. For a review, see: (e) "Two-Directional Synthesis and Its Use in Natural Product Synthesis," Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167-2213. (f) "Formal Synthesis of Uvaricin via Palladium-Mediated Double Cyclization," Burke, S. D.; Jiang, L. *Org. Lett.* **2001**, *3*, 1953–1955. (g) "A Novel Route to the F-Ring of Halichondrin B. Diastereoselection in Pd(0)-Mediated *meso* and *C*2 Diol Desymmetrization," Burke, S. D.; Jiang, L. *Org. Lett.* **2002**, *4*, 3411–3414. (h) "Structure Assignment, Total Synthesis, and Antiviral Evaluation of Cycloviracin B1," Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M.; DeClercq, E. *J. Am. Chem. Soc.* **2003**, *125*, 13132–13142. (i) "Total Synthesis of Efomycine M," Barth, R.; Mulzer, J. *Angew. Chem. Int. Ed*. **2007**, *46*, 5791–5794.

Among these efficient syntheses is the especially striking example shown in Scheme 4. This synthesis of the geodesic molecule dodecahedrane utilized bidirectional transformations in nearly every stage of its synthetic plan involving double cyclopentane.[74] Following organometallic addition to the ketone, elimination of the tertiary alcohol enabled the Nazarov-type dehydrative cyclization to occur with high conversion, effectively doubling the efficiency of the synthetic process.

Scheme 4: Two-Directional Synthesis of Dodecahedrane



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[74] "Synthesis and *X*-ray Crystal Structure of a (*C*2)-C20-Hexaquinane Derivative, a Potential Dodecahedrane Precursor," McKervey, M. A.; Vibuljan, P.; Ferguson, G.; Siew, P. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 912-914.

2.2 *Initial Studies on Scandium(III)-Catalyzed Bidirectional Homologation with Diazoalkanes: Accessing Monomeric Formaldehyde.*

Before attempting to prepare the heterocyclic diazonucleophile needed for the synthesis of cuscohygrine, we decided that thorough investigation of the reaction scope with a range of diazoalkanes should be undertaken. The decision of which specific symmetrical ketones to target would prove to be a guiding factor in our study and, of course, a suitable and compatible method for the generation of monomeric formaldehyde would be paramount in this new method's success.

Typically, to achieve a one-carbon extension of an organic substrate with formaldehyde, the use of organometallic reagents is employed to react with the electrophile in one of its anhydrous, polymeric forms.[75] These nucleophiles are often organolithium reagents that are considered hard anions according to Pearson's hard and soft acid and base theory.[76] This is obviously not the case for the carbon centered anion in a diazoalkane's resonance-stabilized, zwitterionic structure. It has also been noted that titrateable ethereal solutions of monomeric formaldehyde can be obtained by distilling an ether solution containing the depolymerized monomer that results from a Brønsted acid-catalyzed

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(75) Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1986; Vol. 12, pp 232-234.

(76) "Hard and Soft Acids and Bases," Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539.

decomposition of the polymeric structure.[77] The acid source can either be inorganic mineral acids or a solid-supported, acidic reagent. Once the distillation is complete, an aliquot is analyzed by NMR spectroscopy and the formaldehyde's C–H resonance (9.53 ppm) is integrated relative to an internal standard or solutions of monomer can also be quantitated by iodometric titration.[78]

Also pervasive among the methods of isolating monomeric formaldehyde is the use of metallated species to intercept the highly reactive electrophile.[79] Motivation for imparting a known stoichiometry to the formaldehyde reagent was of great interest to us initially because of the potential for synthesizing both symmetric and dissymmetric ketones (Scheme 5). For example, after complete conversion of a given

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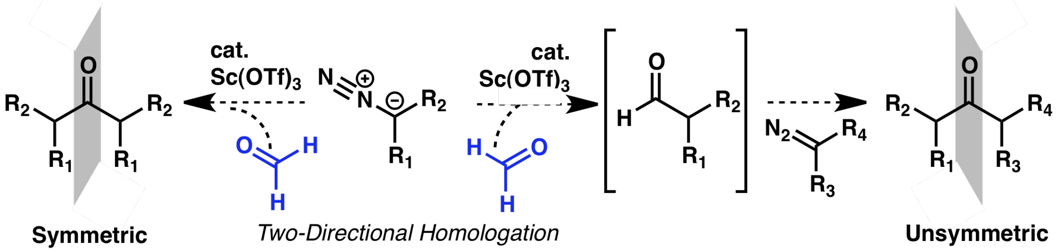
(77) (a) "SCOOPY-Reaktionen: Stereoselektivität der Allyl-alkohol-Synthese via Betain-Ylide," Schlosser, M.; Coffinet, D. *Synthesis* **1971**, 380-381. (b) "Anhydrous Molecular Formaldehyde Solution as a Synthetic Reagent," Rodriguez, L.; Lu, N.; Yang, N-L. *Synlett* **1990**, 227-228. (c) "Monomeric Formaldehyde in Ethereal Solution," Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.

(78) "Eine Beobachtung zur Romijn'schen Formaldehydtitration," Signer, A.; *Helv. Chim. Acta.* **1930**, *13*, 43-46.

(79) For examples with organolithium reagents, see: (a) "Optional *Ortho* or Alpha Hydroxymethylation of Alkylarenes," Guggisberg, Y.; Faigl, F.; Schlosser, M. *J. Organomet. Chem.* **1991**, *415*, 1-6. (b) "Construction of the ABC Ring System of Taxanes via Stereoselective One-Pot Three-Component Coupling and Intramolecular Alkylation of a Protected Cyanohydrin Ether," Serizawa, T.; Miyamoto, S.; Fuse, S.; Doi, T.; Takahashi, T. *Bull. Chem. Soc. Japan* **2010**, *83*, 942-949. (c) "Pentadienyl Type Lithium and Potassium Species: The Regioselectivity of their Reactions with Electrophiles," Schlosser, M.; Zellner, A.; Leroux, F. *Synthesis* **2001**, 1830-1836. For an example with organomagnesium reagents, see: (d) "Total Synthesis of Jerangolid A," Hanessian, S.; Focken, T.; Oza, R. *Org. Lett.* **2010**, *12*, 3172–3175. For examples of lithium enolates, see: (e) "Total Synthesis of (±)- and (−)-Actinophyllic Acid," Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894–4906. (f) "The Carbohydrate−Sesquiterpene Interface. Directed Synthetic Routes to Both (+)- and (−)-Fomannosin from D-Glucose," Paquette, L. A.; Peng, X.; Yang, J.; Kang, H-.J. *J. Org. Chem.* **2008**, *73*, 4548–4558. (g) "A Short, Stereocontrolled, and Practical Synthesis of α-Methylomuralide, a Potent Inhibitor of Proteasome Function," Saravanan, P.; Corey, E. J. *J. Org. Chem.* **2003**, *68*, 2760–2764.

diazoalkane to the corresponding linear aldehyde, the reaction solution could be charged with a different diazo compound to generate a dissymmetric ketone product.

Scheme 5: Titrateable Monomeric Formaldehyde Solutions to Access Diverse Ketones



Although the method has its proven benefits with organometallic reagents, our initial attempts to use prepared solutions of monomeric formaldehyde with phenyldiazomethane failed due to the problem of repolymerization. Therefore, we decided to depolymerize the paraformaldehyde directly and generate the highly reactive methanal electrophile *in situ* in the presence of the diazoalkane. Several methods have been reported with either Lewis or Brønsted acids as catalysts and paraformaldehyde or trioxane as the polymer.[80] Along with solid polymer sources, aqueous solutions of formaldehyde (formalin) are readily

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(80) For examples of paraformaldehyde with Brønsted acids, see: (a) "Organocatalytic Enantioselective Hydroxymethylation of Oxindoles with Paraformaldehyde as C1 Unit," Liu, X.-L.; Liao, Y.-H.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.–M.; Yuan, W.–C. *J. Org. Chem.* **2010**, *75*, 4872–4875. For examples of trioxane with Lewis acids, see: (b) "New Cross-Aldol Reactions. Reactions of Silyl Enol Ethers with Carbonyl Compounds Activated by Titanium Tetrachloride," Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509. (b) "A Practical Synthesis of Chloromethyl Esters from Acid Chlorides and Trioxane or Paraformaldehyde Promoted by Zirconium Tetrachloride," Mudryk, B.; Rajaraman, S.; Soundararajan, N. *Tetrahedron Lett.* **2002**, *43*, 6317–6318. (d) "Total Synthesis of (±)-Ginkgolide B," Corey, E. J.; Kang, M. C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649–651. (e) "Total Syntheses of (+)-Lyconadin A and (−)-Lyconadin B," Beshore, D. C.; Smith, III, A. B. *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149. (f) "New Procedure for the Direct Generation of Titanium Enolates. Diastereoselective Bond Constructions with Representative Electrophiles," Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.

available due to their widespread use in industry[81] and have applications in organic synthesis where an aqueous medium is desireable.[82] Unfortunately, the compatibility of the diazocompounds with the catalysts needed for depolymerization (or water itself) became an issue. We were only able to isolate ketone products in very low yield by these methods.

In spite of these results, we were undeterred from our goal of gaining access to symmetrical ketone products due to the method's power and efficiency. An alternative approach to the depolymerization of paraformaldehyde, known as "cracking" the polymer, is its thermal decomposition to produce gaseous formaldehyde.[83] The temperature for initiating this gaseous liberation is 100 °C, but the presence of water and/or impurities can alter the initiation point because of an increased likelihood for Brønsted acid-catalyzed repolymerization. Therefore, the desiccation of the polymer under high vacuum is a critical requirement before attempting this procedure.[83c]

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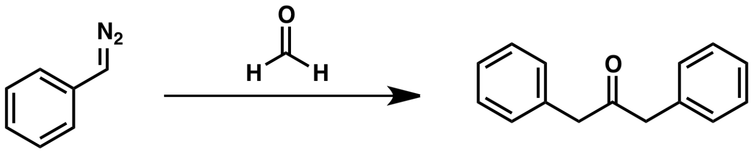
(81) Reuss, G.; Disteldorf, W.; Gamer, A. O.; Hilt, A. Formaldehyde. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2002.

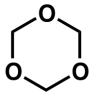
(82) For an informative review of Lewis acid chemistry in water, see: (a) Ogawa, C.; Kobayashi, S. Toward Truly Efficient Organic Reactions in Water In *Process Chemistry in the Pharmaceutical Industry, Challenges in an Ever Changing Climate*; Gadamasetti, K.; Braish, T., Eds.; CRC Press: New York, 2008; Vol. 2, pp 249-266. For a leading example of aqueous solutions of formaldehyde with Lewis acids, see: (b) "Catalytic Asymmetric Hydroxymethylation of Silicon Enolates Using an Aqueous Solution of Formaldehyde with a Chiral Scandium Complex," Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 12236–12237.

(83) (a) "The Adsorption and Decomposition of Formaldehyde and Formic Acid on the Clean and Modified Fe (100) Surface," Hung, W.-H.; Bernasek, S. L. *Surf. Sci.* **1996**, *346*, 165-188. (b) "Adsorption of Formaldehyde on Nickel Oxide Studied by Thermal Programmed Desorption and High-Resolution Electron Energy Loss Spectroscopy," Truong, C. M.; Wu, M. C.; Goodman, D. W. *J. Am. Chem. Soc.* **1993**, *115*, 3647–3653. (c) "Polymerization and Decarbonylation Reactions of Aldehydes on the Pd(111) Surface," Davis, J. L.; Barteau, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 1782–1792.

Upon finding this thermal activation method to introduce monomeric formaldehyde to an anhydrous organic solution, we achieved an exciting and promising opening result simply by heating paraformaldehyde with a heat gun and bubbling the gas through a toluene solution containing scandium(III) triflate with the simultaneous addition of a toluene solution of phenyldiazomethane (Table 1). The desired 1,3-diphenyl-2-propanone was produced in a 96% yield based on ^{1}H NMR integration. We then proceeded to fully establish the generality of the direct approach to 1,3-diaryl propanone derivatives.

Table 1: Preliminary Screening of Reactive Formaldehyde Source



entry	source of formaldehyde	product (NMR yield)
1	distilled "monomeric" formaldehyde sol.	< 10%[a,b]
2	 23 °C, 20 min, Lewis acid	< 20%[b]
3	paraformaldehyde 23 °C, 20 min, Lewis acid; -20 °C while adding diazo	< 10%[b]
4	37 % sol. in H_2O, -20 °C, 20 min	< 10%[b]
5	"cracked" paraformaldehyde, $Sc(OTf)_3$ 10 mol%, toluene, -20 °C, 30 min	96%

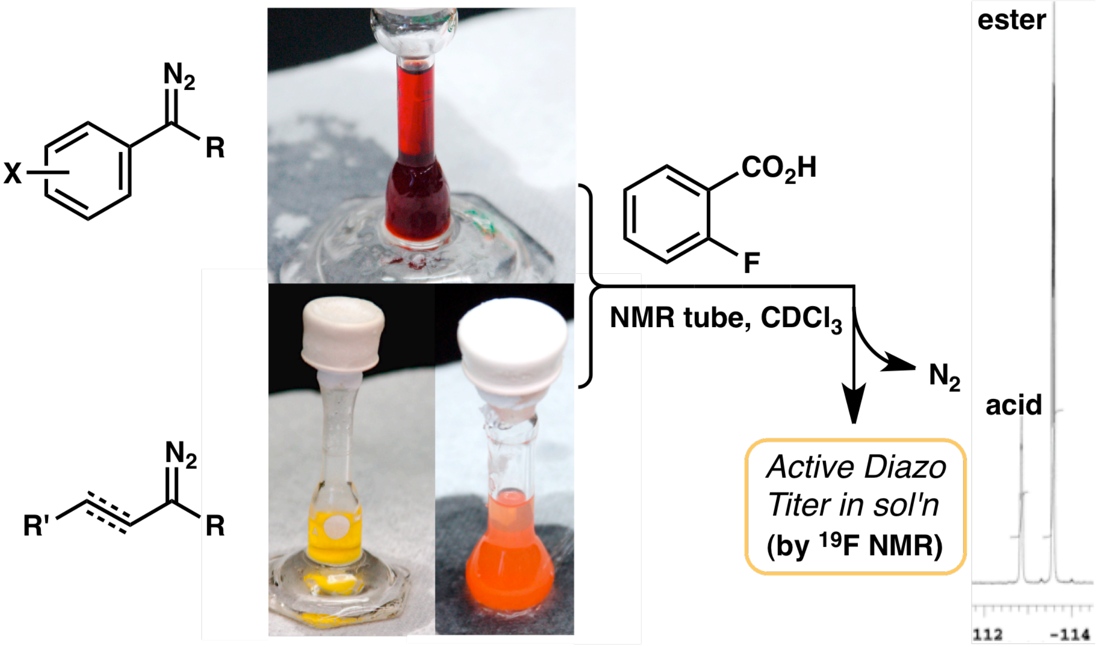
[a]The solution was Et_2O, THF, or toluene. [b]The entry was attempted either in the absence of or with different Lewis acids.

2.3 *Titration of Diazoalkane Solutions with ^{19}F NMR Spectroscopy of ortho-Fluorobenzoate Formation*

In order to accurately determine the yield of ketone product in the bidirectional homologation reaction, we sought to improve the precision and rate at which we titrate the diazoalkane solutions. At the outset of our program, esterification of the nucleophiles was carried out with excess benzoic acid. These reactions proceed with full consumption of the diazoalkane, and the isolated yield of the benzoate ester was used to calculate the active titer for each nucleophile. The shortcoming of this procedure is the need to purify the benzoate ester by silica gel column chromatography. In certain cases, titration of the diazoalkane solution was a function of the user's ability to minimize mechanical loss when performing the isolation of the ester product. Therefore, we sought to use differentially substituted benzoic esters so that we could perform a simple NMR experiment on the crude reaction mixture and reduce such operator inconsistencies. After trials with differently positioned methoxy and methyl substituents on the phenyl ring we still desired an improved choice in the substituted benzoic acid derivative. We next turned to a fluoro-substituted benzoic acid so as to deconvolute the NMR spectra since potential signal overlap was becoming problematic with certain diazoalkane substrates.

Drawing inspiration from Mosher's acid[84] and its use as a chiral derivatizing agent, 2-fluorobenzoic acid was enlisted for esterification and analysis using ^{19}F-NMR spectroscopy. We decided on *ortho* substitution (verses *meta* or *para*) due to its proximity to the carboxylate *ipso* carbon. The greater inductive effect would better translate the fluorine atom's change in chemical environment from benzoic acid to ester with a higher degree of difference in the chemical shift value (Scheme 6).

Scheme 6: Improved Titration of Diazoalkane Solutions with 2-Fluorobenzoic Acid



After recording the ^{19}F NMR spectrum utilizing a 10 sec relaxation delay time (to ensure equilibrating magnetic repopulation) the numerical ratio of acid to ester conversion, assuming only productive consumption of diazoalkane, was derived from integration values and put into the following equation:

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[84] "α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines," Dale, J. A.; Dull, D. L.; Mosher, D. L. *J. of Org. Chem.* **1969**, *34*, 2543–2549.

if total integration area is equal to 100, then

$$\frac{\left[\left(\frac{X}{100}\right)Z\right]}{A} \quad \textit{or} \quad \frac{\left[\left(\frac{X/Y}{1+(X/Y)}\right)Z\right]}{A} = \textbf{Concentration of diazoalkane solution}$$

where X is the integration value for benzoate ester, Y is the integration value for 2-fluorobenzoic acid, Z is the amount of 2-fluorobenzoic acid added in mmol, and A is the volume (in mL) of diazoalkane stock solution used in the titration experiment.

2.4 *Methods Development for the Bidirectional Homologaion of Formaldehyde with Diazoalkanes*

In order to follow up on our promising initial results, we wanted to address questions of reactivity with the goal of producing molecules of synthetic interest – be they within natural products, medicinals, or materials chemistry. The well-known importance of *para*-functionalized 1,3-diarylacetones in the synthesis of graphitic materials[85] presented an excellent platform to expand the scope of this transformation.

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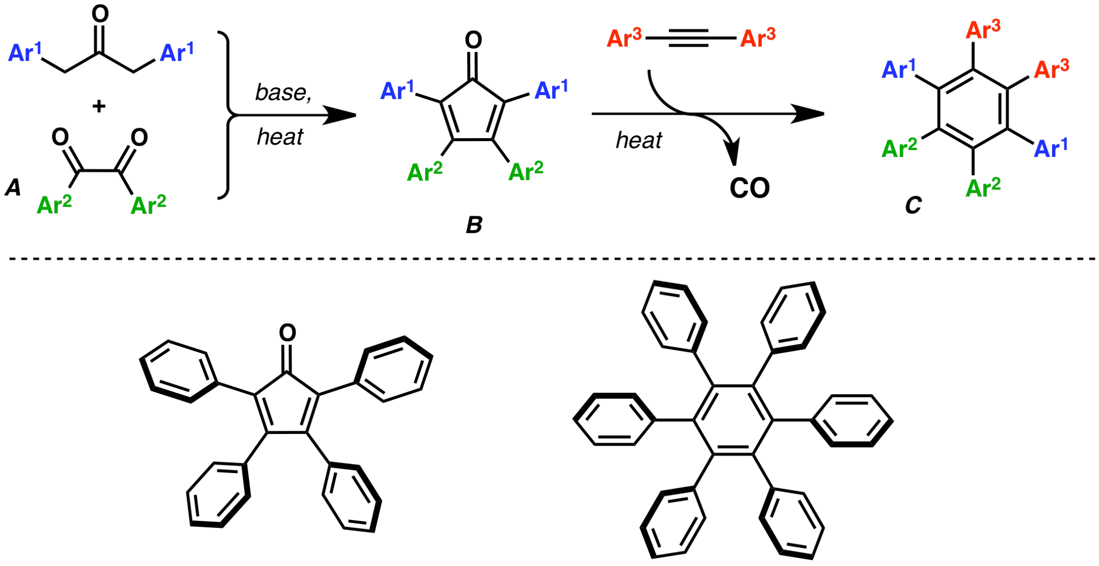
[85] (a) "The Chemistry of Organic Nanomaterials," Grimsdale, A. C.; Müllen, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 5592-5629 and references cited therein. (b) "Nanoscience and Nanotechnology: The Bottom-Up Construction of Molecular Devices and Machines," Balzani. V. *Pure Appl. Chem.* **2008**, *80*, 1631–1650.

2.4.a *1,3-Diarylacetones: important substrates for the synthetic materials chemist*

The Knoevenagel condensation of 1,3-diaryl-2-propanones with diarylethanediones (***A***) delivers products of great interest in the study of aromaticity, since the aryl substituents in tetraarylcyclopentadieneones (***B***) are found to rotate out of the plane of the central cyclopentadienone core (Scheme 7).

Scheme 7: General Access to Diversely-Substituted Hexarylbenzenes



Steric repulsion causes out-of-plane twists.

After Diels-Alder cycloaddition with diarylethynes and carbon monoxide expulsion,[86] the hexarylbenzene products (**C**) also are nonplanar due to

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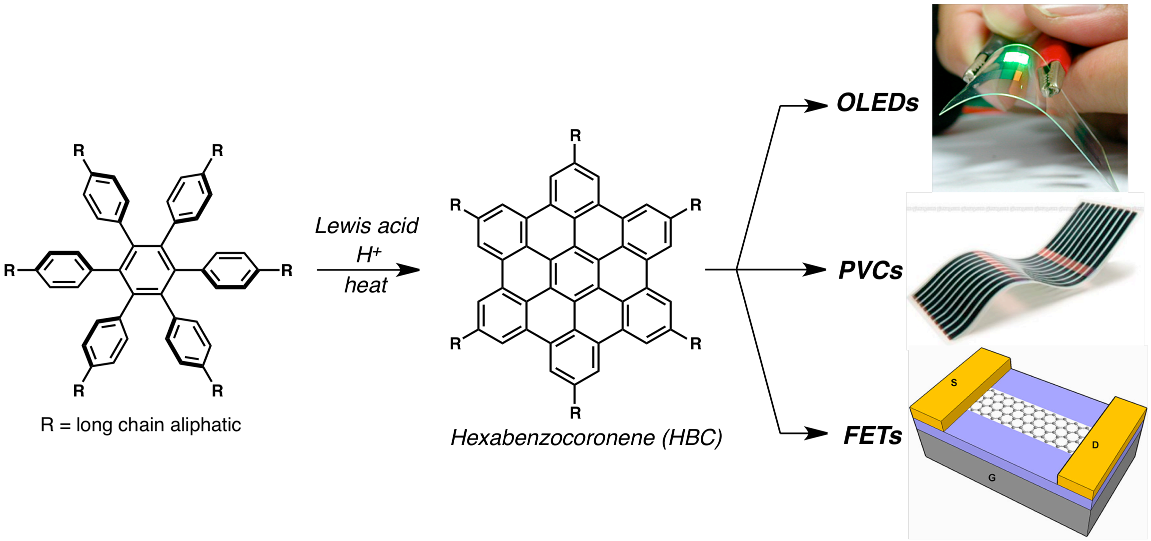
(86) For early examples of the Diels-Alder approach to polysubstituted benzenes, see: (a) "Hexaphenylbenzene," *Org. Syn.* **1966**, *46,* 44. (b) "Corannulene. A Convenient New Synthesis," Scott, L. T.; Hashemi, M. M.; Meyer, D. T.; Warren, H. B. *J. Am. Chem. Soc.* **1991**, *113*, 7082-7084.

the same steric crowding (Scheme 7).[87] Beyond a purely theoretical or academic interest, these materials are of great practical importance in nanoscience.[85] Potential uses of these structures include the construction of graphene sheets to study the material properties of the planar allotrope of carbon by methods that predictably create a material of known dimension. As depicted in Scheme 8, a preferred means for synthesizing such hexabenzocoronenes (HBCs) is also the iron-mediated dehydrogenation of the hexarylbenzene precursors, known as the Scholl reaction.[88]

Scheme 8: From Twisted to Planar, the Scholl Reaction Enabling Applications in Materials Chemistry



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(87) (a) "Restricted Rotation in Hexaarylbenzenes," Gust, D. *J. Am. Chem. Soc.* **1977**, *99*, 6980–6982. (b) "Tampering with Molecular Cohesion in Crystals of Hexaphenylbenzenes," Gagnon, E.; Halperin, S. D.; Mtivaud, V.; Maly, K. E.; Wuest, J. D. *J. Org. Chem.* **2010**, *75*, 399–406.

(88) (a) "Controlling the Scholl Reaction," King, B. T.; Kroulík, J.; Robertson, C. R.; Rempala, P.; Hilton, C. L.; Korinek, J. D.; Gortari, L. M. *J. Org. Chem.* 2007, *72*, 2279–2288. (b) "Gas-phase Diels–Alder Cycloaddition of Benzyne to an Aromatic Hydrocarbon Bay Region: Groundwork for the Selective Solvent-Free Growth of Armchair Carbon Nanotubes," Fort, E. H.; Scott, L. T. *Tetrahedron Lett.* **2011**, *52*, 2051-2053. For a review on dehydgrogenative aryl coupling methods, see: (c) "Catalytic Dehydrogenative Cross-Coupling: Forming Carbon–Carbon Bonds by Oxidizing Two Carbon–Hydrogen Bonds," Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292.

Preparation of these polycyclic aromatic hydrocarbons (PAHs) can only be reliably achieved through controlled chemical synthesis. The alternative methods of materials chemistry, such as combustion or chemical vapor deposition of a carbon rich fuel onto a metal surface, create an array of isomers and structures of varying molecular weight that can be difficult or impossible to separate.[89] These advances in chemical synthesis are particularly exciting because of the difference in properties that microstructures have on the "nano" scale versus properties that the "macromaterial" has with the same molecular composition.[90]

Our studies continued with *para*-butylphenyldiazomethane towards the synthesis of an interesting substrate in the total synthesis of a molecular wire.[91] HBCs that contain an aliphatic periphery are known to be well-behaved discotic liquid crystalline materials, or molecules that non-covalently organize themselves into aligned, stacked, columnar microstructures in their dissolved state.[92] As illustrated in Scheme 8,

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(89) (a) "Chemistry and Kinetics of Chemical Vapor Deposition of Pyrocarbon: VIII. Carbon Deposition from Methane at Low Pressures," Hu, Z.; Huttinger, K. J. *Carbon* **2001**, *39,* 433–441. (b) "Reaction Mechanism of Soot Formation in Flame," Frenklach, M. *Phys. Chem. Chem. Phys.* **2002**, *4*, 2028-2037. For excellent reviews on the subject of the synthesis of planar PAHs, see: (c) "Large Polycyclic Aromatic Hydrocarbons: Synthesis and Discotic Organization," Feng, X.; Pisula, W.; Müllen, K. *Pure Appl. Chem*. **2009**, *81*, 2203-2224. (d) "Big Is Beautiful–"Aromaticity" Revisited from the Viewpoint of Macromolecular and Supramolecular Benzene Chemistry," Watson, M. D.; Fechtenkötter, A.; Müllen, K. *Chem. Rev.* **2001**, *101*, 1267–1300.

(90) "Nanoscience, Nanotechnology, and Chemistry," Whitesides, G. M. *Small* **2005**, *1*, 172-179.

(91) "The Optical and Charge Transport Properties of Discotic Materials with Large Aromatic Hydrocarbon Cores," Debije, M. G.; Piris, J.; de Haas, M. P.; Warman, J. M.; Tomovic, Z.; Simpson, C. D.; Watson, M. D.; Müllen, K. *J. Am. Chem. Soc*. **2004**, *126*, 4641-4645 and references cited therein.

(92) (a) "Fast Photoconduction in the Highly Ordered Columnar Phase of a Discotic Liquid Crystal," Adam, D.; Schuhmacher, P.; Simmerer, J.; Häussling, L.; Siemensmeyer, K.; Etzbach, K. H.; Ringsdorf, H.; Haarer, D. *Nature* **1994**, *371*, 141–143. (b) "Temperature-

these unique carbon-rich nanomaterials have been demonstrated as potential candidates for the active layer in organic-based optoelectronics such as photovoltaic cells (PVCs), organic light emitting diodes (OLEDs), and field-effect transistors (FETs).[93]

As displayed in Table 2, the implementation of our method to access 1,3-bis(4-butylphenyl)propan-2-one (**2a**) is highly efficient. Alternative methods for preparing 1,3-diarylacetones typically require stoichiometric amounts of a metal-based carbonylation reagent, such as in the report by the Hughes group using the van Leusen (tosyl methylisocyanide) reagent or Collman ($Na_2Fe(CO)_4$) reagents or derivatives thereof.[94] More importantly, yields are only moderate when

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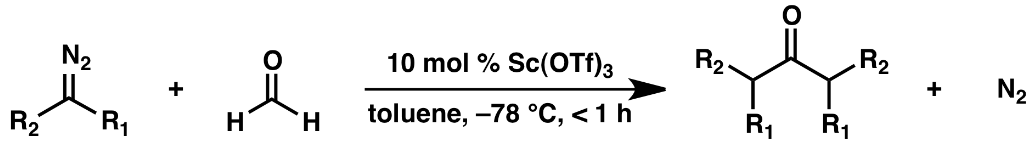
Independent Hole Mobility in Discotic Liquid Crystals," Kreouzis, T.; Donovan, K. J.; Boden, N.; Bushby, R. J.; Lozman, O. R.; Liu, Q. *J. Chem. Phys.* **2001**, *114*, 1797–1802.

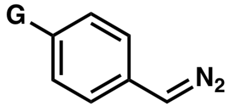
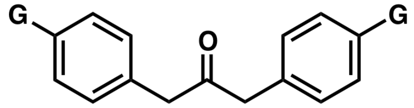
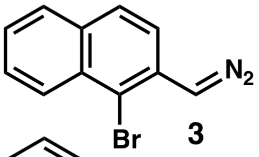
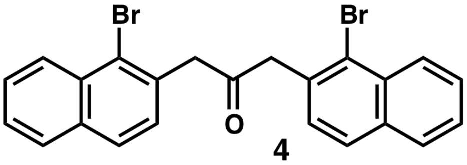
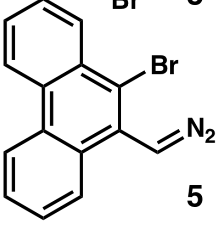
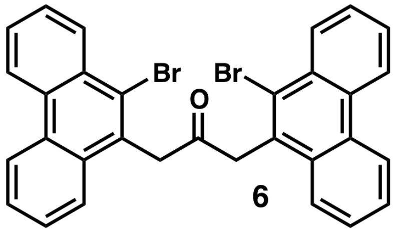
(93) (a) "Self-Organized Discotic Liquid Crystals for High-Efficiency Organic Photovoltaics," Schmidt-Mende, L.; Fechtenkötter, A.; Müllen, K.; Moons, E.; Friend, R. H.; MacKenzie, J. D. *Science* **2001**, *293*, 1119–1122. (b) "Meso-Epitaxial Solution-Growth of Self-Organizing Discotic Liquid-Crystalline Semiconductors," van de Craats, A. M.; Stutzmann, N.; Bunk, O.; Nielsen, M. M.; Watson, M.; Müllen, K.; Chanzy, H. D.; Sirringhaus, H.; Friend, R. H. *Adv. Mater.* **2003**, *15*, 495–499. (c) "Organic Semiconductors for Solution-Processable Field-Effect Transistors (OFETs)," Allard, S.; Forster, M.; Souharce, B.; Thiem, H.; Scherf, U. *Angew. Chem. Int. Ed.* **2008**, *47*, 4070-4098. (d) "Towards high charge-carrier mobilities by rational design of the shape and periphery of discotics," Feng, X.; Marcon, V.; Pisula, W.; Hansen, M. R.; Kirkpatrick, J.; Grozema, F.; Andrienko, D.; Kremer, K.; Müllen, K. *Nat. Mater.* **2009**, *8*, 421-426.

(94) (a) "Synthesis of Heterosubstituted Hexaarylbenzenes via Asymmetric Carbonylative Couplings of Benzyl Halides.," Potter, R. G.; Hughes, T. S. *Org. Lett*. **2007**, *9*, 1187-1190. (b) "Synthesis of Poly(para-phenylene)(2-isocyano-2-tosylpropane-1,3-diyl), Poly(para-phenylene)(2-oxopropane-1,3-diyl) and Oligo(cyclopentadienones) via Carbonylative Coupling of α,α′-Dibromoxylene," Potter, R. G.; Hughes, T. S. *Chem. Comm*. **2007**, 4665-4667. See also: (c) "Dehydrogenation of the Alkane Chain of 1,3-Bis[2-(diphenylphosphino)phenyl]-propane on a Rhodium(I) Centre. Complexes of the Resulting Olefinic Ligand with Rhodium(I), Iridium(I), Rhodium(III) and Nickel(II)," Bennett, M. A.; Neumann, H. *Aust. J. Chem.* **1980**, *33*, 1251-1259. (d) "Iron Pentacarbonyl Mediated Coupling of Benzyl Halides to Ketones under Mild Phase Transfer Conditions," des Abbayes, H.; Clément, J.-C.; Laurent, P.; Tanguy, G.; Thilmont, N. *Organometallics* **1988**, *7*, 2293. (e) "Tosylmethyl Isocyanide Employed in a Novel Synthesis of Ketones. A New Masked Formaldehyde Reagent," Possel, O.; van Leusen, A. M. *Tetrahedron Lett.* **1977**, *48*, 4229-4231.

electron-poor benzyl bromides are applied to these methods.[94C] In addition to the aliphatic result (**2a**), with its prominent place in the potential applications of materials chemistry, we decided to develop further comparison with the methods that utilize stoichiometric iron reagents.

Table 2: Symmetrical Alkanones from the Bidirectional chain Elongation of Formaldehyde[a]



entry	diazoalkane	yield (%)[b]	product	yield (%)[c]
1	 **1a** G = *n*-Bu	82	 **2a** G = *n*-Bu	88
2	**1b** G = OMe	78	**2b** G = OMe	83
3	**1c** G = C≡CTMS	84	**2c** G = C≡CH	81
4	**1d** G = CN	82	**2d** G = CN	86
5	**1e** G = NO_2	94	**2e** G = NO_2	84
6	 **3**	85	 **4**	74
7	 **5**	81	 **6**	57[d]

a) For conditions shown with flash pyrolysis of $(CH_2O)_n$. b) Over three steps based on ^{19}F NMR titration with *o*-$FC_6H_4CO_2H$. c) Yield of chromatographically pure ketone. d) See text.

By contrast, our method forms *para* substituted, electron-poor and electron-rich arenes as demonstrated with the synthesis of 1,3-bis(4-nitrophenyl)propan-2-one (**2e**) and 1,3-bis(4-methoxyphenyl)propan-2-one and (**2b**), respectively to study the extremes in the electronic effects in our phenyldiazomethane starting materials. We were able to access the desired products in high yield with **2b** obtained in 83% yield and **2e** isolated in 84% yield. This seemingly lack of electronic requirement was in stark contrast to the iron-mediated methods whose yields for **2b** and **2e** are 83% and 0%, respectively.[94a] We were also able to confirm the electronic tolerance of electron withdrawing groups in our method with the synthesis of 4,4'-(2-oxopropane-1,3-diyl)dibenzonitrile **2d** in an excellent yield of 86% (Table 2, entry 4).

Another potential use of the downstream tetraphenylcyclopentadienones is to capitalize on their inherent low HOMO-LUMO gap for applications in organic electronics.[95] The targeted product of entry 3, 1,3-bis(4-ethynylphenyl)propan-2-one (**2c**), provides the materials chemist with a functional handle for extending conjugation throughout an oligomeric structure.[96] The production of this synthon (**2c**) towards that goal can be achieved in 81% yield. Interestingly, under the conditions of purification the starting trimethylsilyl protection on the terminal acetylenic position is cleaved to afford the unprotected sp-hybridized carbon centers.

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(95) (a) "Tetrathiafulvalenes, Oligoacenenes, and Their Buckminsterfullerene Derivatives: The Brick and Mortar of Organic Electronics," Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev.* **2004**, *104*, 4891. (b) "Graphenes as Potential Material for Electronics," Wu, J.; Pisula, W.; Müllen, K. *Chem. Rev.* **2007**, *107*, 718–747.

(96) Cornil, J.; Beljonne, D.; Brédas, J. L. In *Electronic Materials*: *The Oligomer Approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 432-446.

2.4.b *1,3-Diarylacetones as Key Synthons in the Controlled Synthesis of Buckybowls and Nanotubes*

A foremost goal within the development of the bidirectional chain elongation method was not only the improvement of synthetic routes to important structures in materials chemistry by increasing the efficient access to previously synthesized compounds, but also to create chemical routes to previously inaccessible compounds. We are fortunate to be in a department where materials-based synthetic chemistry is being carried out at the highest level. The Scott group at Boston College has demonstrated success in accessing complex hydrocarbons for the design and synthesis of well-defined carbon-based nanomaterials. The lab's pioneering work in the first de novo chemical synthesis of C_{60}, or buckminsterfullerene, has caused their group and others to shift their sights to a ground-up synthesis of carbon nanotube endcaps.[97,98] In a templating effect, these curved carbon geometries can set the stage for the complete synthesis of both conducting or semiconducting carbon nanotubes.[99] Such achievements

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(97) For a review, see: (a) "Geodesic Polyarenes by Flash Vacuum Pyrolysis," Tsefrikas, V. M.; Scott, L. T. *Chem. Rev*. **2006,** *106*, 4868–4884. (b) "A Rational Chemical Synthesis of C_{60}," Scott, L. T.; Boorum, M. M.; McMahon, B. J.; Hagen, S.; Mack, J.; Blank, J.; Wegner, H.; de Meijere, A. *Science* **2002**, *295,* 1500-1503.

(98) (a) "Pentaindenocorannulene and Tetraindenocorannulene: New Aromatic Hydrocarbon π Systems with Curvatures Surpassing That of C_{60}," Jackson, E. A.; Steinberg, B. D.; Bancu, M.; Wakamiya, A.; Scott, L. T.; *J. Am. Chem. Soc*. **2007**, *129*, 484–485. (b) "Aromatic π-Systems More Curved Than C_{60}. The Complete Family of All Indenocorannulenes Synthesized by Iterative Microwave-Assisted Intramolecular Arylations," Steinberg, B. D.; Jackson, E. A.; Filatov, A. S.; Wakamiya, A.; Petrukhina, M. A.; Scott, L. T. *J. Am. Chem. Soc*. **2009**, *131*, 10537–10545. (c) "Synthesis of a Basket-Shaped $C_{56}H_{38}$ Hydrocarbon as a Precursor toward an End-Cap Template for Carbon [6,6]Nanotubes," Cui, H.; Akhmedov, N. G.; Petersen, J. L.; Wan, K. K. *J. Org. Chem.* **2010**, *75*, 2050–2056.

(99) (a) "Gas-Phase Diels-Alder Cycloaddition of Benzyne to an Aromatic Hydrocarbon Bay Region: Groundwork for the Selective Solvent-Free Growth of Armchair Carbon

hold many documented promises for improving of a wide range of cutting-edge technologies.[100] Shown in Scheme 9 is a projected route to C_{50}, a [5,5]-single-walled carbon nanotube endcap.[101] The later stages in the pathway are based on Pd-catalyzed coupling chemistry[102] and flash-vacuum pyrolysis (FVP) methods that are routinely used in the Scott lab.

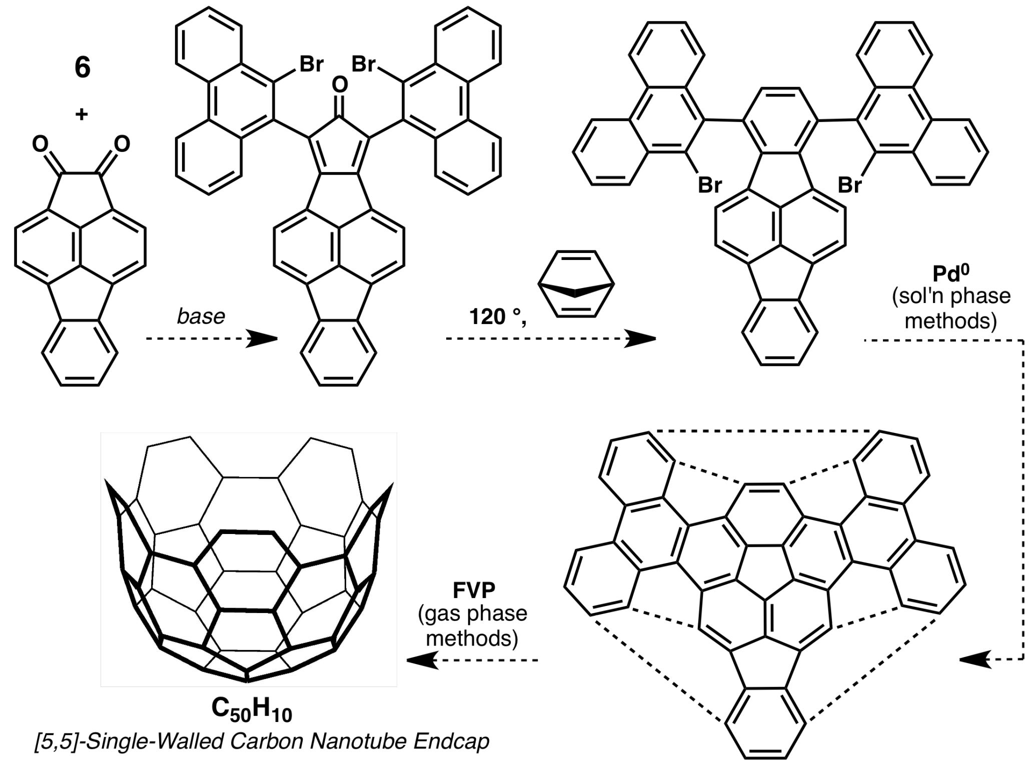
Nanotubes," Fort, E. H.; Scott, L. T. *Tet. Lett.* **2010**, *57*, 2051-2053. (b) "Growing Carbon Nanotubes from Short Hydrocarbon Templates. Energetic Analysis of the Diels-Alder Cycloaddition/Rearomatization Strategy," Fort, E. H.; Scott, L. T. *J. Mater. Chem.* **2011**, *21*, 1373-1381. (c) "One-Step Conversion of Aromatic Hydrocarbon Bay Regions Into New Unsubstituted Benzene Rings. A Reagent for the Low-Temperature, Metal-Free Growth of Single-Chirality Carbon Nanotubes," Fort, E. H.; Scott, L. T. *Angew. Chem. Int. Ed.* **2010,** *49,* 6626-6628. (d) "Diels-Alder Reactivity of Polycyclic Aromatic Hydrocarbon Bay Regions: Implications for Metal-Free Growth of Single-Chirality Carbon Nanotubes," Fort, E. H.; Donovan, P. M.; Scott, L. T. *J. Am. Chem. Soc.* **2009**, *131*, 16006-16007.

(100) (a) "Carbon Nanotubes: Synthesis, Integration, and Properties," Dai, H. *Acc. Chem. Res.* **2002**, *35*, 1035–1044. (b) "Molecular Electronic Devices Based on Single-Walled Carbon Nanotube Electrodes," Feldman, A. K.; Steigerwald, M. L.; Guo, X.; Nuckolls, C. *Acc. Chem. Res.* **2008**, *41*, 1731–1741 (c) "Fundamental Electronic Properties and Applications of Single-Walled Carbon Nanotubes," Ouyang, M.; Huang, J.-L.; Lieber, C. M. *Acc. Chem. Res.* **2002**, *35,* 1018–1025. (d) "Carbon Nanotubes for Photoconversion and Electrical Energy Storage," Dillion, A. C. *Chem. Rev.* **2010**, *110*, 6856–6872.

(101) "Corannulene-based fullerene fragments C20H10-C50H10: when does a buckybowl become a buckytube?" Baldridge, K. K.; Siegel, J. S. *Theor. Chem. Acc*. **1997**, *97*, 67-71.

(102) (a) "Imposing Curvature on a Polyarene by Intramolecular Palladium-Catalyzed Arylation Reactions: A Simple Synthesis of Dibenzo[a,g]corannulene," Reisch, H. A.; Bratcher, M. S.; Scott, L. T. *Org. Lett.* **2000**, *2*, 1427–1430. (b) "Facile Synthesis of Janus "Double-Concave" Tribenzo[*a,g,m*]coronenes," Li, Z.; Lucas, N. T.; Wang, Z.; Zhu, D. *J. Org. Chem.* **2007**, *72*, 3917–3920.

Scheme 9: Potential Synthetic Strategy for the Armchair Nanotube Endcap $C_{50}H_{10}$


6
+
Br
Br
O
O
O
Br
Br
base
120 °,
Pd⁰
(sol'n phase
methods)
FVP
(gas phase
methods)
C₅₀H₁₀
[5,5]-Single-Walled Carbon Nanotube Endcap

For this synthetic pathway to be realized, it is imperative that precursor molecules be accessible in good yield on gram scale.[103] Unfortunately, application of the stoichiometric methods for diarylacetone synthesis is problematic with larger aromatic systems. For example, attempted synthesis of **4** and **6** (Table 2) suffered from poor yields (27%) or failed altogether.[103] Thanks to encouragement from Professor Larry Scott, we have achieved a direct solution to this problem. Simultaneous, bidirectional chain-elongation of formaldehyde with 1-bromo-2-(diazomethyl)naphthalene (**3**) proceeds in 74% yield. The even greater steric hindrance of the phenanthryl-based diazoalkane **5** affords a mono-

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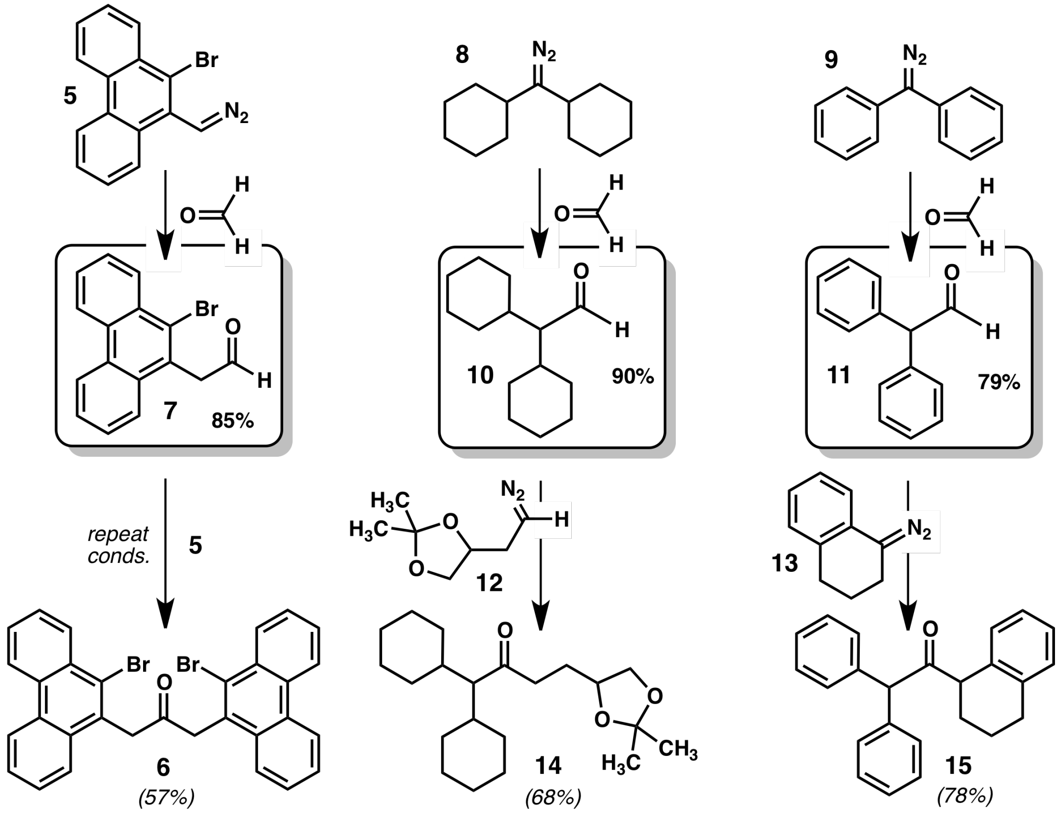
(103) "Extending the Aryl Radical Cyclization Approach to Large Geodesic Polyarenes," Andrusyszyn, P. M., M.S. Thesis, Boston College: Chestnut Hill, MA, 2002.

addition carbaldehyde **7** as the predominant product (Scheme 10). Nonetheless, we are able to obtain the target ketone (**6**) in a respectable 57% yield by resubjecting the arylacetaldehyde to the reaction conditions in the absence of formaldehyde after filtration through a plug of silica gel.

2.4.c *Diazoalkanes with Severe Steric Hindrance Allows Convenient Access to Dissymmetric Ketones.*

Since steric hindrance serves to deter the second C-H insertion event, we wondered whether could enable a general strategy for the production of dissymmetric alkanones. Indeed, dicyclohexyldiazomethane (**8**) and the benzophenone derived diazoalkane (**9**) both deliver the 2,2-disubstituted ethanal products (**10** and **11**, Scheme 10) in high yield when subjected to the standard reaction conditions. Upon isolation and purification of these sterically encumbered aldehydes products, the aldehydes (**10** and **11**) were treated with different diazoalkanes, and this resulted in smooth transformation to the acyclic ketones (**14** and **15,** Scheme 10).

Scheme 10: Steric hinderance provides access to dissymmetric alkanones


5
Br
N2
8
N2
9
N2
O
H
H
7
85%
10
90%
11
79%
repeat conds.
5
H3C
H3C
O
O
12
13
6
(57%)
14
(68%)
15
(78%)
CH3

2.4.d ***Expediant Access to Natural Products and Novel Chemical Entities.***

Armed with these promising results, we performed experiments to extend the method to other, equally challenging substrates. As displayed in entry 1 of Table 3, we achieved a two-step synthesis of the dibenzoic acid natural product (**17b**) by hydrolysis (LiOH, THF) of the corresponding diester, itself being formed in 90% by our methodology. The diacid is isolated from the bark of *Cerbera manghas*. The plant exhibits analgesic, anticonvulsant, cardiotonic, and hypotensive properties.[104]

Hetereoaromatic diazonucleophiles such as the 2-diazomethyl furan (**18**) and thiophene (**20**) are viable functionality as well in (entries 2 and 3, Table 3). The product of entry 4 is a tetrasubstituted acetone (**23**) that we believe is a novel structure. Consistent with other[23] carbon insertion reactions with dialkyldiazomethanes, Sc(tmhd)$_3$ (tmhd = 2,2,6,6-tetramethyl-3,5-heptanedianato or *t*-butyl(acac)) is the preferred catalyst, with no observable byproducts from strain release of the double cyclopropyl substitution. The 55% yield recorded for **23** is quite respectable given that double β-branching is present in the diazonucleophile (**22**) (entry 4, Table 3).

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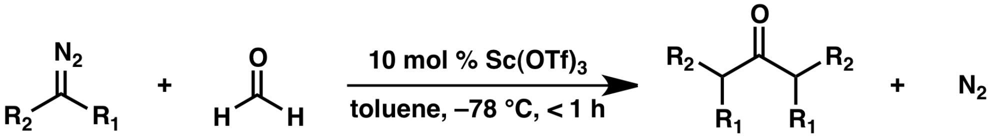
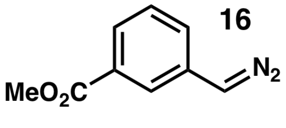
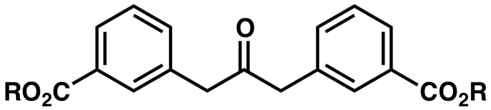
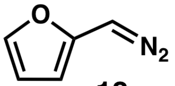
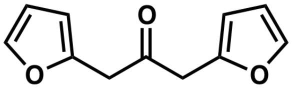
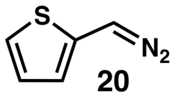
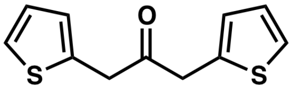
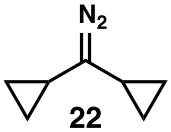
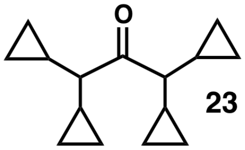
(104) "Chemical constituents from the bark of Cerbera manghas," Zhang, X.-P.; Liu, M.-S.; Zhang, J.-Q.; Kang, S.-L.; Pei, Y.-H. *J. Asian Nat. Prod. Res.* **2009**, *11*, 75-78.

Table 3: Diverse Production of Symmetrical Alkanones from the Bidirectional Chain Elongation of Formaldehyde[a]



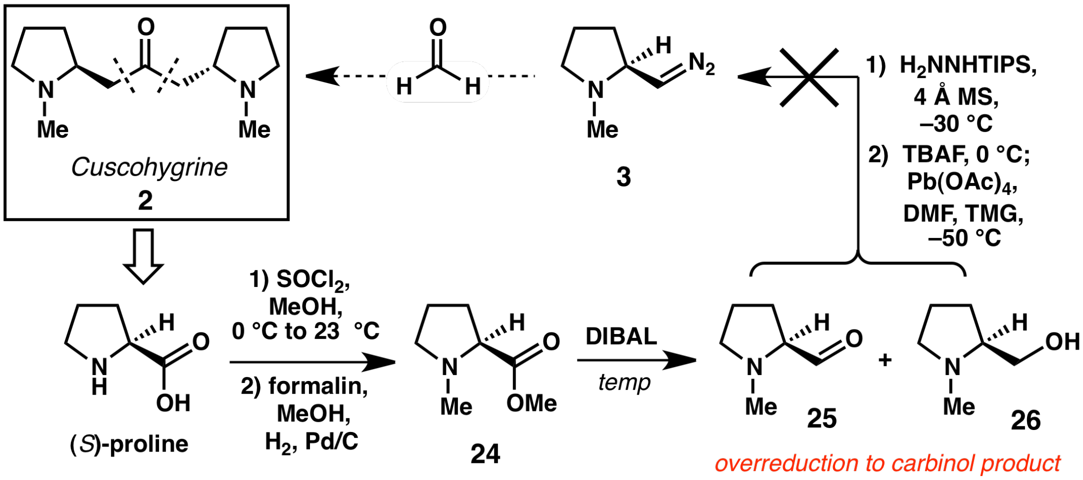
entry	diazoalkane	yield (%)[b]	product	yield (%)[c]
1	 **16**	51	 **17 a** R = Me **17 b** R = H	90
2	 **18**	37	 **19**	73
3	 **20**	45	 **21**	77
4	 **22**	28	 **23**	55[d]

a) For conditions shown with flash pyrolysis of $(CH_2O)_n$. b) Over three steps based on ^{19}F NMR titration with *o*-$FC_6H_4CO_2H$. c) Yield of chromatographically pure ketone. d) Run with $Sc(tmhd)_3$.

2.5 *Application of the Bidirectional Chain Elongation Reaction in the Total Synthesis of Erythroxylon Alkaloids.*

Following the opening study which established bidirectional chain elongation reactions of formaldehyde as an unrivaled entry to important 1,3-diarylacetones, we commenced our investigation into the asymmetric synthesis of the natural product cuscohygrine, the source of the method's inspiration. As originally planned, our synthetic strategy would be to elaborate a chiral *N*-methyl-2-diazomethylpyrrolidine (**3**) that would directly meld onto the target structure. As shown in Figure 3, the challenging formation of the *N*-methylprolinal (**25**) through a reductive pathway was hampered by two important obstacles: (1) The sensitivity of the desired aldehyde (**25**) makes its solvent-free isolation problematic;[105] (2) Despite the testing of numerous reducing agents and reaction conditions, the overreduction of the substrate methyl ester (**23**) complicates an efficient synthesis of diazoalkane **3**.

Figure 3: Complications in an Initial Approach to the Proline-Derived Diazoalkane



Cuscohygrine
2
3
1) $H_2NNHTIPS$, 4 Å MS, –30 °C
2) TBAF, 0 °C; $Pb(OAc)_4$, DMF, TMG, –50 °C
(*S*)-proline
1) $SOCl_2$, MeOH, 0 °C to 23 °C
2) formalin, MeOH, H_2, Pd/C
24
DIBAL
temp
25
26
overreduction to carbinol product

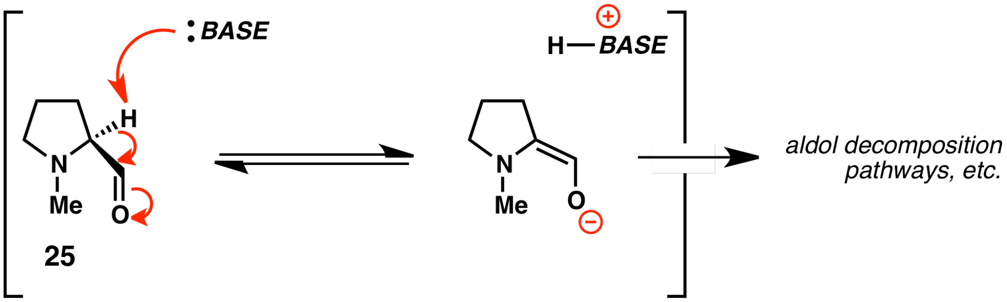
---

[105] The issue of *N*-methylprolinal's sensitivity to isolation has been well documented, see: (a) "Diastereoselective Zwitterionic Aza-Claisen Rearrangement: Synthesis of Nine-Membered Ring Lactams and Transannular Ring Contraction," Diederich, M.; Nubbemeyer, U. *Chem.—Eur. J.* **1996**, *2*, 894–900. (b) "Rigidified Acetylcholine Mimics: Conformational Requirements for Binding to Neuronal Nicotinic Receptors," Villeneuve, G.; Cecyre, D.; Lejeune, H.; Drouin, M.; Lan, R.; Quirion, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3847–3852. (c) "Synthesis and α4β2 nicotinic affinity of 2-pyrrolidinylmethoxyimines and prolinal oxime ethers," Pallavicini, M.; Moroni, B.; Bolchi, C.; Clementi, F.; Fumagalli, L.; Gotti, C.; Vailati, S.; Valoti, E.; Villa, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5827–5830. (d) "A short synthesis of (+)-hygrine," Arevalo-Garcia, E. B.; Colmenares, J. C. Q. *Tetrahedron Lett.* **2008**, *49*, 3995–3996.

2.5.a *N-Benzyl Protection Enables Efficient Production of the Pyrrolidine-Based Diazoalkane.*

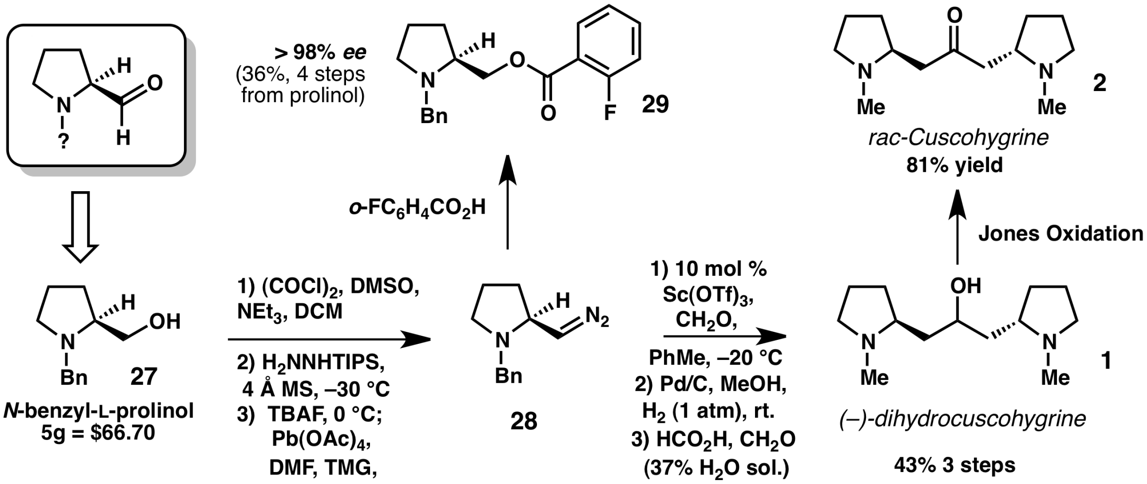
Upon arriving at this temporary roadblock in the synthetic effort, we judged that adding steric bulk to the sensitive amino aldehyde might enhance its stability and decided to use a protection strategy. In considering which protecting group would be suitable for our process, we thought about the demonstrated sensitivity of the proline-derived substrate (Scheme 11). Our aldehyde substrate (**25**) has a tertiary amine that can serve as a Brønsted base and initiate an Aldol-base decomposition pathway. This intermolecular event is frequently observed in solution upon attempted isolation of *N*-methylprolinal (**25**).

Scheme 11: Nitrogenous Tertiary Brønsted Base Enables Decomposition



With our thoughts turned towards the impending hydrazone installation and oxidation, we needed to reflect on how this sensitivity might be diminished based on our experience with different conditions for hydrazone formation. The availability of a highly reactive yet mild hydrazine source can be found in our monosilyl TIPS-protected hydrazine, but in model studies this reagent was shown to deprotect both Boc and Cbz carbamate functions that were protecting the nitrogen atom. The benzyl group emerged as a proper protecting group choice, since its mildly electron-withdrawing nature and large size would discourage the aforementioned deprotonation. We were also attracted to the mild methods of deprotection via metal-catalyzed hydrogenation.

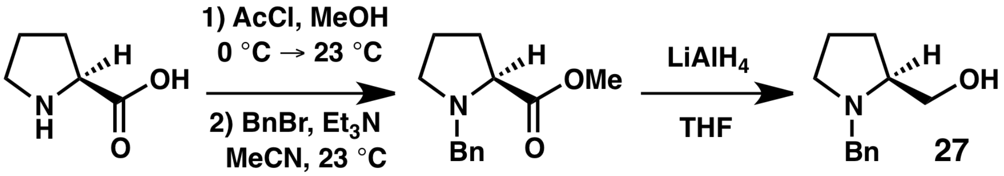
Scheme 12: Protecting Group Enables Stereoretentive Synthesis of (–)-Dihydrocuscohygrine



> 98% *ee*
(36%, 4 steps from prolinol)
29
o-FC$_6$H$_4$CO$_2$H
27
N-benzyl-L-prolinol
5g = $66.70
1) (COCl)$_2$, DMSO, NEt$_3$, DCM
2) H$_2$NNHTIPS, 4 Å MS, –30 °C
3) TBAF, 0 °C; Pb(OAc)$_4$, DMF, TMG,
28
1) 10 mol % Sc(OTf)$_3$, CH$_2$O, PhMe, –20 °C
2) Pd/C, MeOH, H$_2$ (1 atm), rt.
3) HCO$_2$H, CH$_2$O (37% H$_2$O sol.)
1
(–)-dihydrocuscohygrine
43% 3 steps
Jones Oxidation
2
rac-Cuscohygrine
81% yield

Gratifyingly, as demonstrated in Scheme 12, the benzyl group facilitates a smooth transition from proline to diazoalkane **28** via *N*-benzyl prolinal, which can be isolated and stored under inert atmosphere (–20 °C) for prolonged periods with no observable decomposition. To our satisfaction, chiral SFC analysis on the fluorobenzoic ester derivative that obtained following our improved ^{19}F NMR titration method showed the material to be of >98% enantiomeric excess. Importantly, this confirms that hydrazone formation, desilylation, and oxidation under the conditions indicated in Scheme 12 do not cause a stereomutation at the α-position in the amino aldehyde formed by Swern oxidation of **27**. Although the *N*-benzyl-L-prolinol (**27**) is commercially available, we chose to synthesize the alcohol by a convenient two-step, one-pot method involving Fischer esterification, alkylation, and lithium aluminum hydride reduction (Scheme 13).

Scheme 13: Operationally Simple Route to Protected Prolinol



With a route to the proline-based diazoalkane nucleophile in hand, we set out to study the synthesis of cuscohygrine. We were very impressed by the ease at which the *N*-benzyl protected version of cuscohygrine (not shown), could be isolated in 58% unoptimized yield in high enantiomeric purity.[106] However, the goal was not a theoretical synthesis of cuscohygrine (**2**), but a total synthesis. Therefore, investigation into the removal of the benzyl protecting groups under mild conditions was initiated, with continuing concern for accessing one enantiomer of the natural product. Like related alkaloids, cuscohygrine **2** has never been obtained as optically active material because it epimerizes and/or racemizes so readily (for greater discussion, see below). For this reason, we were unsure of the proper method for *N*-methylation, as many traditional protocols are harsh and conducive to epimerization.

Palladium-catalyzed hygrogenative removal of the benzyl protecting groups was our point of departure given the propensity for epimerization problem.[107] Upon testing palladium on carbon as a heterogeneous reagent, we were surprised to find that the central ketone function also undergoes reduction during the course of the deblocking reaction. Without purification and in the same reaction vessel, we proceeded to try literature conditions consistent with the required double methylation via reductive amination.[108] To our delight, this maneuver directly afforded the natural product subtarget in its reduced form, dihydrocuscohygrine in a clean and efficient manner (Scheme 12). This two-stage, one-pot process proved highly reproducible, and a high enantioenrichment for (–)-dihydrocuscohygrine confirmed by polarimetry and gas chromatography in comparison to authentic racemic material.

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[106] See experimental section for details.

2.5.b *The Troublesome 2,2'-Diaminosubstituted Ketone Moiety: Consequences on Homochirality and Product Stability.*

Attempts to translate this enantiomer (**1**) to its oxidized form (**2**) succeeded only when the conditions were strongly oxidizing (Scheme 12). More specifically the only method that was found to deliver the target ketone was the Jones oxidation, which necessitates a strongly acidic reaction medium (Scheme 12). Regrettably, complete racemization and partial degradation of the substrate (**1**) is observed during a moderately high-yielding synthesis (81%) of *rac*–cuscohygrine (**2**). All other oxidation

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(107) (a) Blaser, H.-U.; Steiner, H.; Studer, M. Heterogeneous Hydrogenation: A Valuable Tool for the Synthetic Organic Chemist. In *Transition Metals for Organic Synthesis*; 2nd Ed. Beller, M.; Bolm, C.; Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2 pp 125-143. (b) Wuts, P. G. M.; Greene, T. W.; *Green's Protective Groups in Organic Synthesis*; 4th Ed. Wiley: Hoboken, New Jersey, 2007; pp 748-756.

(108) Freifelder, Morris. *Catalytic Hydrogenation in Organic Synthesis: Procedures and Commentary*. New York: Wiley, 1978.

methods that were attempted either delivered product **2** in low yield, suffering from incomplete conversion or reaction failure altogether.[109] Stapper and Blechert also observed these puzzling results previously in a total synthesis of racemic cuscohygrine.[110] These researchers found it imperative that immediately following this oxidation sequence the crude reaction mixture should be purified carefully to ensure minimal decomposition, as it was found that the natural product was extremely sensitive to decay upon its storage in neat form even under inert atmosphere at low temperature. Following their lead, we purified the natural product quickly and cautiously, and full characterization showed unambiguously the *d,l*-form of cuscohygrine.

Through our efforts (–)-dihydrocuscohygrine is prepared without recourse to isolation of the extremely sensitive cuscohygrine which has never been obtained in optically active form.[110] This is believed to be the result of facile stereomutation, presumably by a retro-Mannich pathway. The existence of a related isomerization within the oxindole family of alkaloids for the natural product horsfiline, one that lacks an α-hydrogen atom, lends further support to this pathway of epimerization (Scheme 14).[111]

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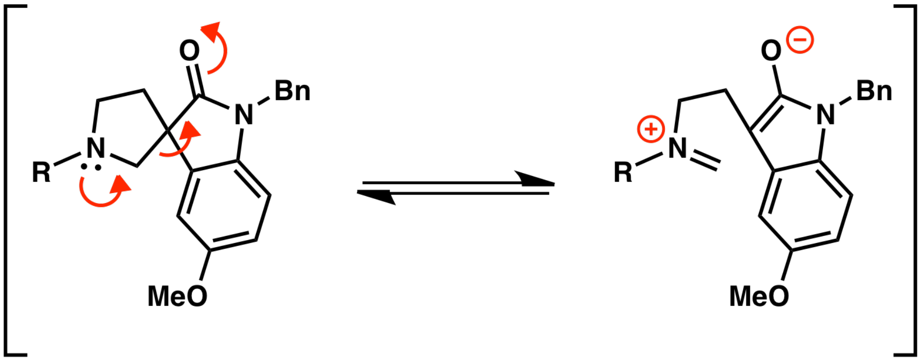
(109) Attempted oxidation conditions (results): Swern oxidation (incomplete conversion), PCC (incomplete after 24 h), PCC on alumina (incomplete after 24 h), PDC (no reaction), $KMnO_4$ (total decomposition), TPAP-NMO (incomplete conversion), IBX (incomplete conversion), Dess−Martin-periodinane (complete after 15 h, complete epimerization, low yield) TEMPO-BAIB (decomposition).

(110) "Total Synthesis of (+)-Dihydrocuscohygrine and Cuscohygrine," Stapper, C.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 6456–6460.

(111) (a) Bindra, J. S. In *Oxindole Alkaloids in The Alkaloids-Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. XIV, pp 83-121. (b) Brown, R.

Scheme 14: Racemization in the Total Synthesis of (–)-Horsfiline



As shown in Scheme 14, retro-Mannich reaction gives an achiral intermediate which upon re-cyclization results in complete loss of enantiopurity (Scheme 14). Support for this pathway is also confirmed in the previously mentioned synthesis of racemic cuscohygrine by Jones oxidation of (+)-dihydrocuscohygrine thereby proving the absolute configuration of the natural enantiomer of (−)-dihydrocuscohygrine (12.9% total yield over 13 steps from the commercially available tropone).[110]

2.5.c *Completion of a Protecting Group-Free Synthesis of Cuscohygrine.*

In spite of the instability of the desired aldehyde **25**, the corresponding diazo compound **3** can be prepared in 23% yield over four steps by careful handling of the amino aldehyde (**25**) after a tightly monitored Swern oxidation. By reaching the aldehyde functionality through an oxidation, rather than the previously problematic reduction

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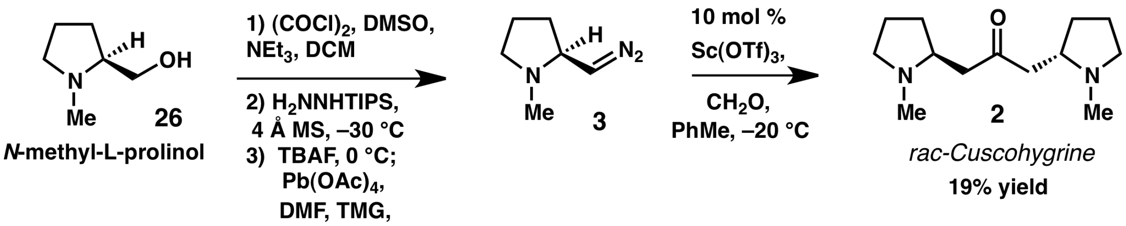
T. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; Wiley Interscience: New York, 1983; Vol. 25, part 4, pp 85-87. (c) "Palladium Asymmetric Allylic Alkylation of Prochiral Nucleophiles: Horsfiline," Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027–2030.

protocol (Figure 4), we were able to immediately initiate formation of the mono-silyl protected hydrazone at a controlled temperature.

Scheme 15: Protecting Group-Free Synthesis of *rac*-Cuscohygrine



26
N-methyl-L-prolinol
1) (COCl)$_2$, DMSO, NEt$_3$, DCM
2) H$_2$NNHTIPS, 4 Å MS, –30 °C
3) TBAF, 0 °C; Pb(OAc)$_4$, DMF, TMG,
3
10 mol % Sc(OTf)$_3$,
CH$_2$O, PhMe, –20 °C
2
rac-Cuscohygrine
19% yield

In a final attempt to access homochiral cuscohygrine, the proline-derived diazoalkane (**3**) was exposed to gaseous monomeric formaldehyde and catalytic Sc(OTf)$_3$ at low temperature, and following the evolution of nitrogen gas, the reaction mixture was promptly filtered through neutral alumina in a rigorously optimized solvent system (TLC R_f = 0.26 in 5:4:1 hexanes/DCM/Et$_2$NH). The natural product forms cleanly, albeit in low yield, but ^{1}H and ^{13}C NMR analysis still show it to be identical to both synthetic and naturally occurring cuscohygrine, which again implies that the *meso* and *d*,*l*- forms are interconverting even under the neutral reaction and purification conditions.[69a]

2.6 *Other Bioactive Synthetic Targets*

A bidirectional method to synthesize a variety of useful molecules with a high level of atom economy and further reduced waste stream can provide structures such as those pictured in Figure 4. The molecules Timcodar and Biricodar were both developed by Vertex pharmaceuticals to increase efficacy of current chemotherapies in the late 1990s.[112] Although these molecules effectively met this medicinal goal, Timcodar was found to aid in the regeneration of epidermal nerve fiber density after a standardized nerve injury in a randomized double blind animal study, although human models have shown conflicting results.[113]

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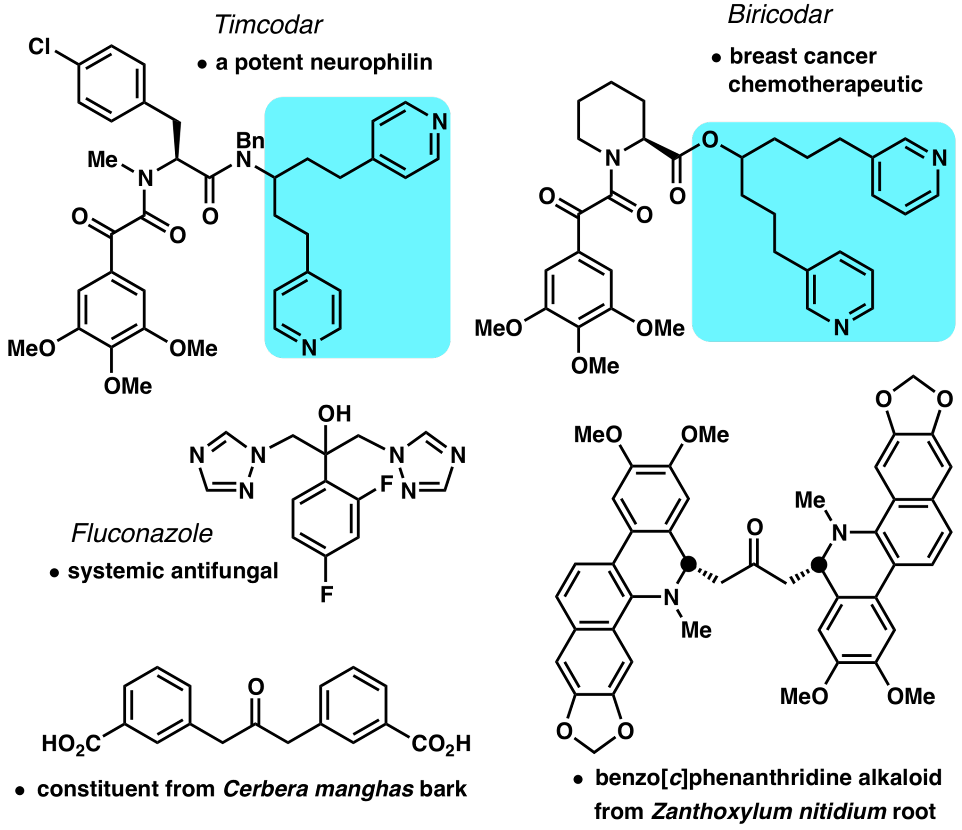
(112) (a) "Inhibition of antibiotic efflux in bacteria by the novel multidrug resistance inhibitors biricodar (VX-710) and timcodar (VX-853)," Mullin, S.; Mani, N.; Grossman, T. H. *Antimicrob. Agents Chemother*. **2004**, *48*, 4171-4176. (b) "VX-710 (Biricodar) Increases Drug Retention and Enhances Chemosensitivity in Resistant Cells Overexpressing P-Glycoprotein, Multidrug Resistance Protein, and Breast Cancer Resistance Protein," Minderman, H.; O'Loughlin, K. L.; Pendyala, L.; Baer, M. A. *Clin. Cancer Res.* **2004**, *10*, 1826-1834. (c) "A Phase II Study of the MDR Inhibitor Biricodar (INCEL, VX-710) and Paclitaxel in Women with Advanced Ovarian Cancer Refractory to Paclitaxel Therapy," Seiden, M. V.; Swenerton, K. D.; Matulonis, U.; Campos, S.; Rose, P.; Batist, G.; Ette, E.; Garg, V.; Fuller, A.; Harding, M. W.; Charpentier, D. *Gynecologic Oncology*, **2002**, *86*, 302–310. (d) "Safety and Efficacy of the Multidrug-Resistance Inhibitor Biricodar (VX-710) with Concurrent Doxorubicin in Patients with Anthracycline-Resistant Advanced Soft Tissue Sarcoma," Bramwell, V. H.; Morris, D.; Ernst, D. S.; Hings, I.; Blackstein, M.; Venner, P. M.; Ette, E.; Harding, M. W.; Waxman, A.; Demetri, G. D. *Clin. Cancer Res.* **2002**, *8*, 383-393.

(113) (a) "Factors Influencing Nerve Regeneration in a Trial of Timcodar Dimesylate," Polydefkis, M.; Sirdofsky, M.; Hauer, P.; Petty, B. G.; Murinson, B.; McArthur, J. C.; *Neurology* **2006**, *66*, 259-261. (b) "Collateral Sprouting of Human Epidermal Nerve Fibers Following Intracutaneous Axotomy," Hahn, K.; Sirdofsky, M.; Brown, A.; Ebenezer, G.; Hauer, P.; Miller, C.; Polydefkis, M. *J Peripher Nerv Syst.* **2006**, *11*, 142-147.

Figure 4: Potential Synthetic and Naturally-Occuring Medicinal Targets


Timcodar
• a potent neurophilin
Cl
Me
N
O
O
Bn
N
N
N
MeO
OMe
OMe
Biricodar
• breast cancer chemotherapeutic
N
O
O
O
O
N
N
MeO
OMe
OMe
OH
N
N
N
N
N
N
F
F
Fluconazole
• systemic antifungal
MeO
OMe
O
O
Me
N
O
N
Me
O
O
MeO
OMe
O
HO2C
CO2H
• constituent from *Cerbera manghas* bark
• benzo[*c*]phenanthridine alkaloid from *Zanthoxylum nitidium* root

Fluconazole was originally developed by Pfizer (Diflucan or Trican) to combat systemic fungal infections in patients with compromised immune response due to chemotherapy or radiation treatment. Our symmetrical ketone synthesis could potentially access the 1,3-ditriazolyl-2-propanone that could be nucleophilically attacked by an appropriately metallated arene. The bottom two natural products are both derived from plants native to Southeast Asia. The benzo[c]phenanthridine alkaloid has been proven effective in improving gingival health when incorporated into toothpaste, which confirms its antibacterial and antibiofilm properties.[114]

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(114) (a) "Dihydrobenzo[c]phenanthridine Alkaloids from Stem Bark of *Zanthoxylum nitidum*," Yang, C.-H.; Cheng, M.-J.; Chiang, M. Y.; Kuo, Y.-H.; Wang, C.-J.; Chen, I.-S. *J. Nat. Prod.* **2008**, *71*, 669–673. (b) "Clinical Observation of Toothpaste Containing

2.7 *Conclusions.*

We have demonstrated an efficient catalytic approach to ketone synthesis by a two-component coupling in a 2:1 ratio of non-stabilized diazoalkanes with formaldehyde. The reaction permits a substantial amount of steric hindrance and is well suited for preparing sterically demanding 1,3-diarylacetone building blocks for materials science. The two-directional strategy has enabled a short enantiospecific total synthesis of the bis(pyrrolidine) alkaloid (–)-dihydrocuscohygrine that requires only five flasks starting from (*S*)-*N*-benzylprolinol. It is noteworthy that sensitive, α-chiral aldehydes are transposed to the corresponding diazo compounds for use in esterification or homologation processes with preservation of enantiopurity.

Zanthoxylum nitidum Extract on Dental Plaque and Gingivitis," Wan, H. C.; Hu, D. Y.; Liu, H. C. *Chinese J. Integ. Trad. W. Med.* **2005**, *25*, 1024-1026.

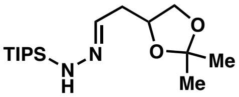
2.8 *Experimentals.*

General. Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, ν_{max} in cm^{-1}. Bands are reported as strong (s), medium (m), weak (w), and broad (br). ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.23). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry Facility (Chestnut Hill, MA) utilizing a JEOL AccuTOF with Data Acquisition in Real Time (DART). Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter. Enantiopurity for 1,3-Bis((*S*)-1-benzylpyrrolidin-2-yl)propan-2-one and (*S*)-(1-benzylpyrrolidin-2-yl)methyl 2-fluorobenzoate (**29**) was determined by Supercritical Fluid Chromatography (SFC) on a Berger instrument with a Daicel CHIRALCEL OD-H column (0.46 cm ϕ x 25 cm). Enantiopurity for (–)-dihydrocuscohygrine **1** was determined by chiral GLC analysis on an

Alltech Associates Chiraldex BDM column (30 m x 0.25 mm) equilibrated to 250 °C.

Unless stated otherwise, all reactions were carried out in flame-dried glassware under an atmosphere of nitrogen in dry, degassed solvents using standard Schlenk or vacuum-line techniques. THF, Et_2O, toluene, CH_2Cl_2, DMF, pentane, and hexanes were dispensed from a Glass Contour solvent purification system custom manufactured by SG Waters, LLC (Nashua, NH). Triisopropylsilylhydrazine was prepared as previously described.[3] 4-Butylbenzaldehyde and 1,1,3,3-tetramethylguanidine were vacuum distilled over calcium hydride. 4-Methoxybenzaldehyde, 4-formylbenzonitrile, 4-((trimethylsilyl)ethynyl)benzaldehyde, methyl 3-formylbenzoate, furfural, thiophene-2-carboxaldehyde, dicyclopropyl-methanone, dicyclohexylmethanone, and 3,4-dihydronaphthalen-1(2*H*)-one were vacuum distilled. 4-Nitrobenzaldehyde was recrystallized from water–isopropanol. $Pb(OAc)_4$, after dissolution in minimal hot glacial acetic acid, deposited as bright white needles upon cooling. The crystals were washed in a fritted Schlenk filter with pentane, dried under high vacuum, and then stored in a glovebox at –20 °C. Hydrazine hydrate (60%), TBAF, 2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde, 9-bromophenanthrene, 1-bromo-2-methylnaphthalene, benzophenone, powdered 4 Å molecular sieves, 2-fluorobenzoic acid, *N*-bromosuccinimide, silver(I) acetate, $Sc(OTf)_3$ and $Sc(tmhd)_3$ were purchased from commercial sources and used as received. The general procedure given below for preparing an unprotected arylhydrazone is based on one described previously.[115] Column chromatography was performed with EMD silica gel 60 (230-400 mesh) and driven with compressed air. Analytical TLC was carried out with EMD silica gel 60 F_{254} precoated plates (250 μm thickness) and a ceric ammonium molybdate, potassium permanganate, ninhydrin, or 2,4-dinitrophenylhydrazine stain for spot visualization.

Representative Procedure for the Synthesis and Handling of an Aliphatic Diazoalkane:



1-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylidene)-2-(triisopropylsilyl)-hydrazone. A 10 mL round-bottom flask equipped with a Teflon-coated stir bar and a jointed vacuum adapter was charged with powdered 4 Å molecular sieves (4 g) and flame-dried under vacuum. After backfilling the flask with nitrogen, the vacuum adapter was swapped for a rubber septum, and 2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (0.166 g, 1.15 mmol) and THF (2.5 mL) were added in succession with stirring. The suspension was then cooled to 0 °C and triisopropylsilylhydrazine (0.216 g, 1.15 mmol, 1.0 equiv; measured by mass difference into a gas tight syringe) was added dropwise over 2 h from a syringe pump. After 30 min of additional stirring, the mixture was

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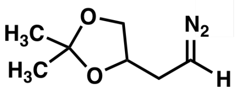
(115) "Oxidation of Hydrazones with Iodine in the Presence of Base," Pross, A.; Sternhill, S. *Aust. J. Chem.* **1970**, *23*, 989-1003.

filtered through a pad of Celite in a sintered glass Schlenk filter into a 100 mL round-bottom flask cooled to 0 ºC. The original flask, molecular sieves, and Celite were washed with two additional 2 mL volumes of cold Et_2O. The resulting homogeneous filtrate was concentrated on a rotovap equipped with an oil-free diaphragm pump (3–10 torr) to provide 0.362 g (1.15 mmol, >98%) of product as a colorless oil (~3:2 *E*:*Z* mixture, >98% pure by ^1H NMR analysis). If not used directly in the subsequent oxidation, this material was stored under nitrogen atmosphere at –20 °C.



12

4-(2-Diazoethyl)-2,2-dimethyl-1,3-dioxolane (12). To a 50 mL round-bottom flask containing a Teflon-coated stir bar, 1-(2-(2,2-dimethyl-1,3-dioxolan-4-yl) ethylidene)-2-(triisopropylsilyl)hydrazone (362 mg, 1.15 mmol) and 10 mL of THF were added. After cooling the colorless solution to 0 ºC, 1.15 mL of TBAF (1.00 M in THF, 1.15 mmol, 1.00 equiv) was added by syringe, at which point a yellow–orange discoloration immediately occurred. The solution was stirred for 10 min and then concentrated under vacuum. Without purification and in the same vessel, the crude hydrazone was freed of residual solvent under high vacuum, backfilled with nitrogen, and redissolved in 7.6 mL of DMF and 2.88 mL 1,1,3,3-tetramethylguanidine (23.0 mmol, 20 equiv). The resulting light pink solution was cooled to –45 °C (dry ice/1:1 ethanol–ethylene glycol)[116] and $Pb(OAc)_4$, finely powdered and weighed into a vial in a glovebox (561 mg, 1.26 mmol, 1.1 equiv), was added in one portion. After 45 min of stirring at –45 °C, 50 mL of ice cold pentane was added and the mixture was poured into a separatory funnel. After removing the colored organic layer, the DMF layer was extracted three times with 25 mL of cold pentane and then the DMF layer was discarded as waste. The pooled extracts were quickly washed once with 25 mL of a cold (–20 °C) 30% aqueous potassium hydroxide solution and twice with cold 25 mL volumes of saturated ammonium chloride. These washes serve (respectively) to remove residual DMF and tetramethylguanidine from the organic extract, a prerequisite for efficient catalytic carbon insertion but not esterification. The diazoalkane solution was then dried over potassium carbonate, filtered with a sintered glass fritted filter, and concentrated under high vacuum at –45 °C to afford 4-(2-diazoethyl)-2,2-dimethyl-1,3-dioxolane (**21**) as a red oil. The oil was immediately dissolved in toluene and transferred (quantitatively, with rinsing) by cannula to a 1 mL volumetric flask. The active titer was determined by an esterification reaction with 2-fluorobenzoic acid. Thus, 100 µL of the stock solution was added to a cold (–45 °C) flask containing a 1 M Et_2O solution of 2-fluorobenzoic acid (16.0 mg, 0.115 mmol, 1.00 equiv based on theoretical) dropwise by syringe. Upon warming from –45 °C, the reaction mixture became colorless and nitrogen evolution was observed. The solvent was then removed under reduced pressure and the crude solids were dissolved in $CDCl_3$ for ^{19}F NMR analysis. Based on integration of the unreacted 2-fluorobenzoic acid to the newly formed benzoate ester (1.44:1), the active titer for the diazoalkane stock solution in toluene was obtained (0.47 M, 41% yield).

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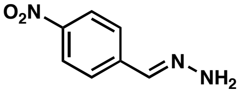
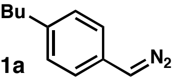
[116] "Dry-Ice Bath Based on Ethylene Glycol Mixtures," Lee, D. O.; Jensen, C. M. *J. Chem. Ed.* **2000**, *77*, 629.

Representative Procedure for the Synthesis of an Unprotected Arylhydrazone:



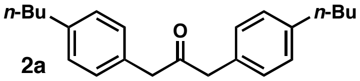
4-Nitrobenzaldehyde hydrazone. In a 2 dram vial equipped with a Teflon-coated stir bar, 4-nitrobenzaldehyde (0.453 g, 3.00 mmol) was suspended in 2.0 mL of hydrazine hydrate. The vial was sealed with a Teflon-lined screw cap and the heterogeneous mixture was stirred rapidly with heating at 100 ºC. After 6 h, the mixture was cooled to 23 °C and the product was extracted with three times with 2 mL portions of CH_2Cl_2. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 0.479 g (2.90 mmol, 96%) of an oil. The material was >98% pure by ^{1}H NMR spectroscopy and proved to be a >98:2 *E*:*Z* mixture.



1a

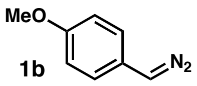
1-Butyl-4-(diazomethyl)benzene (1a). Prepared as a 1.23 M solution in 82% yield from 0.574 g of (4-butylbenzylidene)hydrazone (3.00 mmol) by the known procedure.[24a] Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.

Representative Procedure for the Bidirectional Synthesis of Ketones:

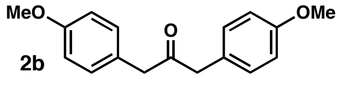


2a

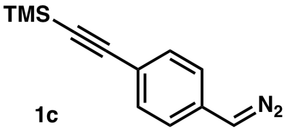
1,3-Bis(4-butylphenyl)propan-2-one (2a). In a glovebox, $Sc(OTf)_3$ (35 mg, 0.071 mmol, 0.095 equiv) was added to a 25 mL round-bottom flask containing a Teflon-coated stir bar. The flask was sealed with a rubber septum, removed from the glovebox, and taken into a fume hood. Under positive nitrogen pressure, the $Sc(OTf)_3$ was suspended in toluene (7.5 mL, 0.1 M) and the flask cooled to –20 °C (dry ice/ethylene glycol–ethanol).[8] Monomeric formaldehyde was then introduced by “cracking” solid paraformaldehyde (<100 mg, thermal depolymerization, >150 °C) in a separate round-bottom flask and allowing the generated gas to pass through a 16G steel cannula into the toluene/$Sc(OTf)_3$ suspension. Care is taken to pre-dry the paraformaldehyde solid by first grinding the polymer pieces into a fine powder followed by overnight desiccation in an Abderhalden drying pistol with P_2O_5. With formaldehyde bubbling through the reaction mixture, a solution of **1a** (0.61 mL of a 1.23 M solution in toluene, 0.75 mmol, 1.0 equiv) was added dropwise over 5 min. At the end of the addition, the bubbling of formaldehyde gas was stopped and the reaction was stirred at –20 °C for 10 min. The reaction mixture was then poured into a separatory funnel, diluted with 20 mL of Et_2O, and washed with 40 mL of water and 40 mL of saturated sodium chloride. After collection of the organic layer, drying over sodium sulfate, filtration, and concentration afforded a yellow oil that was further purified by silica gel chromatography (TLC R_f = 0.30 in 97.5:2.5 hexanes:ethyl acetate). These operations delivered 106 mg (0.33 mmol, 88%) of **2a** as a colorless oil. IR (thin film): 2928 (m), 2857 (m), 1702 (s), 1606 (w), 1512 (w), 1457 (w), 1276 (w), 1103 (m), 823 (w) 650 (w), 537 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.1 Hz, 4H), 7.05 (d, *J* = 8.0 Hz, 4H), 3.67 (s, 4H), 2.85 (t, *J* = 6.4 Hz, 4H), 1.59 (dt, *J* = 6.8, 4.6 Hz, 4H), 1.35 (dd, *J* = 15.0, 7.4 Hz, 4H), 0.92 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.40, 141.89, 131.43, 129.57, 128.97, 48.90, 35.49, 33.81, 22.58, 14.17. HRMS (ESI+) Calcd for $C_{23}H_{31}O^+$ $[M+H]^+$: 323.2330; Found: 323.2416.


1b

(4-Methoxyphenyl)diazomethane (1b). Prepared as a 1.47 M toluene solution in 78% yield from 0.297 g of (4-methoxybenzylidene)hydrazone (1.97 mmol) by the known procedure.[24a] Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.

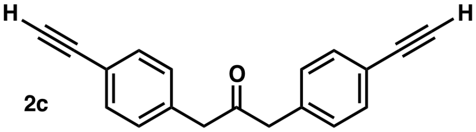

2b

1,3-Bis(4-methoxyphenyl)propan-2-one (2b). Prepared according to the representative procedure given above from 0.248 mmol of **1b** (0.169 mL of a 1.47 M solution in toluene, 1.0 equiv) and 10 mg of Sc(OTf)$_3$ (0.02 mmol, 0.08 equiv). Product **2b** was recovered as a colorless oil (27.8 mg, 83% yield). Full characterization for this material has been previously reported in the literature.[117]



1c

((4-(Diazomethyl)phenyl)ethynyl)trimethylsilane (1c). Prepared as a 1.98 M toluene solution in 84% yield from 0.266 g of (4-((trimethylsilyl)ethynyl)benzyl-idene)hydrazone (1.23 mmol) by the known procedure.[24a] Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.



2c

1,3-Bis(4-ethynylphenyl)propan-2-one (2c). Prepared by the representative procedure given above from 1.00 mmol of **1c** (0.505 mL of a 1.98 M solution in toluene, 1.0 equiv) and 50.0 mg Sc(OTf)$_3$ (0.102 mmol, 0.10 equiv). After purification by silica gel chromatography (TLC R_f = 0.33 in 12:1 hexanes:ethyl acetate), 104 mg of **2c** was recovered as a white crystalline solid in 81% yield (mp = 131-132 °C), and characterization revealed that desilylation had occurred during the chromatography. IR (thin film): 3293 (s), 3032 (w), 2889 (w), 1716 (s) 1508 (m), 1414 (m), 1335 (m), 1303 (m), 1108 (w), 1054 (m), 1020 (w),

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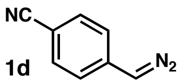
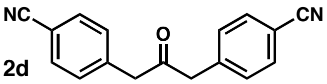
(117) "Synthesis of Heterosubstituted Hexaarylbenzenes via Asymmetric Carbonylative Couplings of Benzyl Halides," Potter, R. G.; Hughes, T. S. *Org. Lett.* **2007**, *9*, 1187-1190.

847 (m), 823 (m), 641 (m), 543 (m), 515 (w), 422 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.42 (m, 1H), 7.12-7.08 (m, 1H), 3.72 (s, 1H), 3.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.48, 147.06, 134.64, 132.62, 129.64, 121.20, 83.41, 49.17. HRMS (ESI+) Calcd for $C_{19}H_{15}O^+$ $[M+H]^+$: 259.1054; Found: 259.1128.



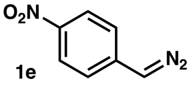
1d

4-(Diazomethyl)benzonitrile (1d). Prepared as a 0.271 M toluene solution in 82% yield from 0.240 g of 4-(hydrazonomethyl)benzonitrile (1.65 mmol) by the known procedure.[24a] Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.



2d

4,4'-(2-Oxopropane-1,3-diyl)dibenzonitrile (2d). Prepared by the representative procedure given above from 0.136 mmol of **1d** (0.502 mL of a 0.271 M solution in toluene, 1.0 equiv) and 6.6 mg $Sc(OTf)_3$ (0.013 mmol, 0.10 equiv). Product **2d** was recovered as a white solid (15.2 mg, 86% yield, mp = 150-151 ºC). Characterization data has been previously reported.[118]



1e

(4-Nitrophenyl)diazomethane (1e). Made as a 1.51 M toluene solution in 95% yield from 0.240 g of 4-nitrobenzaldehyde hydrazone (1.58 mmol) by the known procedure.[24a]

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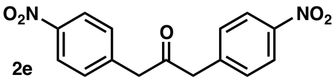
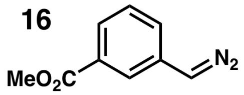
(118) "Metallic Nickel-Mediated Synthesis of Ketones by the Reaction of Benzylic, Allylic, Vinylic, and Pentafluorophenyl Halides with Acid Halides," Inaba, S.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373-1381.

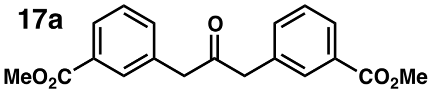
Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.


2e

1,3-Bis(4-nitrophenyl)propan-2-one (2e). Prepared by the representative procedure given above from 1.51 mmol of **1e** (1.00 mL of a 1.51 M solution in toluene, 1.0 equiv) and 44 mg of Sc(OTf)$_3$ (0.090 mmol, 0.06 equiv). Product **2e** was recovered as a crystalline solid (190 mg, 84% yield, mp = 178-179 ºC). Characterization data has been previously reported.[119]


16

Methyl 3-(diazomethyl)benzoate (16). Prepared as a 0.33 M toluene solution in 51% yield by the representative procedure for the synthesis of aliphatic diazoalkanes from 0.310 g of methyl 3-((2-(triisopropylsilyl)hydrazono)methyl)benzoate (0.927 mmol). Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.


17a

Dimethyl 3,3'-(2-oxopropane-1,3-diyl)dibenzoate (17a). Prepared by the representative procedure given above from 0.33 mmol of **16** (1.0 mL of a 0.33 M solution in toluene, 1.0 equiv) and 16.2 mg of Sc(OTf)$_3$ (0.033 mmol, 0.10 equiv). Diester **17a** was isolated as a colorless oil (48.5 mg,

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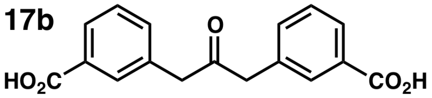
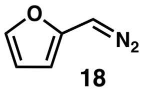
(119) "Predicting the UV–Vis Spectra of Tetraarylcyclopentadienones: Using DFT Molecular Orbital Energies to Model Electronic Transitions of Organic Materials," Potter, R. G.; Hughes, T. S. *J. Org. Chem.* **2008**, *73,* 2995-3004.

90% yield) after silica gel chromatography (TLC R_f = 0.33 in 8:2 hexanes:ethyl acetate). IR (thin film): 2919 (m), 2863 (m), 1722 (m), 1711 (s), 1599 (w), 1562 (w), 1427 (w), 1413 (w), 1337 (m), 1309 (w), 1070 (w) 758 (w), 698 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, *J* = 7.6, 1.4, 1H), 7.82 (s, 1H), 7.40 (t, *J* = 7.6, 1H), 7.34 (dd, *J* = 6.1, 1.5, 1H), 3.91 (s, 3H), 3.81 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.44, 166.91, 134.17, 134.14, 130.79, 130.76, 128.93, 128.58, 52.32, 49.07. HRMS (ESI+) Calcd for $C_{19}H_{19}O_5^+$ $[M+H]^+$: 327.1152; Found: 327.1373.

17b

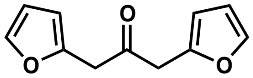


3,3'-(2-Oxopropane-1,3-diyl)dibenzoic acid (17b). A 0.05 M solution of **17a** (27.6 mg, 0.085 mmol) in 1:1 THF–water was added to a 10 mL round-bottom flask equipped with a Teflon-coated stir bar and treated with LiOH (20.0 mg, 0.858 mmol, 10 equiv) as a solid in one portion. Upon dissolution of the base, the colorless solution was stirred for 4 h and diluted with 20 mL of a 1 N HCl solution (20 mL). The contents of the reaction vessel were then poured into a separatory funnel and extracted with 25 mL of CH_2Cl_2 three times. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to a light yellow solid. Purification was achieved by silica gel chromatography (TLC R_f = 0.30 in 9:1 dichloromethane:methanol) to yield a white solid (11.6 mg, 42% yield, 279-282 ºC). Spectroscopic data for diacid **17b** was in agreement with that reported in the isolation literature.[104]



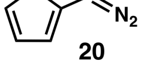
18

2-(Diazomethyl)furan (18). Prepared as a 1.72 M toluene solution in 37% yield from 0.451 g of (furan-2-ylmethylene)hydrazone (4.09 mmol) by the known procedure.[24a] Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.



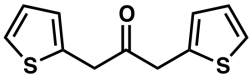
19

1,3-Di(furan-2-yl)propan-2-one (19). Prepared by the representative procedure given above from 0.34 mmol of 2-(diazomethyl)furan (0.20 mL of a 1.72 M solution in toluene, 1.0 equiv) and 16.7 mg of $Sc(OTf)_3$ (0.034 mmol, 0.10 equiv). Purification by silica gel chromatography (TLC R_f = 0.30 in 92:8 hexanes:ethyl acetate) gave 23.8 mg of a colorless oil (74% yield). IR (thin film): 3121 (w), 2924 (w), 2853 (w), 1726 (s), 1598 (w), 1504 (m), 1384 (w), 1329 (w), 1147 (m), 1074 (w), 1011 (m), 913 (w), 806 (w), 734 (s), 599 (m). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, J = 1.9, 0.8 Hz, 2H), 6.34 (dd, J = 3.1, 1.9 Hz, 2H), 6.19 (dd, J = 3.2, 0.7 Hz, 2H), 3.77 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.34, 147.76, 142.42, 110.86, 108.68, 41.64. HRMS (ESI+) Calcd for $C_{11}H_{11}O_3^+$ [M+H]$^+$: 191.0664; Found: 191.0714.

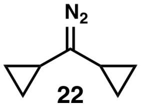


20

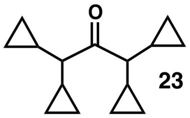
2-(Diazomethyl)thiophene (20). Prepared as a 0.35 M toluene solution in 45% yield from 0.353 g of (thiophen-2-ylmethylene)hydrazone (3.150 mmol) by the known procedure.[24a] Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.


21

1,3-Di(thiophen-2-yl)propan-2-one (21). Prepared by the representative procedure given above from 0.14 mmol of 2-(diazomethyl)furan (0.40 mL of a 0.35 M solution in toluene, 1.0 equiv) and 8.0 mg of Sc(OTf)$_3$ (0.016 mmol, 0.12 equiv). Purification by silica gel chromatography (TLC R$_f$ = 0.30 in 95:5 hexanes:ethyl acetate) provided 11.9 mg of a colorless oil (76% yield). IR (thin film): 3105 (w), 2921 (w), 2898 (w), 2854 (w), 1721 (s), 1612 (w), 1532 (w), 1435 (w), 1401 (w), 1317 (w), 1211 (w), 1079 (m), 851 (w), 696 (s), 537 (w). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.22 (dd, *J* = 5.2, 1.2 Hz, 2H), 6.96 (dd, *J* = 5.2, 3.5 Hz, 2H), 6.87 (d, *J* = 3.5 Hz, 2H), 3.96 (d, *J* = 0.7 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 202.81, 134.85, 127.25, 127.24, 125.46, 42.55. HRMS (ESI+) Calcd for $C_{11}H_{11}S_2O^+$ [M+H]$^+$: 223.0251; Found: 223.2720.

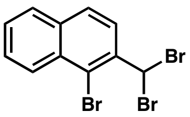

22

(Diazomethylene)dicyclopropane (22). Prepared as a 0.63 M toluene solution in 28% yield by the representative procedure for the synthesis of aliphatic diazoalkanes from 0.516 g of (dicyclopropylmethylene)hydrazine (4.15 mmol). Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.

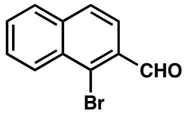


23

1,1,3,3-Tetracyclopropylpropan-2-one (23). Prepared by the representative procedure given above from 0.186 mmol of **9** (0.295 mL of a 0.63 M solution in toluene, 1.0 equiv) and 11.1 mg of Sc(tmhd)$_3$ (0.019 mmol, 0.10 equiv). Purification by silica gel chromatography (TLC R$_f$ = 0.30 in 97.5:2.5 hexanes:ethyl acetate) afforded 11.2 mg of **10** as a colorless oil (55% yield). IR (thin film): 3080 (w), 3006 (w), 2924 (m), 2854 (w), 1731 (s), 1463 (m), 1377 (w), 1272 (w), 1098 (m), 1020 (w), 998 (w), 958 (w), 932 (w), 856 (w), 820 (m). ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.53 (t, *J* = 7.6 Hz, 2H), 0.94 (qt, *J* = 8.2, 5.1 Hz, 4H), 0.51-0.40 (m, 8H), 0.36-0.29 (m, 4H), 0.25-0.18 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 210.92, 27.06, 20.84, 10.69. HRMS (ESI+) Calcd for $C_{15}H_{23}O^+$ $[M+H]^+$: 219.1704; Found: 219.1611.



1-Bromo-2-(dibromomethyl)naphthalene. To a 100 mL round-bottom flask equipped with a Teflon-coated stir bar, 2.21 g of 1-bromo-2-methylnaphthalene (10.0 mmol), 4.45 g of *N*-bromosuccinimide (25.0 mmol, 2.5 equiv), and 0.33 g of azobisisobutyronitrile (2.0 mmol, 0.20 equiv) were added in succession. The flask was outfitted with a reflux condenser, evacuated, and backfilled with nitrogen. The reactants were dissolved in benzene (35 mL, 0.3 M) and stirred at reflux for 24 h. The reaction mixture was then cooled to 23 °C, transferred to a separatory funnel, and washed three times with 25 mL of saturated sodium bisulfite. In each case, the aqueous wash was back-extracted with 5 mL of CH_2Cl_2, and this rinse fraction was added to the organic layer. After drying over sodium sulfate, filtration, and concentration, the crude product was purified by silica gel chromatography (TLC R_f = 0.35 in 97.5:2.5 hexanes:ethyl acetate) to give 3.61 g of the tribromide as a yellow solid (96% yield). Characterization data has been previously reported.[120]



1-Bromo-2-naphthaldehyde. A 200 mL round-bottom flask equipped with a Teflon-coated stir bar was covered with aluminum foil to exclude light and charged with 3.79 g of 1-bromo-2-(dibromomethyl)naphthalene (10.0 mmol) and 3.34 g of silver(I) acetate (20.0 mmol, 2.0 equiv). The solids were dissolved in 16 mL of water, 33 mL of acetone, and 50 mL of ethanol (0.1 M, 1:2:3 ratio). After stirring for 24 h at 23 °C, the reaction mixture was transferred to a separatory funnel and washed with 100 mL of Et_2O. In turn, the organic layer was washed three times with 80 mL of saturated sodium chloride. After collecting the ether layer, it was dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (TLC R_f = 0.33 in 97.5:2.5 hexanes:ethyl acetate) provided 2.21 g of the aldehyde as a yellow solid (95% yield). Characterization data has been previously recorded.[120]

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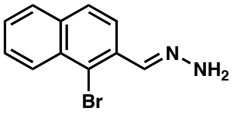
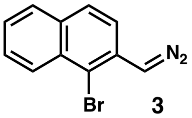
(120) "Synthesis and Cytotoxic Activity of Acronycine Analogues in the Benzo[c]pyrano[3,2-h]acridin-7-one and Naphtho[1,2-b][1,7] and -[1,10]-phenanthrolin-7(14H)-one," Bongui, J.; Elomri, A.; Cahard, D.; Tillequin, F.; Pfeiffer, B.; Pierre, A.; Seguin, E. *Chem. Pharm. Bull.* **2005**, *53,* 1540-1547.

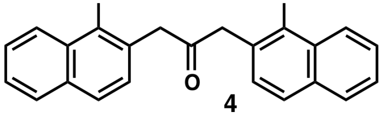


((1-Bromonaphthalen-2-yl)methylene)hydrazone. In a 20 mL vial equipped with a Teflon-coated stir bar, 1-bromo-2-naphthaldehyde (0.710 g, 3.02 mmol, 1.0 equiv) was suspended in 0.50 mL of hydrazine hydrate (15 mmol, 5.0 equiv) and 6 mL of ethanol (0.5 M). After sealing the vial with a Teflon-lined screw cap, the heterogeneous mixture was stirred rapidly with heating at 80 ºC. After 2 h, the mixture was cooled to 23 °C for 12 h of stirring. The product was then extracted with three 5 mL volumes of $CHCl_3$. The pooled extracts were dried over sodium sulfate, filtered, and concentrated to afford 0.479 g (2.90 mmol, 96% yield) of a white solid. This material was >98% pure and consisted of a >98:2 *E*:*Z* mixture on the basis of ^{1}H NMR analysis.



3

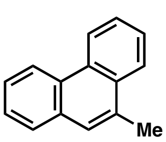
1-Bromo-2-(diazomethyl)naphthalene (3). Prepared as a 0.25 M toluene solution in 85% yield from 0.252 g of ((1-bromonaphthalen-2-yl)methylene)hydrazone (1.01 mmol) by the known procedure.[24a] Used in a homologation reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.



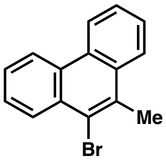
4

1,3-Bis(1-bromonaphthalen-2-yl)propan-2-one (4). Prepared by the representative procedure given above from 0.50 mmol of **3** (2.0 mL of a 0.25 M solution in toluene, 1.0 equiv) and 25 mg of $Sc(OTf)_3$

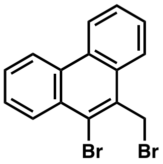
(0.050 mmol, 0.10 equiv). Purification by silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate) delivered 86.6 mg of **12** as a white solid in 74% yield (mp = 163 °C). IR (thin film): 3087 (w), 3052 (w), 1716 (s), 1603 (w), 1585 (w), 1488 (w), 1452 (w), 1392 (m), 975 (w), 822 (m), 760 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.60 (dd, J = 8.4, 6.9 Hz, 2H), 7.52 (dd, J = 8.4, 6.8 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.24 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.33, 133.85, 132.77, 132.70, 128.74, 128.28, 128.00, 127.74, 127.58, 126.63, 125.31, 51.31. HRMS (ESI+) Calcd for $C_{23}H_{17}Br_2O^+$ $[M+H]^+$: 469.9439; Found: 469.9527.



9-Methylphenanthrene. To a solution of 5.00 g (19.4 mmol) of 9-bromophenanthrene in Et_2O (100 mL, 0.2 M) at 0 °C was added 10.7 mL of *n*-BuLi (2.0 M in hexanes, 21.4 mmol, 1.1 equiv) dropwise over 10 min. After warming the solution to 23 °C for 10 min and recooling it to 0 °C, 3.52 mL of dimethyl sulfate (36.9 mmol, 1.9 equiv) was added dropwise over a 30 min period. The reaction mixture was then heated to reflux for 5 h. After cooling to 23 °C, the reaction was quenched with 40 mL of ammonium hydroxide and transferred to a separatory funnel. The organic layer was washed three times with 50 mL of saturated sodium chloride and then collected, dried over sodium sulfate, filtered, and concentrated. The resulting solid was recrystallized from hot hexanes to afford 3.59 g of colorless needles (72% yield). Characterization data has been previously reported.[121]



9-Bromo-10-methylphenanthrene. A 100 mL round-bottom flask containing a Teflon-coated stir bar and covered with aluminum foil to exclude light was charged with 2.44 g (12.7 mmol) of 9-methylphenanthrene and 2.71 g of *N*-bromosuccinimide (15.2 mmol, 1.2 equiv). After the flask was flushed with nitrogen and sealed with a rubber septum, the reactants were dissolved in acetonitrile (21.2 mL, 0.6 M) for 24 h of stirring at 23 °C. At the end of the reaction period, 20 mL of 1 N NaOH was added with 10 min of stirring. The mixture was then poured into a separatory funnel and extracted with three 25 mL volumes of CH_2Cl_2. Organic layers were pooled, dried over sodium sulfate, filtered, and concentrated to give 3.10 g (90% yield) of bromide that was used directly in the next reaction without further purification. Characterization data has been previously reported.[121]



9-Bromo-10-(bromomethyl)phenanthrene. A 250 mL round-bottom flask containing a Teflon-coated stir bar was charged with 3.10 g of 9-bromo-10-methylphenanthrene (11.4 mmol), 4.27 g of *N*-bromosuccinimide (24.0 mmol, 2.1 equiv), and 0.280 g of azobisisobutyronitrile (1.71 mmol, 0.15 equiv). The flask was outfitted with a reflux condenser, evacuated, and backfilled with nitrogen. The

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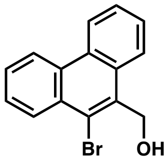
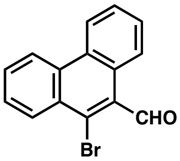
(121) "A Novel Nickel(0)-Catalyzed Cascade Ullmann—Pinacol Coupling: From *o*-Bromobenzaldehyde to trans-9,10-Dihydroxy-9,10-dihydrophenanthrene.,"Lin, S.; Chen, Q.; You, T. *Synlett* **2007**, *13*, 2101-2105.

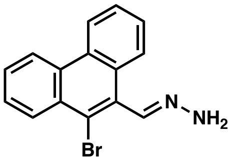
reactants were dissolved in benzene (60 mL, 0.2 M) and stirred at reflux for 24 h. The reaction mixture was then cooled to 23 °C, transferred to a separatory funnel, and washed three times with 50 mL of saturated sodium bisulfite. In each case, the aqueous wash was back-extracted with 20 mL of CH_2Cl_2, and this rinse fraction was added to the organic layer. The solution was dried over sodium sulfate, filtered, and concentrated to give 3.91 g (98%) of dibromide that was directly used without further purification. Characterization data has been previously reported.[121]



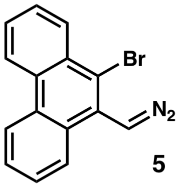
(10-Bromophenanthren-9-yl)methanol. A 250 mL round-bottom flask equipped with a Teflon-coated stir bar and covered with aluminum foil to exclude light was charged with 4.12 g (11.0 mmol) of 9-bromo-10-(bromomethyl)phenanthrene and 4.00 g of silver(I) acetate (24.2 mmol, 2.2 equiv). After dissolving the solids in 10 mL of water, 30 mL of acetone, and 60 mL of ethanol (0.1 M, 1:2:3 ratio), the solution was stirred at 23 °C for 24 h. The reaction mixture was then transferred to a separatory funnel and washed with 100 mL of Et_2O. In turn, the organic layer was washed three times with 80 mL of saturated sodium chloride before being dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (TLC R_f = 0.33 in 9:1 hexanes:ethyl acetate) afforded 2.94 g of the alcohol as a white solid (93% yield). Characterization data has been previously reported.[121]



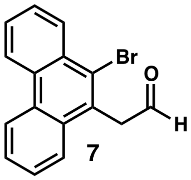
10-Bromophenanthrene-9-carbaldehyde. A –60 °C solution of 0.22 mL of dimethyl sulfoxide (3.13 mmol, 1.10 equiv) in THF (20 mL) was treated with 0.26 mL of oxalyl chloride (2.99 mmol, 1.05 equiv) dropwise over 5 min. After 15 min of stirring, 0.820 g (2.84 mmol, 1.0 equiv) of (10-bromophenanthren-9-yl)methanol was added as a solution in THF (8 mL). After 15 min 0.84 mL of triethylamine (5.97 mmol, 2.1 equiv) was added, and the vessel was allowed to slowly warm to 23 °C. The reaction mixture was then diluted with 50 mL of water, transferred to a separatory funnel, and extracted three times with 20 mL of ethyl acetate. The combined organic layers were then washed three times with 30 mL of saturated sodium chloride before being dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate) gave 0.72 g of the aldehyde as a white solid (88% yield). Characterization data has been previously reported.[121]



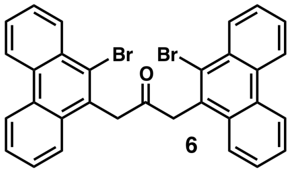
((10-Bromophenanthren-9-yl)methylene)hydrazone. In a 2 dram vial equipped with a Teflon-coated stir bar, 0.190 g of 10-bromophenanthrene-9-carbaldehyde (0.666 mmol) was suspended in 0.150 mL of hydrazine hydrate (3.33 mmol, 5.0 equiv) and ethanol (1.5 mL, 0.5 M). The vial was sealed with a Teflon-lined screw cap and the mixture was stirred rapidly with heating at 80 ºC. After 2 h, the mixture was cooled to 23 °C for 12 of stirring. The product was then extracted with three 5 mL volumes of $CHCl_3$. Combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 0.197 g of a white solid (99% yield). This material was >98% pure and consisted of a >98:2 *E*:*Z* mixture based on ^{1}H NMR analysis.


5

9-Bromo-10-(diazomethyl)phenanthrene (5). Prepared as a 0.42 M toluene solution in 81% yield from 0.200 g of ((10-bromophenanthren-9-yl)methylene)hydrazone (0.668 mmol) by the known procedure.[24a] Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.

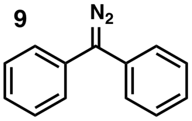

7

2-(10-Bromophenanthren-9-yl)acetaldehyde (7). The near exclusive product when using the representative procedure given above with 0.110 mmol of **5** (0.262 mL of a 0.42 M solution in toluene, 1.0 equiv) and 5.4 mg of $Sc(OTf)_3$ (0.011 mmol, 0.10 equiv). Purification by silica gel chromatography (TLC R_f = 0.35 in 9:1 hexanes:ethyl acetate) gave 28.0 mg of the product as a white solid in 85% yield (mp = 198 °C). IR (thin film): 3068 (w), 2923 (w), 2850 (w), 2723 (w), 1721 (s), 1488 (w), 1445 (w), 753 (s), 720 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, *J* = 1.9 Hz, 1H), 8.65 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.62 (d, *J* = 9.5 Hz, 1H), 8.41 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.84 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.64-7.60 (m, 3H), 7.58-7.53 (m, 1H), 4.52 (d, *J* = 1.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.55, 131.62, 131.32, 30.60, 130.14, 129.19, 128.03, 128.01, 127.91, 127.39, 127.10, 125.00, 123.62, 122.85, 49.08. HRMS (ESI+) Calcd for $C_{16}H_{12}BrO^+$ $[M+H]^+$: 300.0021; Found: 299.9973.



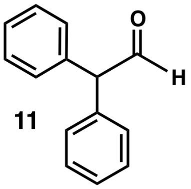
6

1,3-Bis(10-bromophenanthren-9-yl)propan-2-one (6). Prepared by a general procedure given below for the synthesis of dissymmetric ketones from 45.6 mg of 2-(10-bromophenanthren-9-yl)acetaldehyde (0.152 mmol), 0.168 mmol of **5** (0.4 mL of a 0.42 M solution in toluene, 1.10 equiv), 8.3 mg of $Sc(OTf)_3$ (0.017 mmol, 0.10 equiv), and 1.8 mL of toluene (0.1 M). Purification by silica gel chromatography (TLC R_f = 0.35 in 9:1 hexanes:ethyl acetate) provided 57.8 mg of **6** as a white solid in 67% yield (mp = 249 °C). Characterization that follows is in agreement with the previously documented spectra.[103] IR (thin film): 3073 (w), 2954 (w), 2923 (w), 2852 (w), 1712 (s), 1488 (m), 1444 (m), 1333 (w), 1066 (w), 1050 (w), 901 (w), 749 (s), 718 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 8.2 Hz, 2H), 8.69 (dd, J = 6.4, 3.1 Hz, 2H), 8.48 (dd, J = 7.6, 2.0 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.71-7.65 (m, 6H), 7.53 (t, J = 8.3 Hz, 2H), 4.73 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.88, 131.69, 131.27, 130.69, 130.48, 130.06, 129.17, 127.88, 127.81, 127.70, 127.23, 127.09, 125.27, 123.48, 122.81, 48.78. HRMS (ESI+) Calcd for $C_{31}H_{21}Br_2O^+$ $[M+H]^+$: 569.9840; Found: 569.9792.



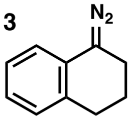
9

Diphenyl diazomethane (9). Prepared as a 0.89 M toluene solution in 85% yield from 1.82 g (10.0 mmol) of benzophenone by the known procedure.[24a] Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.



11

2,2-Diphenylacetaldehyde (11). The predominant product when using the representative procedure given above with 0.178 mmol of diphenyl diazomethane (0.200 mL of a 0.89 M solution, 1.0 equiv) and 8.9 mg of $Sc(OTf)_3$ (0.018 mmol, 0.10 equiv). Purification by silica gel chromatography (TLC R_f = 0.30 in 97.5:2.5 hexanes:ethyl acetate) gave 13.8 mg of the monoinsertion carbaldehyde adduct as a colorless oil in 79% yield. Characterization data was previously reported.[122]



13

1-Diazo-1,2,3,4-tetrahydronaphthalene (13). Prepared as a 0.37 M toluene solution in 80% yield from 55.0 mg (0.343 mmol) of α-tetralone hydrazone by the known procedure.[24a] Used in a homologation reaction immediately after its preparation, otherwise stored cold at –78 °C.

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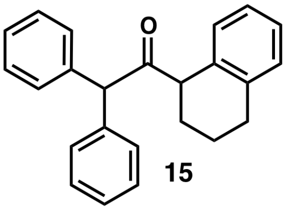
(122) "A Facile Work-up – Free Catalytic Rearrangement of Epoxides on Immobilized Organoaluminum Columns.," Nagahara, S.; Maruoka, K.; Yamamoto, H. *Chem. Lett.* **1992**, *21*, 1193-1196.

Representative Procedure for the Synthesis of Dissymmetric Ketones:

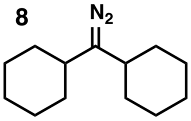


15

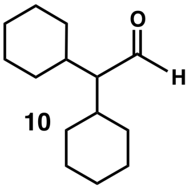
2,2-Diphenyl-1-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanone (15). To a stirring suspension of 38.2 mg (0.195 mmol) of 2,2-diphenylacetaldehyde and 9.8 mg of Sc(OTf)$_3$ (0.020 mmol, 0.10 equiv) in 2.0 mL toluene at –78 °C was added 0.214 mmol of 1-diazo-1,2,3,4-tetrahydronaphthalene (0.578 mL of a 0.37 M in solution in toluene, 1.1 equiv). After stirring for 10 min at –78 °C, the reaction mixture was diluted with 20 mL of Et$_2$O, poured into a separatory funnel, and washed three times with 20 mL of water and once with 20 mL of saturated sodium chloride before being dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (TLC R$_f$ = 0.33 in 97.5:2.5 hexanes:ethyl acetate) afforded 49.7 mg of **15** as a white solid in 78% yield (mp = 81 °C). IR (thin film): 3059 (m), 3026 (m), 2936 (m), 2867 (w), 1715 (s), 1658 (m), 1598 (w), 1494 (m), 1448 (m), 1317 (w), 1277 (m), 1075 (w), 1044 (w), 941 (w), 919 (w), 743 (m), 701 (s), 638 (m). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.81 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.33 (dd, *J* = 9.1, 5.6 Hz, 2H), 7.28 (d, *J* = 2.3 Hz, 2H), 7.21 (dd, *J* = 6.4, 4.7 Hz, 2H), 7.12 (d, *J* = 5.7 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 5.35 (s, 1H), 4.06 (t, *J* = 6.3 Hz, 1H), 2.75 (dd, *J* = 13.7, 6.9 Hz, 2H), 2.11-1.93 (m, 2H), 1.77 (dd, *J* = 74.1, 4.9 Hz, 2H). ^{13}C NMR (100

MHz, $CDCl_3$): δ 209.41, 139.11, 138.46, 138.12, 137.83, 133.63, 132.63, 130.28, 129.81, 129.59, 129.28, 129.13, 129.02, 128.65, 128.49, 127.50, 127.21, 127.11, 125.96, 61.98, 53.24, 29.31, 26.22, 20.64. HRMS (ESI+) Calcd for $C_{24}H_{23}O^+$ $[M+H]^+$: 327.1748; Found: 327.1774.

8

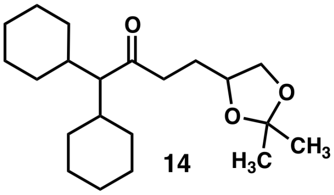


(Diazomethylene)dicyclohexane (8). Prepared as a 0.42 M toluene solution in 48% yield by following the general procedure for the synthesis of aliphatic diazoalkanes with 0.510 g (2.62 mmol) of dicyclohexylmethanone. Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at –78 °C.



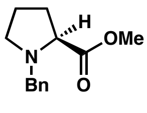
10

2,2-Dicyclohexylacetaldehyde (10). The near exclusive product when the representative procedure given above is applied with 1.36 mmol of **8** (3.24 mL of a 0.42 M solution in toluene, 1.0 equiv) and 66.9 mg of $Sc(OTf)_3$ (0.136 mmol, 0.10 equiv). Purification by silica gel chromatography (TLC R_f = 0.30 in 49:1 hexanes:ethyl acetate) gave 129 mg of **10** as a colorless oil (91% yield). IR (thin film): 2923 (s), 2851 (m), 1721 (m), 1447 (w), 991 (w). ^1H NMR (400 MHz, $CDCl_3$): δ 9.66 (d, *J* = 4.6 Hz, 1H), 1.89-1.57 (m, 13H), 1.35-1.07 (m, 6H), 1.10-0.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.82, 63.23, 35.65, 30.20, 26.74, 26.64. HRMS (ESI+) Calcd for $C_{14}H_{25}O^+$ $[M+H]^+$: 209.1824; Found: 209.1859.



14

1,1-Dicyclohexyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butan-2-one (14). Prepared by the general procedure given above for the synthesis of dissymmetric ketones from 25.1 mg of 2,2-dicyclohexylacetaldehyde (0.120 mmol), 0.132 mmol of 4-(2-diazoethyl)-2,2-dimethyl-1,3-dioxolane (0.281 mL of a 0.47 M solution in toluene, 1.1 equiv), 7.1 mg of Sc(tmhd)$_3$ (0.012 mmol, 0.10 equiv), and 1.2 mL of toluene (0.1 M). Purification by silica gel chromatography (TLC R$_f$ = 0.30 in 97.5:2.5 hexanes:ethyl acetate) afforded 27.5 mg of **14** as a colorless oil (68% yield). IR (thin film): 2920 (s), 2874 (m), 1719 (s), 1420 (w), 1347 (w), 1237 (w), 1009 (w), 984 (w), 955 (w), 928 (w). ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.11-4.09 (m, 1H), 3.64 (dd, *J* = 8.3, 6.0, 1 H), 3.58 (dd, *J* = 8.3, 6.7, 1H), 2.53-2.66 (m, 2H), 2.38-2.35 (m, 1H), 1.89-1.59 (m, 14H), 1.42 (s, 3H), 1.37 (s, 3H) 1.35-1.07 (m, 6H), 1.12-0.90 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 208.32, 108.81, 69.34, 63.23, 39.79, 35.58, 30.20, 29.91, 27.64, 26.90, 26.74, 26.64, 25.80. HRMS (ESI+) Calcd for $C_{14}H_{25}O^+$ [M+H]$^+$: 337.2588; Found: 337.2579.



(*S*)-Methyl 1-benzylpyrrolidine-2-carboxylate. Prepared according to a previously disclosed method[123] in which acetylchloride (9.26 mL, 130 mmol) was added dropwise with stirring to a

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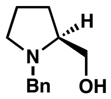
(123) Trost, B. M.; Ito, H. "Catalytic Compositions and Methods for Asymmetric Aldol Reactions." U.S. Patent 147367-A1, 2002.

0 °C solution of (*S*)-proline (5.00 g, 43.4 mmol) in methanol (80 mL). After the addition, the ice bath was removed and the stirring was continued for 15 h at 23 °C. Volatile organics were then removed under reduced pressure and the residual oil was redissolved in dry acetonitrile (70 mL). Triethylamine (18.0 mL, 130 mmol) and benzyl bromide (6.20 mL, 52.1 mmol, 1.2 equiv) was added to give a white suspension. After 12 h of stirring at 23 °C, the acetonitrile was evaporated and the residue was partitioned between saturated ammonium chloride (200 mL) and Et_2O (200 mL). The phases were separated and the aqueous layer was washed twice with 40 mL of Et_2O. The pooled organic layers were washed with equal volumes of water and saturated sodium chloride, dried over magnesium sulfate, and concentrated. Purification by silica gel chromatography (TLC R_f = 0.30 in 92:8 hexanes:ethyl acetate) gave 6.37 g of a colorless oil (69% yield). Spectroscopic data was in full agreement with the previously reported values.[124]



(*S*)-(1-Benzylpyrrolidin-2-yl)methanol (27). To a solution of lithium aluminum hydride (0.570 g, 15.1 mmol, 1.1 equiv) in THF (10 mL) at 0 °C was added (*S*)-methyl 1-benzylpyrrolidine-2-carboxylate (3.00 g, 13.7 mmol, 1.00 equiv) in THF (25 mL) dropwise with rapid stirring. The reaction mixture was warmed slowly to 23 °C and stirred for 6 h. The mixture was then diluted with 15 mL of Et_2O, transferred to a

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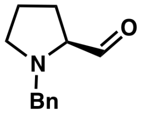
(124) "A Catalytic Enantioselective Synthesis of Denopamine, a Useful Drug for Congestive Heart Failure," Corey, E. J.; Link, J. O. *J. Org. Chem*. **1991**, *56*, 442-444.

separatory funnel, and washed with 50 mL volumes of saturated ammonium chloride and saturated sodium chloride. Before being discarded, the pooled aqueous washes were back-extracted extracted with 50 mL of Et_2O. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford 2.46 g of a colorless oil (12.9 mmol, 94% yield) whose spectral data matched that reported in the literature[125] and was used without further purification.



(*S*)-1-Benzylpyrrolidine-2-carbaldehyde. Prepared by the known procedure[126] by adding a DCM solution (11 mL, 1.5 M) of $(COCl)_2$ (1.445 mL, 16.56 mmol, 1.51 equiv) dropwise to a stirring –78 °C solution of DMSO (2.18 mL, 32.90 mmol, 3.00 equiv) in methylene chloride (22 mL, 1.5 M). Stirring was continued at this temperature for 45 min, then a methylene chloride (18 mL, 0.5 M) solution of (*S*)-(1-benzylpyrrolidin-2-yl)methanol (2 mL, 10.97 mmol, 1.00 equiv) was added slowly over 10 min. This mixture was stirred for 20 min at –78 °C, then triethylamine (6.16 mL, 43.87 mmol, 4.00 equiv) was added and the reaction was warmed to 0 °C and stirred for 2h. The reaction was then transferred to a seperatory funnel for DCM extraction with water, $NaHCO_3$ saturated sol. and brine washes. The organic layers were combined and

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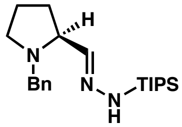
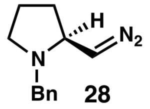
(125) "Highly Efficient Copper-Catalyzed N-Arylation of Nitrogen-Containing Heterocycles with Aryl and Heteroaryl Halides," Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737-2743.

(126) "Photochemical Reaction between Tertiary Allylic Amines and Chromium Carbene Complexes: Synthesis of Lactams via a Zwitterion Aza Cope Rearrangement," Deur, C. J.; Miller, M. W.; Hegedus, L. S. *J. Org. Chem.* **1996**, *61*, 2871-2876.

dried with Na_2SO_4, filtered and the volatile organics were then removed under reduced pressure to afford 1.89 g of a colorless oil (9.98 mmol, 91%), which was used without further purification.



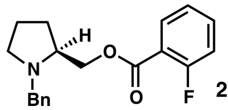
(*S*)-1-Benzyl-2-((2-triisopropylsilyl) hydrazono) methyl) pyrrolidine. Prepared by the known procedure for aliphatic triisopropylhydrazone synthesis[2a] by slow addition of triisopropylhydrazine (0.78 g, 4.19 mmol, 1.50 equiv) to a 0 °C solution of (*S*)-1-benzylpyrrolidine-2-carbaldehyde (0.53 g, 2.79 mmol, 1.00 equiv) in THF (4.0 mL, 0.7 M) with extensively flame-dried 4 Å molecular sieves (0.53 g, 1:1 w/w) while rapidly stirring. This was brought to ambient temperature and allowed to stir under an argon atmosphere for 36 h. Then the reaction medium was filtered through a cotton plug and the product was isolated upon removal of volatile organics under reduced pressure. The clear oil (1.00 g, >99%) was used immediately without further purification.



28

(*S*)-1-Benzyl-2-(diazomethyl)pyrrolidine (28). Swern: To a THF solution (4 mL, 0.04 M) of (*S,E*)-1-benzyl-2-((2-triisopropylsilyl)hydrazono)methyl)pyrrolidine (0.055 g, 0.154 mmol, 1.00 equiv) was added a 1 M solution of TBAF (0.15 mL, 0.155 mmol, 1.01 equiv) at 0 °C with rapid stirring. After 10 min of stirring at 0 °C, the THF was removed under reduced pressure. Prior to the preparation of the deprotected hydrazone, a methylene chloride solution (0.155 mL, 1.5 M) of $(COCl)_2$ (0.021 mL, 0.232 mmol, 1.51 equiv) dropwise to a stirring –78 °C solution of DMSO (0.031 mL, 0.462 mmol, 3.00 equiv) in methylene chloride (0.3 mL, 1.5 M). Stirring was continued at this temperature for 45 min, then a methylene chloride (0.3 mL, 0.5 M) solution of the freshly prepared free hydrazone was added slowly over 10 min. This mixture was stirred for 20 min at –78 °C, then triethylamine (6.16 mL, 43.87 mmol, 4.00 equiv) was added and the reaction was warmed to 0 °C and stirred for 30 min. The reaction was then transferred to a seperatory funnel for methylene chloride extraction with water, $NaHCO_3$ saturated sol. and brine washes. The organic layers were combined and dried with Na_2SO_4, filtered and the volatile organics were then removed under reduced pressure to leave a yellow oil that was redissolved in toluene (1 mL). An aliquot (0.100 mL) of this diazo solution was taken into an esterification reaction as previously described determine the active titer (33% yield).

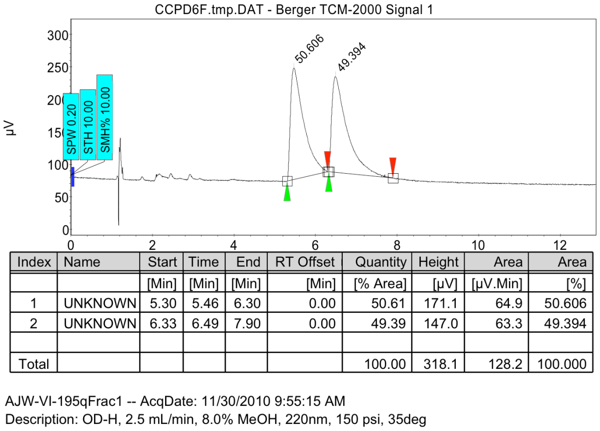
Note: (*S*)-1-Benzyl-2-(diazomethyl)pyrrolidine (26) could also be prepared reliably (32-36% yield) according to the general procedure for the synthesis of aliphatic diazoalkanes with $Pb(OAc)_4$. The diazoalkane was used in reaction with formaldehyde immediately following the preparation of a concentrated solution in toluene and titration with 2-fluorobenzoic acid.



29

(*S*)-(1-Benzylpyrrolidin-2-yl)methyl 2-fluorobenzoate (29). To obtain appreciable amounts of the desired benzoate, the esterification reaction was conducted as follows. Thus, 400 µL of the 0.45 M diazoalkane stock solution (0.18 mmol, 1.00 equiv) is added to a 2-fluorobenzoic acid (25.2 mg, 0.18 mmol, 1.0 equiv) solution in Et_2O (0.50 mL, 0.36 M) at –45 °C dropwise by syringe. Upon slow warming from –45 °C, the reaction mixture became colorless and nitrogen evolution was observed. The solvent is then removed under reduced pressure and the crude product is further purified by silica gel column chromatography (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate) affording the ketone product as a viscous, colorless oil (56 mg, 99%, 99% ee). $[\alpha]^{23}_{D}$ = –59.6 (c = 0.80 g • cm^{-3}, in $CHCl_3$) IR (thin film): 2950 (m), 2843 (w), 2779 (m), 1712 (s), 1612 (m), 1488 (m), 1454 (m), 1293 (s), 1247 (s), 1228 (m), 1157 (m), 1124 (m), 1081 (s), 1033 (s), 967 (w), 754 (s), 691 (w), 655 (w). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (td, *J* = 7.6, 1.8, 1H), 7.55-7.49 (m, 1H), 7.38 (d, *J* = 7.0, 2H), 7.33 (t, *J* = 7.3, 2H), 7.26 (t, *J* = 7.3, 1H), 7.21 (td, *J* = 7.7, 1.1, 1H), 7.15 (ddd, *J* = 10.7, 8.4, 1.0, 1H), 4.37 (qd, *J* = 11.0, 5.7, 2H), 4.21 (d, *J* = 13.1, 1H), 3.49 (d, *J* = 13.1, 1H), 3.06-2.94 (m, 2H), 2.32 (ddd, *J* = 9.1, 6.0, 2.3, 1H), 2.12-2.01 (m, 1H), 1.87-(m, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.42, 164.39, 163.01, 160.94, 139.68, 134.44, 134.37, 132.15, 132.14, 128.83, 128.21, 126.86, 123.96, 123.93, 118.97, 118.90, 117.08, 116.90, 68.02, 61.98, 59.49, 54.49, 28.65, 23.03. HRMS (ESI+) Calcd for $C_{19}H_{21}FNO_2^+$ $[M+H]^+$: 314.1568; Found 314.1556.

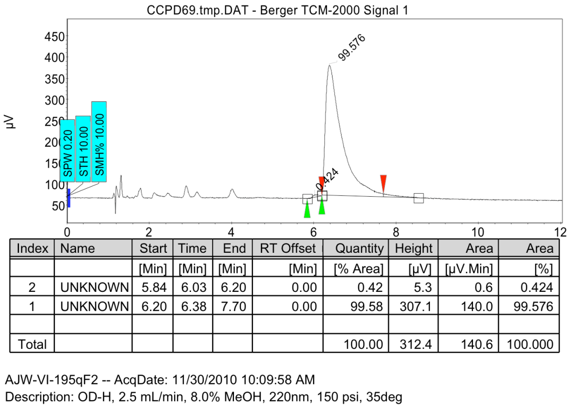
Racemic **29**:



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	5.30	5.46	6.30	0.00	50.61	171.1	64.9	50.606
2	UNKNOWN	6.33	6.49	7.90	0.00	49.39	147.0	63.3	49.394
Total						100.00	318.1	128.2	100.000

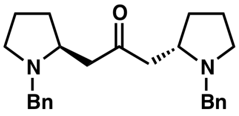
AJW-VI-195qFrac1 -- AcqDate: 11/30/2010 9:55:15 AM
Description: OD-H, 2.5 mL/min, 8.0% MeOH, 220nm, 150 psi, 35deg

Enantioenriched **29:**



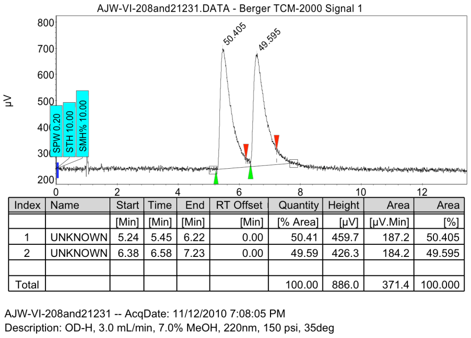
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
2	UNKNOWN	5.84	6.03	6.20	0.00	0.42	5.3	0.6	0.424
1	UNKNOWN	6.20	6.38	7.70	0.00	99.58	307.1	140.0	99.576
Total						100.00	312.4	140.6	100.000

AJW-VI-195qF2 -- AcqDate: 11/30/2010 10:09:58 AM
Description: OD-H, 2.5 mL/min, 8.0% MeOH, 220nm, 150 psi, 35deg



1,3-Bis((*S*)-1-benzylpyrrolidin-2-yl)propan-2-one. Prepared according to the general procedure for bidirectional synthesis of ketones. Purified by SiO_2 column chromatography (TLC R_f = 0.30 in 70:30 hexanes:ethyl acetate) affording a colorless oil (31 mg, 58%, 98% ee). $[\alpha]_D^{23}$ = –35.2 (c = 1.53 g • cm^{-3}, in $CHCl_3$)IR (thin film): 3086 (m), 3058 (w), 3027 (m), 2966 (m), 2872 (m), 1711 (s), 1601 (m), 1495 (m), 1444 (m), 1370 (w), 1317 (w), 1262 (w), 1221 (w), 1167 (m), 1078 (m), 1043 (w), 1029 (m), 908 (w), 807 (w), 718 (w), 697 (s), 615 (m). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 10H), 3.90 (d, *J* = 13.1, 2H), 3.47 (d, *J* = 13.1, 2H), 3.01 (dd, *J* = 8.8, 7.4, 2H), 2.88-2.80 (m, 2H), 2.48-2.36 (m, 4H), 2.36-2.25 (m, 2H), 2.17-2.04 (m, 2H), 1.92-1.80 (m, 2H), 1.80-1.68 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 209.52, 138.12, 129.20, 128.46, 127.33, 62.91, 61.51, 56.36, 53.03, 35.10, 25.04. HRMS (ESI+) Calcd for $C_{25}H_{33}N_2O^+$ [M+H]$^+$: 377.2612; Found 377.2593.

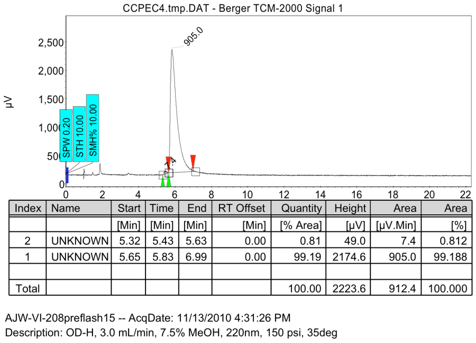
Racemic: *N*-benzylcuscohygrine



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	5.24	5.45	6.22	0.00	50.41	459.7	187.2	50.405
2	UNKNOWN	6.38	6.58	7.23	0.00	49.59	426.3	184.2	49.595
Total						100.00	886.0	371.4	100.000

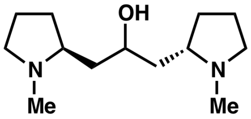
AJW-VI-208and21231 -- AcqDate: 11/12/2010 7:08:05 PM
Description: OD-H, 3.0 mL/min, 7.0% MeOH, 220nm, 150 psi, 35deg

Enantioenriched: *N*-benzylcuscohygrine from (*S*)-proline:



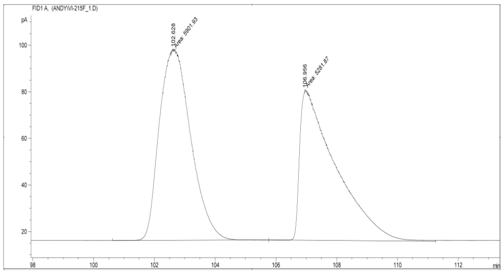
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
2	UNKNOWN	5.32	5.43	5.63	0.00	0.81	49.0	7.4	0.812
1	UNKNOWN	5.65	5.83	6.99	0.00	99.19	2174.6	905.0	99.188
Total						100.00	2223.6	912.4	100.000

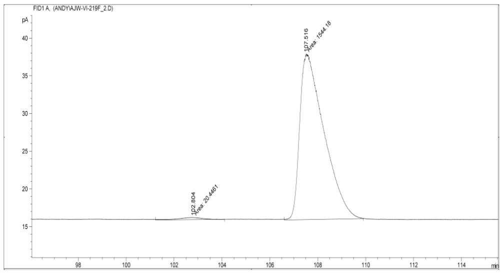
AJW-VI-208preflash15 -- AcqDate: 11/13/2010 4:31:26 PM
Description: OD-H, 3.0 mL/min, 7.5% MeOH, 220nm, 150 psi, 35deg



1

(–)-Dihydrocuscohygrine (1). To a solution of Pd/C (10% w/w) in methanol (1 mL) was added the crude 1,3-bis((*S*)-1-benzylpyrrolidin-2-yl)propan-2-one (0.156 mmol theoretical) in dry methanol (2.6 mL, 0.06M based on theoretical) via cannula under argon atmosphere. The reaction vial was then purged with hydrogen gas and the 1 atm environment was maintained for 16 h at ambient temperature. The reaction mixture was then filtered through a pad of neutral alumina under argon atmosphere using standard Schlenk techniques. The crude product in methanol was then added dropwise to a flame-dried 5 mL round-bottom flask that contained a stirring solution of 30 μL formic acid (0.0.78 mmol, 5 equiv) in a 37% formaldehyde solution (0.23 mL, 20 equiv) at ambient temperature. This light yellow reaction mixture was then heated at 80 °C for 6 h and then recooled to RT for extraction into cold $CHCl_3$ and the organic layer was washed with a cold 1N NaOH solution (3x), the organic layer was separated and dried with Na_2SO_4, filtered and the solvent was removed to leave a yellow oil, which was further purified with silica gel chromatography (TLC R_f = 0.38 in 5:4:1 hexanes/DCM/Et_2NH) to give the product alcohol as a colorless oil that rapidly yellows upon RT standing (7.6 mg, 0.034 mmol, 43% yield over three steps). $[\alpha]^{23}_D = -102$ (c = 0.76 g • cm^{-3}, acetone) IR (thin film): 3254 (m,b), 2937 (s), 2839 (m), 2781 (s), 1658 (w), 1547 (w), 1543 (s), 1370 (m), 1352 (w), 1289 (w), 1209 (m), 1110 (m), 1037 (s), 957 (w), 901 (m), 827 (m), 745 (w), 700 (w), 575 (w), 459 (w). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.12-4.03 (m, 1H), 3.07 (t, J = 7.8, 2H), 2.41-2.36 (m, 2H), 2.35 (s, 6H), 2.14 (td, J = 9.4, 7.7, 2H), 2.00-1.89 (m, 2H), 1.83-1.76 (m, 2H), 1.75-1.65 (m, 4H), 1.63-1.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.42, 64.49, 57.33, 41.00, 39.35, 30.27, 23.12 HRMS (ESI+) Calcd for $C_{13}H_{27}N_2O^+$ $[M+H]^+$: 227.2112; Found 227.2123. Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (99:1 e.r. sample below; CDBDM column, 15 psi, 120 °C).





#	Time	Area	Height	Width	Area%	#	Time	Area	Height	Width	Area%
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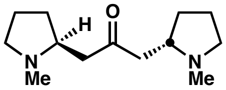
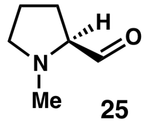
2	106.96	5281.9	64.7	1.3611	47.228	2	107.52	1544.2	22	1.1706	98.693



(±)-Cuscohygrine (2). Following the procedure of Stapper and Blechert,[110] to a stirring solution of 1,3-bis((*S*)-1-methylpyrrolidin-2-yl)propan-2-ol **29** (7 mg, 0.031 mmol, 1 equiv) in acetone (0.2 mL, 0.15 M) at 0 °C was added freshly prepared Jones' reagent (0.034 mL, 0.062 mmol, 2.0 equiv). The reaction mixture was then stirred for 1 h at the temperature. Then an ice-cold solution of saturated $NaHCO_3$ was added in equal volume to the reaction vessel to quench, followed by a cold extraction with chloroform and a –20 °C solution of 30 % KOH to wash the organic layer. The chloroform layer was then separated, dried with Na_2SO_4, filtered and the solvent was removed to leave a yellow oil, which was further purified (TLC R_f = 0.26 in 5:4:1 hexanes/DCM/Et_2NH) to give the product **30** as a colorless oil (5.6 mg, 0.025 mmol, 81%). The racemic material, which undergoes the known epimerization mechanism[111] was immediately characterized.[125] IR (thin film): 3386 (m), 2924 (s), 2853 (m), 2780 (m), 1712 (s), 1456 (m), 1375 (m) 1210 (w), 1115 (w), 1031 (w), 966 (w), 906 (w). ^{1}H NMR (400

MHz, $CDCl_3$): δ = 3.13-3.04 (m, 2H), 2.88-2.79 (m, 2H), 2.68-2.43 (m, 4H), 2.33 (s, 6H), 2.27-2.18 (m, 2H), 2.16-2.01 (m, 2H), 1.86-1.66 (m, 4H), 1.50-1.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.67, 208.58, 61.99, 61.91, 56.82, 48.20, 48.12, 40.60, 40.57, 31.38 , 22.22 HRMS (ESI+) Calcd for $C_{13}H_{25}N_2O^+$ $[M+H]^+$: 225.1959; Found 225.1967.


25

(*S*)-1-Methylpyrrolidine-2-carbaldehyde (25). Prepared according to the known procedure by adding $(COCl)_2$ (0.179 mL, 2.05 mmol, 1.025 equiv) dropwise to a stirring –78 °C solution of DMSO (0.150 mL, 2.11 mmol, 1.055 equiv) in methylene chloride (3 mL, 0.70 M). Stirring was continued at this temperature for 20 min, then at –50 °C a methylene chloride (1 mL, 2.0 M) solution of (*S*)-(1-methylpyrrolidin-2-yl)methanol[127] (230 mg, 2.00 mmol, 1.00 equiv) was added dropwise down the sidewalls of the reaction vessel. This mixture was stirred for 30 min at –50 °C, then the cooling bath was changed to –78 °C for the triethylamine (0.307 mL, 2.20 mmol, 1.10 equiv) addition to the center of the reaction solution, and the reaction was warmed to –60 °C and stirred for 30 min. Pentane was then added to the reaction mixture for 10 min of stirring, then the septa was removed for Celite filtration with multiple pentane rinses the volatile organics were then removed under reduced pressure to afford 0.196 g of a colorless oil (1.73 mmol, 86%), which was

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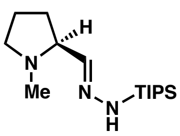
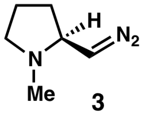
(127) "NMR Spectroscopy in Distinguishing Between 3-Piperidyl- and 2-Pyrrolidylmethyl Alcohols, Amines, Esters, and Amides," Cannon, J.G.; Milne, L.D. *J. Het. Chem.* **1976**, *13*, 686-689.

kept under nitrogen atmosphere at all times and used without further purification.

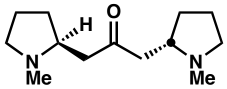


(*S*)-1-Methyl-2-((2-triisopropylsilyl)hydrazono)methyl) pyrrolidine. Prepared according to the known procedure for aliphatic triisopropylhydrazone synthesis[2a] by slow addition of triisopropylhydrazine (0.489 g, 2.59 mmol, 1.50 equiv) to a 0 °C solution of (*S*)-1-methylpyrrolidine-2-carbaldehyde (0.196 g, 1.73 mmol, 1.00 equiv) in THF (3.5 mL, 0.5 M) with extensively flame-dried 4 Å molecular sieves (0.20 g, 1:1 w/w) while rapidly stirring. This was brought to ambient temperature and allowed to stir under an argon atmosphere for 36 h. Then the reaction medium was filtered through a cotton plug and the product was isolated upon removal of volatile organics under reduced pressure. The light yellow oil (0.485 g, 99%) was used immediately without further purification.

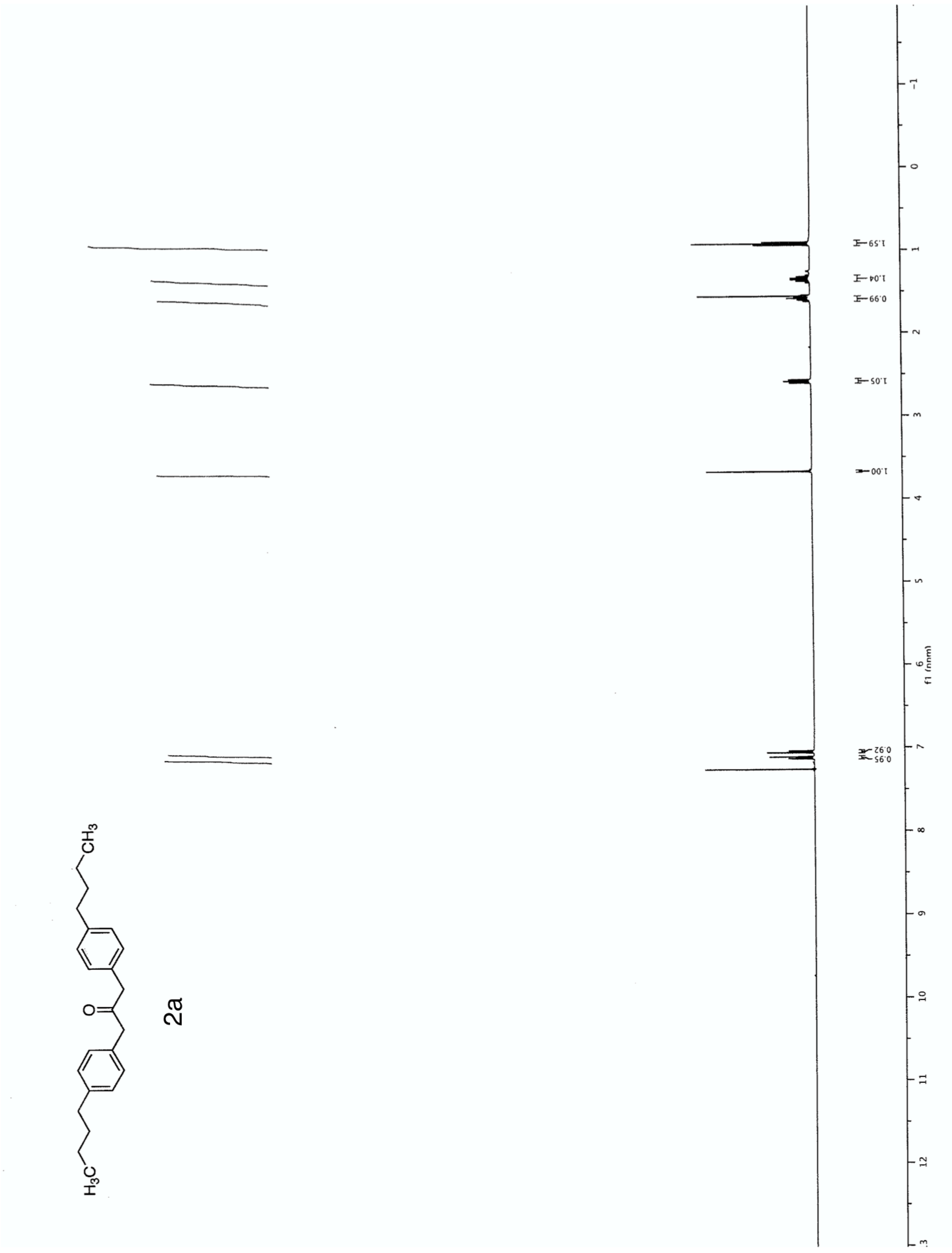


3

(*S*)-1-Methyl-2-(diazomethyl)pyrrolidine (3). Prepared as a 0.21 M solution in toluene (23% yield) by the general procedure for the synthesis of aliphatic diazoalkanes using 0.485 g of (*S,E*)-1-methyl-2-((2-triisopropylsilyl)hydrazono)methyl)pyrrolidine (2.05 mmol). Used in the homologation reaction with formaldehyde immediately following the preparation of a concentrated solution in toluene and titration.

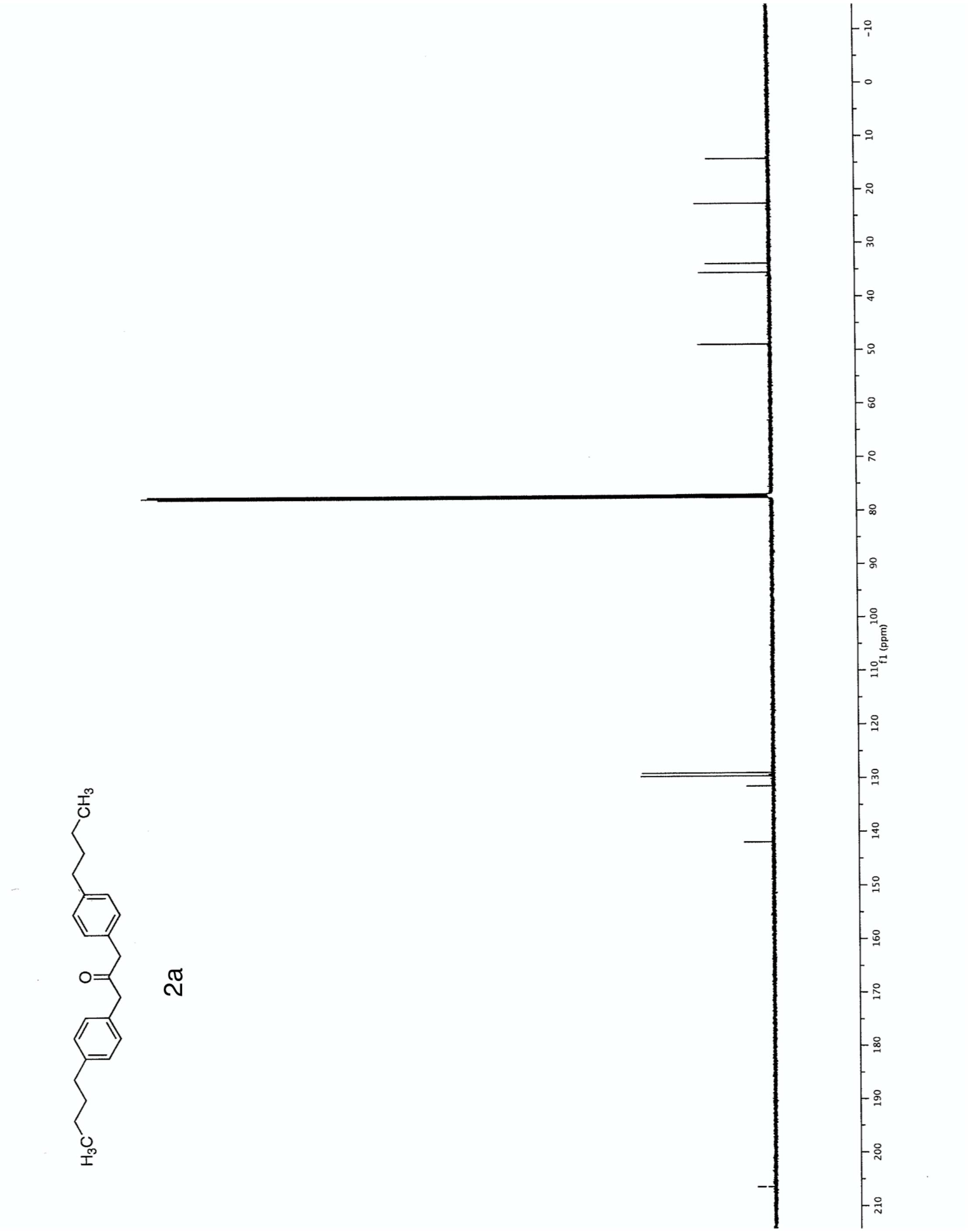


(±)-Cuscohygrine (2). Prepared according to the general procedure for bidirectional synthesis of ketones using 2 mL of (*S*)-1-Methyl-2-(diazomethyl)pyrrolidine (0.410 mmol, 0.33 M, 1.00 equiv) and 19.6 mg Sc(OTf)$_3$ (0.041 mmol, 0.10 equiv). Purified by neutral alumina column chromatography (TLC R_f = 0.31 in 5:4:3 hexanes/DCM/Et$_3$N) affording a colorless oil in 18% yield (8.3 mg). Characterization data is documented above and has been previously described.[110,125]



2a

H3C
CH3
O
1.59
1.04
0.99
1.05
1.00
0.92
0.95
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)



2a

H$_3$C
CH$_3$
O
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
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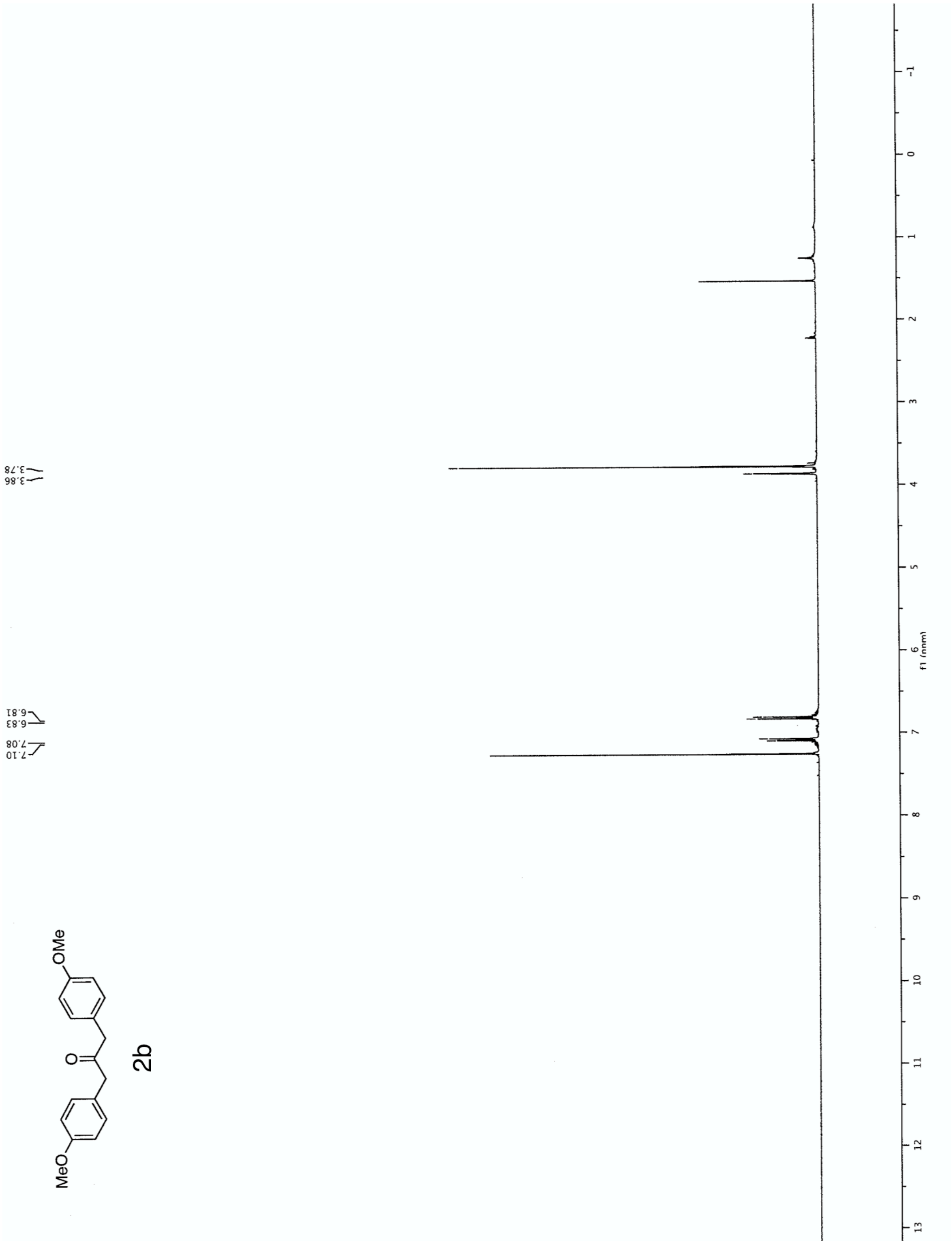
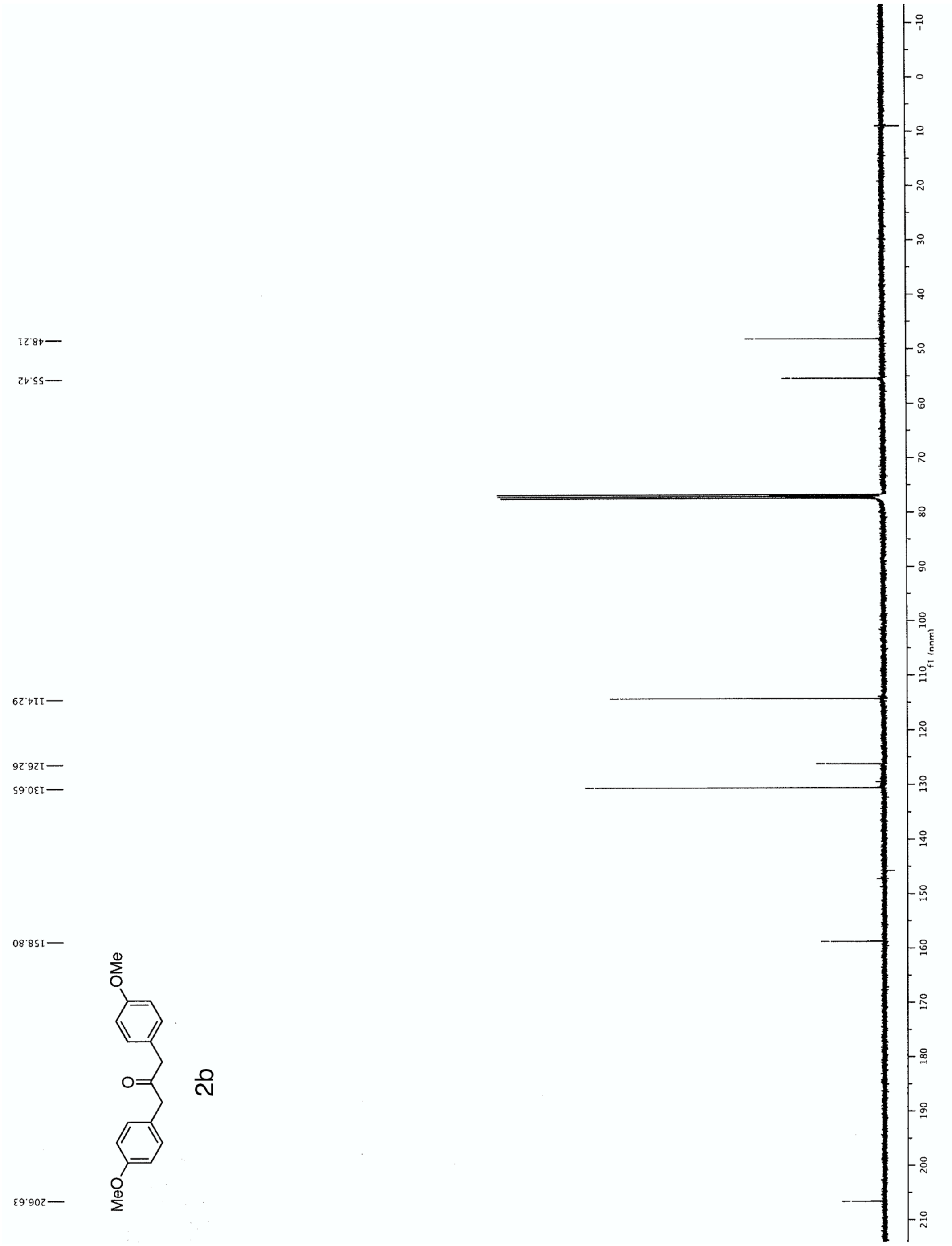
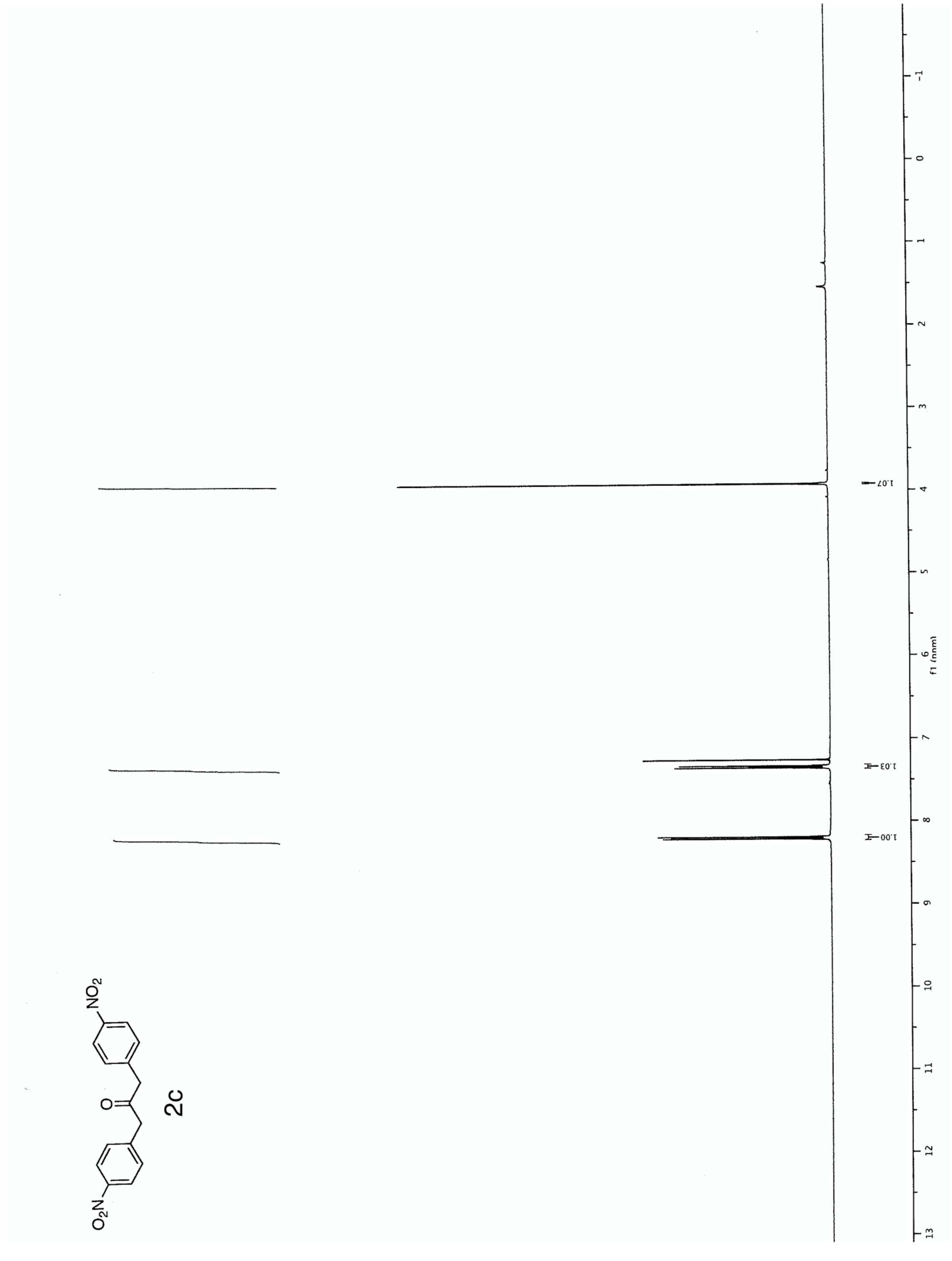
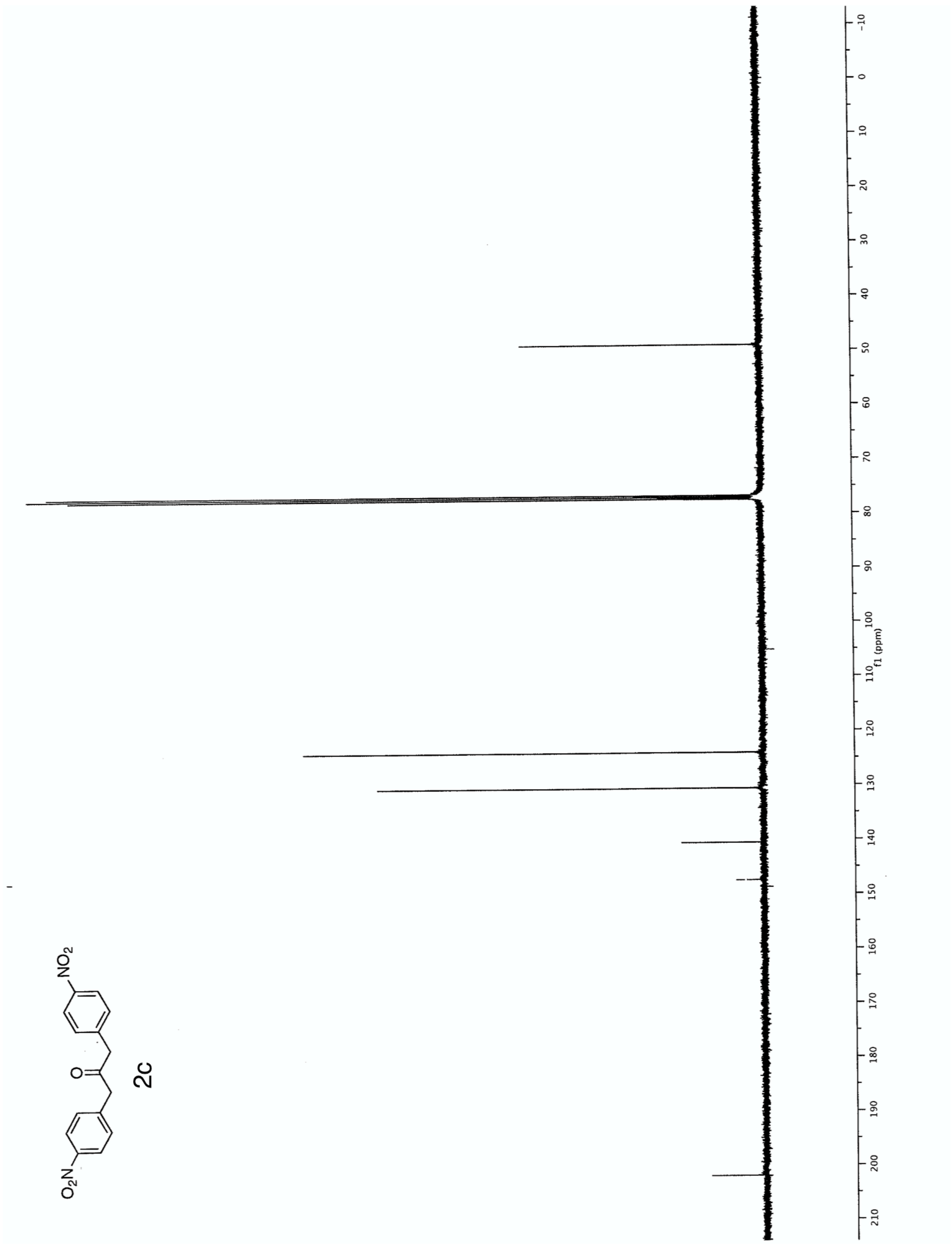
160
170
180
190
200
210


MeO
O
OMe
2b
3.78
3.86
6.81
6.83
7.08
7.10
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


2b
206.63
158.80
130.65
126.26
114.29
55.42
48.21
MeO
O
OMe
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

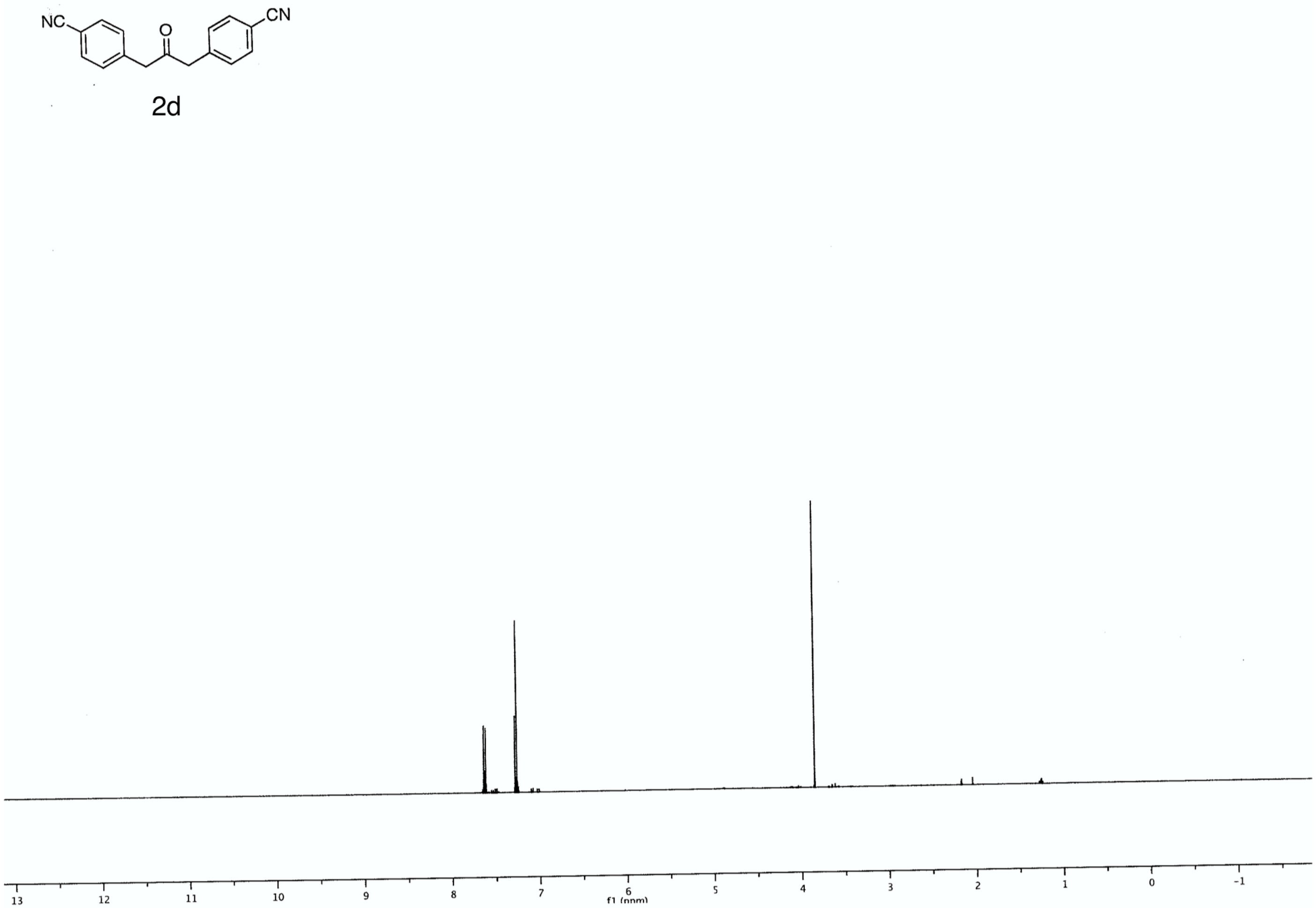


O$_2$N
NO$_2$
O
2c
1.07
1.03
1.00
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)

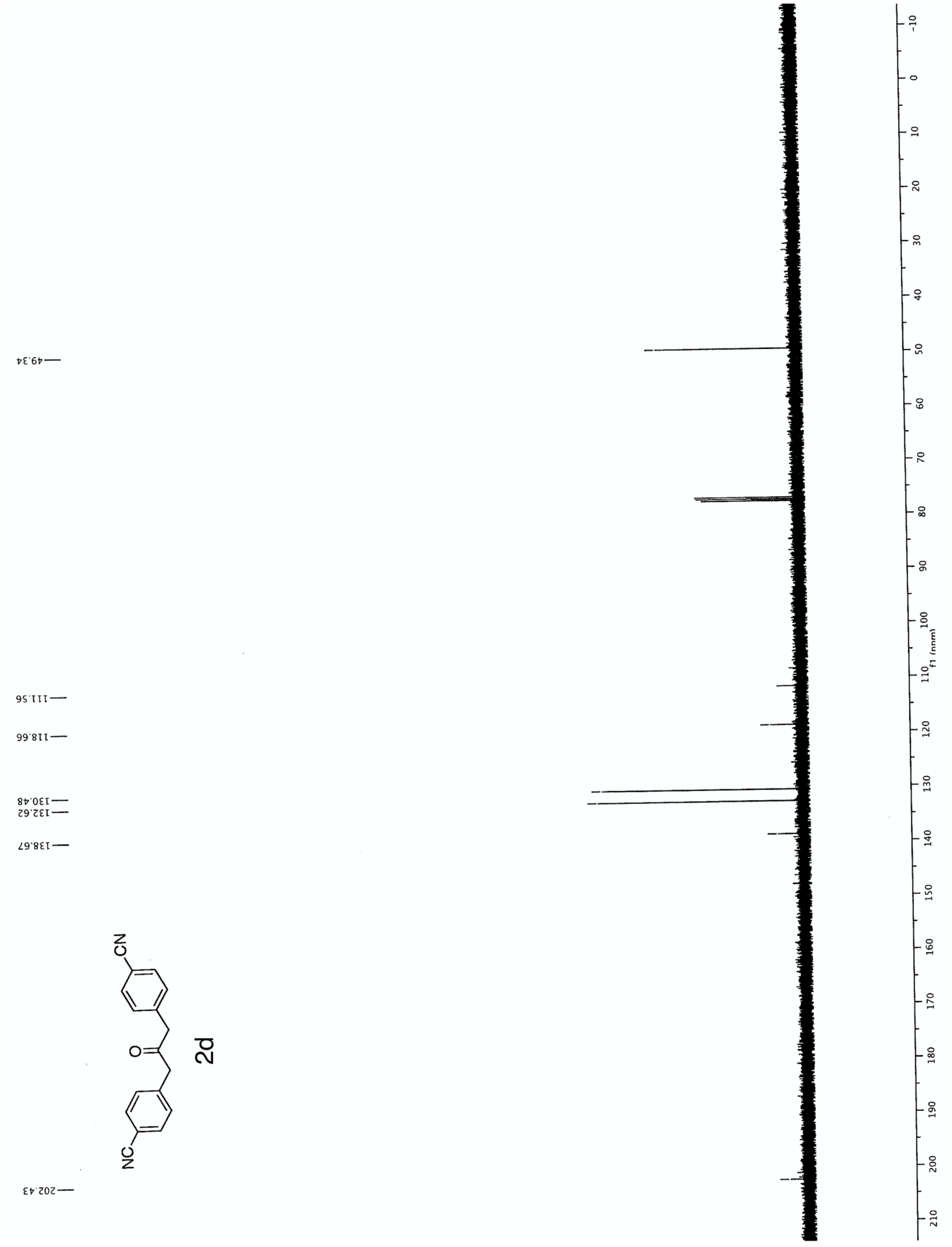


O₂N
O
NO₂
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

2c



2d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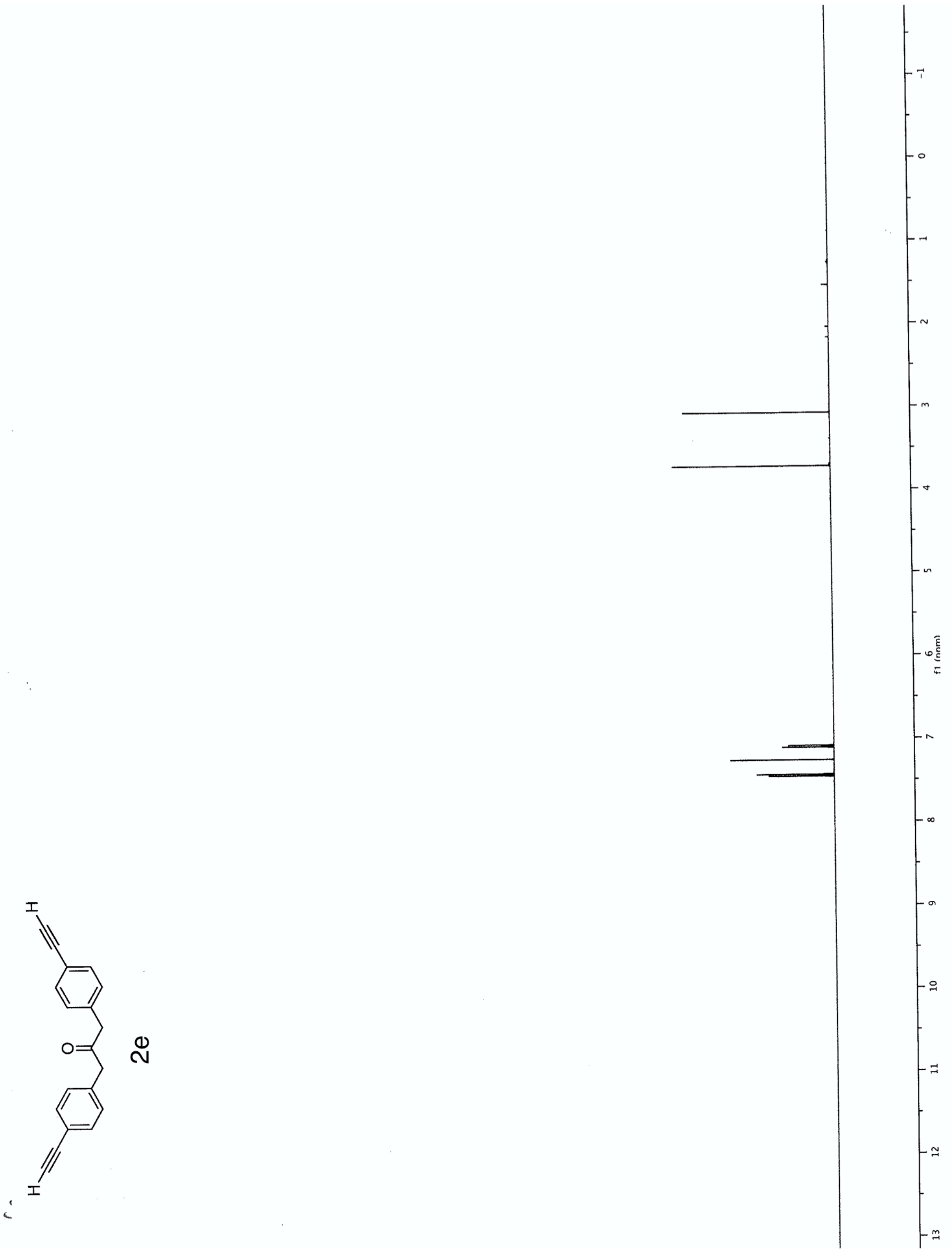
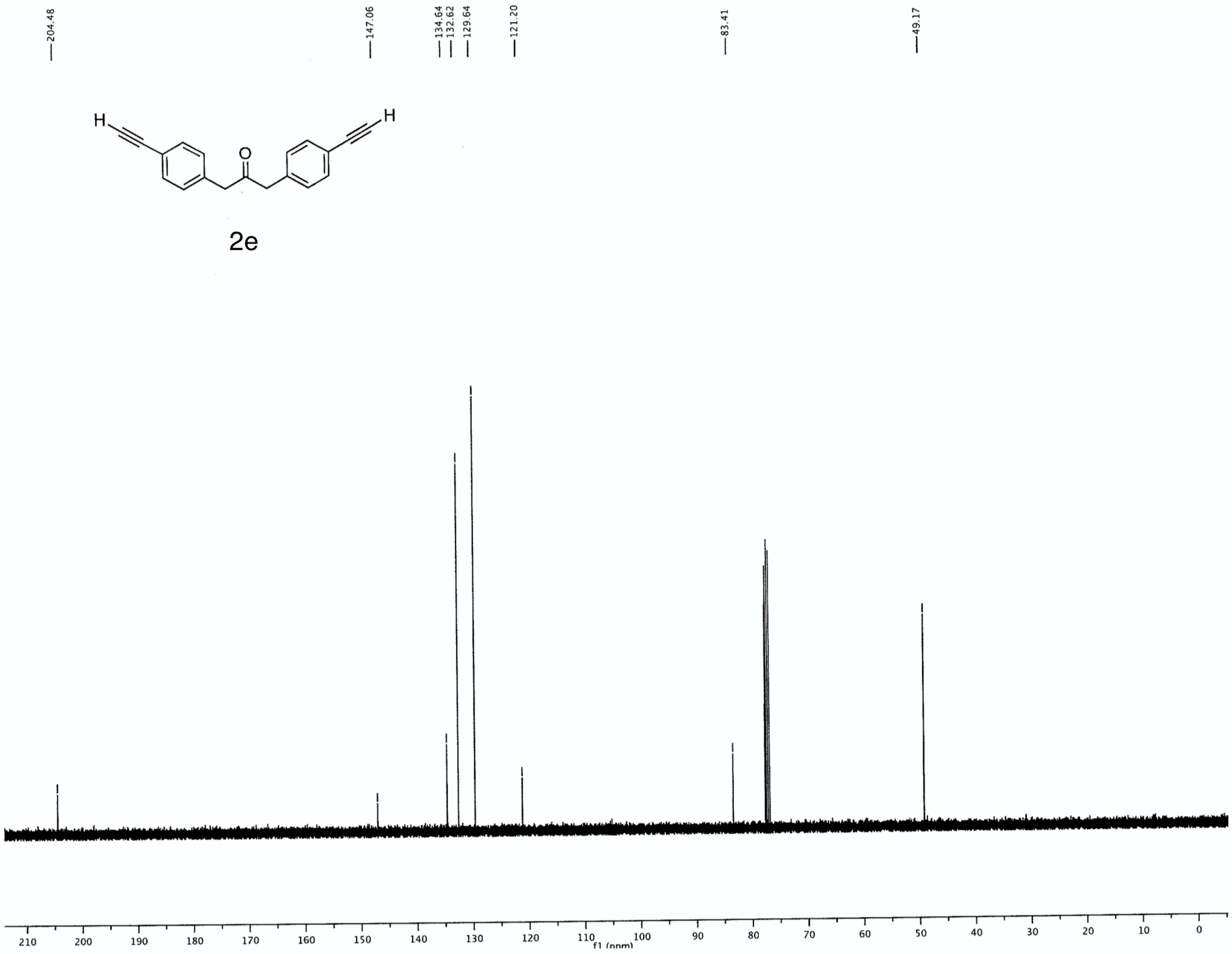
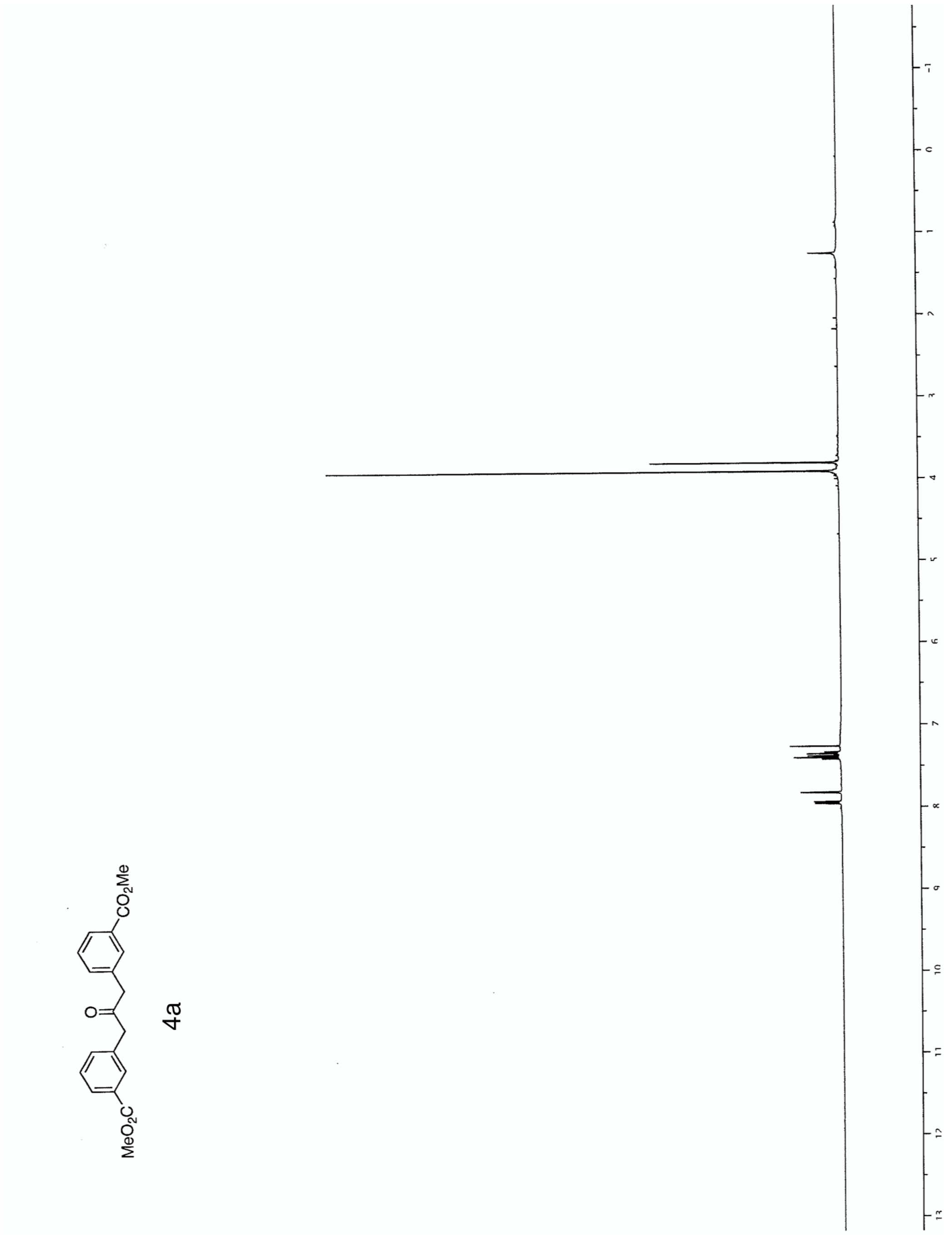
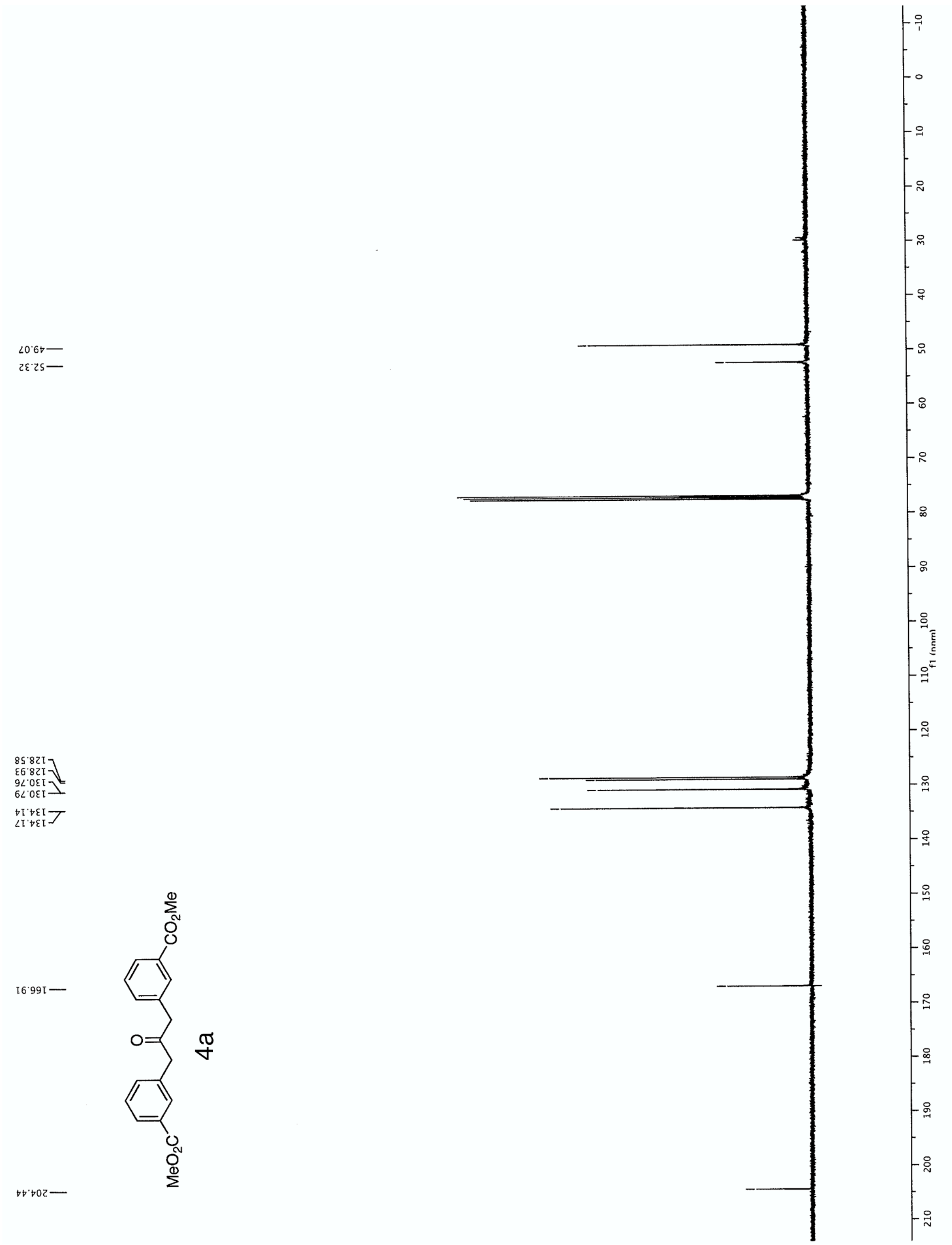
138.67
132.62
130.48
118.66
111.56
49.34
NC
CN
O
2d
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

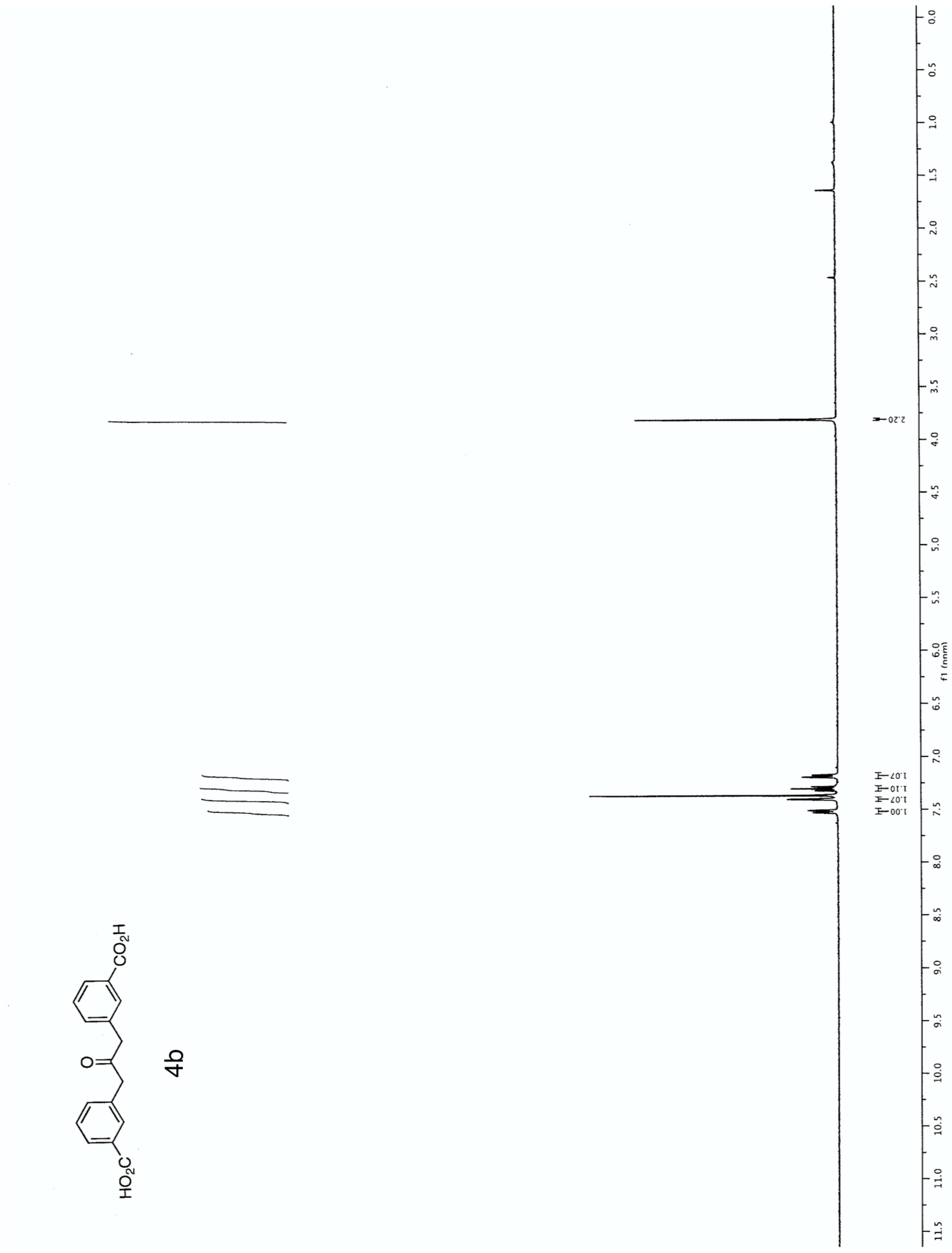

2e

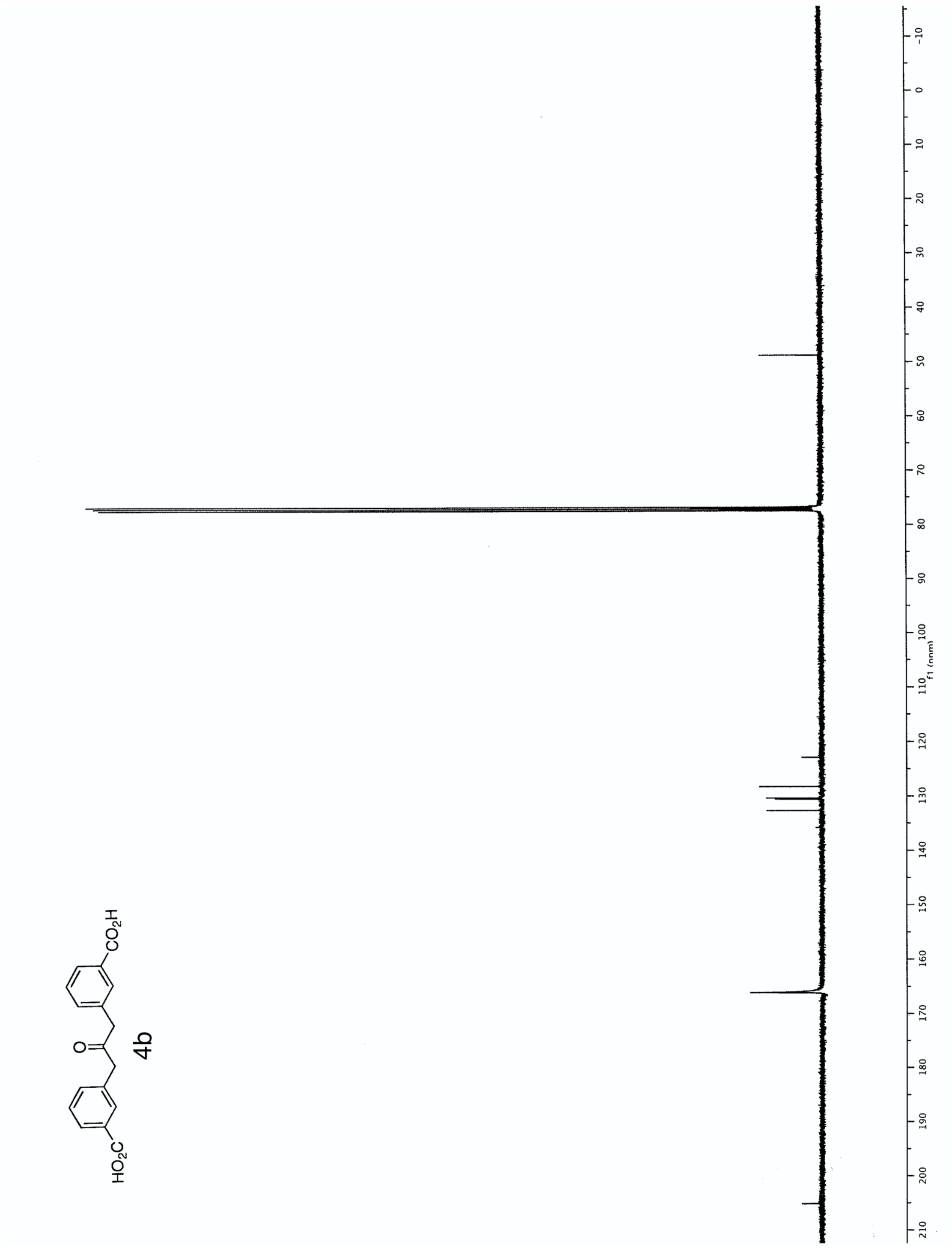

204.48
147.06
134.64
132.62
129.64
121.20
83.41
49.17
H
O
H
2e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



4a

204.44
166.91
134.17
134.14
130.79
130.76
128.93
128.58
52.32
49.07
MeO2C
O
CO2Me
4a
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


HO$_2$C
O
CO$_2$H
4b
2.20
1.07
1.10
1.07
1.00
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


4b

HO$_2$C
CO$_2$H
O
-10
0
10
20
30
40
50
60
70
80
90
100
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120
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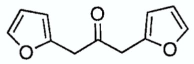
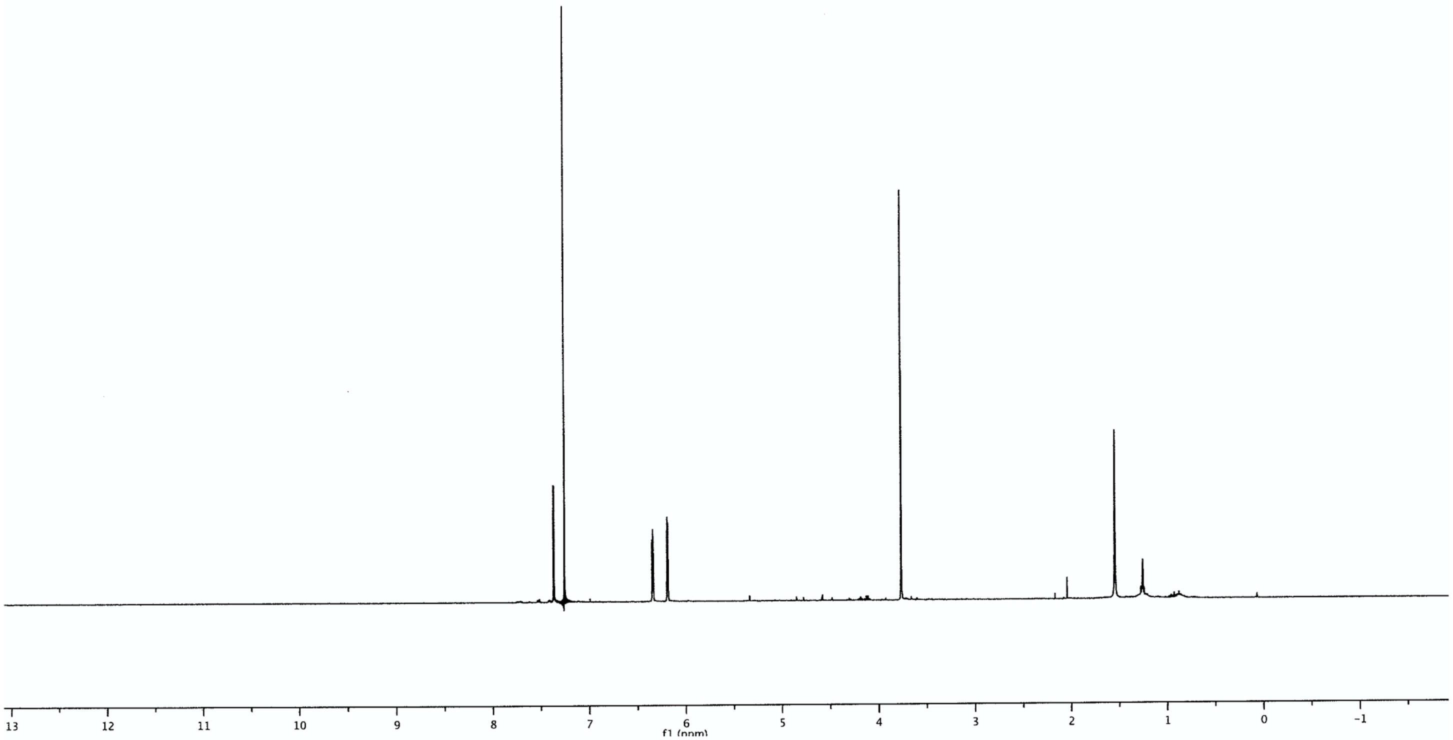
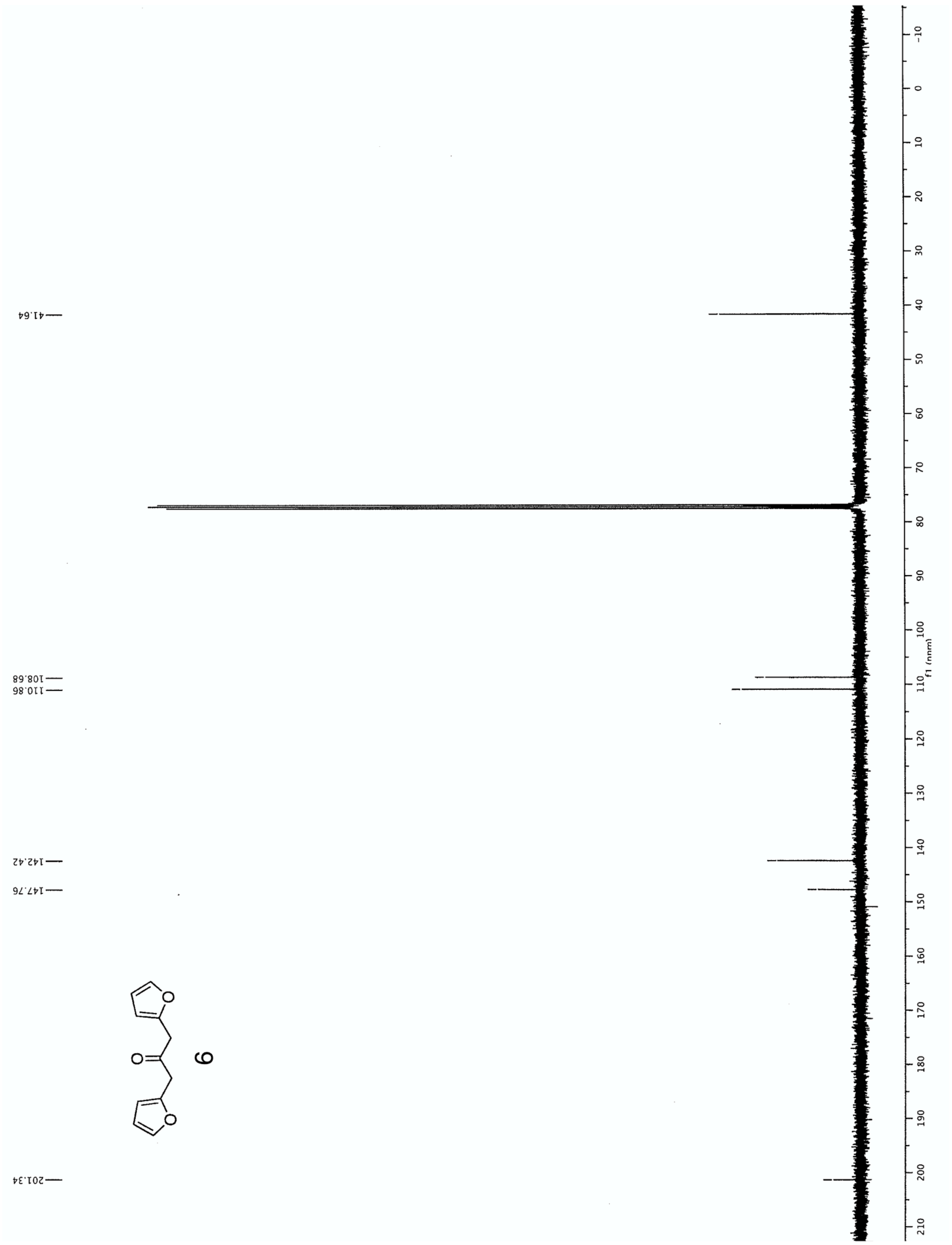
180
190
200
210
f1 (ppm)



6




201.34
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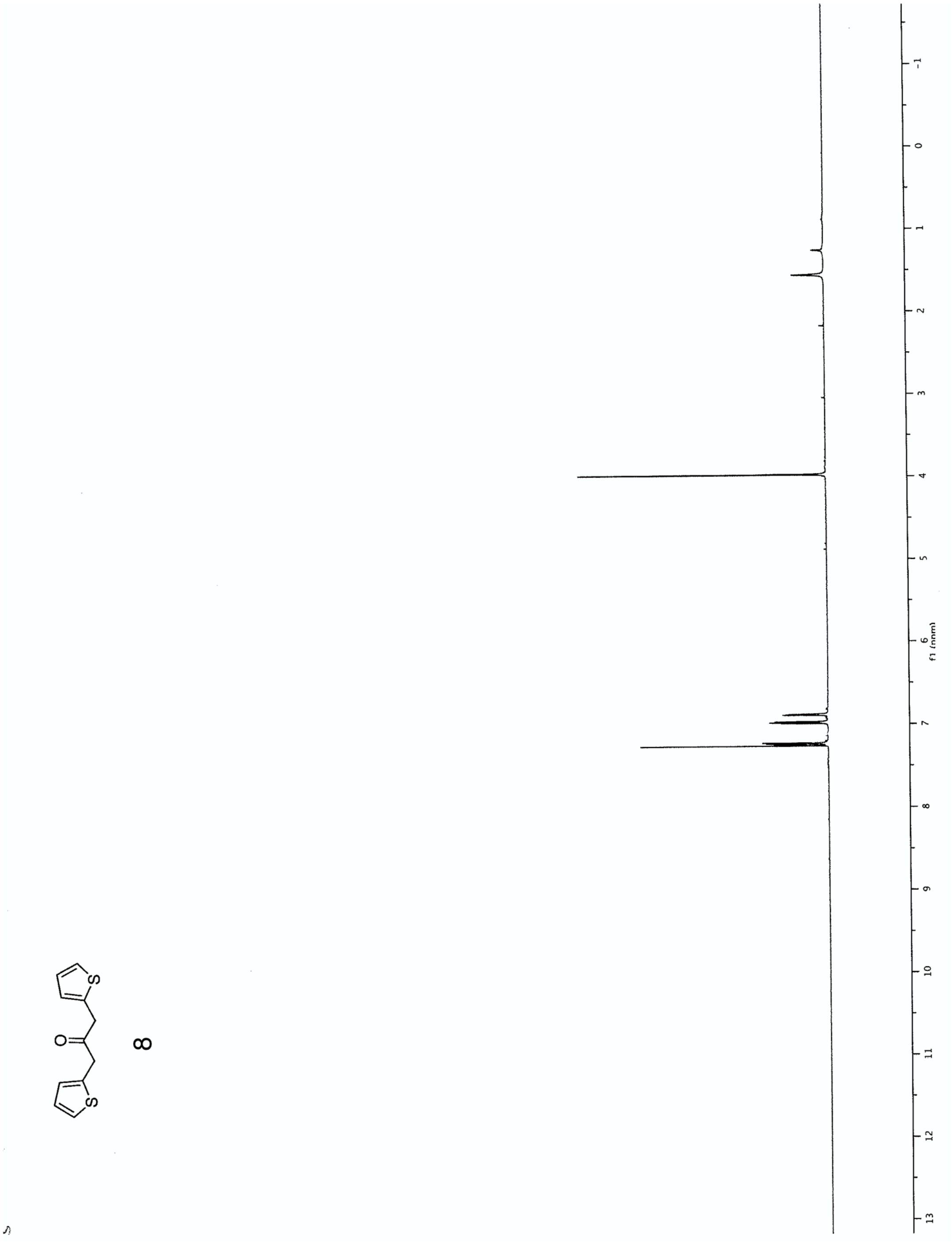
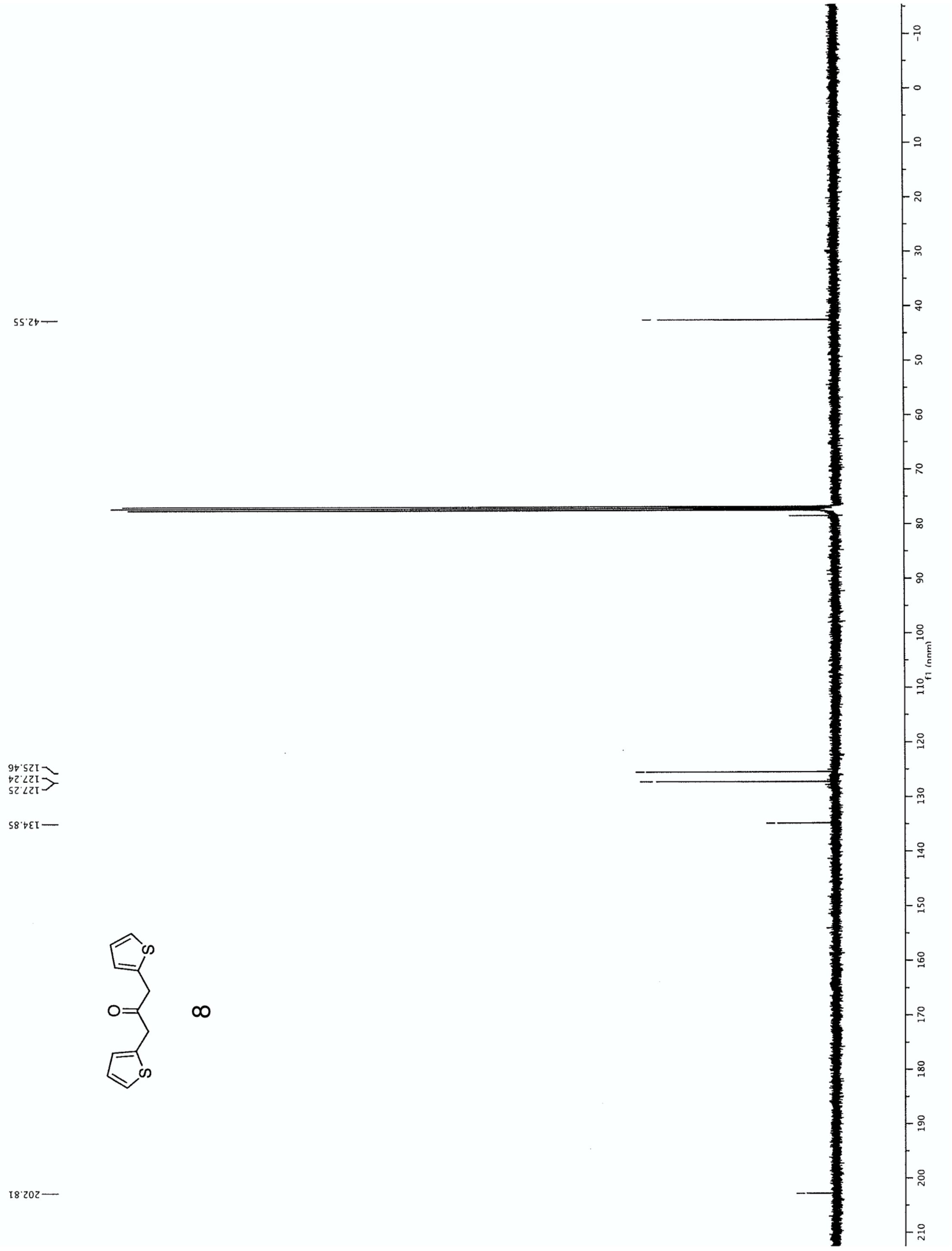
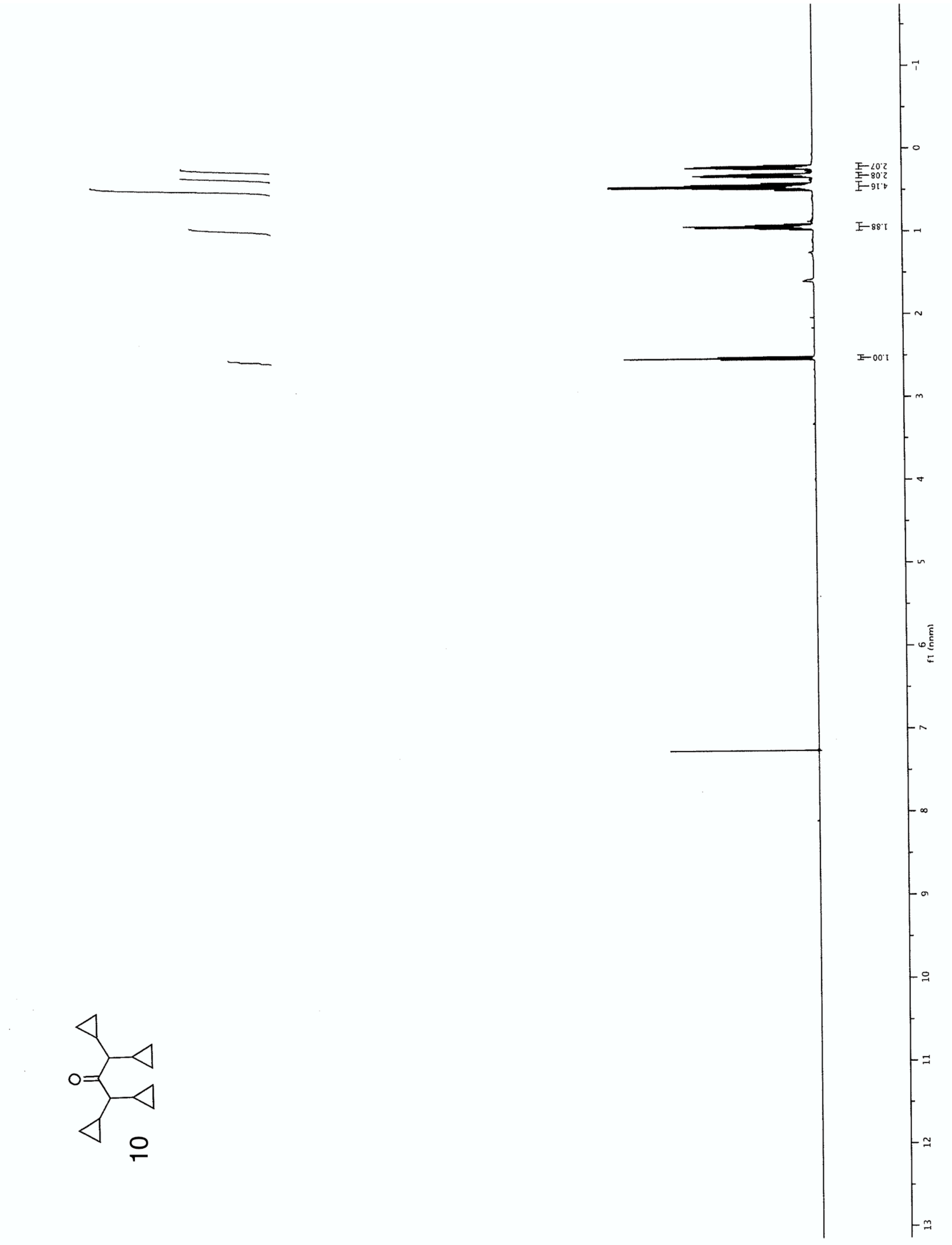
142.42
110.86
108.68
41.64
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

6

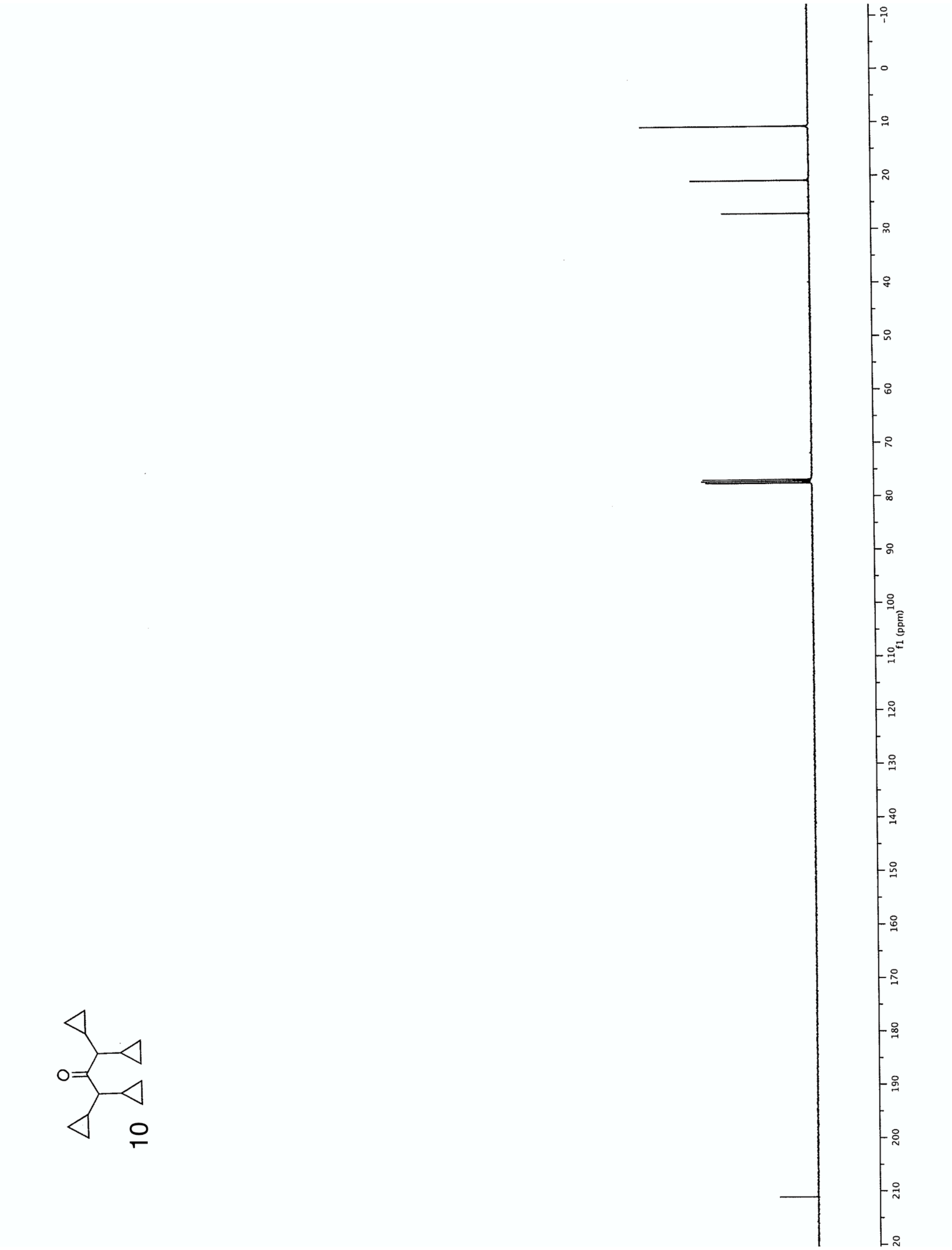

8

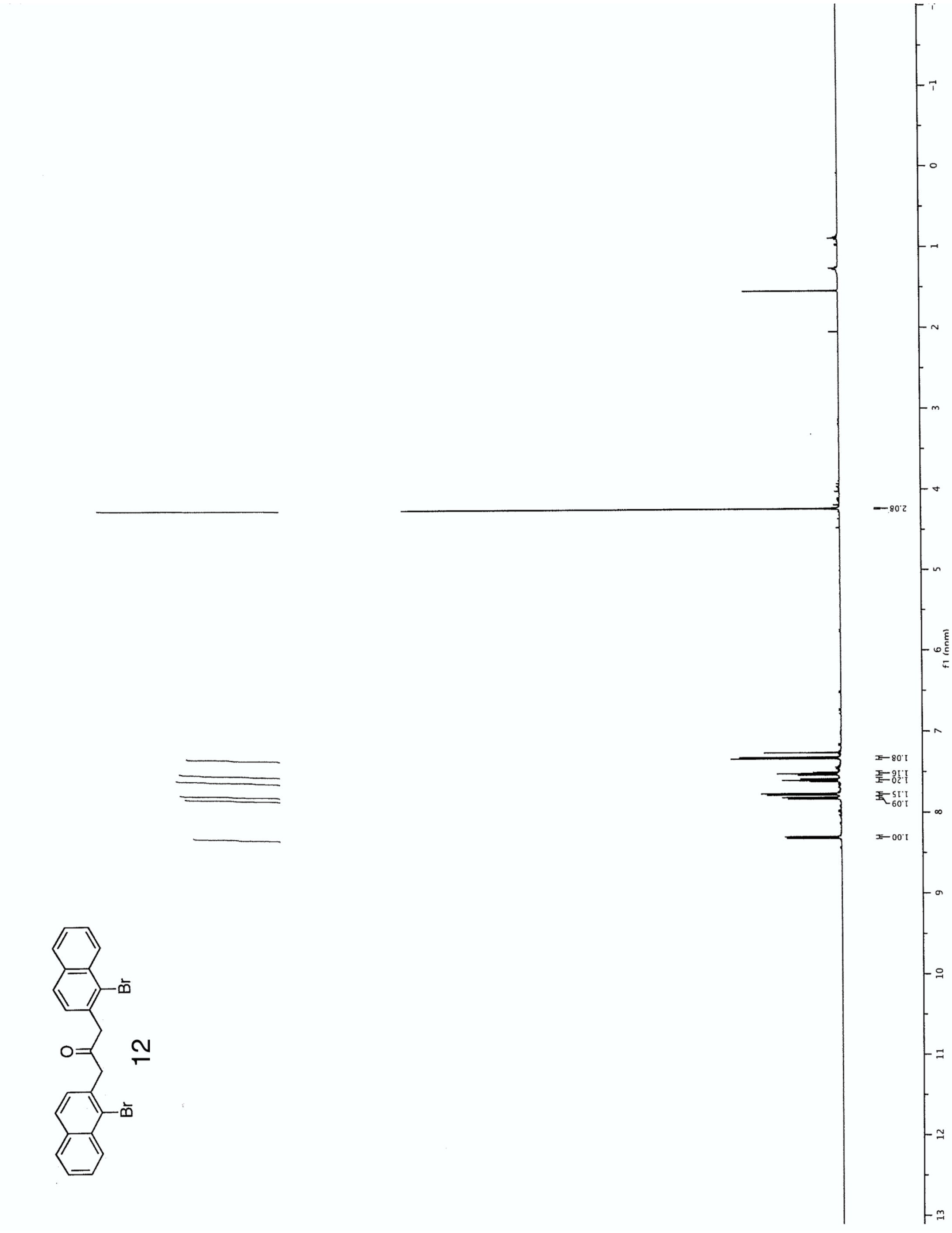

8

42.55
125.46
127.24
127.25
134.85
202.81
O
S
S
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)



10


10
-10
0
10
20
30
40
50
60
70
80
90
100
110
f1 (ppm)
120
130
140
150
160
170
180
190
200
210
20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Br
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1.15
1.09
1.00
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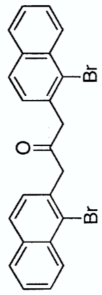
10
9
8
7
6
f1 (ppm)
5
4
3
2
1
0
-1

12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Br
Br

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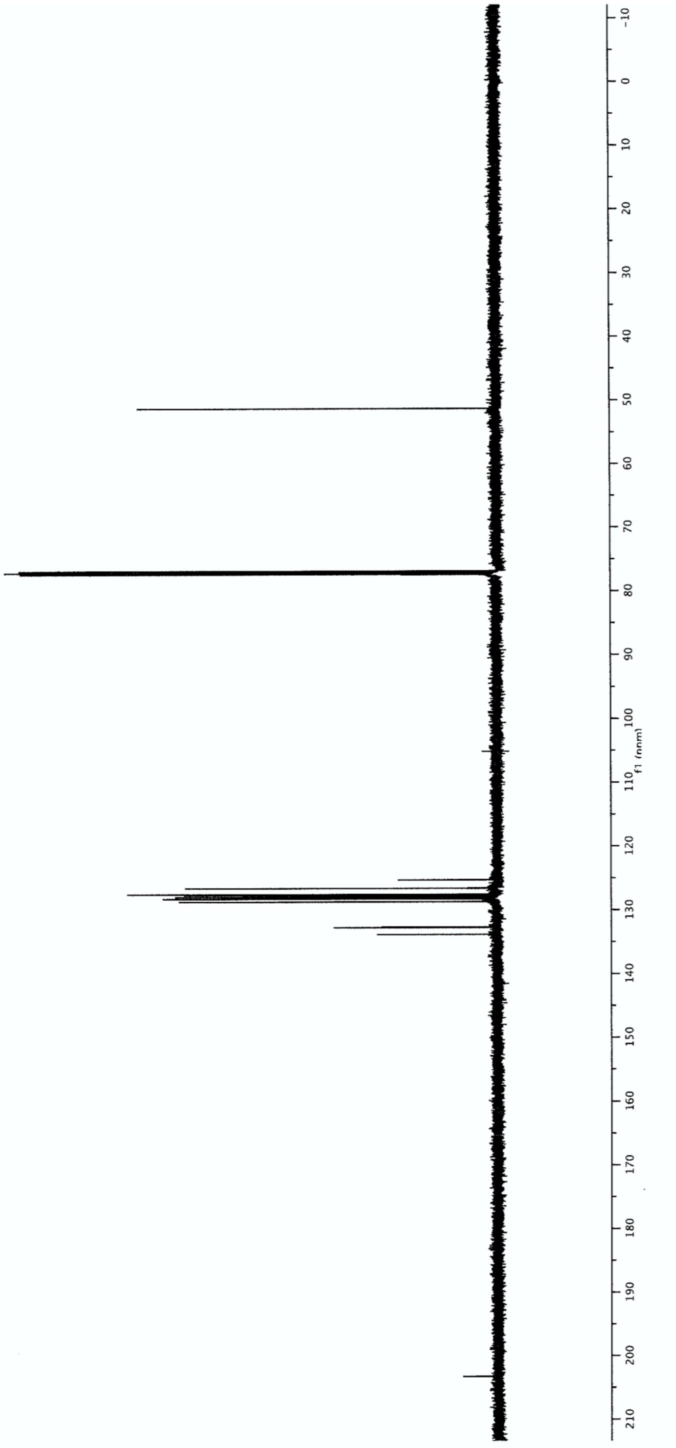
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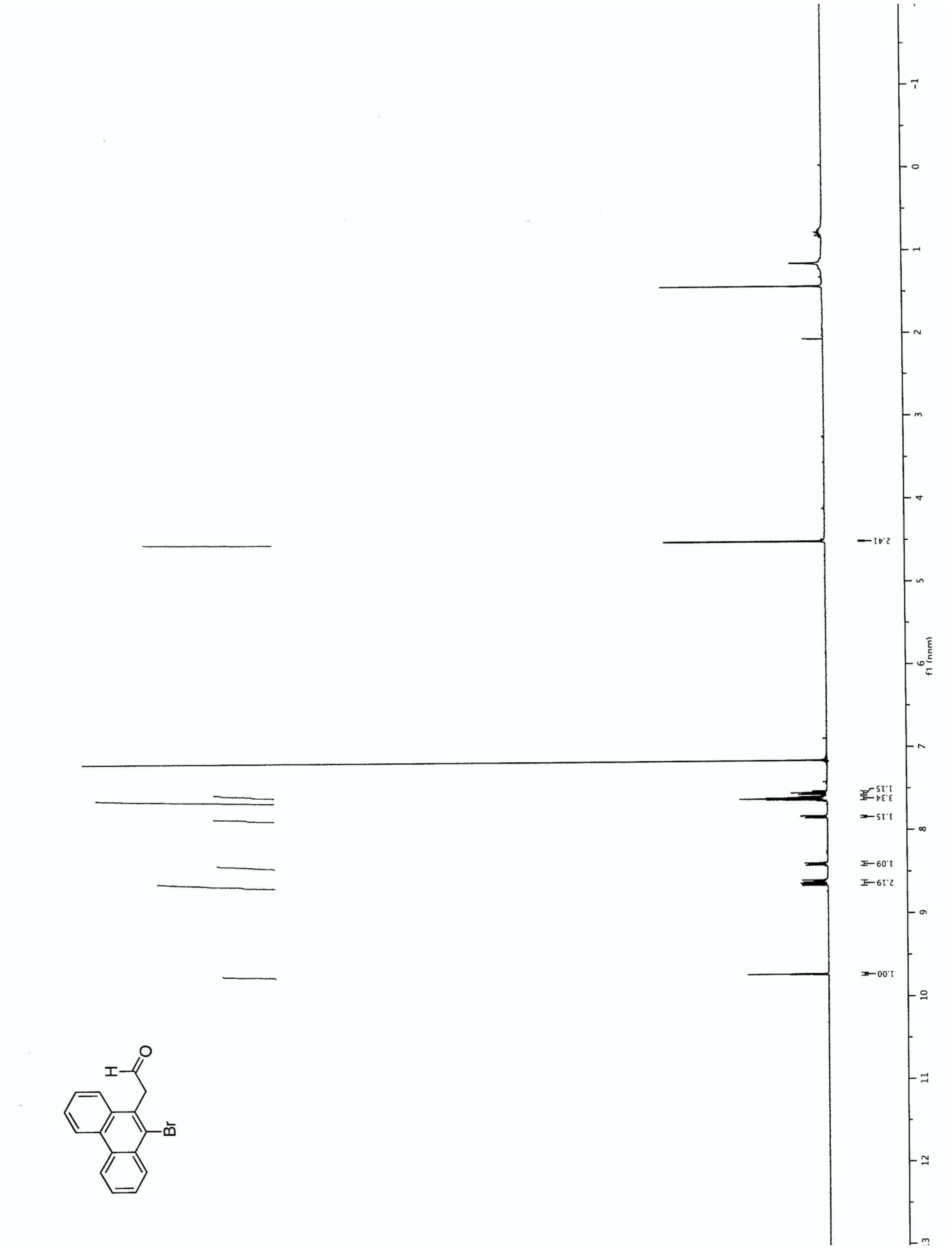
f1 (ppm)



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1.15
3.34
1.15
2.41
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11
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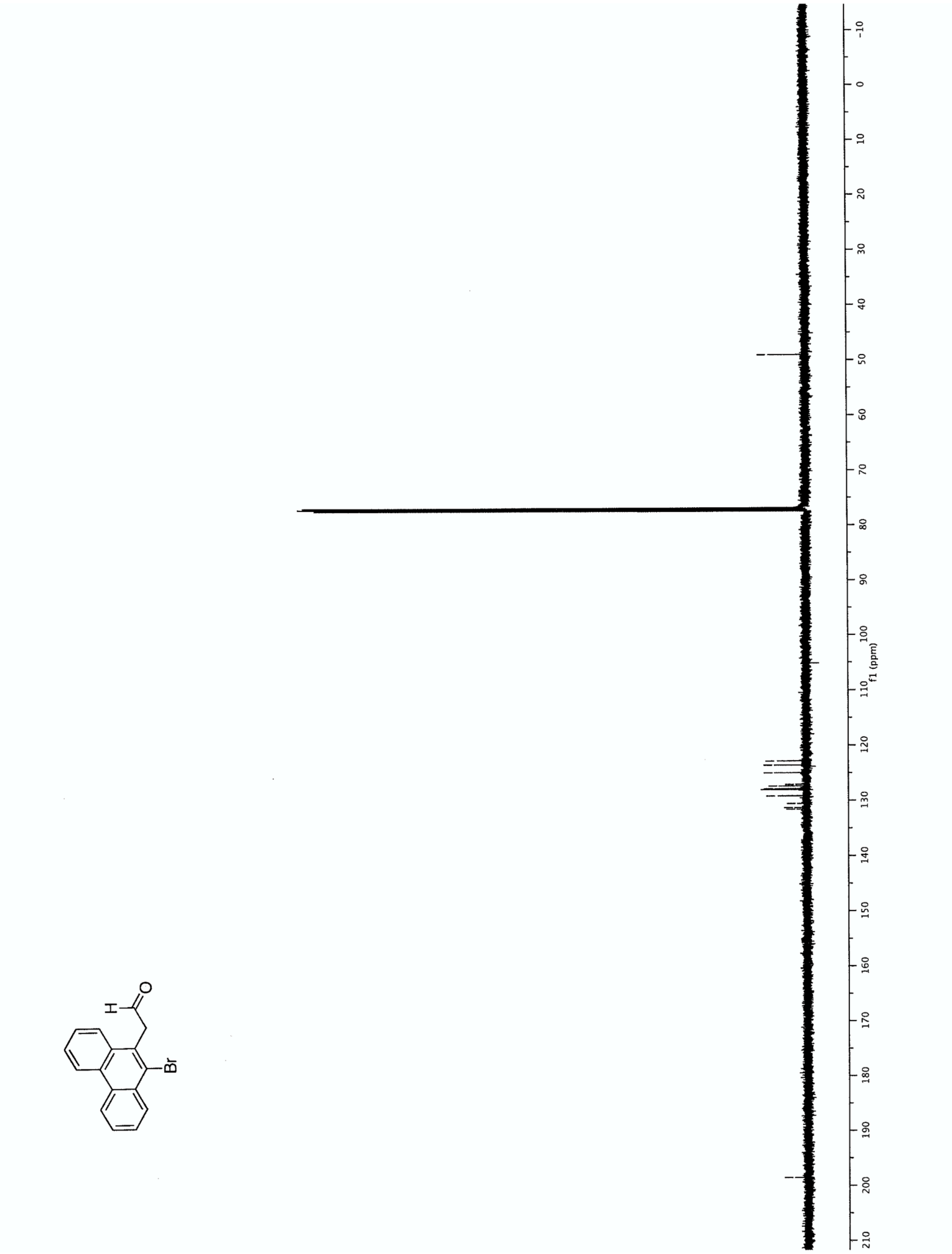
8
7
6
f1 (ppm)
5
4
3
2
1
0
-1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O
Br
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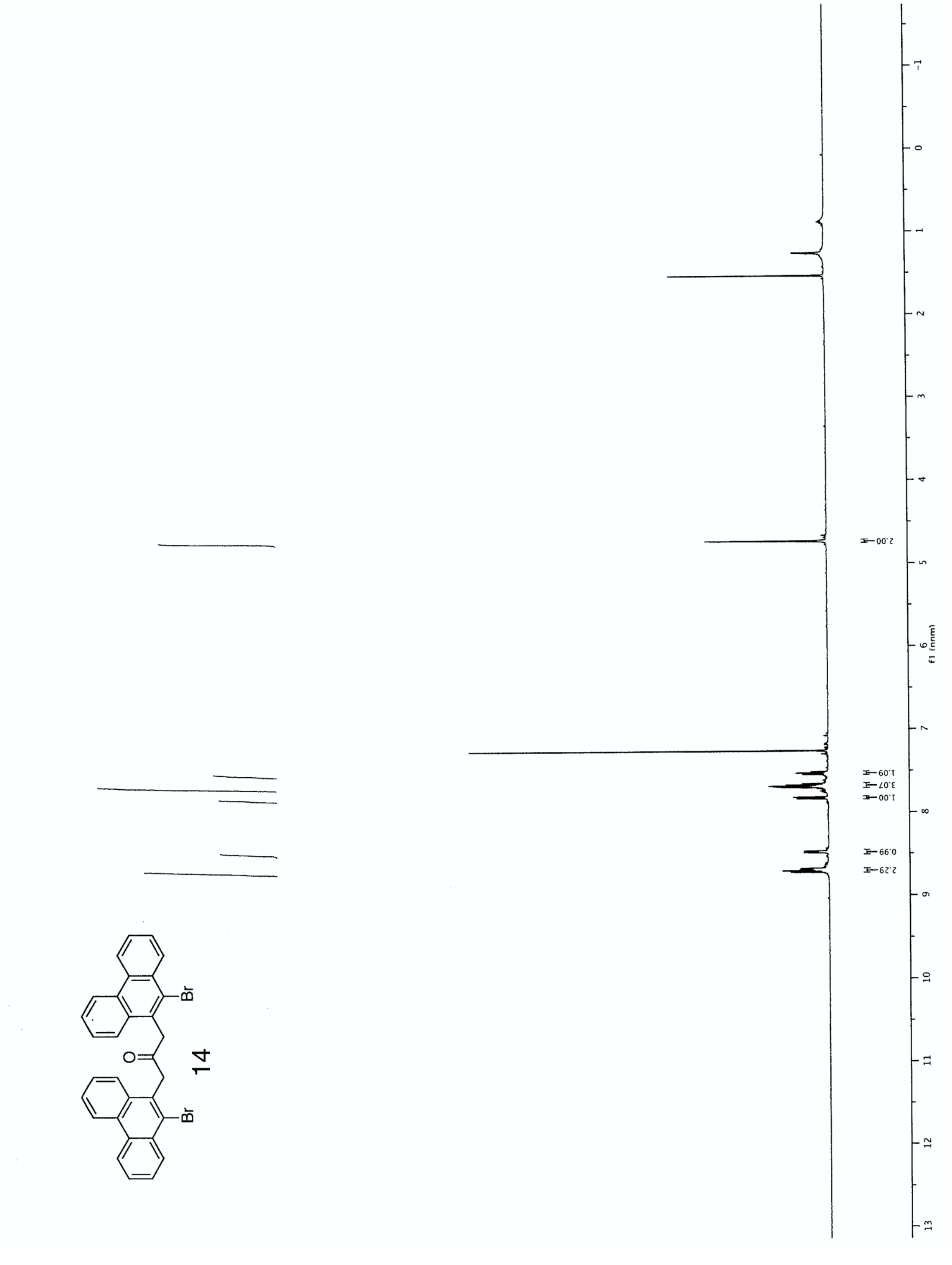
200
210
f1 (ppm)



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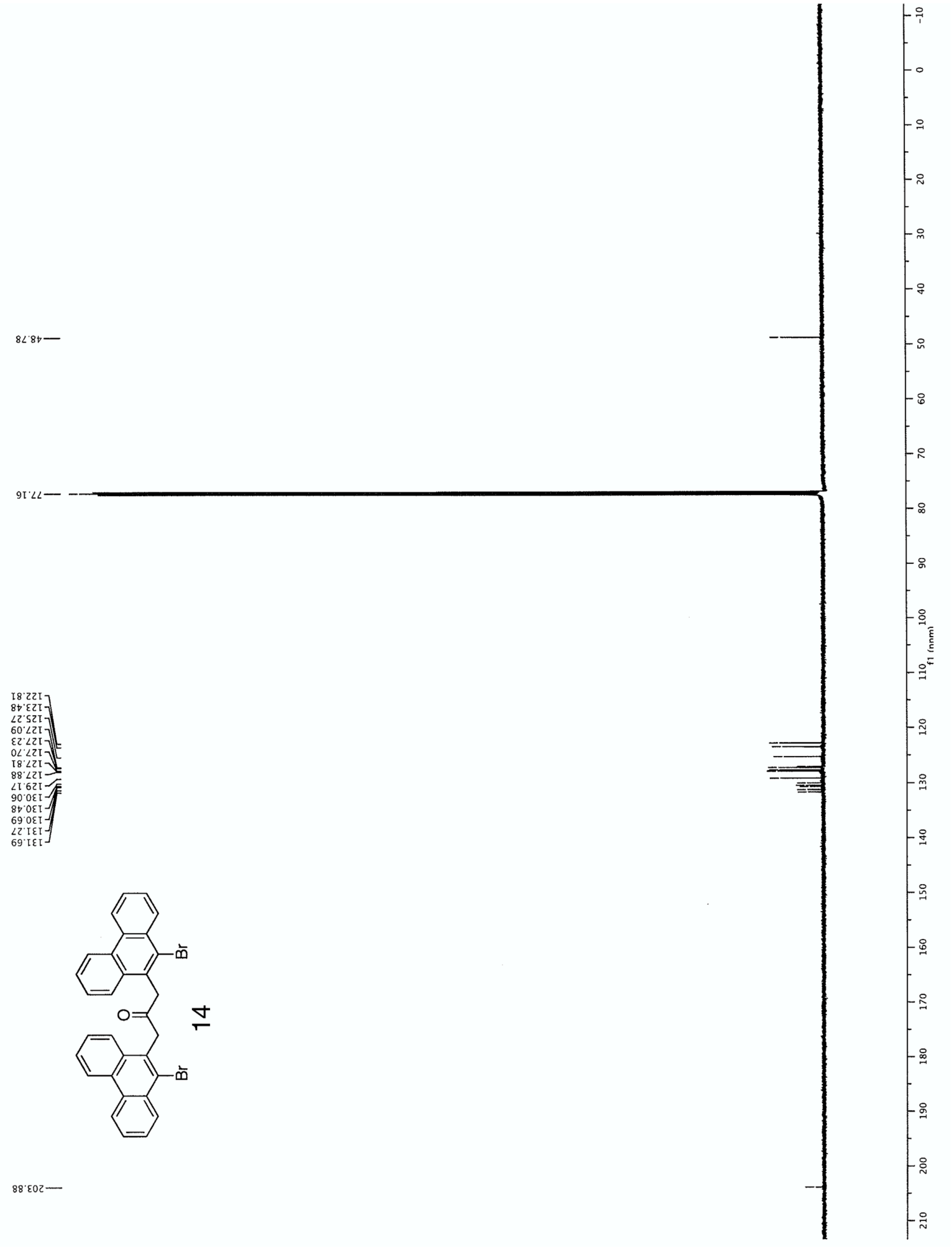
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130.48
130.06
129.17
127.88
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127.23
127.09
125.27
123.48
122.81
77.16
48.78
O
Br
Br
210
200
190
180
170
160
150
140
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110
100
90
80
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60
50
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30
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10
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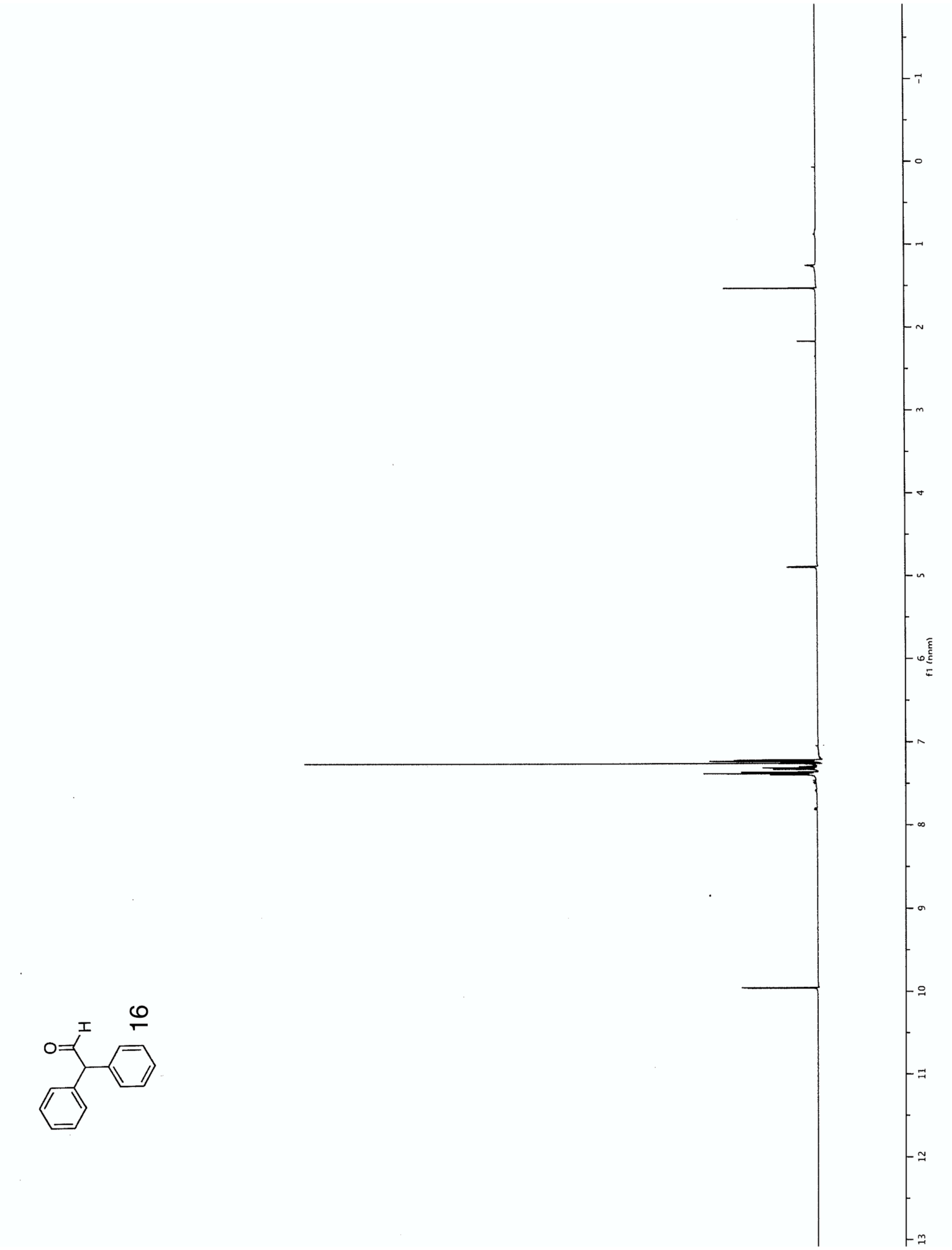
f1 (ppm)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O
H
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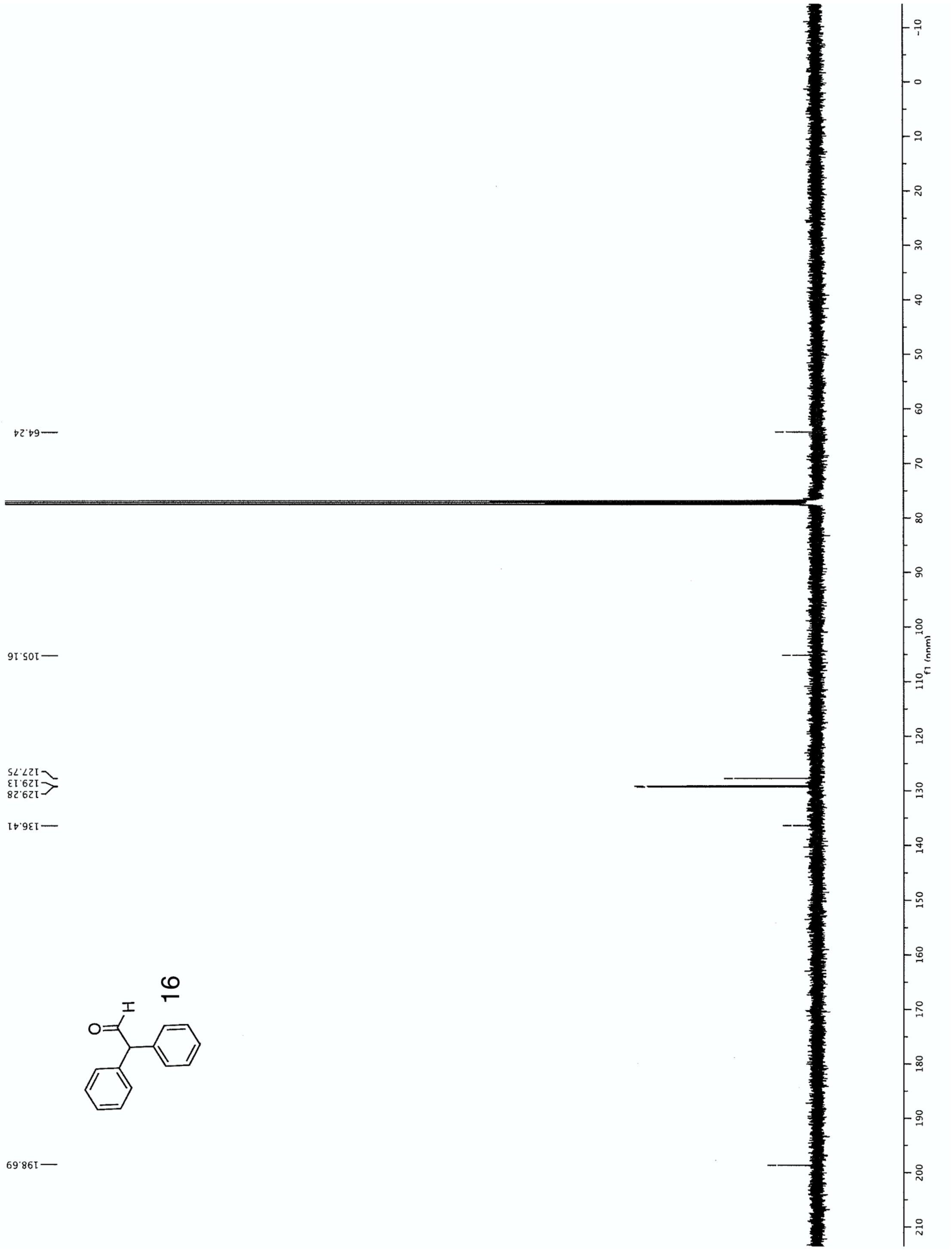
6
f1 (ppm)
7
8
9
10
11
12
13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127.75
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129.28
136.41
198.69
-10
0
10
20
30
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90
100
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120
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140
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160
170
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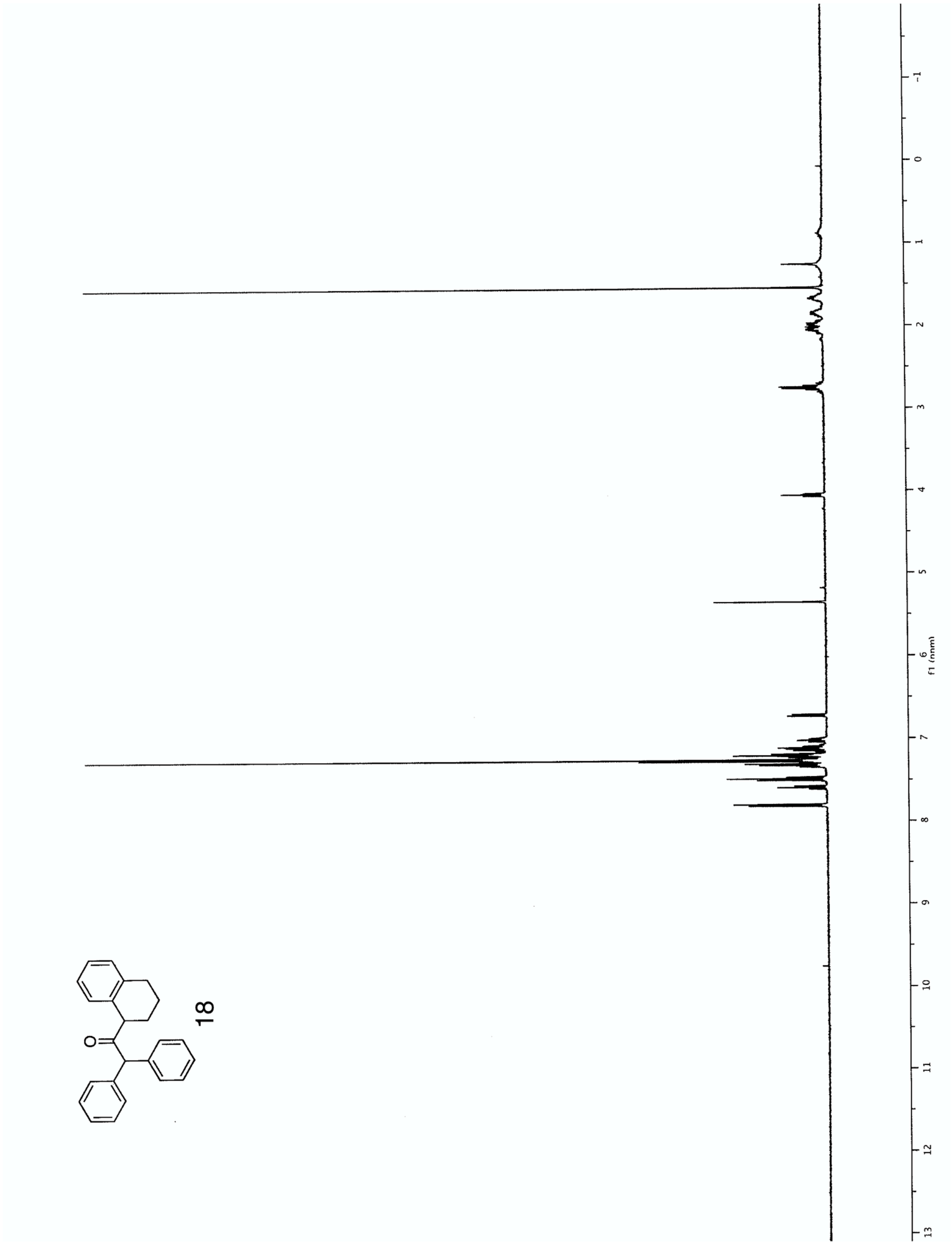
190
200
210
f1 (ppm)



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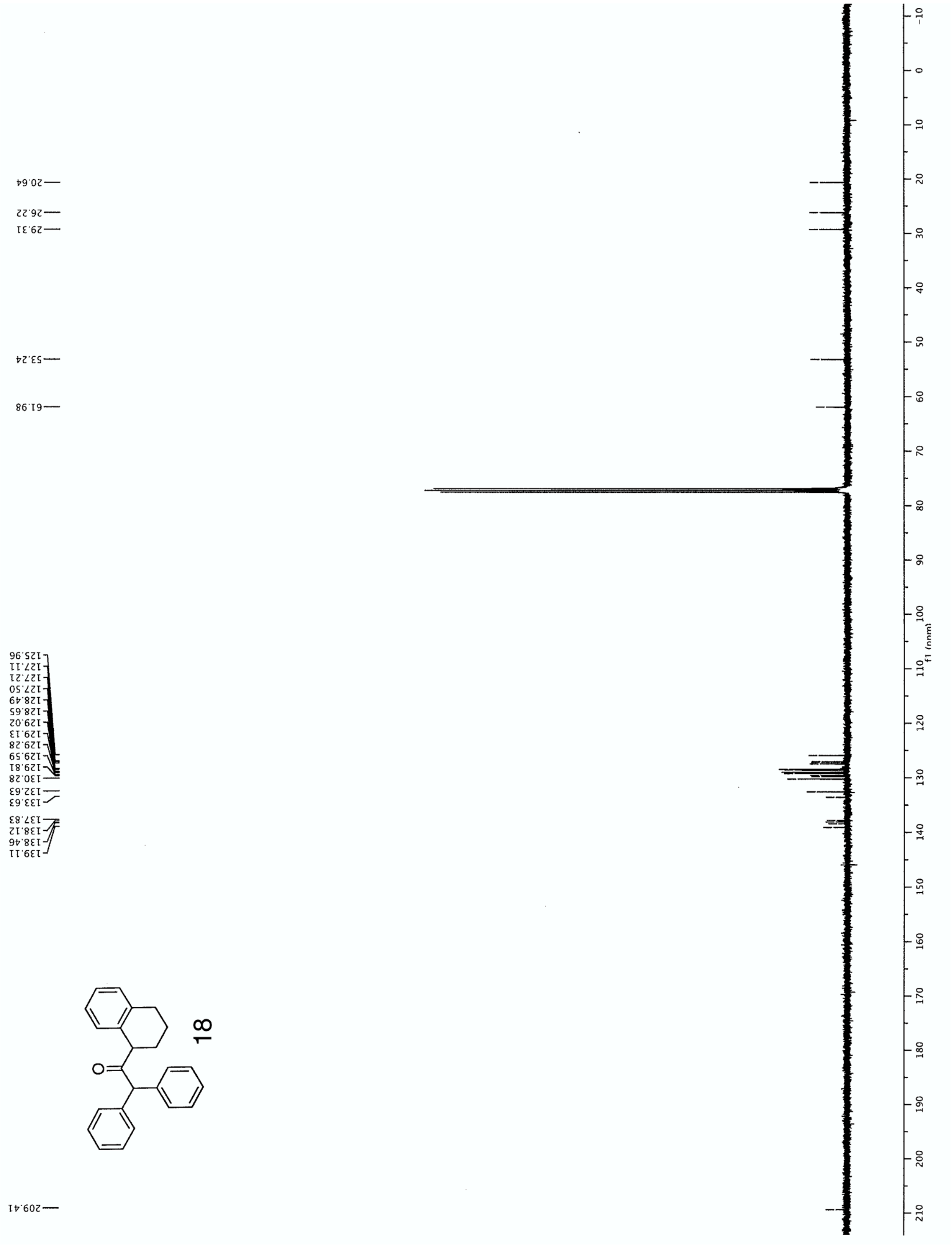
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138.12
137.83
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132.63
130.28
129.81
129.59
129.28
129.13
129.02
128.65
128.49
127.50
127.21
127.11
125.96
61.98
53.24
29.31
26.22
20.64
O
18
-10
0
10
20
30
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50
60
70
80
90
100
110
120
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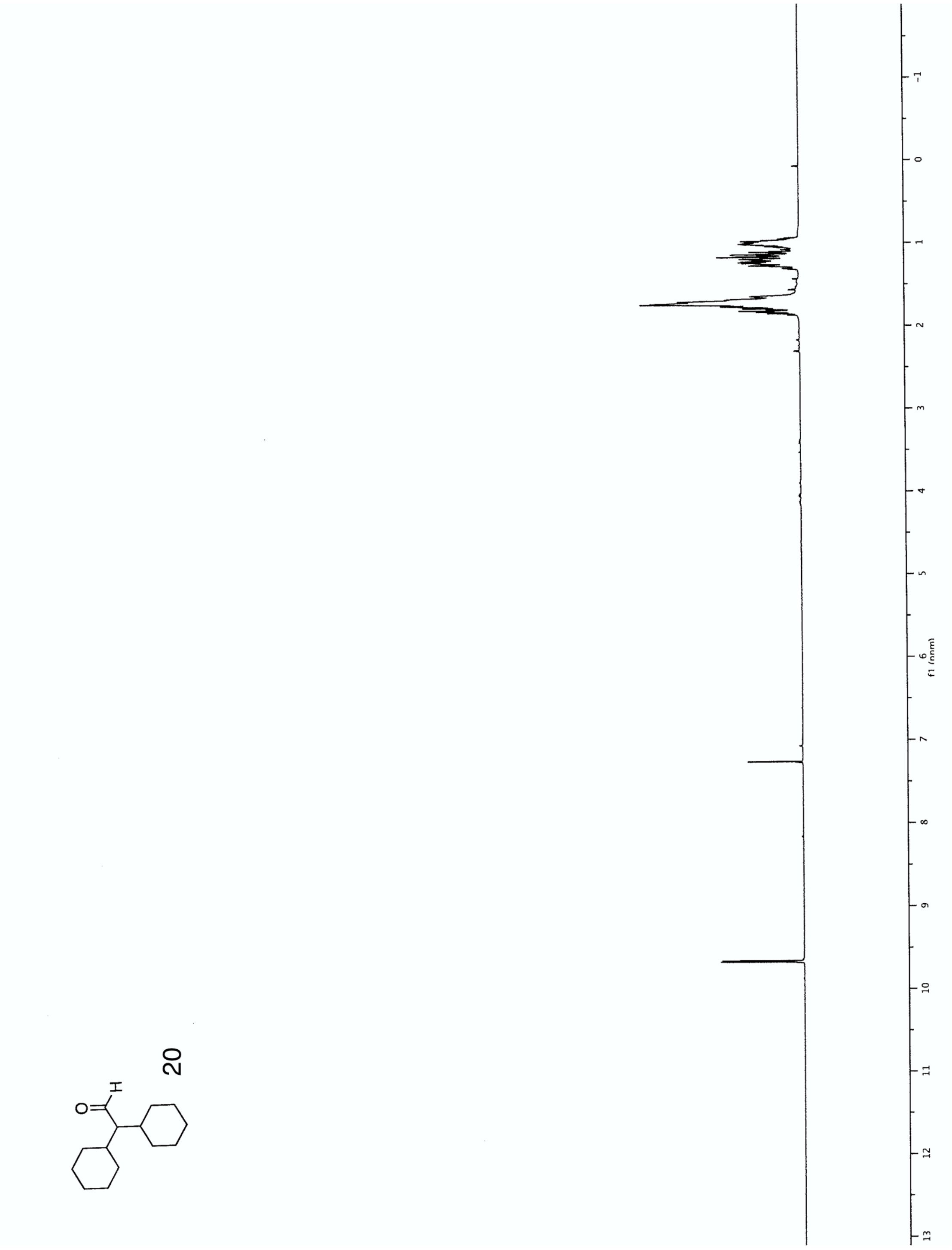
140
150
160
170
180
190
200
210
f1 (ppm)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O
H
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0
1
2
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4
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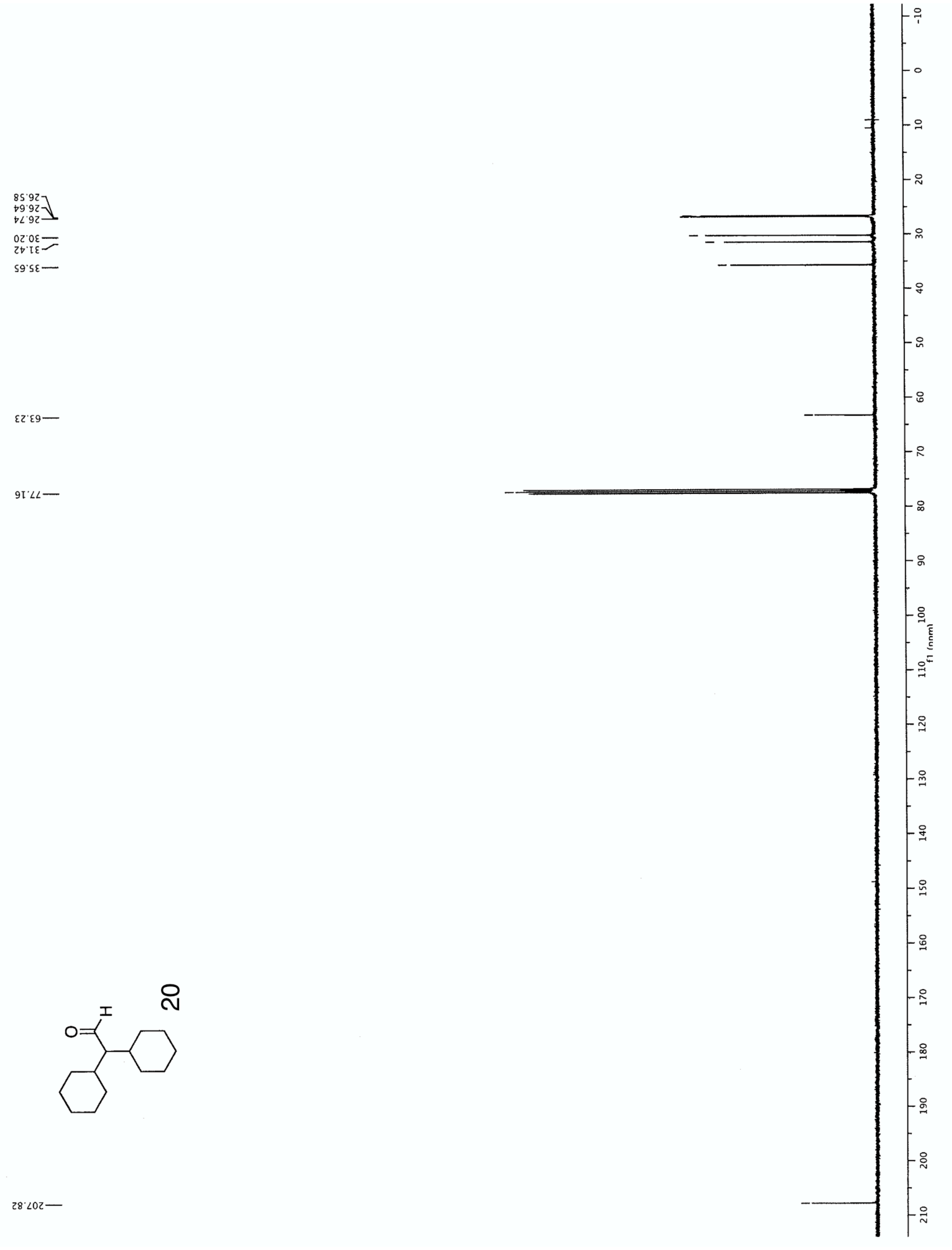
6
f1 (ppm)
7
8
9
10
11
12
13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26.64
26.74
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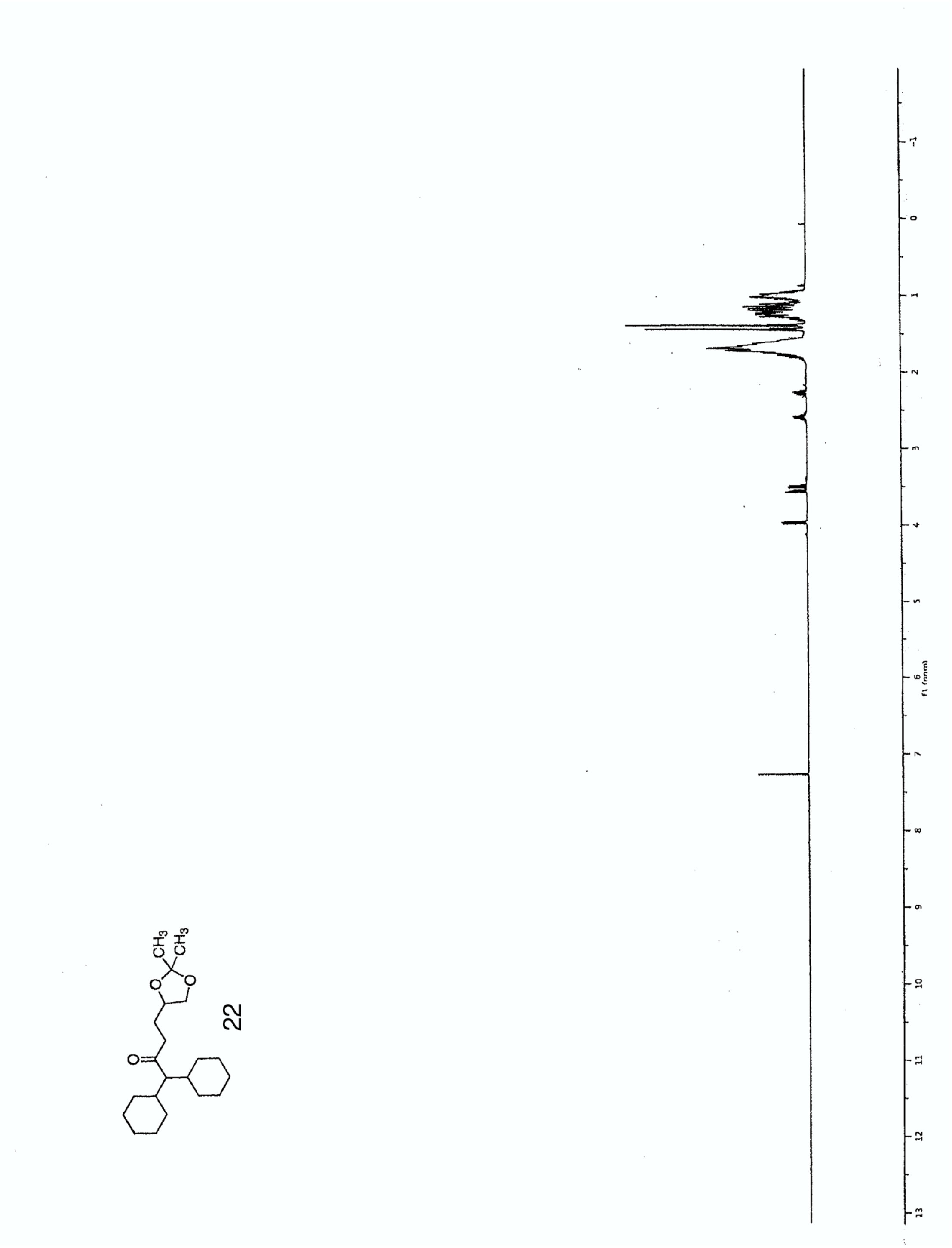
35.65
63.23
77.16
207.82
O
H
20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)



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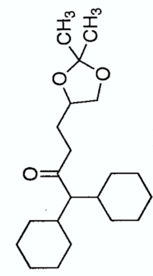

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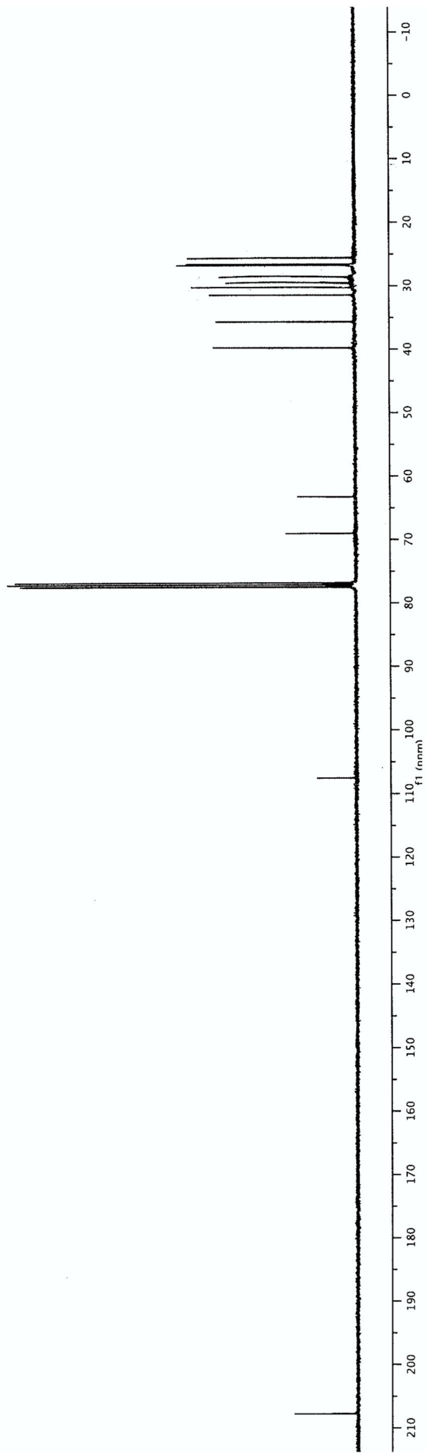
-10
0
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20
30
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100
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120
130
140
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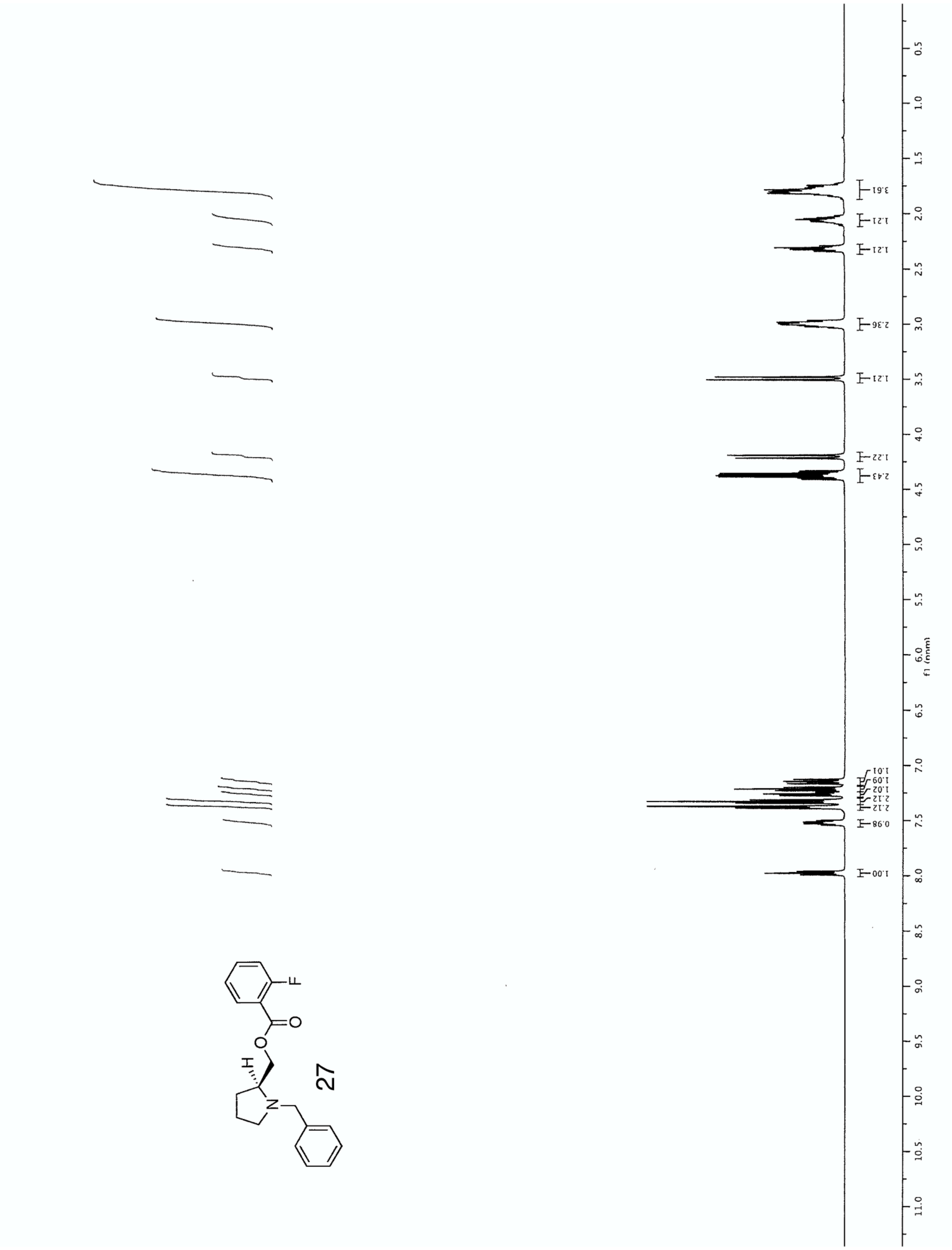
180
190
200
210
f1 (ppm)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1.09
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1.00
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
f1 (ppm)
6.5
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8.5
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9.5
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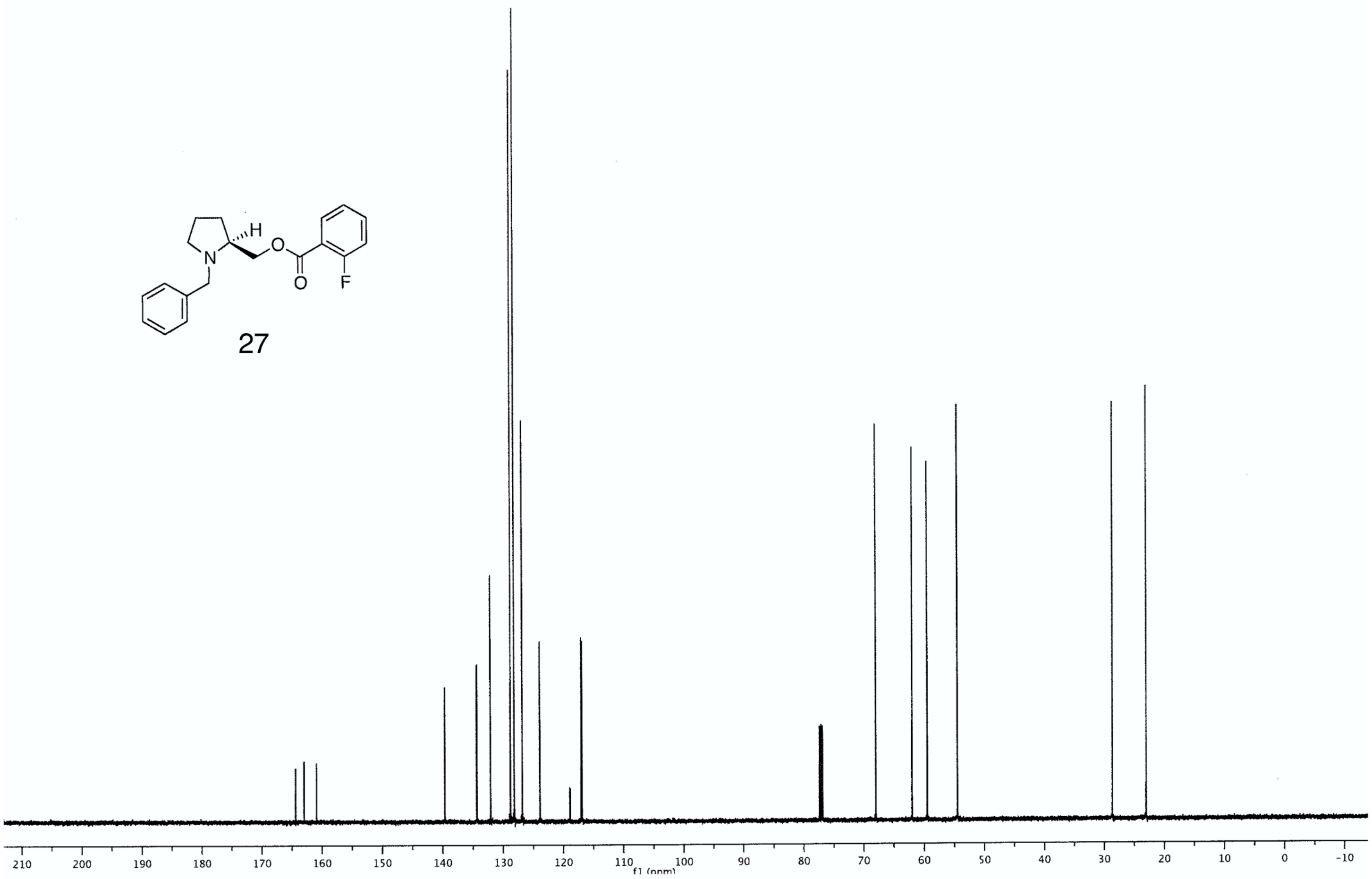
10.5
11.0
H
N
O
O
F

27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200
190
180
170
160
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140
130
120
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100
90
80
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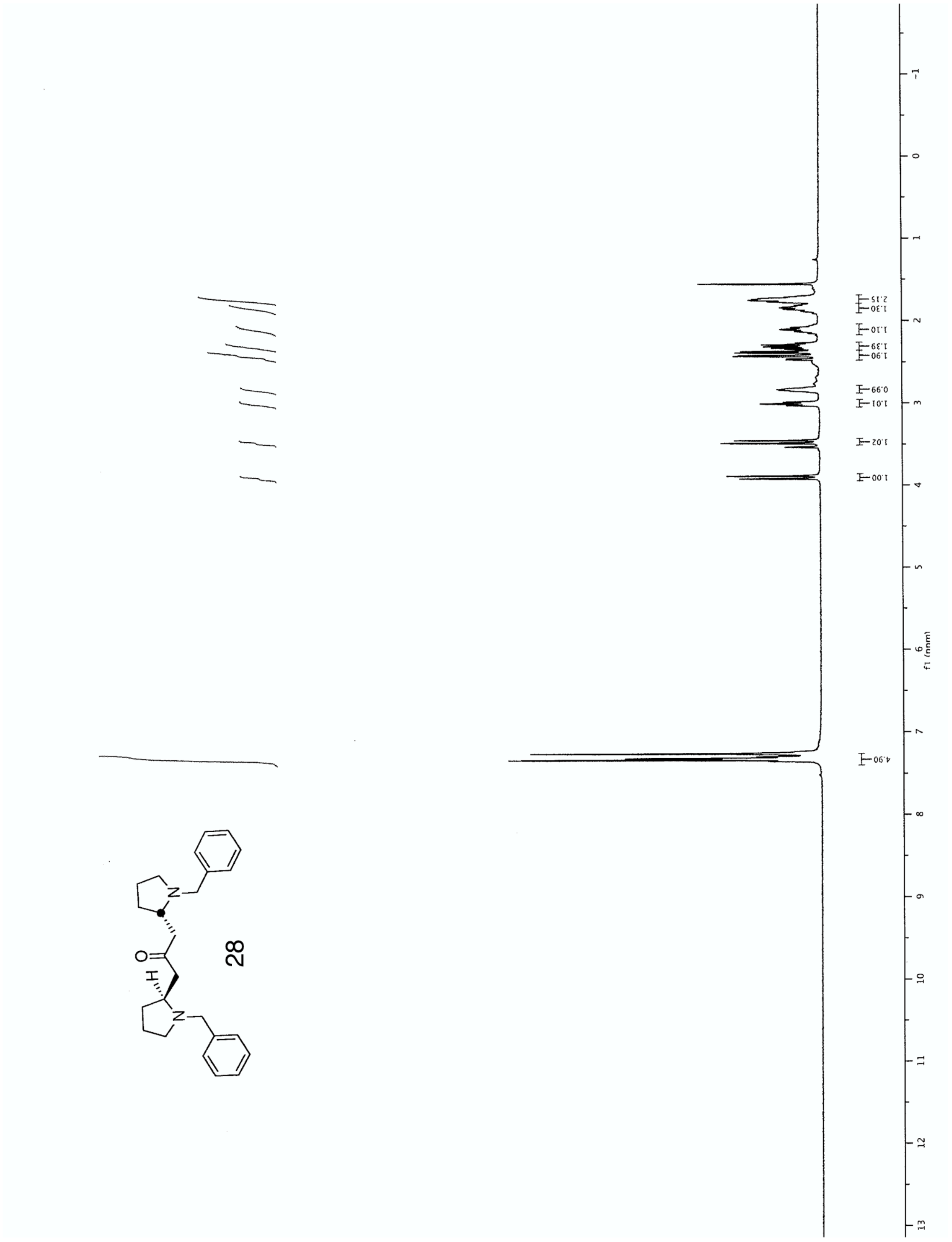
60
50
40
30
20
10
0
-10
f1 (ppm)
N
H
O
O
F



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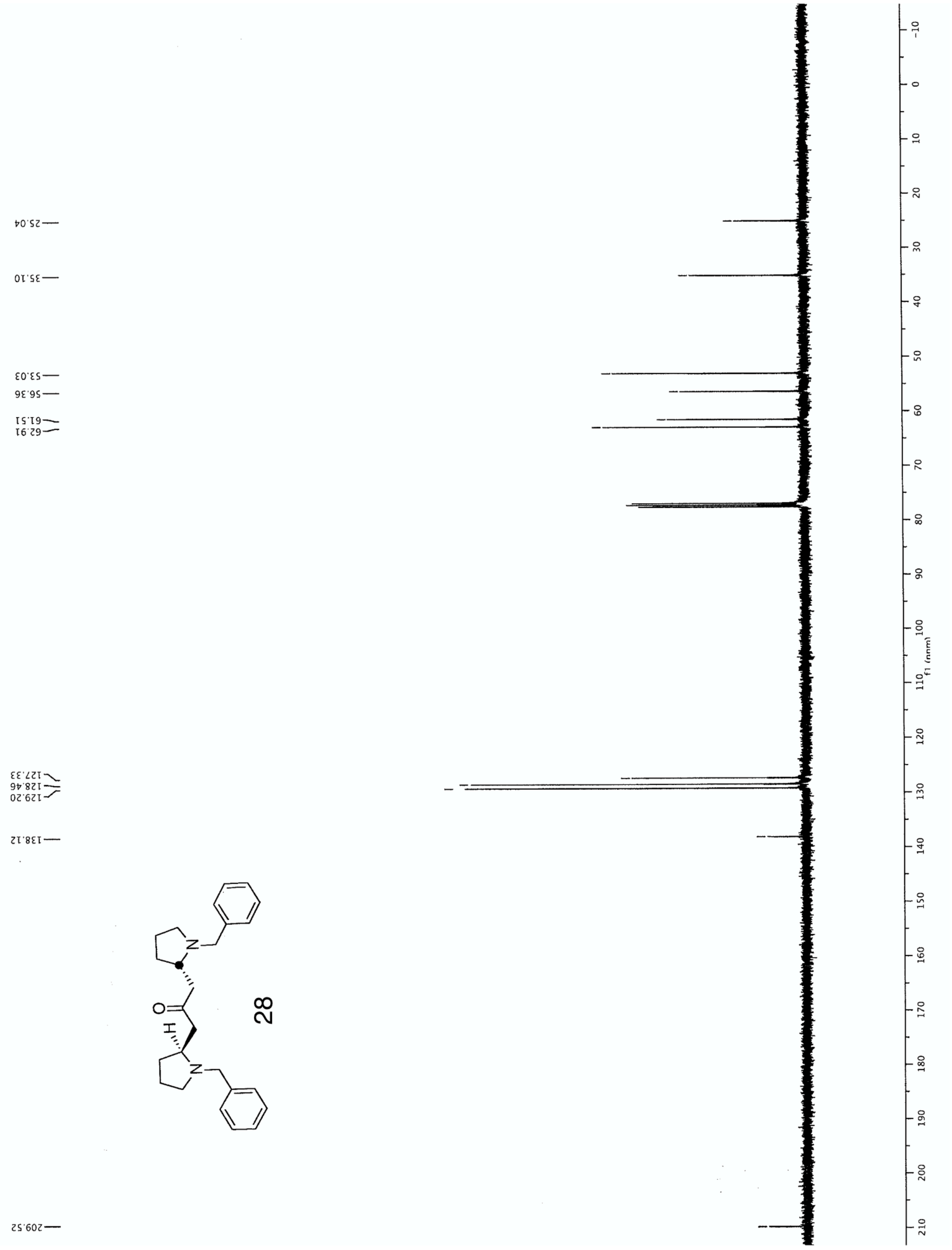
N
O
H
2.15
1.30
1.10
1.39
1.90
0.99
1.01
1.02
1.00
4.90
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)



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56.36
61.51
62.91
127.33
128.46
129.20
138.12
209.52
O
H
N
N
28
-10
0
10
20
30
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60
70
80
90
100
110
120
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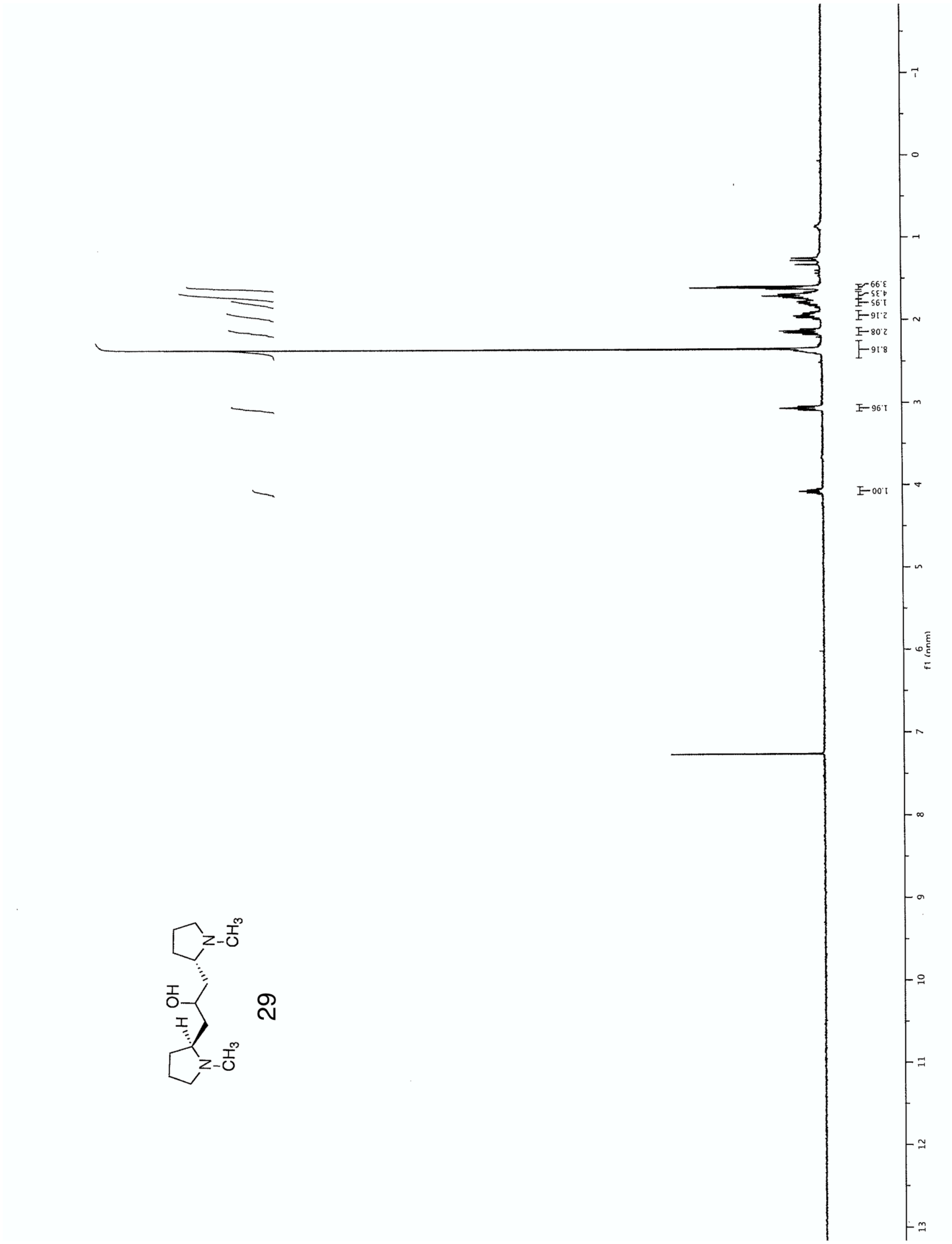
140
150
160
170
180
190
200
210
f1 (ppm)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N
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2.08
8.16
1.96
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12
11
10
9
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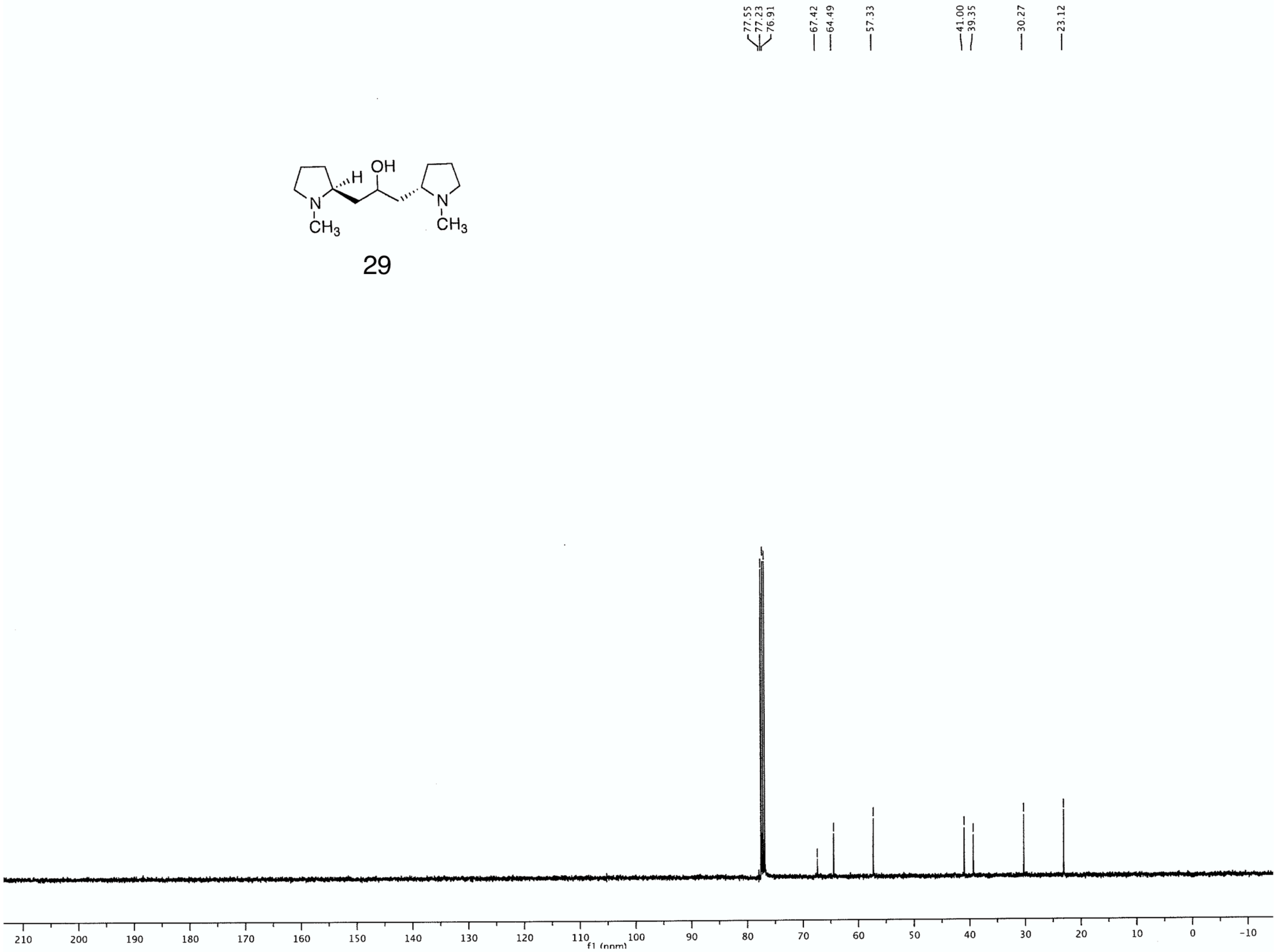
7
6
5
4
3
2
1
0
-1
f1 (ppm)

29


29

77.55
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64.49
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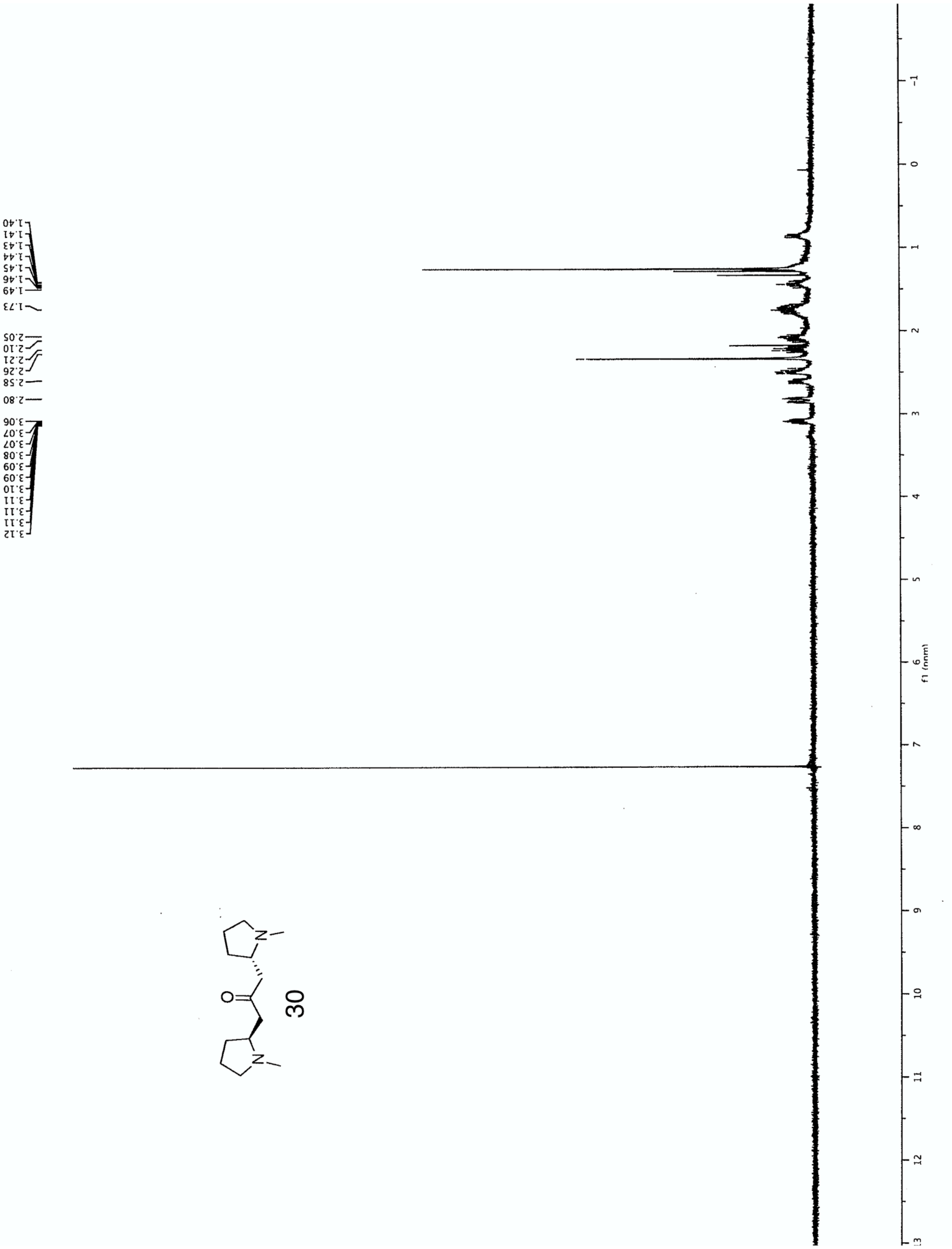
41.00
39.35
30.27
23.12
OH
H
N
CH3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


30

1.40
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1.45
1.46
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2.21
2.26
2.58
2.80
3.06
3.07
3.07
3.08
3.09
3.09
3.10
3.11
3.11
3.11
3.12
O
N
N
-1
0
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2
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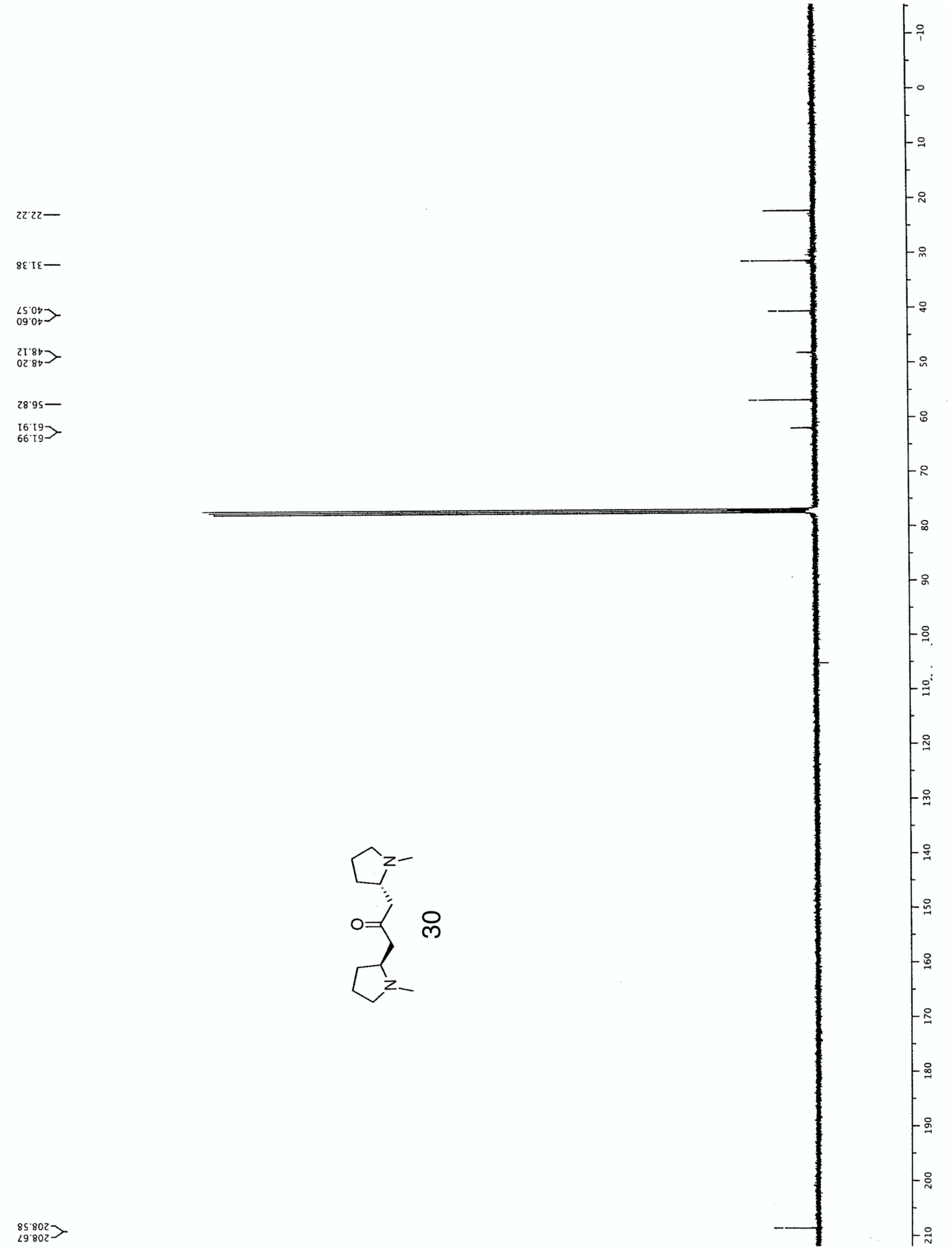
4
5
6
7
8
9
10
11
12
13
f1 (ppm)


22.22
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61.99
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30
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0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

Chapter 3. The Platinum-Catalyzed Geminal Diboration of Diazoalkanes: Access to Boronic Ester-Stabilized Carbanions.

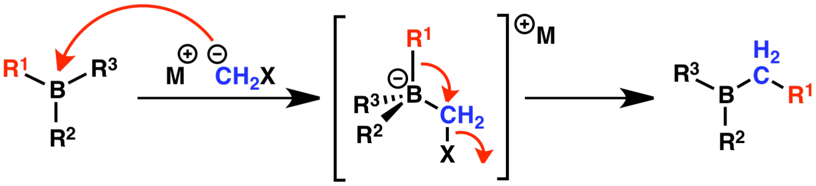
3.1 *Introduction and Background*

Chapters 1 and 2 of this thesis can attest to the fact that our group is experienced in the preparation and handling of substituted diazomethane nucleophiles. As our research has progressed, we have grown curious about electrophiles other than aldehydes or ketones and opportunities for new reactivity. Current research efforts in the organic division at Boston College reflect our community's need to access synthons that are diverse and modular for the planning and execution of target-oriented syntheses.[128] Amongst the most enabling synthetic scaffolds stands the carbon-boron bond as a key effector in the diversification of carbon connectivity.[129] Interest in preparing these valuable organoborons by catalytic, enantioselective approaches can be seen in many current research efforts.[130] In particular, work encompassing nucleophilic attack of a carbenoid (donor/acceptor) reagent onto a suitable electrophilic boron atom has been significant (Scheme 1).

---

[128] (a) "Development, Mechanism, and Scope of the Palladium-Catalyzed Enantioselective Allene Diboration," Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766–8767. (b) "Asymmetric 1,4-Dihydroxylation of 1,3-Dienes by Catalytic Enantioselective Diboration," Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134–9135. (c) "Regio- and Stereoselective Ni-Catalyzed 1,4-Hydroboration of 1,3-Dienes: Access to Stereodefined (Z)-Allylboron Reagents and Derived Allylic Alcohols," Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534–2535. (d) "A Boron-Based Synthesis of the Natural Product (+)-*trans*-Dihydrolycoricidine," Poe, S. L.; Morken, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 4275-4278. (e) "Highly Selective Methods for Synthesis of Internal (-) Vinylboronates through Efficient NHC-Cu-Catalyzed Hydroboration of Terminal Alkynes. Utility in Chemical Synthesis and Mechanistic Basis for Selectivity," Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859–7871. (f) "Enantioselective Synthesis of Allylboronates Bearing a Tertiary or Quaternary B-Substituted Stereogenic Carbon by NHC-Cu-Catalyzed Substitution Reactions," Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637. (g) Enantioselective Synthesis of Boron-Substituted Quaternary Carbons by NHC-Cu-Catalyzed Boronate Conjugate Additions to Unsaturated Carboxylic Esters, Ketones or Thioesters," O'Brien, J. M.; Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630–10633.

Scheme 1: Organoborane Mediated Homologarion of Carbeniod Reagents



Matteson and coworkers pioneered the now frequently used method of combining highly reactive lithium halomethane reagents with organoborane electrophiles as a tool for dependable, stereodirected synthesis.[131] These protocols constitute a reliable, stereoretentive functionalization that can be applied following enantioselective hydroborations or other organoboron installations. Additional variations on

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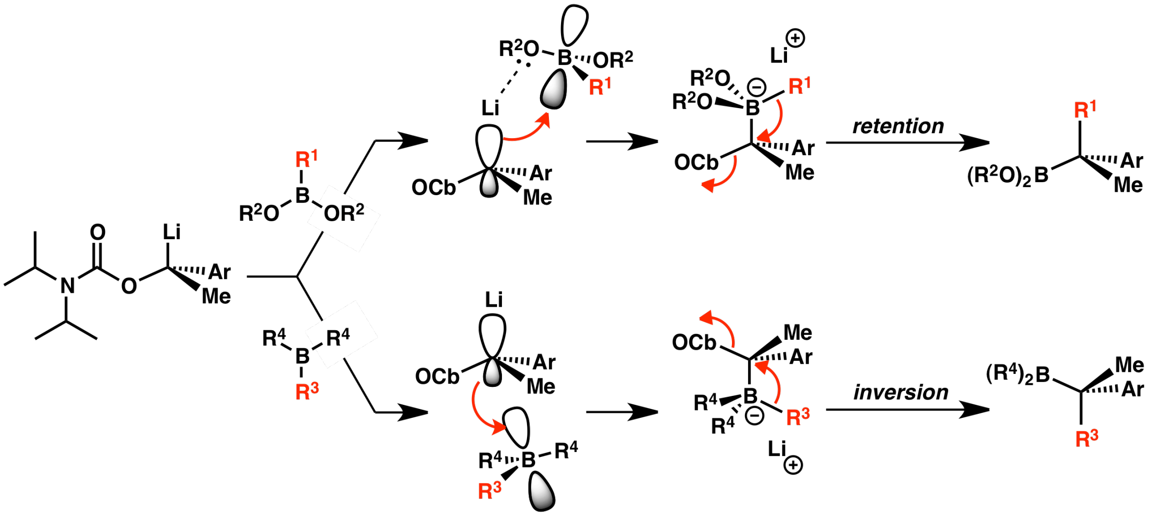
(129) (a) "Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds," Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) "Organoboranes for synthesis—substitution with retention," Brown, H. C.; Singaram, B. *Pure Appl. Chem.* **1987**, *59*, 879–894. (c) "The β-Alkyl Suzuki–Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis," Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.

(130) Leading references in enantioselective synthesis of tertiary boronic esters: (a) "Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to Five-, Six-, and Seven-Membered β-Substituted Cyclic Enones: Enantioselective Construction of All-Carbon Quaternary Stereocenters," Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M.; *J. Am. Chem. Soc.* **2011**, *133*, 6902–6905. (b) "Enantioselective Construction of Quaternary Stereogenic Centers from Tertiary Boronic Esters: Methodology and Applications." Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3760–3763. (c) "Enantiodivergent Conversion of Chiral Secondary Alcohols into Tertiary Alcohols," Stymiest, J. L.; Bagutski, V.; French, R.; Aggarwal, V. K. *Nature* **2008,** *456*, 778–782.

(131) "α-Halo Boronic Esters: Intermediates for Stereodirected Synthesis," Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535–1551.

the original theme include the merger of sulfur-based ylides with trialkylboranes, wherein the sulfur reagent often bears a chiral auxiliary.[132] Blakemore has shown that lithiation or magnesation of enantiomerically pure α-chloro sulfoxides can also offer similar utility as lithiated halomethanes in the addition/1,2-rearrangement reaction with boronic esters.[133] Aggarwal has also made an excellent contribution in the context of stereocontrol with the use of lithiated, enantiomerically pure, secondary carbamates as the nucleophile with either trialkylboranes or boronic esters. As shown in Scheme 2, the use of different organoboron electrophiles dictates the outcome of the tetrahedral borate migration event.

Scheme 2: Stereodivergent Reactivity with Different Organoboron Species



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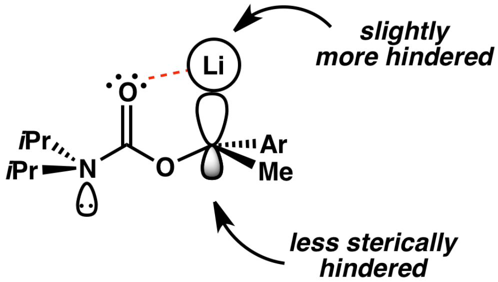
(132) "Asymmetric Sulfur Ylide Reactions with Boranes: Scope and Limitations, Mechanism and Understanding," Fang, G. Y.; Wallner, O. A.; Di Blasio, N.; Ginesta, X.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2007**, *129*, 14632–14639.

(133) "Reagent-Controlled Asymmetric Homologation of Boronic Esters by Enantioenriched Main-Group Chiral Carbenoids," Blakemore, P. R.; Marsden, S. P.; Vater, H. W. *Org. Lett.* **2006**, *8*, 773–776.

The observed divergent reactivity with different boron species is rationalized by the directing effect of the oxygen lone pair on the boronic ester to the lithiated carbamate. As illustrated in Figure 1, with the use of non-Lewis basic trialkylborane reagents, the anion, which has a partially planarized geometry, can now approach the vacant *p*-orbital of boron from the less hindered face, assuming the reactive conformation is the most populated (i.e. most energetically favorable).

Figure 1: Lithium Carbamate Provides Steric Bias



3.1.a ***The Hooz Reaction: Use of Carbonyl-Stabilized Diazo Compounds in Organoboron Homologation.***

Literature precedent concerning electrophilicity at the vacant *p*-orbital of boron using diazo compounds has, for the most part, been limited to carbonyl-stabilized diazoalkanes. As illustrated in Scheme 3, Hooz *et al.* have extensively studied this reaction as well as the products' subsequent utility.[134] Initially, their research demonstrated that efficient

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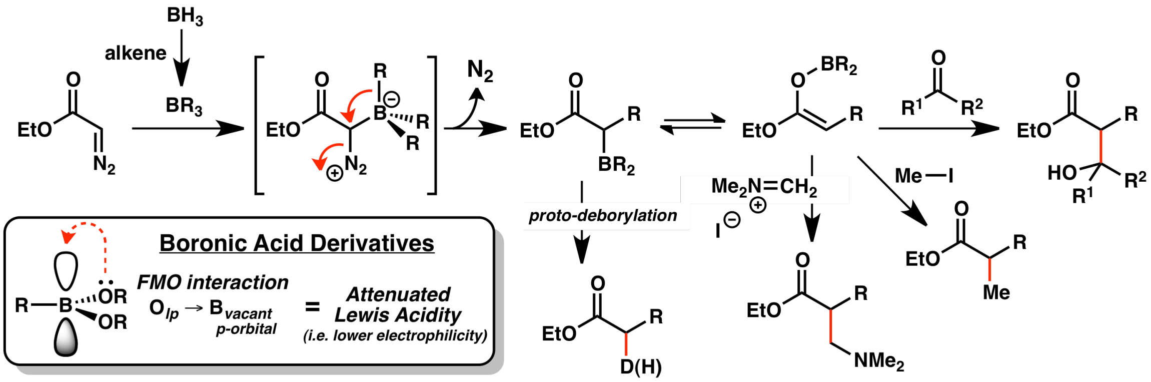
(134) (a) Francis A. Carey and Richard J. Sundberg Carbon-Carbon Bond-Forming Reactions of Compounds of Boron, Silicon, and Tin Advanced Organic Chemistry, Fourth Edition Part B: Reactions and Synthesis 2002, 547-59. (b) "The Reaction of Trialkylboranes with Diazoacetone. A New Ketone Synthesis," Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936-5937. (c) "Alkylation of Diazoacetonitrile and Ethyl Diazoacetate by Organoboranes. Synthesis of Nitriles and Esters," Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968,** *90*, 6891-6892. (d) "Reaction of Dialkylchloroboranes with Ethyl Diazoacetate at Low Temperatures. Facile Two-Carbon Homologation under Exceptionally Mild

reaction is limited to trialkylboranes because of their greater electrophilicity relative to boronic acids or esters (Scheme 3). As illustrated, after exhaustive hydroboration to generate the saturated electrophile, nucleophilic attack by ethyl diazoacetate forms the betaine intermediate. The tetrahedral boronate species then decomposes by migration of a carbon-boron sigma bond to displace dinitrogen, which is an excellent, irreversible nucleofuge. The resulting α-borylcarbonyl compound can then be translated into a range of useful functionality (Scheme 3).

Scheme 3: General Hooz Reaction and α-Borylcarbonyl Derivatization



BH3
alkene
BR3
EtO
O
N2
R
B
N2
EtO
R
BR2
O
BR2
R1
R2
HO
proto-deborylation
Me2N=CH2
I
Me—I
D(H)
NMe2
Me
Boronic Acid Derivatives
FMO interaction
Olp → Bvacant p-orbital
=
Attenuated Lewis Acidity
(i.e. lower electrophilicity)
R—B
OR
OR

Modern examples of this reactivity have appeared in the literature[135] and further encouraged our research into the use of non-

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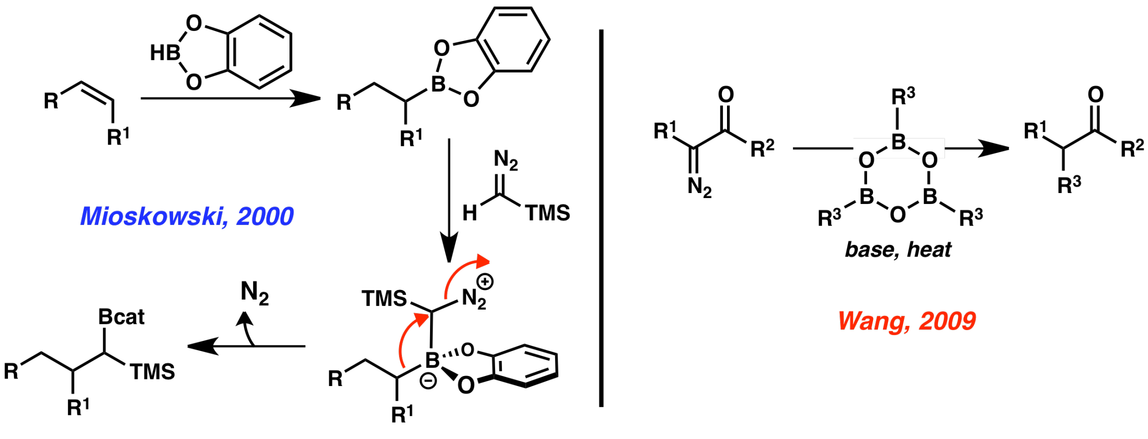
Conditions," Brown, H. C.; Midland M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1972**, *94*, 3662-3664. (e) "Reaction of Alkyl- and Aryldichloroboranes with Ethyl Diazoacetate at Low Temperature," Hooz, J.; Bridson, J. N.; Calzada, J. G.; Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Org. Chem.* **1973**, *38*, 2574–2576. (f) "Reaction of Organoboranes with Diazo Esters and Diazo Ketones in the Presence of Deuterium Oxide. A New Synthesis of α-Deuterio- and α,α-Dideuterio Esters and Ketones," Hooz, J.; Gunn, D. M. *J. Am. Chem. Soc.* **1969**, *91*, 6195-6196. (g) "Transfer Reactions Involving Boron. XXII. Position-Specific Preparation of Dialkylated Ketones from Diazo Ketones and Methyl Vinyl Ketone via Vinyloxyboranes," Pasto, D. J.; Wojtkowski, P. W. *J. Org. Chem.* **1971,** *36,* 1790-1792. (h) "A New Regiospecific Synthesis of Enol Boranes of Methyl Ketones," Hooz; J.; Oudenes, J.; Roberta, J. L.; Benderly, A. *J. Org. Chem.* **1987,** *52*, 1347.

(135) (a) "Preparation of Alcohols from Alkenes via the Homologation of Boronates with (Trimethylsilyl)diazomethane," Goddard, J. P.; Le Gall, T.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1455-1456. (b) "Regioselective Homologation of Bis(boronate) Intermediates Derived from Rhodium Catalyzed Diboration of Simple Alkenes." Kalendra, D. M.;

stabilized diazoalkanes as nucleophiles towards boron electrophiles (Scheme 4).

Scheme 4: Modern Examples of Organoboron Reactivity with Diazonucleophiles



3.1.b *Initial Inspiration Towards an Enantioselective Hooz Reaction with Non-Stabilized Diazoalkanes.*

Among the different methods capable of forging chiral, enantiomerically enriched organoboron species via catalyst control[136], hydroboration with a chiral pool-derived borane continues to be the most general and widely used.[137] Our vision was to introduce a readily

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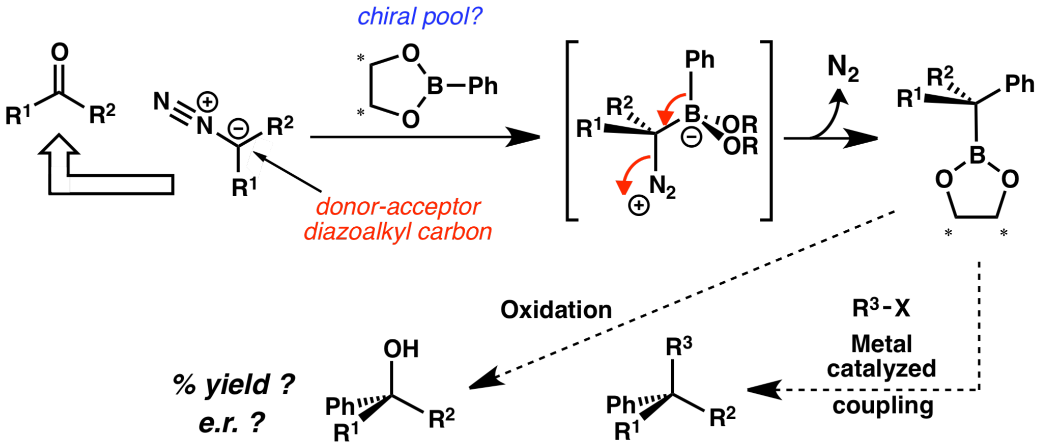
Duenes R. A.; Morken, J. P. *Synlett* **2005**, 1749-1751. (c) "Arylation and Vinylation of α-Diazocarbonyl Compounds with Boroxines," Peng, C.; Zhang, W.; Yan, G.; Wang, J. *Org. Lett.* **2009**, *11*, 1667–1670. (d) "Multicomponent Mannich Reactions with Boron Enolates Derived from Diazo Esters and 9-BBN," Luan, Y.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 2510–2513.

(136) (a) For a review of early developments in metal-catalyzed hydroborations, see: "Transition-Metal Promoted Hydroborations of Alkenes, Emerging Methodology for Organic Transformations," Burgess K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179-1191. (b) For an updated review, see: "Catalytic Asymmetric Hydroboration: Recent Advances and Applications in Carbon−Carbon Bond-Forming Reactions," Crudden, C. M.; Edwards, D. R. *Eur. J. Org. Chem.* **2003**, 4695-4712.

(137) (a) H. C. Brown, Organic Syntheses via Boranes, John Wiley and Sons, London, 1975 (b) "Versatile α-Pinene-Based Borane Reagents for Asymmetric Syntheses," Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1-19. (c) "9-Borabicyclo[3.3.2]decanes and the Asymmetric Hydroboration of 1,1-Disubstituted

accessible source of asymmetry onto the boron reagent to allow for diastereofacial selection during approach of the diazoalkane (Scheme 5). Assuming complete stereospecificity in the migration step, and barring any equilibrating pathway that could potentially erode the stereocenter, enantioenriched products would result. Given the fact that stereoretentive derivatizations of the C–B bond in the products is a routine operation,[138] we judged that the enantioselectivity imparted by various chiral controllers of boron could be evaluated quickly and effectively (Scheme 5).

Scheme 5: The Asymmetric Hooz Reaction: Access to Valuable Enantioenriched Products?



Alkenes," Gonzalez, A. Z.; Roman, J. G.; Gonzalez, E. J. Martinez, E. J.; Medina, J. R.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.*, **2008**, *130*, 9218-9219.

(138) For an excellent review, see: "Expanding the Scope of Transformations of Organoboron Species: Carbon–Carbon Bond Formation with Retention of Configuration," Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.*, **2009**, 6704-6716, and references therein.

3.1.c *Initial Studies on the Asymmetric Hooz Reaction.*

Our investigation commenced with the preparation of the phenylboronic ester derived from the condensation of the commercially available C_2–symmetric diol, (*R,R*)-(+)-hydrobenzoin with phenylboronic acid.[139] As illustrated in Scheme 6, we planned to engage this potential electrophile with *para*-tolyldiazomethane to afford an enantiomerically enriched diarylmethanol. This type of product would be difficult to access through the currently available protocols for asymmetric reduction due to the steric and electronic similarity of the two aryl rings (i.e. CBS reduction).[140] Additionally, if the reaction conditions could be optimized to high levels of enantiopurity, the product could be taken on to the physiologically active diarylmethane product, (*R*)-neobenodine (Scheme 6).[141]

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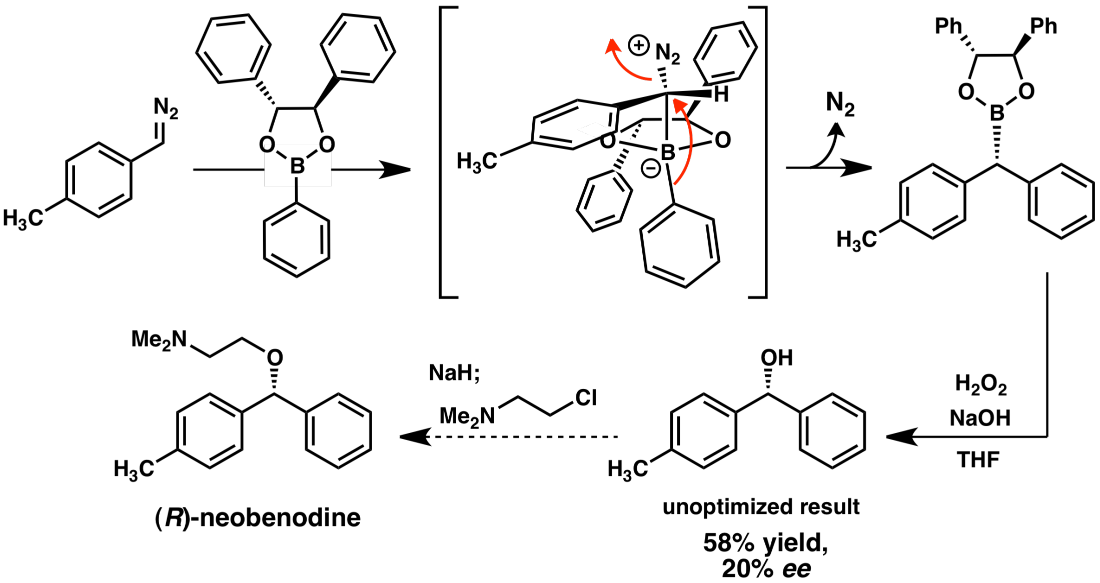
(139) "Efficient Synthesis of Substituted Terphenyls by Suzuki Coupling Reaction," Chaumeil, H.; Drian, C. L.; Defoin, A. *Synthesis* **2002**, *6,* 757–760.

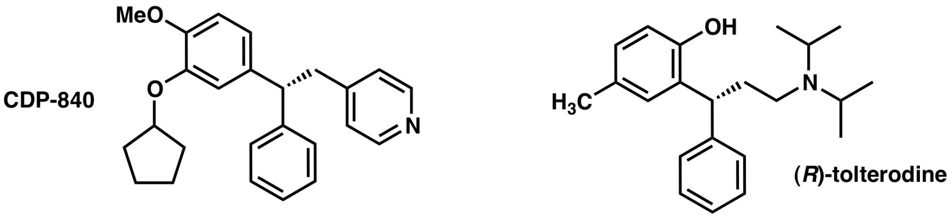
(140) The most effective enantioselective methodology is currently enzymatic in origin, see: (a) "Enzyme-Catalyzed Enantioselective Diaryl Ketone Reductions," Truppo, M. D.; Pollard, D.; Devine, P. *Org. Lett.* **2007**, *9*, 335. For organic methodology relating to enantioselective reduction of diaryl ketones, see: (b) "Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful New Synthetic Method," Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012. (c) "Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones," Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (d) "Asymmetric Reductions of Ketones using Lithium Aluminium Hydride Modified with *N,N*-Dialkyl Derivatives of (*R*)-(–)-2-Aminobutan-1-ol," Brown, E.; Penfornis, A.; Bayma, J.; Touet, J. *Tetrahedron: Asymmetry* **1991**, *2*, 339–342. (e) "Nonracemic Diarylmethanols From CuH-Catalyzed Hydrosilylation of Diaryl Ketones," Lee, C.-H.; Lipshutz, B. H. *Org. Lett.* **2008**, *10*, 4187–4190.

(141) "The Antihistaminic and Anticholinergic Activities of Optically Active Diphenhydramine Derivatives. The Concept of Complementarity," Rekker, R. F.; Timmerman, H.; Harms, A. F.; Nauta, W. T. *Arzneim.-Forsch.* **1971,** *21*, 688–691.

Scheme 6: Model Study to Access Chiral Diarylmethanols


N$_2$
H$_3$C
O
B
O
⊕
N$_2$
H
⊖
N$_2$
Ph
Ph
H$_2$O$_2$
NaOH
THF
OH
NaH;
Me$_2$N
Cl
Me$_2$N
O
(*R*)-neobenodine
unoptimized result
58% yield,
20% *ee*

Alternative Bioactive Diarylmethane Targets


MeO
O
N
CDP-840
OH
H$_3$C
N
(*R*)-tolterodine

Upon initial investigations into reactivity and selectivity of the process, we obtain measurable enantioselectivities and a reasonable yield of product (Scheme 6). Attempts to increase reactivity by the addition of a Lewis acid (for coordination to a boronic ester oxygen lone pair) were made in the hopes that the reaction would proceed at lower tempurature and allow for higher selectivity.[142] Through the potential Lewis acid coordination of the lone pair on oxygen of the boronic ester, the donation of that oxygen lone pair into the vacant *p*-orbital will be attenuated, thereby increasing the electrophilic character of the boron atom and

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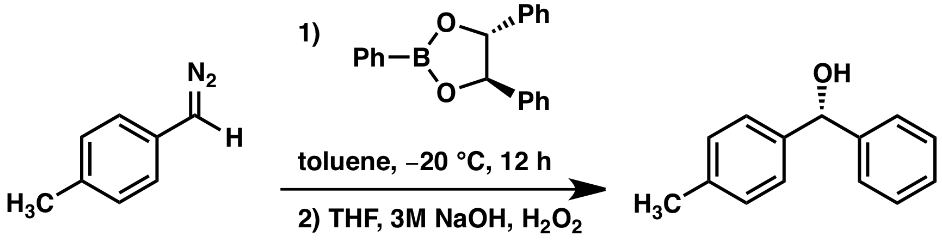
(142) "Lewis Acids Catalyze the Addition of Allylboronates to Aldehydes by Electrophilic Activation of the Dioxaborolane in a Closed Transition Structure," Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, 126, 4518-4519.

increasing reactivity. Entry 1 and 2 of Table 1 show diminished product yield which is presumably due to the decreased diazoalkane survival at 0 ºC. A screen of Lewis acids[143] in entries 5–15 illustrates the absence of boronic ester activation towards increasing productive reagent union or selectivity.

Table 1: Attempts to Increase Reactivity with Lewis Acid Activation



entry	Lewis Acid	temp	conc.	yield	% ee
1	none	0 °C	0.25 M	36%	12%
2	none	0 °C	1.00 M	41%	14%
3	none	–20 °C	0.20 M	58%	20%
4*	none	–20 °C	0.20 M	29%	14.7%
5	$Sc(OTf)_3$	–20 °C	0.20 M	no rxn	--
6	$Ti(O\textit{i}Pr)_4$	–20 °C	0.20 M	52%	9%
7	$Sc(acac)_3$	–20 °C	0.20 M	53%	22%
8	$Sm(OTf)_3$	–20 °C	0.20 M	no rxn	--
9	$Al(O\textit{i}Pr)_3$	–20 °C	0.20 M	47%	12%
10	$Yb(OTf)_3$	–20 °C	0.20 M	no rxn	--
11	$La(OTf)_3$	–20 °C	0.20 M	no rxn	--
12	$Sc(TMHD)_3$	–20 °C	0.20 M	31%	12%
13	$Sc(hfacac)_3$	–20 °C	0.20 M	28%	13%
14	$TiCl_4$	–20 °C	0.20 M	no rxn	--
15	$BF_3 \cdot OEt_2$	–20 °C	0.20 M	no rxn	--

All reactions run for 12 h. *$NaBO_3$ in oxidation.

The modest nature of these data, in combination with the fact that more exciting results in a related arena were forthcoming (see below), led us to postpone further optimization of this system (such as ideas toward

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(143) All Lewis acids employed in Table 1 were used in a stoichiometric equivalent of Lewis acid to boronic ester.

alternating the diol ligand[144,145]). Although we did foresee potential applications in the synthesis of other biologically active molecules[146] with alternative carbon-boron bond derivatizations (Scheme 6), we decided to reexamine our choice of electrophile.

As mentioned previously, the use of boronic esters would benefit our method since the esters possess superior stability relative to trialkylborane reagents and are more compatible with diazoalkane reagents in comparison to Brønsted acidic boronic acids. Unfortunately, the stability of boronic esters comes at a cost to reactivity due to the aforementioned reduction in Lewis acidity (Scheme 3). Previous research has shown the futility of using trialkylboranes, since competition among the available migration pathways in betaine borate intermediates can lead to multiple products. With three C_{alkyl}-B bonds possessing a nearly equivalent migratory preference, the product distribution would be far from ideal in a proposed methodology based on diazoalkane nucleophiles, such

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(144) The diol ligand can be quantitatively recovered following silica gel chromatography of the oxidized product.

(145) (a) "Bidirectional Metalation of Hydrobenzoin: Direct Access to New Chiral Ligands and Auxiliaries," Cho, I.; Meimetis, L.; Britton, R. *Org. Lett.* **2009**, *11*, 1903-1906. (b) "Catalytic Enantioselective Allyl- and Crotylboration of Aldehydes Using Chiral Diol•$SnCl_4$ Complexes. Optimization, Substrate Scope and Mechanistic Investigations," Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481-8490. (c) "Practical and Efficient Multigram Preparation of a Camphor-Derived Diol for the Enantioselective Lewis Acid Catalyzed Allylboration of Aldehydes," Lachance, H.; St-Onge, M.; Hall, D. G.; *J. Org. Chem.* **2005**, *70*, 4180–4183.

(146) (a) "CDP840. A Prototype of a Novel Class of Orally Active Anti-Inflammatory Phosphodiesterase 4 Inhibitors," Alexander, R. P.; Warrellow, G. J.; Eaton, M. A. W.; Boyd, E. C.; Head, J. C.; Porter, J. R.; Brown, J. A.; Reuberson, J. T.; Hutchinson, B.; Turner, P.; Boyce, B.; Barnes, D.; Mason, B.; Cannell, A.; Taylor, R. J.; Zomaya, A.; Millican, A.; Leonard, J.; Morphy, R.; Wales, M.; Perry, M.; Allen, R. A.; Gozzard, N.; Hughes, B.; Higgs, G. *Bioorg. Med. Chem. Lett.* **2002,** *12*, 1451-1456. (b) "Tolterodine – a New Bladder-Selective Antimuscarinic Agent," Nilvebrant, L.; Andersson, K.-E.; Gillberg, P.-G.; Stahl, M.; Sparf, B. *Eur. J. Pharmacol.* **1997** 327 195-207.

as in the potential use of a diisopinocampheylboron platform (Ipc$_2$BR)[147] or an analogy to the *C*$_2$-symmetric, 2,5-dimethylborolane reagent developed by Masamune.[148] After analysis of boron derivatives that could be used in the proposed reaction, one class of boron reagents remained to be tested – diboron reagents.

3.1.d *Investigations into the Reaction of Diazoalkanes with Diboron Reagents: Literature Precedent*

Reactivity of commercially available diboron reagents, bis(catecholato)diboron (B$_2$cat$_2$) and bis(pinacolato)diboron (B$_2$pin$_2$), has been studied by Wang and coworkers by engaging ethyldiazoacetate in reaction with boroxines (Scheme 4). Recent reports from Hoveyda and coworkers demonstrate the reactivity of B$_2$pin$_2$ with *N*-heterocyclic carbenes (NHC) in the absences of metal catalyst.[149] Therefore, we were uncertain as to whether or not a transition metal catalyst was required to activate the vacant boron *p*-orbital in the diboron reagent. They propose Lewis basic activation of B$_2$pin$_2$ for Michael-type addition by a catalytic amount of a chiral NHC. Whereas there is no leaving group attached to the carbene carbon in the NHC catalyst, the diazoalkane, with its excellent dinitrogen nucleofuge, may undergo similar reversible Lewis base addition to the boron atom in B_2pin_2 forming the borate complex, followed by 1,2-migration of the B–B bond through an antiperiplanar geometry to the dinitrogen leaving group (Scheme 7).

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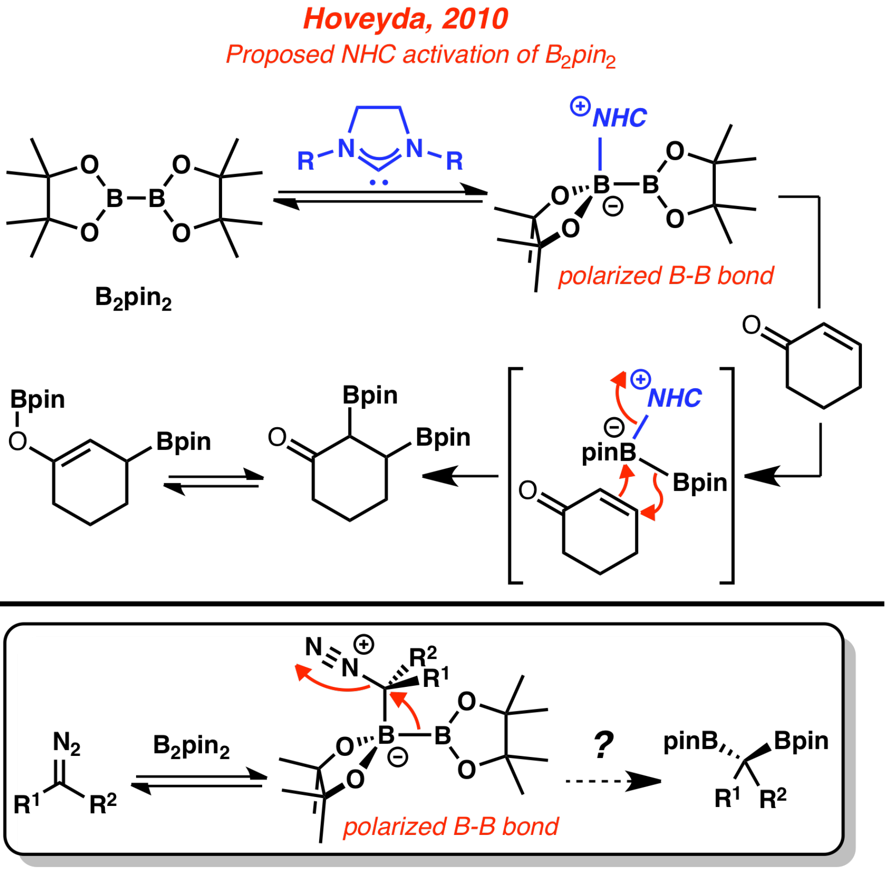
[147] "An Asymmetric Synthesis of the Diastereomeric 1-(2-Cyclohexenyl)-1-alkanols in High Optical Purity via a Stereochemically Stable Allylic Borane, β-2-Cyclohexen-1-yldiisopinocampheylborane," Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564–2565.

[148] (a) "Organoboron Compounds in Organic Synthesis. 1. Asymmetric Hydroboration," Masamune, S.; Kim, B. M.; Petersen, J. S.; Sato, T.; Veenstra, S. J.; Imai, T. *J. Am. Chem. Soc.*, **1985**, *107*, 4549–4551. (b) "Organoboron Compounds in Organic Synthesis. 2. Asymmetric Reduction of Dialkyl Ketones with (*R,R*)- or (*S,S*)-2,5-Dimethylborolane," Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T. A.; Kennedy, R. M.; Masamune, S. *J. Am. Chem. Soc.* **1986**, *108*, 7402–7404.

[149] "Efficient C–B Bond Formation Promoted by N-Heterocyclic Carbenes: Synthesis of Tertiary and Quaternary B-Substituted Carbons through Metal-Free Catalytic Boron Conjugate Additions to Cyclic and Acyclic α,β-Unsaturated Carbonyl," Lee, K.-s.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–7255.

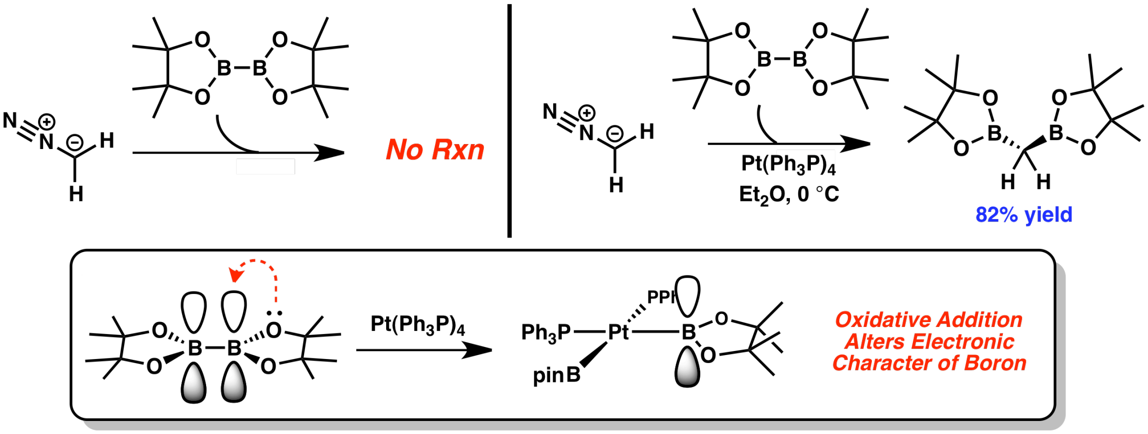
Scheme 7: Potential Hooz-Type Reactivity with Diboron Reagents.



Literature investigations returned reports from Srebnik and coworkers using non-stabilized diazoalkanes in reaction with B_2pin_2 that demonstrated the need for a metal catalyst to alter the electronic character of the boron atom in order to facilitate reaction with diazomethane

(Scheme 8).[150] Upon oxidative addition of tetrakis(triphenylphosphine)platinum catalyst into the B–B bond, the electron density on boron is pulled toward the more electronegative platinum nucleus thereby enabling favorable reaction with the presumed platinum carbenoid from the diazoalkane nucleophile.[150,152]

Scheme 8: Reactivity of Diboron Reagents and Diazomethane by Srebnik



3.1.e *Preliminary Studies of the Pt-Catalyzed Geminal Diboration of Diazomethane.*

Mechanistic detail has been initially aided by control experiments that support the need for platinum catalysis. Upon attempted reaction of diazomethane in the absence of metal catalyst, no productive conversion was observed. Furthermore, in absence of the platinum catalyst, no reaction was observed for ethyldiazoacetate. To support the platinum-boron complex (highlighted box, Scheme 8), isolation of the platinum tetrakis(triphenylphosphene) complex after insertion into the B–B bond of

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(150) "Addition Reactions of Bis(pinacolato)diborane(4) to Carbonyl Enones and Synthesis of (Pinacolato)$_2$BCH$_2$B and (pinacolato)$_2$BCH$_2$CH$_2$B by Insertion and Coupling," Ali, H. A.; Goldberg, I.; Srebnik, M. *Organometallics* **2001**, *20,* 3962–3965.

B_2pin_2 has been reported with x-ray crystallography.[151] Additionally, platinum-catalyzed addition of diazomethane into a tetrakis(dialkylamino)diboron reagent failed in multiple trials with different *N*-alkyl substitutions, presumably due to higher N_{lp} → B_{σ^*} FMO contributions. While this data supports of non-Hooz mechanism, additional experimentation is needed to conclusively determine the mechanistic sequence.

3.1.f *Previous Scope in the Pt-Catalyzed Geminal Diboration of Diazoalkanes.*

Srebnik and coworkers demonstrate the use of 1,1-diborylmethane in Michael additions to α,β-unsaturated ketones. Our desire is to use the reactivity of our diverse range of non-stabilized diazoalkanes synthesize *gem*-disubstituted diboronic esters and effeciently convert them to other important functional groups. The Srebnik communication disclosing a formal methylene insertion into B_2pin_2 represents the only method of using non-stabilized diazoalkanes to achieve this transformation. The standard method employed for this desired goal is typically the use of lithiumchloromethane, by a Matteson homologation sequence. Srebnik and coworkers have communicated the synthesis of four other *gem*-diboronic esters products to publish their novel structures with

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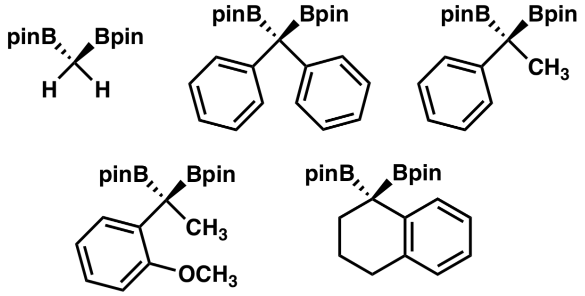
(151) "Platinum(0)-Catalyzed Diboration of Alkynes with Tetrakis(alkoxo)diborons: An Efficient and Convenient Approach to *cis*-Bis(boryl)alkenes," Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N. *Organometallics* **1996**, *15*, 713–720.

crystallography studies (Figure 2).[152] The narrow substrate scope is potentially due to perceived hazards in non-stabilized diazoalkane synthesis.

Figure 2: Limited Exploration in Substrate Scope



While reaction of diazomethane is conducted at 0 ºC with the prescribed method, more sterically hindered examples, shown in Figure 2, are constructed under relatively harsh reaction conditions, refluxing toluene for 12 hours. Our experience has shown us the remarkable stability of aryl-substituted diazomethanes and therefore we were unsure of high temperatures as a requirement for reactivity. Before commencing studies of Pt-catalyzed insertion of our diverse selection of diazoalkanes into B_2pin_2, we wanted to acquire an understanding regarding reactivity of diazoalkanes with transition metal catalysts.

3.1.g *Relevant Metal-Catalyzed Reactions of α-Diazocarbonyl Compounds.*

The use of diazoalkanes as entry into their metal carbenoid chemistries is extensive.[153] We were interested into the mechanism of

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(152) "Novel C1-Bridged Bisboronate Derivatives by Insertion of Diazoalkanes into Bis(pinacolato)diborane," Ali, H. A.; Goldberg, I.; Kaufmann, D.; Burmeister, C.; Srebnik, M. *Organometallics* **2002**, *21*, 1870–1876.

platinum-catalyzed carbenoid formation from diazoalkanes and a literature survey finds that palladium metal more often serves as a catalyst in the coupling of boron-based reagents and diazoalkanes.[154] In order to understand the development of these current methods, we wanted to familiarize ourselves with the research background of these authors' works into metal-catalyzed diazoalkane insertion reactions.

Reports by Van Vranken and coworkers have utilized the presumed formation of a palladium carbenoid from trimethylsilyldiazomethane (TMSD) in the presence of soft carbon nucleophiles, such as malonate esters, or secondary amines, to intercept π–allyl palladium intermediates (Scheme 9).[155]

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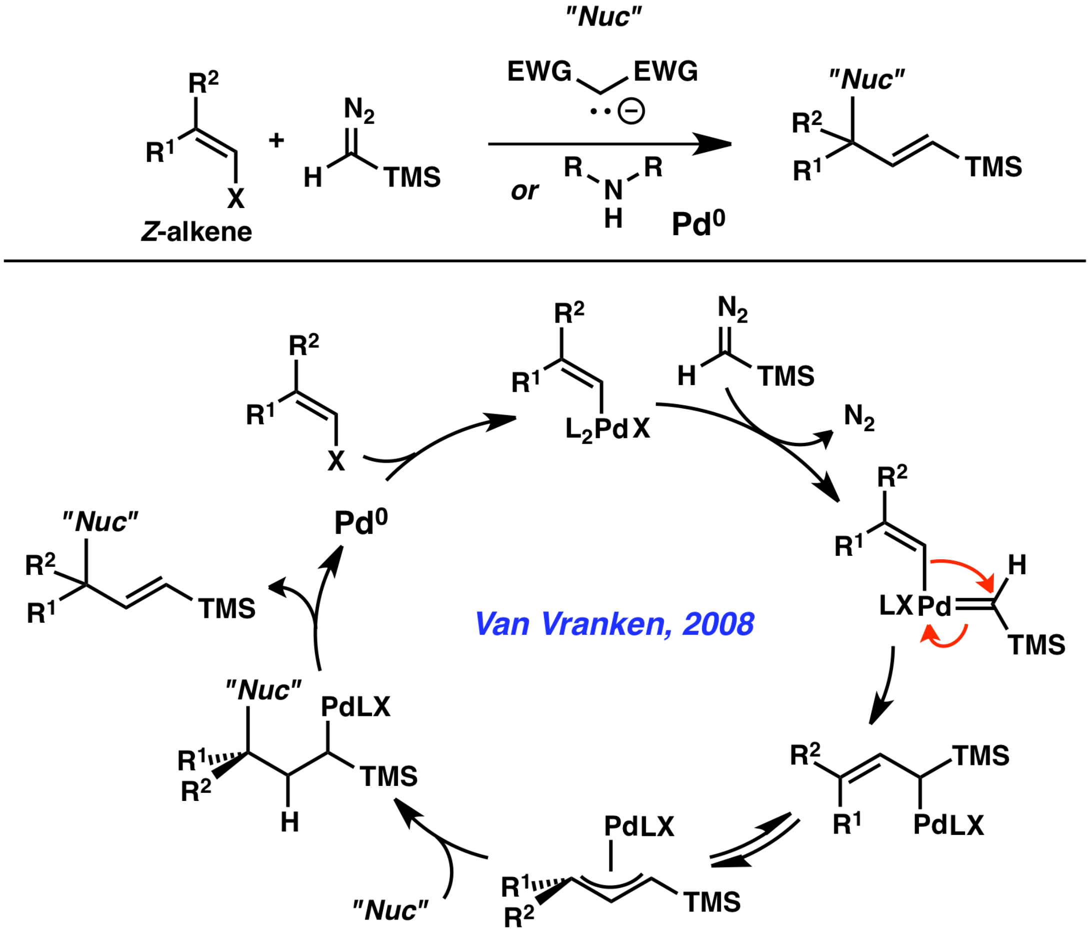
(153) (a) "Recent Advances in Asymmetric Catalytic Metal Carbene Transformations," Michael P. Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–936. (b) "Catalytic Carbene Insertion into C−H Bonds," Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704–724. (c) "Catalytic Enantioselective C−H Activation by Means of Metal−Carbenoid-Induced C−H Insertion," Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2904. (d) "Stereoselective Cyclopropanation Reactions," Lebel, H.; Marcoux, J.-F.; Carmela Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (e) "Enantioselective Catalytic Aziridinations and Asymmetric Nitrene Insertions into CH Bonds," Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2920.

(154) (a) "Palladium-Catalyzed Cross-Coupling of α-Diazocarbonyl Compounds with Arylboronic Acids," Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566–1567. (b) "Palladium-Catalyzed Oxidative Cross-Coupling Reaction of Arylboronic Acids with Diazoesters for Stereoselective Synthesis of (*E*)-α,β-Diarylacrylates," Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 4506–4509.

(155) (a) "Palladium-Catalyzed Carbene Insertion into Vinyl Halides and Trapping with Amines," Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2007**, *9*, 2047–2049. (b) "Palladium-Catalyzed Carbene Insertion and Trapping with Carbon Nucleophiles," Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909–1911. (c) "Cyclization Reactions Involving Palladium-Catalyzed Carbene Insertion into Aryl Halides," Kudirka, R.; Van Vranken, D. L. *J. Org. Chem.* **2008**, *73*, 3585–3588.

Scheme 9


"Nuc"
EWG
EWG
R^2
R^1
X
Z-alkene
+
N_2
H
TMS
or
R
N
R
H
Pd^0
"Nuc"
R^2
R^1
TMS
R^2
R^1
X
R^2
R^1
L_2PdX
N_2
H
TMS
N_2
R^2
R^1
LXPd
H
TMS
Van Vranken, 2008
Pd^0
"Nuc"
R^2
R^1
TMS
"Nuc"
PdLX
R^1
R^2
TMS
H
R^2
TMS
R^1
PdLX
PdLX
R^1
R^2
TMS
"Nuc"

These authors perturb the donor-acceptor properties of the diazoalkane functionality in TMSD by engaging it as a palladium carbenoid in order for the carbenoid carbon to behave in analogy carbon monoxide via palladium(0)-catalyzed carbonylative coupling reaction.[156]

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(156) Originally pioneered by Heck (a) "A Synthesis of Diaryl Ketones from Arylmercuric Salts," Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5546–5548. (b) "Palladium-Catalyzed Carboalkoxylation of Aryl, Benzyl, and Vinylic Halides," Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318–3326. The extension of the method has been adapted to a wide range of nucleophiles. For Tin, see: (c) "Unsymmetrical Ketone Synthesis from Organic Halides, Carbon Monoxide, and Organotin Compounds Catalyzed by a Palladium Complex," Tanaka, M. *Tetrahdron Lett.* **1979,** *20*, 2601-2602. (d) "Palladium-Catalyzed Carbonylative Coupling of Aryl Triflates with Organostannanes," Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557–1565. For Copper, see: (e) "Convergent Synthesis of the Quinolone Substructure of BILN 2061 via Carbonylative Sonogashira Coupling/Cyclization," Haddad, N.; Tan, J.; Farina, V. *J. Org. Chem.* **2006**, *71*, 5031–5034. For boron, see: (f) "Palladium-Catalyzed

Alternatively, Chen and Wang have communicated the successful merging of a π-allyl palladium intermediate and α-diazocarbonyl compounds to access conjugated dienyl carbonyl compounds invoking the mechanistically plausible carbenoid intermediate.[157] The evolution of their research became a combination of two methods in which the carbenoid derived from α-diazocarbonyl compounds is cabonylated to form ketene intermediates presumably through carbon monoxide ligand migration,[158] which is a mechanistic analogy to metal-catalyzed carbonylative coupling reactions.[156]

Shown in Scheme 10, palladium-catalyzed coupling of ethyldiazoacetate (EDA) with aryl- or vinyl-iodides is productively combined in the presence of carbon monoxide atmosphere to amazingly retain the diazo functionality, without formation of the palladium carbenoid,

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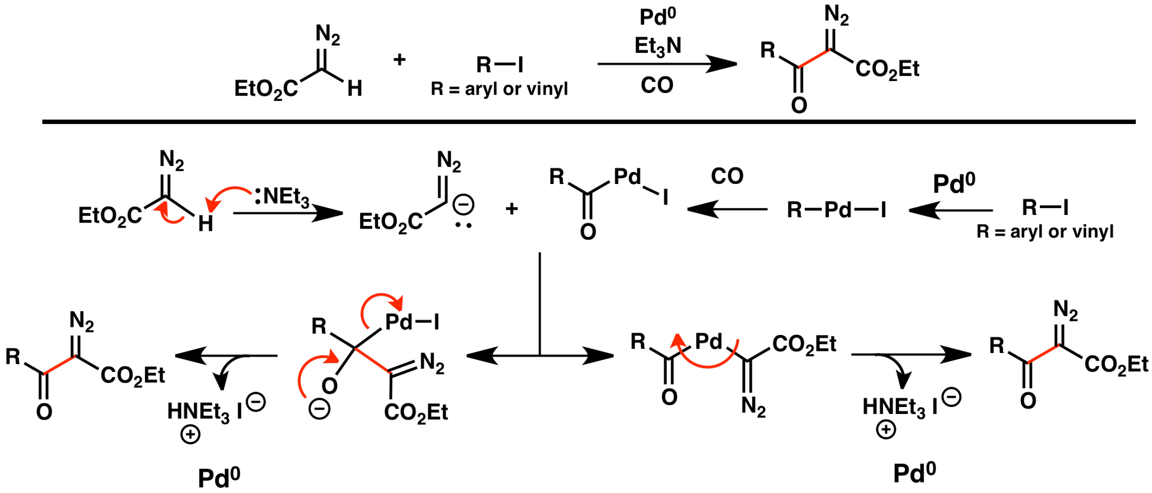
Carbonylative Cross-Coupling Reaction of Arylboronic Acids with Aryl Electrophiles: Synthesis of Biaryl Ketones," Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726–4731. (g) "Palladium(0)-Catalyzed Carbonylation of Alkenyl- and Aryl- Borates and Boronic Acids with Carbon Monoxide," Ohe, T.; Ohe, K.; Uemura, S.; Sugita, N. *J. Organomet. Chem.* **1988** 344 C5-C7. For nickel, see: (h) "Nickel-Catalyzed Carbonylative Negishi Cross-Coupling Reactions," Wang, Q.; Chen, C. *Tetrahedron Lett.* **2008,** *49*, 2916-2921. For aluminum, see: (i) "Ketone Synthesis via Palladium-Catalyzed Carbonylation of Organoaluminium Compounds," Bumagin, N. A.; Ponomaryov, A. B.; Beletskya, I. P. *Tetrahedron Lett.* **1985,** *26*, 4819-4822. For magnesium, see: (j) "Selectvie Formation of Ketone, Diketone and Aldehyde by the CO Insertion into the Nickel-Alkyl Bonds of Dialkylnickel Complexes. A Novel Nickel-Catalyzed Synthesis of Ketones and Tertiary Alcohols from Grignard Reagents, Aryl Halides, and Carbon Monoxide," Yamamoto, T.; Kohara, T.; Yamamoto, A. *Chem. Lett.* **1976,** *5*, 1217-1220. For silicon, see: (k) "Highly Selective Cross-Coupling Reactions of Organosilicon Compounds Mediated by Fluoride Ion and a Palladium Catalyst," Hatanaka, Y.; Hiyama, T. *Synlett* **1991,** 845-853.

(157) "Palladium-catalyzed reaction of allyl halides with α-diazocarbonyl compounds," Chen, S.; Wang, J. *Chem. Commun.* 2008, 4198-4200.

(158) "Pd-Catalyzed Carbonylation of Diazo Compounds at Atmospheric Pressure: A Catalytic Approach to Ketenes," Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330–4341.

and delivers β-keto α-diazocarbonyl compounds.[159] This work proves the efficient nucleophilic use of diazoalkanes in palladium-catalyzed coupling reactions under basic conditions, although the authors refrain from comment regarding the mechanistic fate of the ethyldiazoacetate anion. Select plausible mechanistic pathways are shown in Scheme 10.

Scheme 10: The Pd(0)-Catalyzed Carbonylative Coupling of EDA with Aryl- or Vinyl-Iodides



After presumed deprotonation with an amine base, the diazo compound possesses sufficiently localized carbanionic character and thus demonstrates that carbonyl-stabilized diazoalkanes are compatible nucleophiles.

Separate from this unique demonstration of palladium-catalyzed derivatization of ethyldiazoacetate, the use of a boron-transition metal bond, which is catalytically generated, has not been extensively investigated. Limited research towards metal-catalyzed coupling of boronic acids and boroxine derivatives with stabilized diazoalkanes relies on their conversion to carbenoid equivalents in order to insert into the carbon-boron bond.[160] These results further encouraged us to extend the limited scope of the Srebnik method by employing our diverse scope of the generally more nucleophilic, non-stabilized diazoalkanes in our planned metal-catalyzed process (Scheme 8 and Figure 2).

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[159] "Palladium-Catalyzed Cross-Coupling of Aryl or Vinyl Iodides with Ethyl Diazoacetate," Peng, C.; Cheng, J.; Wang, J. *J. Am. Chem. Soc.* **2007**, *129*, 8708–8709.

3.1.j *Previous Synthetic Methods to Access Geminal Diborylalkanes.*

We wanted to be aware of the previously developed methodology to access monosubstituted geminal diborylmethanes before entering into active research toward the diversification of the known disubstituted, geminal diborylmethanes via our expanded non-stabilized diazoalkane scope (Figure 2). The most common protocol to access these trisubstituted variants is through double hydroboration reaction of terminal alkynes (Scheme 11).

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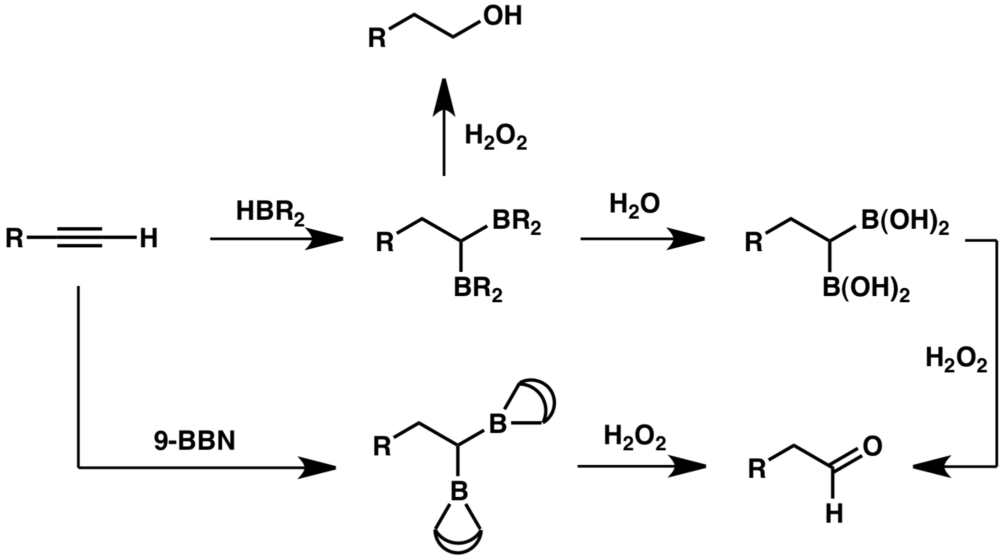
(160) (a) "Palladium-Catalyzed Cross-Coupling of α-Diazocarbonyl Compounds with Arylboronic Acids," Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566–1567. (b) "Palladium-Catalyzed Oxidative Cross-Coupling Reaction of Arylboronic Acids with Diazoesters for Stereoselective Synthesis of (*E*)-α,β-Diarylacrylates," Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 4506–4509.

Scheme 11: Dihydroboration to Yield Geminally Diborylated Products



As illustrated in Scheme 11, use of an excess of borane with a terminal alkyne yields 1,1-diborane intermediates where upon direct oxidation the sole product is the primary alcohol due to the rate of proteodeborylation outcompeting the rate of a second oxidation that would form the primary hydrate.[161] However, if the aldehyde product is desired, the geminal diborane must first undergo hydrolysis to the boronic acid and then introduction of peroxide will yield the carbonyl oxidation state. It was later discovered that use of the sterically bulky borane, 9-borabicyclo(3.3.1)nonane (9-BBN),[162] in the double hydroboration event will deliver the aldehyde product following direct peroxide oxidation of the

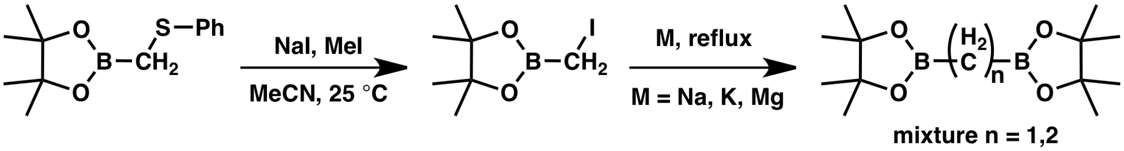
---

(161) "Reactions avec le diborane," Dulou, R.; Chretien-Bessière, Y. *Bull. Soc. Chim. Fr.* **1959**, 1362.

(162) "Simple, Remarkably Efficient Route to High Purity, Crystalline 9-Borabicyclo[3.3.1]nonane (9-BBN) Dimer," Soderquist, J. A.; Brown, H. C. *J. Org. Chem.* **1981**, *46*, 4599–4600.

9-(BBN) dihydroboration product (Scheme 11).[163] Alternatively, the desired production of geminally substituted diboronic esters can be achieved as a mixture using a reductive coupling of (pinacolato)boratamethylene iodide (Scheme 12),[150] which is generated from simple substitution and alkylative trap of the nucleofuge.[164]

Scheme 12: Matteson-Srebnik Synthesis of (Pinacolato)$_2$BCH$_2$B



Synthesis of 1,1-diborylated cyclopropanes is achieved following a similar mechanistic pathway as the previous example (Scheme 12) with metal-halogen exchange that enables nucleophilic reactivity on a diboron reagent, similar to the original Hooz-Matteson work.[165] Very few variations from these reports exist to synthesize the desired *gem*-diboryl products, with dihydroboration predominating.[166] Due to this frequency for employing hydroboration protocols there are a limited number of reports that attempt to obtain disubstituted *gem*-diboryl compounds as the

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(163) (a) "Hydroboration. 50. Hydroboration of Representative Alkynes with 9-Borabicyclo[3.3.1]nonane - A Simple Synthesis of Versatile Vinyl Bora and *gem*-Dibora Intermediates," Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc.* **1979**, *101*, 96–99. (b) "Synthesis of β-Cyclopropyl- and β-Cyclobutylbicyclo[3.3.1]nonane via Ring Closure of Boron Intermediates. A Convenient Entry into Cyclopropyl and Cyclobutyl Derivatives via Hydroboration," Brown, H. C.; Rhodes, S. P. *J. Am. Chem. Soc.* **1969**, *91*, 4306–4307.

(164) "Iodomethaneboronic Esters and Aminomethane Boronic Esters," Matteson, D. S.; Majumdar, D. *J. Organomet. Chem*. **1979**, *170*, 259-264.

(165) "Synthesis and Applications of 1,1-Diborylated Cyclopropanes: Facile Route to 1,2-Diboryl-3-methylenecyclopentenes," Shimizu, M.; Schelper, M.; Nagao, I.; Shimono, K.; Kurahashi, T.; Hiyama, T. *Chem. Lett.* **2006**, *35*, 1222–1223.

(166) "Synthesis and Reactivity of sp^3-Geminated Organodimetallics," Marek, I.; Normant, J.-F. *Chem. Rev.* **1996**, *96*, 3241–3268, and references therein.

targeted product.[165] This stems from a limitation of the dihydroboration method – it only tolerates the use of terminal alkynes. The dihydroboration methods that do report the synthesis of disubstituted *gem*-diboryl products are accounting for presence as byproducts.[167]

3.2 *Access to Novel Disubstituted gem-Diborylalkanes*

Initially envisioning the Hooz reaction as a protocol to efficiently access tertiary alcohols, tertiary amines, and/or all-carbon quaternary centers was found to be unsuccessful due the requirement of catalyst activation of the diboron reagent. This limited reactivity of boronic esters in the original Hooz process motivated us to address the scope of diazoalkane compatibility with platinum-catalyzed insertion into diboron reagents. However, the discovery of the platinum-catalyzed method now serves as a conduit to the same highly substituted products. We were now aware of a gap in chemical space that we could potentially fill stemming from our experience in non-stabilized, disubstituted diazoalkane synthesis. We wanted to not only efficiently synthesize a range of disubstituted *gem*-diboryl compounds, but also use this unique chemical moiety towards our original goal of accessing important functional groups in organic chemistry. Literature investigations immediately revealed a

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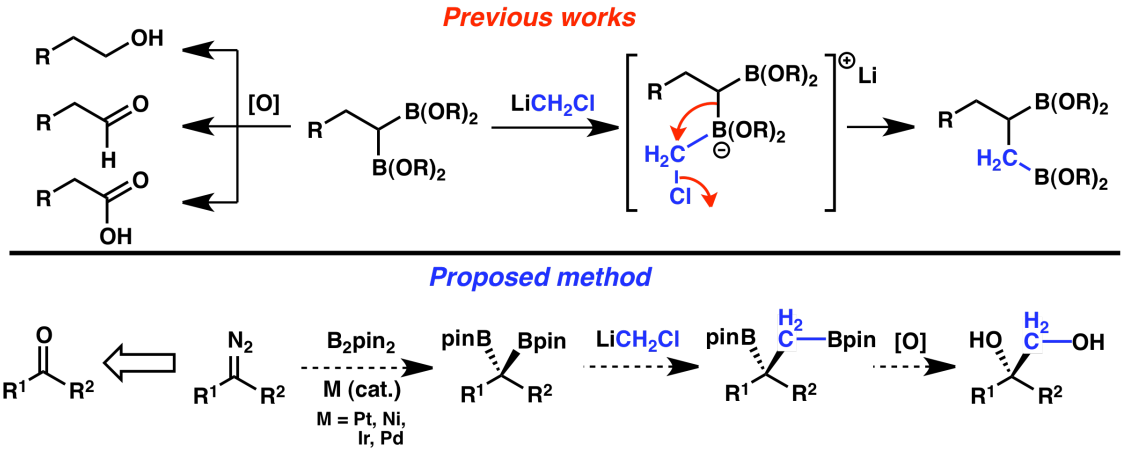
(167) "Bis(imidazoline-2-thione)–Copper(I) Catalyzed Regioselective Boron Addition to Internal Alkynes," Kim, H. R.; Jung, I. G.; Yoo, K.; Jang, K.; Lee, E. S.; Yun, J.; Son, S. U. *Chem. Commun.* **2010**, *46*, 758-760.

wide range of minimally developed chemical transformations of the *gem*-diboryl functional group.

In addition to the common oxidation of the carbon-boron bond, Morken and others have reported the use of a Matteson homologation with $LiCH_2Cl$ to precede the oxidation event for the synthesis of methanol substituents at each site of the newly formed carbon-boron bond(s) (Scheme 13).[168] With this targeted strategy, we initially planned to functionalize the disubstituted geminal diboronic ester products with the reported Matteson homologation/oxidation sequence[168] to afford racemic 1,2-diol products.

Scheme 13



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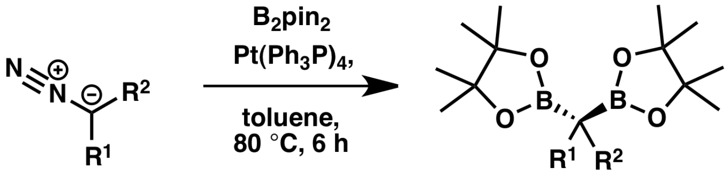
[168] (a) "(Chloromethyl)lithium: Efficient Generation and Capture by Boronic Esters and a Simple Preparation of Diisopropyl (chloromethyl)boronate," Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687–1689. (b) "Catalytic Asymmetric Carbon–Carbon Bond Forming Reactions: Preparation of Optically Enriched 2-Aryl Propionic Acids by a Catalytic Asymmetric Hydroboration–Homologation Sequence," Chen, A. C.; Ren, L.; Crudden, C. M. *Chem. Commun.* **1999**, 611-612. (c) "Catalytic Asymmetric Hydrocarboxylation and Hydrohydroxymethylation. A Two-Step Approach to the Enantioselective Functionalization of Vinylarenes," Chen, A. C.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, *64*, 9704–9710. (d) "Homologations of Boronate Esters: the First Observation of Sequential Insertions," Ren, L.; Crudden, C. M. *Chem. Commun.* **2000**, 721-722. (e) "Pt-Catalyzed Enantioselective Diboration of Terminal Alkenes with B_2pin_2," Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210–13211.

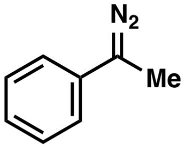
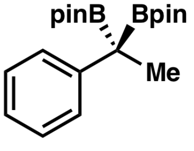
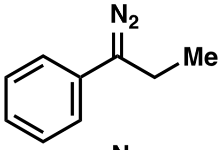
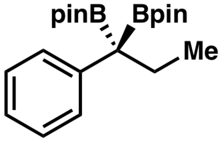
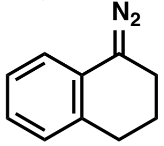
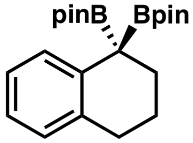
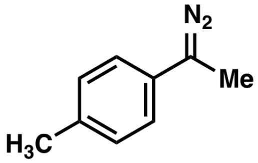
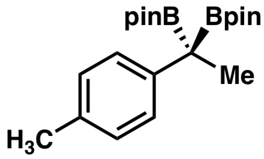
As shown in scheme 13, this reaction sequence was proposed because of its documented efficiency and this double functionalization of the carbon-boron bond(s) would quickly engender a dramatic polarity difference from the nonpolar starting geminal diboronic esters to ease the purification of the diol products. We then began our research into expanding the scope of disubstituted *gem*-diboryl methanes by enlisting our experience in the synthesis of novel and unusual non-stabilized diazoalkanes.

3.2.a *Scope of the Pt-Catalyzed Geminal Diboration of Non-Stabilized Diazoalkanes.*

The initial non-stabilized diazoalkane reagent chosen for model studies was methyl phenyl diazomethane. This aryl-based diazoalkane would facilitate reaction progress monitoring by UV analysis of reaction mixture aliquots after TLC development. The initial results were quite gratifying where the desired disubstituted geminal diboronic ester was received in high yield (79% yield isolated). As seen in Table 2, the substrate scope was originally studied with aryl-based hydrocarbon substituted variants of the model compound, so as to confirm the work of Srebnik *et al.* and optimize the reaction conditions. The temperature of the toluene reaction was found not to require a refluxing environment for the efficient production of the desired *gem*-diboronic ester, also the reduced temperature allows prolonged diazoalkane survival during the shortened 6 hour reaction period.

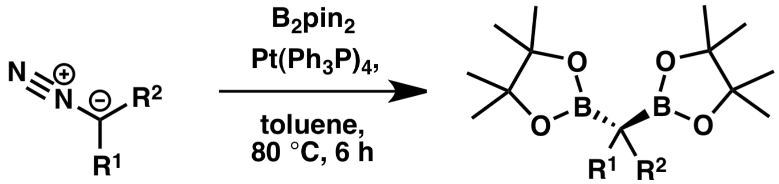
Table 2: Geminal Diboronic Ester Products from $Pt(Ph_3P)_4$ Catalyzed Diboration of Diazoalkanes

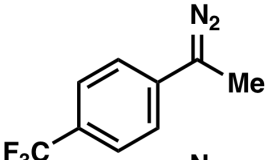
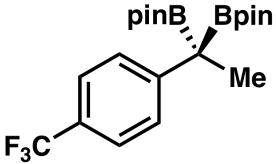
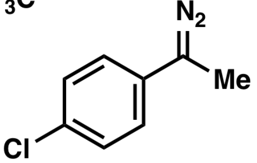
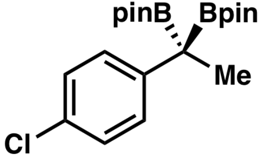
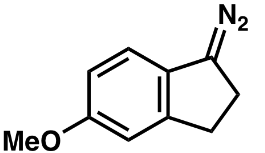
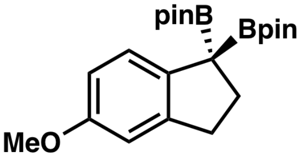
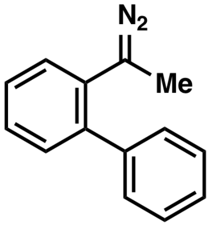
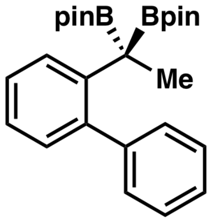


entry	diazo	product	yield
1			79%
2			74%
3			78%
4			80%

Brief studies were undertaken to investigate alternative metal-catalyst that are known to oxidatively insert between the boron-boron bond in other settings. Although much more research would be needed to conclusively state that platinum tetrakis(triphenylphosphine) is the optimal catalyst, nickel (0) complexes (i.e. $Ni(PCy_3)_2$) and palladium (0) catalysts ($Pd(Ph_3P)_4$ and Pd_2dba_2) failed to deliver the desired products as detected by mass spectrometric analysis of crude organic mixtures. Interestingly, there have been reports of significant reactivity differences between $Pt(Ph_3P)_4$ and $Pt(dba)_2$ during 1,2-diboration of alkenes as illustrated with the large contrast in reaction temperature requirements.[169] We did not use Pt(dba)$_x$ catalysts in our initial trials. Instead, our attention turned to extending the substrate scope with the Pt(Ph$_3$P)$_4$ catalyst first using aryl-based diazoalkanes and altering their electronic and steric characteristics (Table 3).

Table 3: Geminal Diboronic Ester Products from Pt(Ph$_3$P)$_4$ Catalyzed Diboration of Diazoalkanes: Steric and Electronic Arene Modifications



entry	diazo	product	yield
1			68%
2			61%
3			76%
4			71%

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[169] "Platinum(0)-Catalyzed Diboration of Methylenecyclopropanes with Bis(pinacolato)diboron: A Selective Route to 2,4-Bis(boryl)-1-butenes," Ishiyama, T.; Momota, S.; Miyaura, N. *Synlett* **1999**, *11,* 1790-1792 and references therein.

Although the yields are generally moderate for the electronically and sterically modified examples shown in Table 3, the tolerance of extreme steric hindrance in entry 4 demonstrates the method's potential use in crowded synthetic settings. Also of note is entry 2, which preserves the aryl chloride during the reaction sequence and speaks to the slow oxidative addition of platinum(0) with these substrates in Miyaura borylation methodologies.[170]

Further extension of the protocol is provided with the tolerance of alkyl-based diazoalkanes as shown in Table 4. In general, a slight increase in yield was observed for the alkyl-based nucleophiles, which is in agreement with the general increase in reactivity amongst these diazoalkanes. Also, the absence of any resonance stabilization from a π-system, such as in the alkyl-based diazoalkanes, slightly increases the nucleophilicity of the platinum carbenoid.[153]

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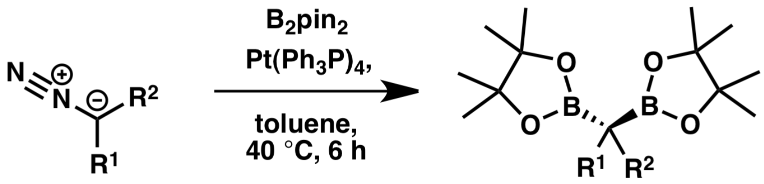
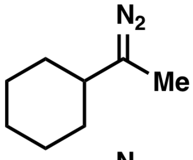
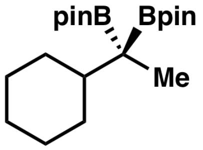
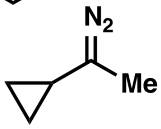
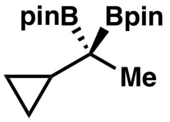
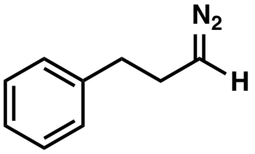
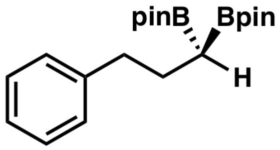
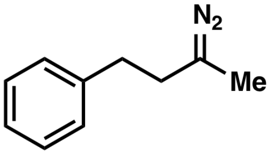
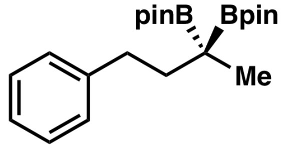
(170) (a) "Palladium(0)-Catalyzed Cross-Coupling Reaction of Alkoxydiboron with Haloarenes: A Direct Procedure for Arylboronic Esters," Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508-7510. (b) "The Conversion of Phenols to the Corresponding Aryl Halides Under Mild Conditions," Thompson, A. L. S.; Kabalka, G. W.; Akula, M. R.; Huffman, J. W. *Synthesis* **2005**, 547-550.

Table 4: Geminal Diboronic Ester Products from Pt(Ph_3P)$_4$ Catalyzed Diboration of Alkyl-Based Diazoalkanes



entry	diazo	product	yield
1			81%
2			75%
3			70%
4			84%

3.2.b *Mechanistic Questions: Carbenoid versus Borate Mechanism*

As illustrated in Scheme 14, there remains a question as to the electrophilic target of the diazoalkane during the course of the reaction. The originally proposed mechanism is given on the left, whereby, following oxidative addition of the diboron reagent to give **A**,[171] the diazoalkane nucleophilicly attacks the platinum metal, *d*-electrons from the metal help to extrude the dinitrogen leaving group, which forms **C** via **B**. Then the carbenoid migrates to form the first carbon-boron bond (**D**).[150,152,172] A plausible alternative mechanism is also shown in which the vacant *p*-orbital on the boron atom in **A** is attacked by the diazoalkane nucleophile to generate the borate intermediate **G**, then be followed by reductive elimination to the product (**E**), instead of forming a carbenoid (Scheme 14).

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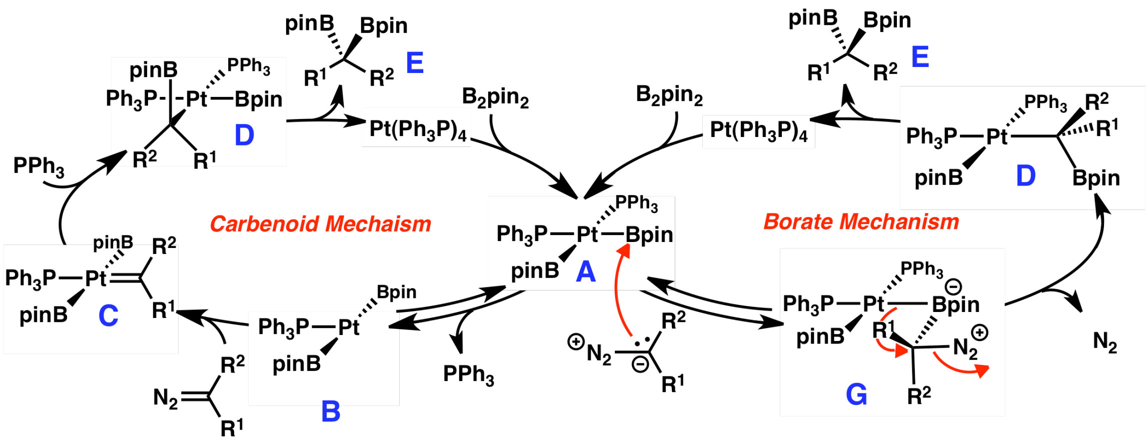
[171] "Chemistry of Group 13 Element-Transition Metal Linkage — the Platinum- and Palladium-Catalyzed Reactions of (Alkoxo)diborons," Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611,* 392-402.

Scheme 14



pinB Bpin R1 R2 E
pinB PPh3 Ph3P-Pt-Bpin R2 R1 D
B2pin2
Pt(Ph3P)4
PPh3
Carbenoid Mechaism
Borate Mechanism
PPh3 Ph3P—Pt—Bpin pinB A
pinB R2 Ph3P—Pt pinB C R1
Bpin Ph3P—Pt pinB B
R2 N2 R1
PPh3
N2 R2 R1
PPh3 Ph3P—Pt—Bpin pinB R1 N2 R2 G
PPh3 R2 Ph3P—Pt R1 pinB D Bpin
N2

3.2.c *Mechanistic Answers Through Spectroscopy*

A potential solution towards the discernment of these mechanistic questions could be found in heteronuclear NMR study. The use of ^{11}B or ^{31}P NMR would give insight into the geometry of the distinct reaction intermediates. As illustrated in Scheme 14, there are two unsymmetrical intermediates in the borate mechanism (**G** and **D**) while there is only one unsymmetrical intermediate in the carbenoid pathway (**D**). If current thinking into the reversible nature of diazoalkane/borate formation is true,[135,149,182] then this reactive intermediate (**G**) should be observable by

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(172) "Mechanism of Rhodium-Catalyzed Carbene Formation from Diazo Compounds," Wong, F. M.; Wang, J.; Hengge, A. C.; Wu, W. *Org. Lett.* **2007**, *9*, 1663–1665.

either ^{11}B or ^{31}P NMR spectroscopy, with potential variable temperature adjustments as an enabling tool. NMR spectroscopy is uniquely suited to study dynamic molecular events as it is a spectroscopic method that detects the molecular motion itself, rather the number of molecules in different states. Due to the electromagnetic frequency used, radio waves, the effects of magnetic spin flip typically have little physical change on the system's energetic state. Because of this characteristic, NMR is able to detect chemical exchange even when the system is in equilibrium. A potential drawback to using the boron nucleus is the well-documented line-broadened peak shapes and loss of resolution.[173] Alternatively, using the isotope ^{195}Pt in the tetrakis (triphenylphosphine) platinum complex, which may be prohibitively expensive to enrich,[174] scalar couplings could be determined between different points with these intermediates thereby providing spatial information during the course of an appropriately designed stoichiometric reaction.[174b] With a convenient spin number of ½ the ^{195}Pt nucleus, which has a high natural abundance and a receptivity value[175] of 20.7, relative to ^{13}C = 1.00, could enable the use of commercially available $Pt(Ph_3P)_4$ in such experiments.

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(173) "Three-Coordinated Boron-11 Chemical Shifts in Borates," Kroeker, S.; Stebbins, J. F. *Inorg. Chem.* **2001**, *40*, 6239–6246 .

(174) The price of platinum on June 23rd, 2011 was $1750 USD per ounce. (a) For a review, see: "An Overview of ^{195}Pt Nuclear Magnetic Resonance Spectroscopy," Priqueler, J. R. L.; Butler, I. S.; Rochon, F. D. *Appl. Spectrosc. Rev.* **2006**, *41*, 185-226. For an example of ^{195}Pt NMR spectroscopy used to study Pt oxidative addition into B_2pin_2, see: (b) "Platinum(0)-Catalyzed Diboration of Alkynes," Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.*, **1993**, *115*, 11018–11019.

(175) The receptivity value is an algebraic combination of natural abundance, gyromagnetic ratio, and nuclear spin and is typically defined realative to the commonly observed nuclei ^{1}H and ^{13}C. Berger, S.; Braun, S. Heteronuclear NMR Spectroscopy. In *200 and More NMR Experiments: A Practical Course*; Wiley-VCH: Weinheim, 2004.

3.2.d ***Differentially Protected Diboron Reagents for Chemoselective Synthesis.***

In analogy to work by the Suginome and Santos groups,[176] platinum-catalyzed *gem*-diboration of diazoalkanes was attempted on a mixed diboron reagent, (pin)B-B(dan), where dan is diaminonaphthalene. To corroborate the initial report of Srebnik et al.,[150] the reaction mixture contained no geminally disubstituted desired product as determined NMR spectroscopy and mass spectrometric analysis of the crude product mixture. Although the installation of differentially protected boron atoms would be enabling to chemoselective processes, initial empirical results show the absence of productive union. Further research is needed to conclusively determine these initial outcomes. Additionally, the use of silylboranes[177] towards the synthesis of analogously mixed *gem*-dimetallics has not been investigated.

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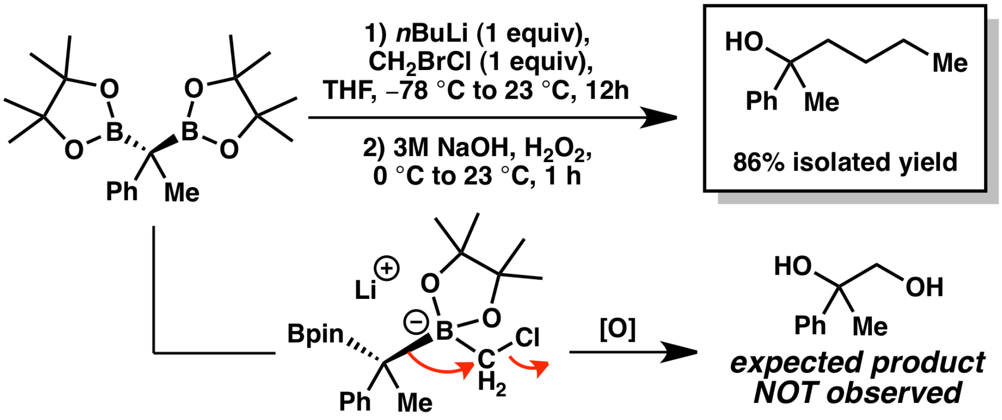
(176) For representative examples, see: (a) "Anthranilamide: A Simple, Removable *ortho*-Directing Modifier for Arylboronic Acids Serving also as a Protecting Group in Cross-Coupling Reactions," Ihara, H.; Koyanagi, M.; Suginome, M. *Org. Lett.* **2011**, *13*, 2662–2665. (b) "Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki−Miyaura Coupling," Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758–759. (c) "Structure and Reactivity of a Preactivated sp^2–sp^3 Diboron Reagent: Catalytic Regioselective Boration of α,β-Unsaturated Conjugated Compounds," Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slebodnick, C.; Marder, T. B.; Santos, W. L. *J. Org. Chem.* **2011**, *76*, 3997–4007. (d) "sp^2–sp^3 Hybridized Mixed Diboron: Synthesis, Characterization, and Copper-Catalyzed β-Boration of α,β-Unsaturated Conjugated Compounds," Gao, M.; Thorpe, S. B.; Santos, W. L. *Org. Lett.* **2009**, 11, 3478-3481. (e) "Differentially Protected Diboron for Regioselective Diboration of Alkynes: Internal-Selective Cross-Coupling of 1-Alkene-1,2-diboronic Acid Derivatives," Iwadate, N.; Suginome, M. *J. Am. Chem. Soc.* **2010**, 132, 2548-2549.

(177) (a) "Unusual Palladium-Catalyzed Silaboration of Allenes Using Organic Iodides as Initiators: Mechanism and Application," Chang, K.-J.; Rayabarapu, D. K.; Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2005**, *127*, 126-131. (b) "Palladium-Catalyzed Asymmetric Silaboration of Allenes," T. Ohmura, H. Taniguchi, M. Suginome, *J. Am. Chem. Soc.* **2006**, *128*, 13682-13683.

3.2.e *Matteson Protocol Results in Unexpected Alkylation.*

The originally planned double Matteson homologation/oxidation sequence was attempted on the diboronic ester product from methyl phenyl diazomethane (Table 1, entry 1), but the desired 1,2-diol product was entirely absent from crude reaction mixtures, as determined by mass spectrometry and ^{1}H NMR spectroscopy. Instead the major product of the reaction sequence was a tertiary alcohol, as initially concluded through IR and NMR analysis (Scheme 15).

Scheme 15: Initial Matteson Homologation/Oxidation: Efficient Tertiary Alcohol Production

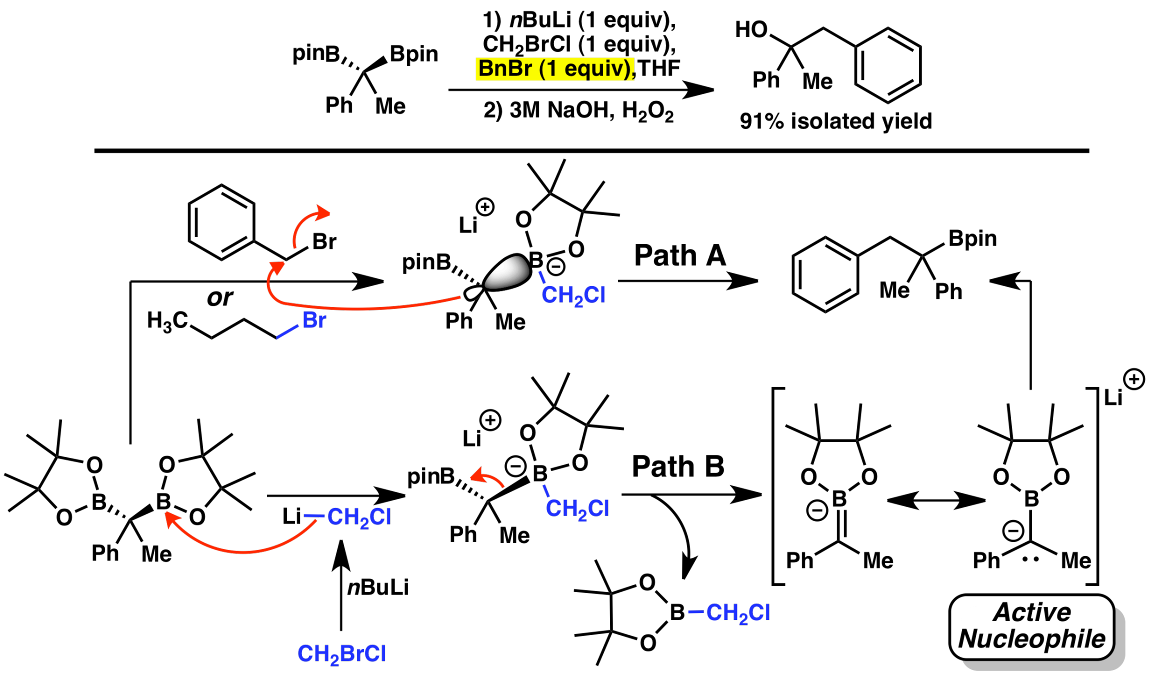

1) *n*BuLi (1 equiv),
CH_2BrCl (1 equiv),
THF, –78 °C to 23 °C, 12h
2) 3M NaOH, H_2O_2,
0 °C to 23 °C, 1 h
HO
Me
Ph
Me
86% isolated yield
O
B
Ph
Me
Li
Bpin
Cl
C
H_2
[O]
HO
OH
Ph
Me
expected product
NOT observed

Although this was a fantastic empirical result, with the one-pot formation of a C_{sp^3}-C_{sp^3} bond and a C_{sp^3}-O bond, the mechanism to account for this transformation remained unprobed. Following the reproduction of the result, a hypothesis was formed as to the in situ generation of an *n*-butyl electrophile. It was presumed that, following the lithium-halogen exchange of *n*BuLi and CH_2BrCl, formation of 1-bromobutane would expose the geminal diboronic ester starting material to a stoichiometric amount of the primary alkyl halide (Scheme 16). An experiment was performed that exposes the *gem*-diboronic ester, under the same reaction conditions, to an additional equivalent of benzyl bromide, which is a much better electrophile than the in situ generated 1-bromobutane. We gratifyingly received the benzyl-containing tertiary alcohol product in excellent yield to lend support to our proposed mechanism.

3.2.f *Initial Experiments Supporting the Proposed Alkylation Mechanism.*

There were still questions as to the nature of the nucleophile in this supposed S_N2 reaction. After the *gem*-diboron species is activated by chloromethyl lithium reagent, the antibonding lobe of the C-B bond could then act in an anionic nucleophilic manner (path A), as in Scheme 2, or the chloromethyl borate could dissociate to leave the carbanion (path B), which then undergoes substitution.

Scheme 16: Mechanistic Questions of Nucleophilic Carbanion Formation.



pinB
Bpin
Ph
Me
1) *n*BuLi (1 equiv), CH₂BrCl (1 equiv), BnBr (1 equiv),THF
2) 3M NaOH, H₂O₂
HO
91% isolated yield
or
Br
H₃C
Li
O
B
CH₂Cl
Path A
Path B
Li—CH₂Cl
*n*BuLi
CH₂BrCl
B—CH₂Cl
Active Nucleophile

The extreme steric hindrance of the incoming nucleophile in path A suggests that the formation of the tertiary boronic ester intermediate would not be formed as efficiently as observed. In addition to being a less hindered carbanion, the nucleophile that is formed following path B will have further stabilization from the illustrated resonance structure where the anion uses boron's vacant *p*-orbital to delocalize and potentially afford a longer lifetime of the reactive intermediate.

3.2.g *Literature precedent of the Alkylation of Geminal Diboronic Esters.*

After this promising result, the usefulness of these geminal diboronic esters was fully investigated in the literature. As previously discussed, using 1,1-diboryl compounds has limited literature precedent due to the inaccessibility of this unique carbon substitution. Using these compounds as reagents in organic synthesis is, with few exceptions,[165] limited to monosubstituted, acyclic geminal diboryl compounds accessed through dihydroboration of terminal alkynes.[166] Even so, there are numerous reports of using 1,1-diboryl compounds in a wide variety of methodologies, albeit vary few with disubstituted *gem*-diboryl reagents which are readily available through our methodology and experience in non-stabilized disubstituted diazoalkane synthesis.

The reaction of monosubstituted *gem*-diboryl compounds with alkyllithium reagents to transiently form 1,1-borolithio intermediates dominates the known chemistry of previously reported *gem*-diboryl substrates. Our discovery of the alkylation/oxidation sequence to form tertiary alcohols (Scheme 15) with the same reagents as required for a Matteson-type homologation/oxidation[168] is not a new development. Indeed, the reaction of a geminal borolithio intermediate derived from a 1,1-diboryl starting material, with an internal electrophilic moiety forms cyclized products such as cyclopropyl and cyclobutyl was first reported in 1962 with narrow scope.[178] The generation of geminal borolithio intermediates was also utilized for the synthesis of secondary alcohols by beginning from the corresponding alkyne that undergoes dihydroboration

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(178) (a) "Darstellung und Eigenschaften von Cyclopropyl-boranen," Binger, P.; Köster, R. *Angew. Chem.* **1962**, *74*, 652-652. (b) "Synthesis of β-Cyclopropyl- and β-Cyclobutylbicyclo[3.3.1]nonane via Ring Closure of Boron Intermediates. A Convenient Entry into Cyclopropyl and Cyclobutyl Derivatives via Hydroboration," Brown, H. C.; Rhodes, S. P. *J. Am. Chem. Soc.* **1969**, *91*, 4306-4307.

with various dialkylborane reagents.[179] It was observed that in these primary and secondary alcohol syntheses the reactivity of alkyllithiums with the diboron reagents was improved through either increasing the base's steric bulk or placing sterically large substituents on the boron atom itself.[180] The extension of this organometallic exchange reaction uses of 2 equivalents of *n*BuLi followed by introduction of carbon dioxide, and upon acidification of the corresponding dicarboxylate salts, the synthesis of malonic acid derivatives is achieved in high yield.[181] These researchers recognized the stabilization of these carbanion equivalents by the boron *p*-orbital as an analogy to both enolates and phosphorus ylides for the study of aldol and Wittig chemistries, respectively. To study these reactions, the use of carbonyl electrophiles was shown to produce 1,2-diols when employed with bulky alkylboron reagents such as with dimesityl boryl carbanions, following oxidation of the boron-carbon bond.[182] These bulky

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(179) "A Convenient Procedure for the Synthesis of Secondary Alcohols From 1-Alkynes via the Alkylation of Boron-Stabilized Carbanions," Zweifel, G.; Fisher, R. P.; Horng, A. *Synthesis* **1973**, 37-38.

(180) (a) "The Dimesitylboron Group in Organic Synthesis 2. The *C*-Alkylation of Alkyldimesitylboranes," Pelter, A.; Williams, L.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 627-630. (b) "Hindered Organoboron Groups in Organic Chemistry 20. Alkylations and Acylations of Dimesitylboron Stabilized Carbanions," Pelter, A.; Warren, L.; Wilson, J. W. *Tetrahedron* **1993**, *49*, 2988-2990. (c) "Generation of Boron-Stabilized Carbanions," Rathke, M. W.; Kow, R. *J. Am. Chem. Soc.* **1972**, *94,* 6854–6856. (d) "The Dimesitylboron Group in Organic Synthesis 1. Introduction," Pelter, A.; Singaram, B.; Williams, L.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 623-626. (e) "Hindered Organoboron Groups in Organic Chemistry. 18. The Production of Boron Stabilised Carbanions," Pelter, A.; Singaram, B.; Williams, L.; Wilson, J. W. *Tetrahedron* **1993**, *49*, 2965-2978. (f) "Synthesis of Boron Stabilised Carbanions," Wilson, J. W. *J. Organomet. Chem.* **1980**, *186*, 297-300.

(181) Three examples in "*gem*-Dimetallic Compounds: On the Metal-Metal Interconversion Between *gem*-Organoboron Compounds and *n*-Butyllithium," Cainelli, G.; Dal Bello, G.; Zubiani, G. *Tetrahedron Lett.* **1965**, 3429-3432.

(182) (a) "The Dimesitylboron Group in Organic Synthesis 7. A Unique Variant of the Boron-Wittig Reaction which Stereoselectively Yields 1,2-Diols," Pelter, A.; Buss, D.; Pitchford, A. *Tetrahedron Lett.* **1985**, *26*, 5093-5096. (b) "Hindered Organoboron Groups in

(dimesitylborio)lithioalkanes also react with substituted epoxides to give the corresponding 1,3-diol products after oxidation.[183] The authors demonstrate that regiochemistry is governed by steric constraints rather than electronic factors. The reactions of monosubstituted boron-stabilized carbanion compounds with aldehydes and ketones to deliver the respective disubstituted and trisubstituted alkenes have been briefly studied and proceed in moderate to good yields.[184]

3.3 *Access to Tertiary Alcohols and Tertiary Boronic Esters.*

We wanted to confirm the reactivity of our disubstituted *gem*-diboronic ester products (Tables 2-4) in some of the previously

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Organic Chemistry. 30. The Production of *erythro*-1,2-Diols by the Condensation of Dimesitylboron Stabilised Carbanions with Aromatic Aldehydes," Pelter, A.; Peverall, S.; Pitchford, A. *Tetrahedron* **1996**, *52*, 1085-1094. (c) "Synthesis, Structure, and Thermolysis of a Tetracoordinate 1,2-Oxaboretanide: An Intermediate of the Boron-Wittig Reaction under Basic Conditions," Kawashima, T.; Yamashita, N.; Okazaki, R. *J. Am. Chem. Soc.* **1995**, *117*, 6142-6143.

(183) (a) "The Dimesitylboron Group in Organic Synthesis 8. Preparations of 1,3-Diols from Oxiranes," Pelter, A.; Bugden, G.; Rosser, R. *Tetrahedron Lett.* **1985**, *26*, 5097-5100. (b) "Hindered Organoboron Groups in Organic Chemistry. 21. The Reactions of Dimesitylboron Stabilised Carbanions with Oxiranes," Pelter, A.; Vaughan-Williams, G. F.; Rosser, R. M. *Tetrahedron* **1993**, *49*, 3007-3034.

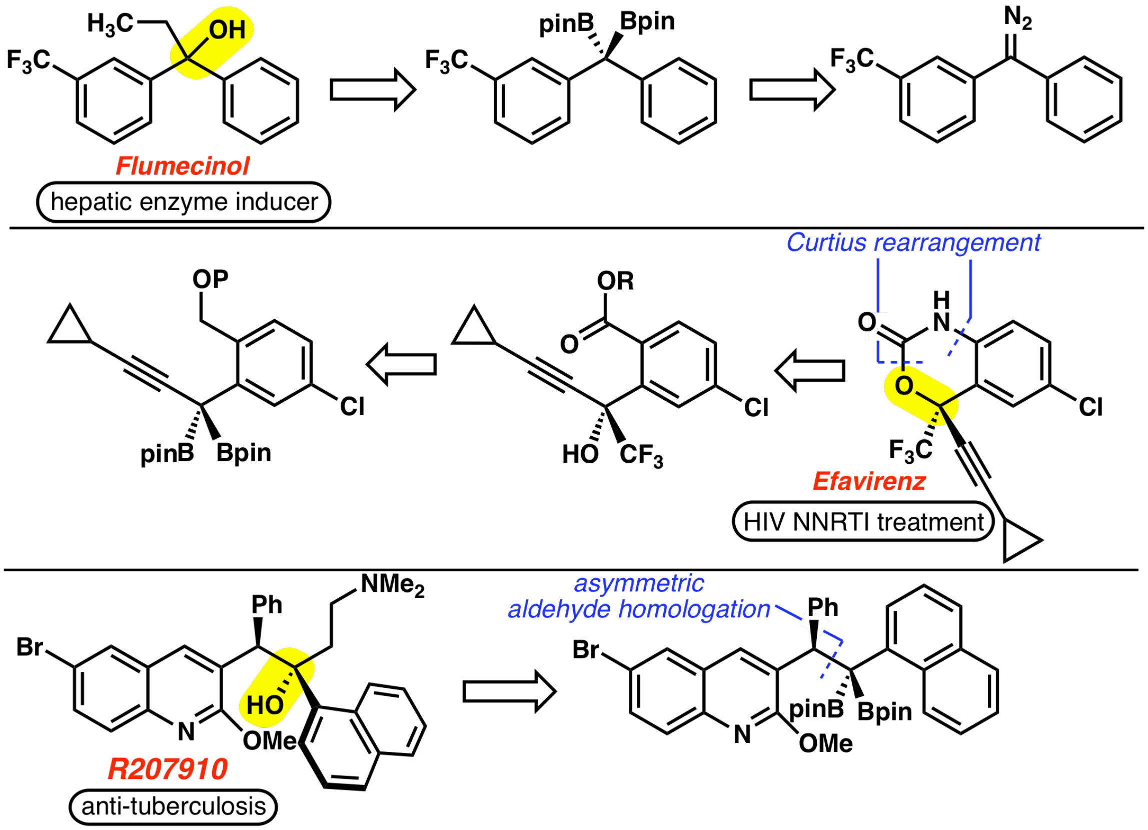
(184) (a) "*gem*-Dimetallic Compounds; A Novel Approach to Olefins Starting from Carbonyl Compounds and Acetylenic Derivatives," Cainelli, G.; Dal Bello, G.; Zubiani, G. *Tetrahedron Lett.* **1966**, 4315-4318. (b) "The Dimesitylboron Group in Organic Synthesis. 4. The 'Boron-Wittig' Reaction," Pelter, A.; Singaram, B.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 635-636. (c) "Stereoselective Synthesis of *E*- and *Z*-Alkenes by the Boron–Wittig Reaction," Pelter, A.; Buss, D.; Colclough, E. *J. Chem. Soc., Chem. Commun.* **1987**, 297-299. (d) "Hindered Organoboron Groups in Organic Chemistry. 23. The Interactions of Dimesitylboron Stabilised Carbanions with Aromatic Ketones and Aldehydes to Give Alkenes." Pelter, A.; Buss, D.; Colclough, E.; Singaram, B. *Tetrahedron* **1993**, *49*, 7077-7103. (e) "Hindered Organoboron Groups in Organic Synthesis. 14. Stereoselective Synthesis of Alkenes by the Boron-Wittig Reaction using Aliphatic Aldehydes," Pelter, A.; Smith, K.; Elgendy, S.; Rowlands, M. *Tetrahedron Lett.* **1989**, *30*, 5647-5650. (f) "Hindered Organoboron Groups in Organic Chemistry. 25. The Condensation of Aliphatic Aldehydes with Dimesitylboryl Stabilised Carbanions to give Alkenes," Pelter, A.; Smith, K.; Elgendy, S. M. A. *Tetrahedron* **1993**, *49*, 7119-7132.

reported methods in order to expand the scope of these methodologies to include the user-friendly pinacolatoboryl substituent, relative to dimesitylboryl groups, which is currently the most thoroughly studied system within these reports.

3.3.a *Potential Synthetic Applications of Tertiary Alcohol-Containing Bioactive Products.*

Our efforts toward the full development of this historical method could enable access towards several bioactive targets (Scheme 17).

Scheme 17: Bioactive Synthetic Targets Containing Tertiary Alcohols



H_3C
OH
F_3C
Flumecinol
hepatic enzyme inducer
pinB
Bpin
F_3C
N_2
F_3C
OP
Cl
pinB
Bpin
OR
O
Cl
HO
CF_3
Curtius rearrangement
H
N
O
O
Cl
F_3C
Efavirenz
HIV NNRTI treatment
Br
Ph
NMe_2
HO
N
OMe
R207910
anti-tuberculosis
asymmetric
aldehyde homologation
Ph
Br
N
pinB
Bpin
OMe

The potential synthesis of *rac*-flumecinol[185] could be easily accomplished following the synthesis of the diarylketone required for the diazoalkane preparation. Efavirenz is a commonly prescribed antiviral agent used in management of HIV infection that acts as a non-nucleoside reverse transcriptase inhibitor (NNRTI).[186] Starting from the alkynyl aryl diazomethane reagent to produce the *gem*-diboryl product, alkylation of iodotrifluoromethane and subsequent oxidation would produce the tertiary benzylic alcohol. The interception of the isocyanate intermediate following a Curtius rearrangement of a benzoic acid derivative would be valuable to the synthetic step- and atom-economy, but the synthetic plan may be complicated by the acid-lability of the newly formed benzylic alcohol. Janssen Pharmaceutica first developed the experimental anti–tuberculosis medicinal agent R207910 for clinical trials in 2007.[187] Following development of an asymmetric aldehyde homologation method with diazoalkanes, the required benzylic ketone could also be translated into an aryl-based diazoalkane for platinum(0)-catalyzed synthesis of sterically

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(185) "Flumecinol for the Treatment of Pruritus Associated with Primary Biliary Cirrhosis," Turner, I. B.; Rawlins, M. D.; Wood, P.; James, O. F. *Aliment Pharmacol Ther.* **1994**, *8*, 337-342.

(186) (a) "Efavirenz plus Zidovudine and Lamivudine, Efavirenz plus Indinavir, and Indinavir plus Zidovudine and Lamivudine in the Treatment of HIV-1 Infection in Adults," Staszewski, S.; Morales-Ramirez , J.; Tashima, K. T.; Rachlis, A.; Skiest, D.; Stanford, J.; Stryker, R.; Johnson, P.; Labriola, D. F.; Farina, D.; Manion, D. J.; Ruiz, N. M. *N. Engl. J. Med.* **1999**, *25*, 1865-18673. (b) "Practical Asymmetric Synthesis of Efavirenz (DMP 266), an HIV-1 Reverse Transcriptase Inhibitor," Pierce, M. E.; Parsons, R. L., Jr.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C. Y.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D. L.; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536–8543.

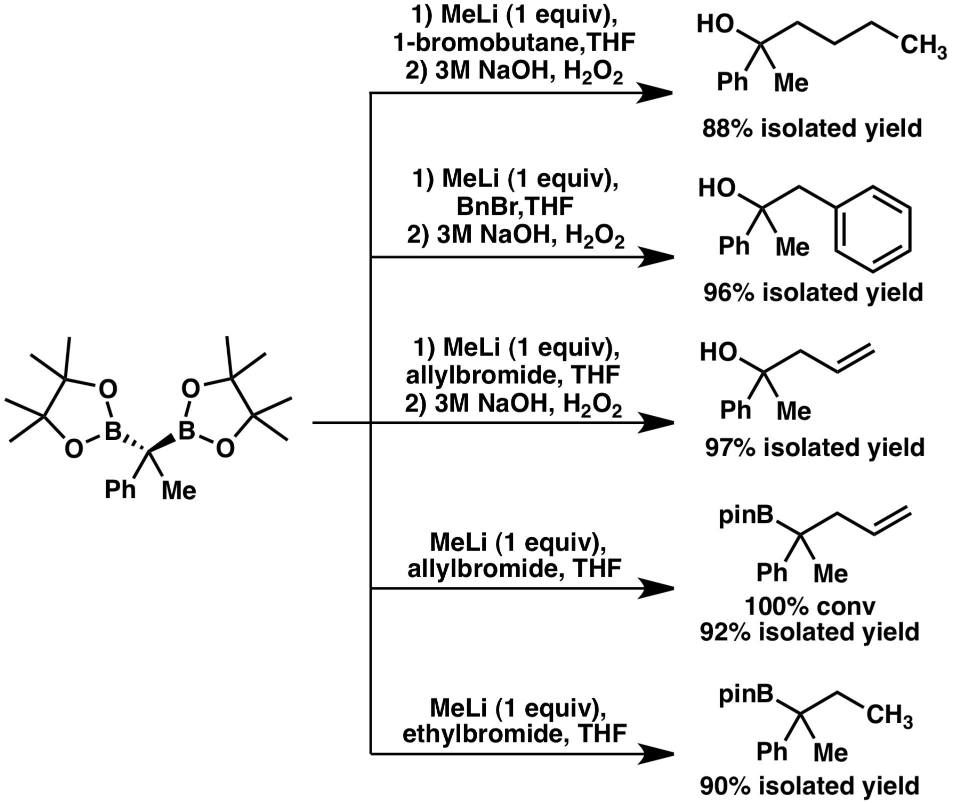
(187) "A Computational Model of the Inhibition of Mycobacterium Tuberculosis ATPase by a New Drug Candidate R207910," de Jonge, M. R.; Koymans, L. H.; Guillemont, J. E.; Koul, A.; Andries, K. *Proteins* **2007**, *67*, 971–980.

hindered *gem*-diboryl products shown (Scheme 17). Completing the potential synthesis of this pharmaceutical could proceed through the alkylation of the diarylquinoline *gem*-diboryl substrate shown in Scheme 18 with 2-chloro-*N*,*N*-dimethylethanamine followed by careful oxidation of the tertiary pinacol boronic ester.

3.3.b *Synthesis of Tertiary Alcohols and Tertiary Boronic Esters.*

Before any potential synthetic studies could begin, we needed to confirm our initial alkylation/oxidation result (Scheme 16) to test the efficiency of alkylation with different electrophiles as well as isolate the tertiary boronic ester products.

Scheme 18



1) MeLi (1 equiv),
1-bromobutane,THF
2) 3M NaOH, H_2O_2
HO
CH_3
Ph
Me
88% isolated yield
1) MeLi (1 equiv),
BnBr,THF
2) 3M NaOH, H_2O_2
HO
Ph
Me
96% isolated yield
1) MeLi (1 equiv),
allylbromide, THF
2) 3M NaOH, H_2O_2
HO
Ph
Me
97% isolated yield
O
B
O
O
B
O
Ph
Me
MeLi (1 equiv),
allylbromide, THF
pinB
Ph
Me
100% conv
92% isolated yield
MeLi (1 equiv),
ethylbromide, THF
pinB
CH_3
Ph
Me
90% isolated yield

As seen in Scheme 18, we confirmed our initial results and found that the selected carbon-bromide electrophiles undergo alkylation in very high yield. We efficiently produced a small array of both tertiary alcohols and tertiary boronic esters.

3.3.c *The Boron-Wittig Reaction for E-Selective Trisubstituted Alkene Synthesis.*

Even though efficient production of biologically active tertiary alcohol targets could be conceived (Scheme 17) and as a consequence of the multiple methods in the modern literature toward the synthesis of these important functionalities,[130,188] we were persuaded to study the reactivity of the boron-stabilized carbanion in the boron-Wittig reaction to form trisubstituted alkenes and potentially tetrasubstituted alkenes stereoselectively (Table 5).

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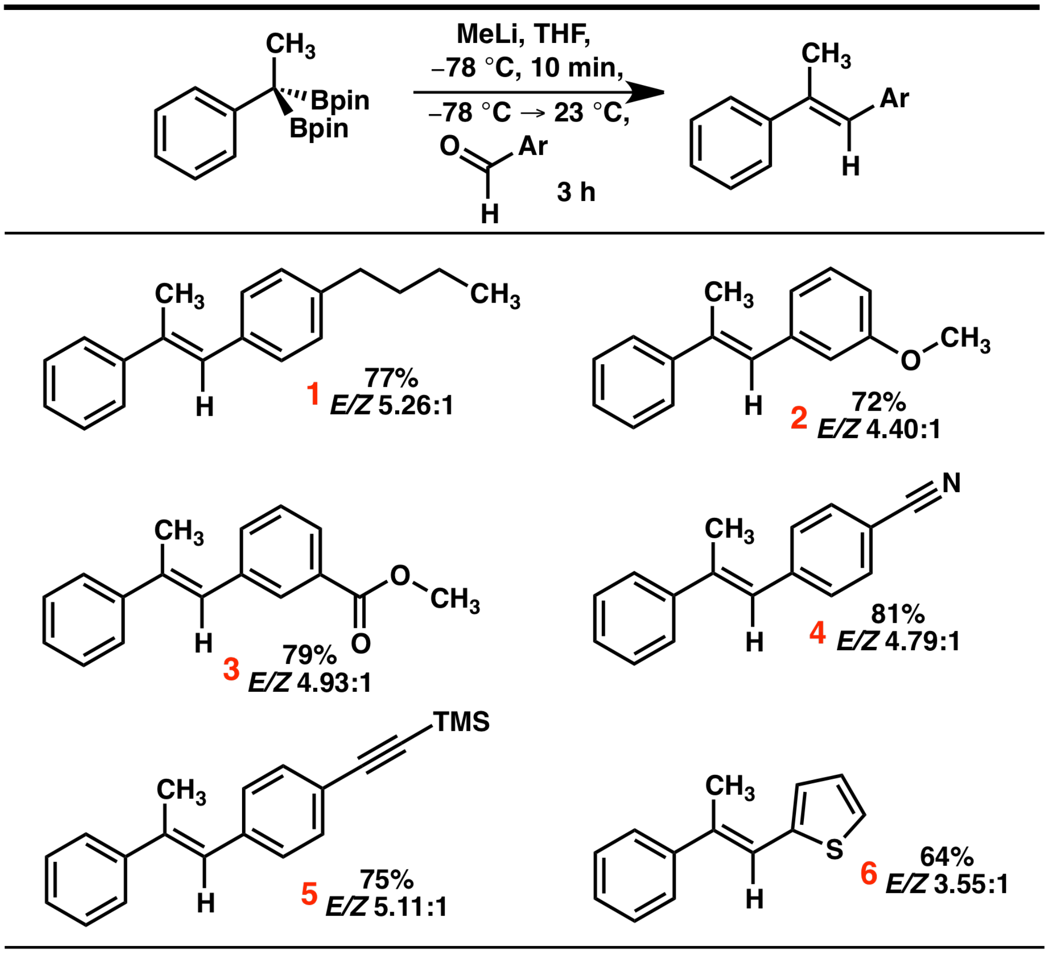
(188) For reviews on nucleophilic additions to ketones, see: (a) "Asymmetric Catalysis for the Construction of Quaternary Carbon Centers: Nucleophilic Addition on Ketones and Ketimines," Riant, O.; Hannedouche, *J. Org. Biomol. Chem.* **2007**, *5*, 873-888. (b) "Asymmetric Addition to Ketones: Enantioselective Formation of Tertiary Alcohols," García, C.; Martín, V. S. *Curr. Org. Chem.* **2006**, *10*, 1849-1889. (c) "Asymmetric Synthesis of Tertiary Alcohols and α-Tertiary Amines via Cu-Catalyzed C–C Bond Formation to Ketones and Ketimine," Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853–2873.

Table 5: Initial Studies for the Boron-Wittig Reaction



MeLi, THF,
−78 °C, 10 min,
−78 °C → 23 °C,
3 h
1 77% E/Z 5.26:1
2 72% E/Z 4.40:1
3 79% E/Z 4.93:1
4 81% E/Z 4.79:1
5 75% E/Z 5.11:1
6 64% E/Z 3.55:1

All yields are isolated major isomer. *E/Z* ratios were derived from intergration of the crude NMR spectra.

As illustrated in Table 5, a range of electronic perturbations are well tolerated within compounds **2**, **3**, and **4** in the *E*-selective synthesis of trisubstituted alkenes. The full preservation of the potentially sensitive trimethyl silyl group on the terminal alkyne demonstrates the chemoselective nucleophilic attack of the methyl lithium reagent on the boron atom.

A consequence of the proposed mechanism is the generation of methyl-Bpin as an innocuous, stoichiometric byproduct (Scheme 16). This may serve as a means to inhibit excess methyl lithium during and/or after the desired reaction sequence. With this hypothesis, we still only observed the need for approximately one equivalent of alkyl lithium reagent. Heterocycles are also reasonably well tolerated, as evidenced in the olefination of thiophene-2-carboxaldehyde (**6**).

Our experimental design to enhance the stereoselectivity was initially influenced by Pelter and coworkers.[182,184] In order for the elimination of a proposed "boroxetane-type" intermediate or a *trans*-elimination to outcompete the reversible nature of the boron-stabilized carbanion addition to the carbonyl, we chose low temperature reaction conditions. These conditions were found to lower the unproductive consumption of the aldehyde electrophile through an alkoxide-mediated Cannizzaro disproportionation mechanism, as has been previously documented.[184d]

3.3.d *Potential Synthetic Targets in Trisubstituted Alkene Synthesis.*

As shown in Scheme 19, using trisubstituted alkenes in developing molecular understanding is pervasive throughout the spectrum of chemical disciplines. The synthetic substitution of a *trans*-amide linkage with all-carbon sp^2-hybridization enables the structure/function analysis from the loss of hydrogen bond acceptors that is potentially vital to secondary structure (α-helix, β-barrel, etc.) and tertiary behavior.[189] This isosteric

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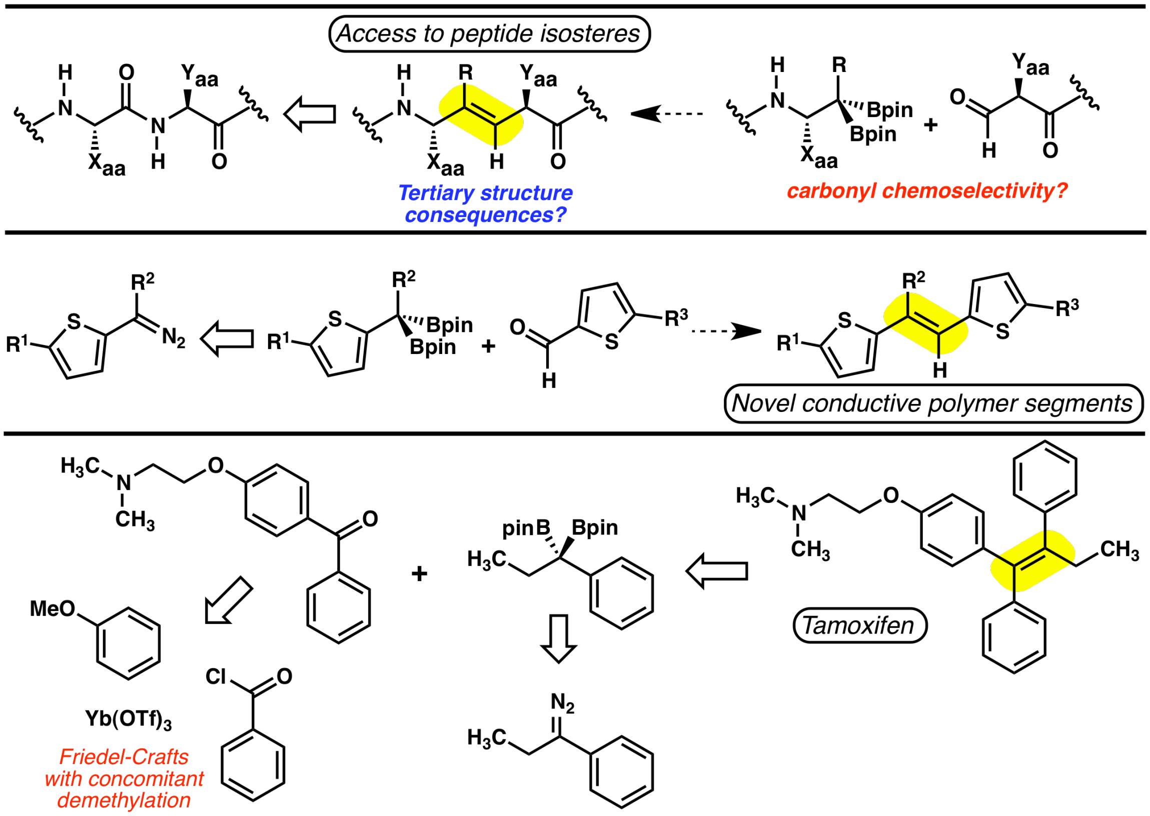
(189) "Solid-Phase Syntheses of β-Turn Analogues To Mimic or Disrupt Protein−Protein Interactions," Burgess, K. *Acc. Chem. Res.* **2001**, *34*, 826–83. (b) "Peptide Science: Exploring the Use of Chemical Principles and Interdisciplinary Collaboration for Understanding Life Processes," Hruby, V. J. *J. Med. Chem.* **2003**, *46*, 4215–4231.

replacement is a current strategy toward the goal of increased bioavailability of peptide-based pharmaceuticals as a result of decreased proteolytic cleavage.[190] Another use for trisubstituted alkene synthesis is their employment in materials chemistry as functionality to continue π-conjugation within functional materials.[191]

Scheme 19: Potential Alkene Targets: Chemical Biology, Materials Chemistry, and Pharmaceuticals


Access to peptide isosteres
H
N
O
Yaa
N
H
O
Xaa
R
Tertiary structure consequences?
Bpin
Bpin
+
carbonyl chemoselectivity?
R2
S
R1
N2
R3
Novel conductive polymer segments
H3C
N
CH3
O
+
pinB
Bpin
Tamoxifen
MeO
Yb(OTf)3
Friedel-Crafts with concomitant demethylation
Cl
CH3

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(190) (a) “Designing Non-Peptide Peptidomimetics in the 21st Century: Inhibitors Targeting Conformational Ensembles,” Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541–558. (b) “Efficient Synthesis of Trifluoromethyl and Related Trisubstituted Alkene Dipeptide Isosteres by Palladium-Catalyzed Carbonylation of Amino Acid Derived Allylic Carbonates,” Inokuchi, E.; Narumi, T.; Niida, A.; Kobayashi, K.; Tomita, K.; Oishi, S.; Ohno, H.; Fujii, N. *J. Org. Chem.* **2008**, *73*, 3942–3945. (c) “Amino Acid-Based Synthesis of Trifluoromethylalkene Dipeptide Isosteres by Alcohol-Assisted Nucleophilic Trifluoromethylation and Organozinc–Copper-Mediated S_N2' Alkylation,” Kobayashi, K.; Narumi, T.; Oishi, S.; Ohno, H.; Fujii, N. *J. Org. Chem.* **2009**, *74*, 4626–4629.

(191) (a) “‘Synthetic Metals’: A Novel Role for Organic Polymers (Nobel Lecture),” MacDiarmid, A. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 2581-2590. (b) “About Supramolecular Assemblies of π-Conjugated Systems,” Hoeben, F. J. M.; Jonkheijm, P.; Meijer, E. W.; Schenning, A. P. H. J. *Chem. Rev.* **2005**, *105*, 1491–1546.

The last example in Scheme 19 shows a different retrosynthetic analysis to the common synthetic target Tamoxifen.[192] The diaryl ketone that is required for boron-Wittig reaction could be derived from a lanthanide-catalyzed Friedel-Crafts reaction between readily available anisole and benzoyl chloride.[193] With ytterbium(III)-catalyzed dimethylation of anisole, this reaction sequence provides alternative activation of the Friedel-Crafts nucleophile, rather than the typical electrophilic activation, which thereby increases the arene's nucleophilicity.[193] Following alkylation of the product's phenolic oxygen with a suitable electrophile, 2-chloro-*N*,*N*-dimethylethanamine, the diaryl ketone efficiently obtained.

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(192) (a) "Carbolithiation of Diphenylacetylene as a Stereoselective Route to (*Z*)-Tamoxifen and Related Tetrasubstituted Olefins," McKinley, N. F.; O'Shea, D. F. *J. Org. Chem.* **2006**, *71*, 9552–9555. (b) "(*Z*)-Tamoxifen and Tetrasubstituted Alkenes and Dienes via a Regio- and Stereospecific Three-Component Magnesium Carbometalation Palladium(0) Cross-Coupling Strategy," Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989–2992. (c) "Diversity-Oriented Synthesis of Tamoxifen-type Tetrasubstituted Olefins," Itami, K.; Kamei, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2003**, *125*, 14670–14671. (d) "Stereoselective Synthesis of (*E*)-(Trisubstituted alkenyl)borinic Esters: Stereochemistry Reversed by Ligand in the Palladium-Catalyzed Reaction of Alkynylborates with Aryl Halides," Ishida, N.; Shimamoto, Y.; Murakami, M. *Org. Lett.* **2009**, *11*, 5434–5437. (e) Stereoselective Cross-Coupling Reaction of 1,1-Diboryl-1-alkenes with Electrophiles: A Highly Stereocontrolled Approach to 1,1,2-Triaryl-1-alkenes," Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506–12507. (f) "Stereoselective Synthesis of Tetrasubstituted Alkenylboronates via 1,1-Organodiboronates," Endo, K.; Hirokami, M.; Shibata, T. *J. Org. Chem.* **2010**, *75*, 3469–3472.

(193) "One-Step Reaction of Friedel-Crafts Acylation and Demethylation of Aryl-Methyl Ethers Catalyzed by Ytterbium(III) Triflate," Su, W.; Jin, C. Synth. Commun. **2004**, *34*, 4199-4205.

3.4 Future directions

In the modern era of organic chemistry the development of most methods that produce organoboron compounds also investigates the potential for metal-catalyzed cross coupling reactions for carbon-carbon bond formation. The literature precedent is extensive for palladium-catalyzed cross coupling of organoboron compounds to other organic species of varying electrophilic activation.[194] The development of Suzuki-Miyaura coupling reaction is a very active area of modern research.[129a,194] Current limitations to accessing disubstituted *gem*-diboron organics has prevented the development of Pd-catalyzed

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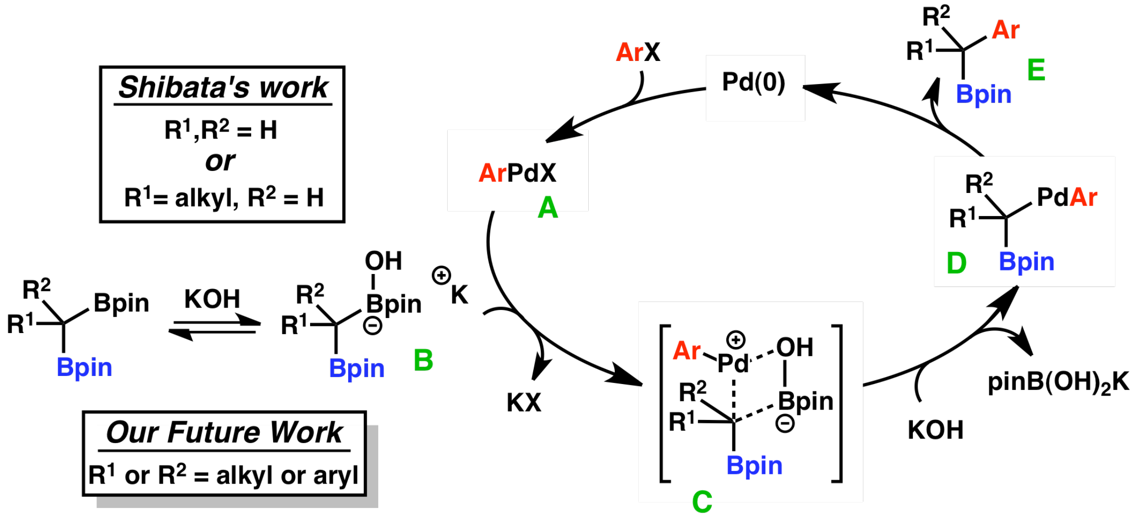
(194) (a) "Boronic Acids: New Coupling Partners in Room-Temperature Suzuki Reactions of Alkyl Bromides. Crystallographic Characterization of an Oxidative-Addition Adduct Generated under Remarkably Mild Conditions," Kirchhoff, J. H.; Netherton, M. R.; Hill, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662-13663. (b) "Suzuki-Miyaura Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates," G. A. Molander, C. R. Bernardi, *J. Org. Chem.* **2002**, *67*, 8424-8429. (c) "The First General Palladium Catalyst for the Suzuki-Miyaura and Carbonyl Enolate Coupling of Aryl Arenesulfonates," H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818-11819. (d) "An N-Heterocyclic Carbene Ligand with Flexible Steric Bulk Allows Suzuki Cross-Coupling of Sterically Hindered Aryl Chlorides at Room Temperature," G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem. Int. Ed.* **2003**, *42*, 3690-3693. (e) "Phosphine-Free Palladium Acetate Catalyzed Suzuki Reaction in Water," Liu, L.; Zhang, Y. Wang, *J. Org. Chem.* **2005**, *70*, 6122-6125. (f) "A Highly Active Catalyst for Suzuki-Miyaura Cross-Coupling Reactions of Heteroaryl Compounds," Billingsley, K. L; Anderson, K. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 3484-3488. (g) "Alkyl-Alkyl Suzuki Cross-Couplings of Unactivated Secondary Alkyl Halides at Room Temperature," B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 9602-9603. (h) "*N*-Vinylpyridinium and -Ammonium Tetrafluoroborate Salts: New Electrophilic Coupling Partners for Pd(0)-Catalyzed Suzuki Cross-Coupling Reactions," Buszek, K. R.; Brown, N. *Org. Lett.* **2007**, *9*, 707-710. (i) "A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki−Miyaura Coupling of β-Protected Haloboronic Acid Building Blocks," Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716−6717. (j) "Suzuki-Miyaura Cross-Coupling of Potassium Trifluoroboratohomoenolates," G. A. Molander, D. E. Petrillo, *Org. Lett.* **2008**, *10*, 1795-1798. (k) "General Reaction Conditions for the Palladium-Catalyzed Vinylation of Aryl Chlorides with Potassium Alkenyltrifluoroborates," E. Alacid, C. Nájera, *J. Org. Chem.* **2009**, *74*, 8191-8195. (l) "Stereoconvergent Amine-Directed Alkyl–Alkyl Suzuki Reactions of Unactivated Secondary Alkyl Chlorides," Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157.

coupling of these uniquely functionalized materials. Nevertheless, Shibata and coworkers, working with monosubstituted diboronic esters, have communicated initial developments toward these goals. This work illustrates the unique reactivity of the geminal diboron functionality in this synthetic transformation.[195] The authors provide insight into the directing effect of the neighboring boron atom, as shown in Scheme 20.

Scheme 20: Shibata's Proposed Reaction Mechanism: Potential Extension to Disubstituted *gem*-Diboronic Esters.


Shibata's work
R^1,R^2 = H
or
R^1= alkyl, R^2 = H
Our Future Work
R^1 or R^2 = alkyl or aryl
R^2
R^1
Bpin
Bpin
KOH
OH
Bpin
K
B
ArX
Pd(0)
ArPdX
A
KX
Ar
Pd
OH
Bpin
C
KOH
pinB(OH)$_2$K
PdAr
D
Ar
E

After careful optimization of base stoichiometry, the mono-activated borate species (**B**) can direct the arylpalladium species (**A**) via Lewis basic coordination to the metal catalyst as it approaches the geminal carbon (**C**). In addition to this directing affect, the second boronic ester (shown as blue in **C**) can serve to stabilize the α-carbanion character of both the hydroxy borate (**B** and **C**) and the σ-palladium species (**D**) in order to preclude

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(195) (a) "Chemoselective and Regiospecific Suzuki Coupling on a Multisubstituted sp^3-Carbon in 1,1-Diborylalkanes at Room Temperature," Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033–11035. (b) "Chemoselective Suzuki Coupling of Diborylmethane for Facile Synthesis of Benzylboronates," Endo, K.; Ohkubo, T.; Shibata, T. *Org. Lett.* **2011**, *13*, 3368–3371.

β-hydride elimination. With our convenient synthesis of disubstituted geminal diboronic esters, the synthesis of tertiary boronic esters (**E**) could be enabled under this manifold. This would provide alternative tertiary boronic ester products that would be inaccessible with our current alkylation protocol (i.e. vinyl- or aryl-halides) and further expand the scope of Suzuki couplings.

3.4.a *Initial Trials in Suzuki Couplings to Extend the Crudden Method.*

In addition to other methods,[130] tertiary boronic esters are accessed in extremely high yield (Scheme 18). The potential use of Suzuki-Miyaura coupling reactions with these boronic esters would facilitate the synthesis of all-carbon quaternary centers, which are historically difficult to access.[196] Pd-catalyzed Suzuki couplings occurring in such a hindered environment is unprecedented, but the work of Crudden and coworkers demonstrates that a less hindered boronic ester can undergo productive Suzuki coupling after careful optimization.[197] With this communication, Crudden *et al.* provides a detailed account of the experimentation needed

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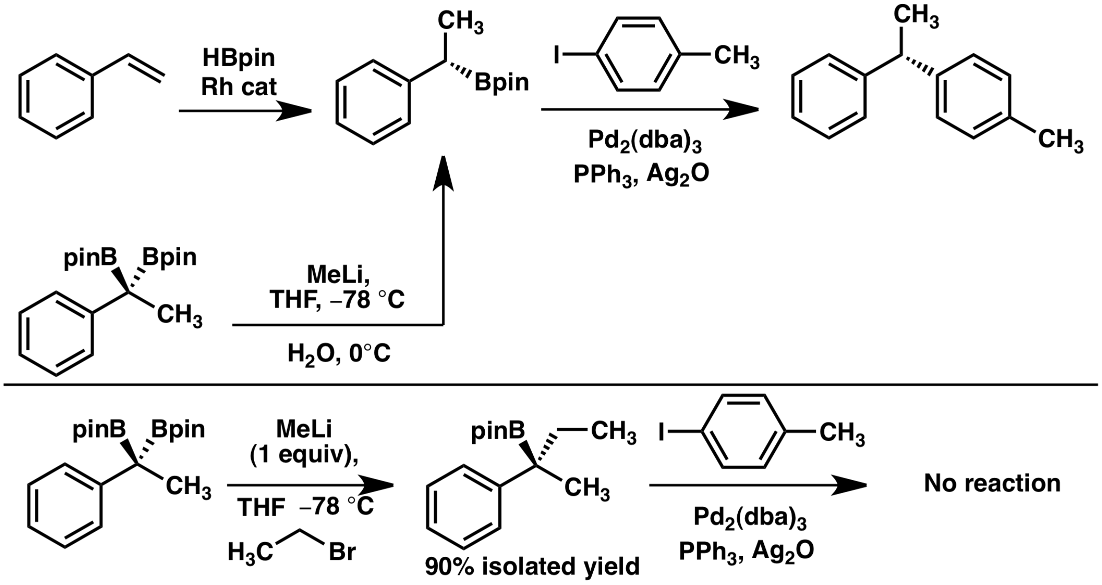
(196) (a) "Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners," Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. (b) "Enantioselective Construction of All-Carbon Quaternary Centers by Branch-Selective Pd-Catalyzed Allyl–Allyl Cross-Coupling," Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716–9719. (c) "The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters," Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, 37, 388-401. (d) "Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters," Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369-396. (e) "Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers in Acyclic Aystems," Das, J. P.; Marek, I. *Chem. Commun.* **2011**, 47, 4593-4623.

(197) "Cross Coupling Reactions of Chiral Secondary Organoboronic Esters With Retention of Configuration," Imao, D.; Glasspoole, B. W.; Vronique S. Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025.

to successfully couple aryl iodides with benzylic secondary boronic esters. While we were able to reproduce the coupling of *p*-iodotoluene to the secondary boronic ester shown in Scheme 21, we were unable to detect any productive coupling of *p*-iodotoluene to our tertiary boronic ester after multiple trials. While these very preliminary results are not promising for the Pd-catalyzed coupling of tertiary boronic esters, much more research will be need to definitively determine the outcome of this potential synthetic method.

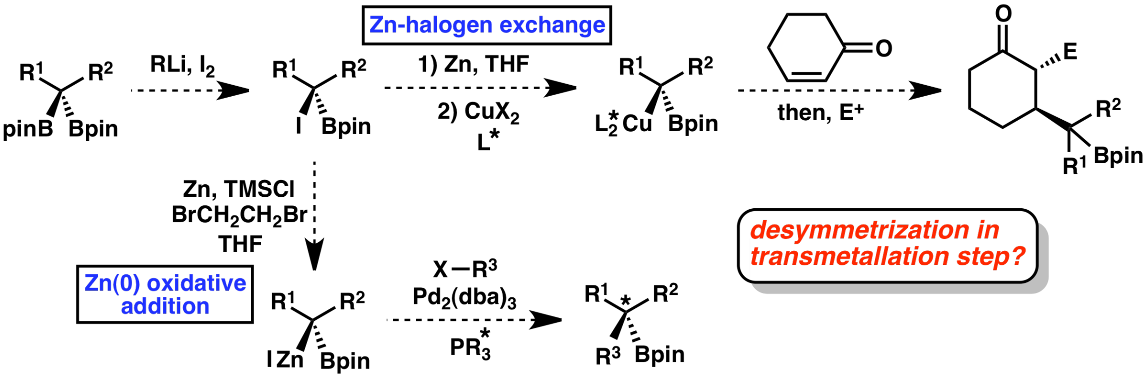
Scheme 21: Attempted Pd-Catalyzed Coupling of Tertiary Boronic Ester


HBpin
Rh cat
CH3
Bpin
I
CH3
Pd2(dba)3
PPh3, Ag2O
CH3
CH3
pinB
Bpin
CH3
MeLi,
THF, −78 °C
H2O, 0°C
pinB
Bpin
CH3
MeLi
(1 equiv),
THF −78 °C
H3C
Br
pinB
CH3
CH3
90% isolated yield
I
CH3
Pd2(dba)3
PPh3, Ag2O
No reaction

3.4.b *Potential Synthesis of Mixed Geminal Diorganometallics.*

Additional future directions could utilize the unique chemistry that mixed geminal diorganometallics can afford. The special characteristics of boron's stabilization of an α-carbanion-like intermediate should enable organometallic reactions to have diminished levels of β-hydride elimination as an unwanted, destructive pathway. With the observation that the lithium carbanion starting from a monosubstituted geminal diboronic ester can be successfully iodinated,[131] the oxidative insertion of multiple transition metals (as well as main group metals) can provide potential entry to many different organometallic chemistries.[198] For example, in Scheme 22, after successful iodination of the lithium anion, the iodoorganoboronic ester can undergo oxidative addition with zinc metal to generate the d^{10} Zn^{2+} organometallic reagent.

Scheme 22: Potential Applications of *gem*-Boron Stabilized Organometallics


R1 R2
pinB Bpin
RLi, I2
R1 R2
I Bpin
Zn-halogen exchange
1) Zn, THF
2) CuX2
L*
R1 R2
L*2Cu Bpin
then, E+
O
E
R2
R1 Bpin
Zn, TMSCl
BrCH2CH2Br
THF
Zn(0) oxidative addition
R1 R2
IZn Bpin
X—R3
Pd2(dba)3
PR*3
R1 * R2
R3 Bpin
desymmetrization in transmetallation step?

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(198) (a) "A New Approach to Boron-Stabilized Organometallics," Knochel, P. *J. Am. Chem. Soc.* **1990**, *112*, 7431–7433. (b) "Preparation of Functionalized Dialkylzinc Reagents via an Iodine-Zinc Exchange Reaction. Highly Enantioselective Synthesis of Functionalized Secondary Alcohols," Rozema, M. J.; Sidduri, A. R.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956–1958. (c) "Stereoselective Synthesis of Allylic Boronates via Palladium-Catalyzed Cross-Coupling Reaction of Knochel's (Dialkoxyboryl) Methylzinc Reagents with 1-Halo-1-alkenes," Watanabe, T.; Miyaura, N.; Suzuki, A. *J. Organomet. Chem.* **1993**, *444*, C1-C3. (d) "Preparation and Reactions of Polyfunctional Organozinc Reagents in Organic Synthesis," Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188.

This hindered organometallic could find use in Negishi couplings[199] to quickly build complexity. With a different organometallic entry into the carbon-zinc bond, Zn-halogen exchange could enable dialkylzinc formation. These species could undergo cuprate formation towards novel extensions of important existing conjugate addition chemistries.[200] The potential to influence spatial trajectory in the approach of the organozinc to the metal catalyst (Pd and Cu shown) could be realized by appropriate choice of ligand.[201] If the chiral organometal adduct is produced, then reductive elimination will afford enantioenriched tertiary boronic esters. Although far from atom economical, dialkylzinc reagents have distinct advantages, compared with Grignard or organoaluminum reagents, because they show low reactivity in uncatalyzed reactions and high tolerance for functional groups both in the zinc reagent and in the substrate. Alternatively these functionalized organozinc reagents could be made available through an alkyl-transfer procedure, similar to the sequence of carbon-zinc formation from alkenes via hydroboration.[202] The transmetallation of the lithium *gem*-boronic ester carbanion with

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(199) "Palladium- or nickel-catalyzed cross coupling. A new selective method for carbon-carbon bond formation," Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340–348.

(200) "Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions," Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pämies, O.; Diguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823.

(201) (a) "Phosphoramidites: Marvelous Ligands in Catalytic Asymmetric Conjugate Addition," Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353. (b) "Ligand Bite Angle Effects in Metal-catalyzed C−C Bond Formation," van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741–2770. (c)

(202) "Preparation and Reaction of New Dialkylzincs Obtained by a Boron-Zinc Transmetalation," Langer, F., Waas, J. & Knochel, P. *Tetrahedron Lett.* **1993** *34*, 5261–5264.

trialkylstannyl halides also provides potential access to chemoselective Stille couplings reagents.[203]

3.5 *Conclusions.*

With our expertise in non-stabilized diazoalkane synthesis, access to novel disubstituted geminal diboronic esters is enabled and awaits further exploration. The previous literature examples set the stage for their potential synthetic impact. By not having access to the fully substituted *gem*-diboronic esters that our chemistry can provide, the prior studies have been limited. The distinctive stabilization of carbanion-like character by the geminal boron atom's vacant *p*-orbital has been shown to provide efficient and reliable access to highly functionalized carbon centers. The opportunity is now before us to contribute to these useful synthetic methods.

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(203) "An α-Lithio Boronic Ester from an α-Trimethylstannyl Boronic Ester," Matteson, D. S.; Wilson, J. W. *Organometallics* **1985**, *4*, 1690-1692.

3.6 Experimentals.

General. Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer, ν_{max} in cm^{-1}. Bands are reported as strong (s), medium (m), weak (w), and broad (br). ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.23). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry Facility (Chestnut Hill, MA) utilizing a JEOL AccuTOF with Data Acquisition in Real Time (DART).

Unless stated otherwise, all reactions were carried out in flame-dried glassware under an atmosphere of nitrogen in dry, degassed solvents using standard Schlenk or vacuum-line techniques. THF, Et_2O, toluene, CH_2Cl_2, DMF, pentane, and hexanes were dispensed from a Glass Contour solvent purification system custom manufactured by SG Waters, LLC (Nashua, NH). 4-Butylbenzaldehyde and 1,1,3,3-

tetramethylguanidine were vacuum distilled over calcium hydride. 3-Methoxybenzaldehyde, 4-formylbenzonitrile, 4-((trimethylsilyl)ethynyl)benzaldehyde, methyl 3-formylbenzoate, thiophene-2-carboxaldehyde, cyclopropyl methyl ketone, cyclohexyl methyl ketone, dihydrocinnemaldehyde, and α-tetralone were vacuum distilled. 1-Bromobutane, benzyl bromide, allyl bromide, and ethyl iodide were fractionally distilled and stored over silver wool prior to use. Bis(pinacolato)diboron was recrystallized from hexanes as with needles. $Pb(OAc)_4$, after dissolution in minimal hot glacial acetic acid, deposited as bright white needles upon cooling. The crystals were washed in a fritted Schlenk filter with pentane, dried under high vacuum, and then stored in a glovebox at –20 °C. 1-([1,1'-biphenyl]-2-yl)ethanone and 4-phenylbutan-2-one were purified prior to use by silica gel column chromatography. Hydrazine hydrate, 2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde, $Pt(Ph_3P)_4$, 9-bromophenanthrene, 1-(4-chlorophenyl)ethanone1-(4-(trifluoromethyl)phenyl)ethanone, 1-bromo-2-methylnaphthalene, 1-(*p*-tolyl)ethanone, benzophenone, propiophenone, 5-methoxy-2,3-dihydro-1*H*-inden-1-one, powdered 4 Å molecular sieves, and 2-fluorobenzoic acid were purchased from commercial sources and used as received. The general procedure given below for preparing an unprotected arylhydrazone is based on one described previously.[52] Methyllithium was titrated before use using *N*-benzylbenzamide according

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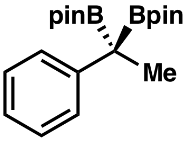
(52) "Oxidation of Hydrazones with Iodine in the Presence of Base," Pross, A.; Sternhill, S. *Aust. J. Chem.* **1970**, *23*, 989-1003.

to a literature procedure.[204] Column chromatography was performed with EMD silica gel 60 (230-400 mesh) and driven with compressed air. Analytical TLC was carried out with EMD silica gel 60 F_{254} precoated plates (250 μm thickness) and a ceric ammonium molybdate, potassium permanganate, *para*-anisaldehyde, or 2,4-dinitrophenylhydrazine stain for spot visualization.

Representative Procedure for the Synthesis and Handling of a Disubstituted Geminal Bis(pinalocato)boronic Ester:



2,2'-(1-Phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). To a 50 mL round bottom flask was added bis(pinacolato)diboron with (0.375 g, 1.584 mmol, 1.00 equiv) and a Teflon-coated stir bar. The flask was taken into a N_2 atmosphere glovebox and $Pt(Ph_3P)_4$ (0.059 g, 0.0475 mmol, 0.03 equiv) was added as a solid. The reaction flask was then sealed in the inert atmosphere with a rubber septa and brought into the fumehood. Under active nitrogen atmosphere, the solids were dissolved with toluene (15.8 mL, 0.10 M) at ambient temperature (23 °C) with stirring. Methyl phenyl diazomethane was then added as solution in toluene in one portion (2.50 mL, 1.742 mmol, 1.10 equiv). The rubber septa was then replaced with a condensing column and set to heating at 80 °C for 6 h under N_2

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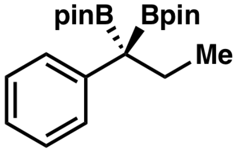
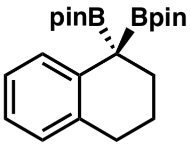
(204) "Titration of Alkyllithiums with a Simple Reagent to a Blue Endpoin," Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281-283.

atmosphere. After the reaction period, the solvent and volatile organics were removed under reduced pressure. To the remaining solids in the reaction flask was added hexanes for extractive isolation of the crude product. This hexanes solution was separated from the remaining organic solids and then repeated three times with fresh solvent. The hexanes solvent was then removed to leave the crude crystalline product, which was further purified by silica gel chromatorgraphy (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). These operations delivered 0.449 g (1.254 mmol, 79%) of 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) as a clear crystalline solid (mp = 71.3 °C). IR (thin film): 2978 (m), 2927 (w), 1504 (w), 1383 (m), 1348 (s), 1298 (s), 1244 (m), 1139 (m), 1097 (m), 971 (m), 855 (m), 772 (w), 698 (m). ^{1}H NMR (400 MHz, $CDCl_3$): 7.34 (d, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 1.45 (s, 3H), 1.23 (d, *J* = 2.0 Hz, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.29, 128.40, 128.02, 124.54, 83.50, 24.83, 18.77, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{20}H_{33}B_2O_4^+$ $[M+H]^+$: 359.254; Found: 359.252.

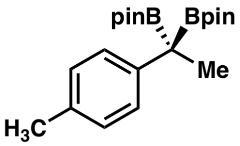


2,2'-(1-Phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.432 g (1.818 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.050 g (0.040 mmol, 0.02 equiv) $Pt(Ph_3P)_4$ in 20.0 mL of toluene (0.10 M) with 1.25 mL of ethyl phenyl diazomethane (1.999 mmol, 1.10 equiv) added as a 0.625 M solution in toluene. 2,2'-(1-Phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a clear crystalline solid (0.501 g, 74% yield, mp = 77.1 °C) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 2977 (m), 2931 (w), 2873 (w), 1495 (w), 1459 (w), 1371 (m), 1350 (s), 1311 (s), 1254 (s), 1214 (w), 1139 (s), 1105 (m), 972 (m), 853 (m), 764 (w), 699 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.3 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 1.98 (q, *J* = 7.3 Hz, 2H), 1.25 (d, *J* = 2.9 Hz, 24H), 0.77 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.23, 130.32, 128.04, 124.83, 83.46, 27.36, 24.91, 24.86, 12.38, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{21}H_{35}B_2O_4^+$ $[M+H]^+$: 373.264 Found: 373.269.



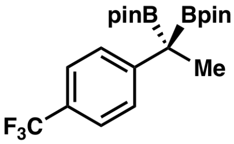
2,2'-(1,2,3,4-Tetrahydronaphthalene-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.432 g (1.818 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.050 g (0.040 mmol, 0.02

equiv) $Pt(Ph_3P)_4$ in 20.0 mL of toluene (0.10 M) with 1.139 mL of 1-diazo-1,2,3,4-tetrahydronaphthalene (1.838 mmol, 1.01 equiv) added as a 1.613 M solution in toluene. 2,2'-(1,2,3,4-Tetrahydronaphthalene-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a clear crystalline solid (0.544 g, 78% yield, mp = 104.0 °C) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 2986 (w), 2928 (m), 2878 (w), 1494 (w), 1455 (w), 1347 (s), 1306 (s), 1244 (s), 1202 (w), 1140 (s), 1109 (m), 969 (m), 850 (m), 763 (w), 699 (m). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 7.7 Hz, 1H), 7.11 – 7.03 (m, 1H), 7.00 (dd, J = 4.8, 1.0 Hz, 2H), 2.76 (t, J = 6.4 Hz, 2H), 2.08 – 2.00 (m, 2H), 1.76 (dt, J = 12.1, 6.2 Hz, 2H), 1.23 (d, J = 1.6 Hz, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.70, 135.89, 130.69, 129.15, 124.88, 123.97, 83.38, 30.49, 27.99, 24.88, 24.72, 23.25, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{22}H_{35}B_2O_4^+$ $[M+H]^+$: 385.231 Found: 385.239.

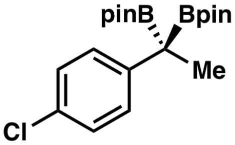


2,2'-(1-(*p*-Tolyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.139 g (0.584 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.022 g (0.017 mmol, 0.03 equiv) $Pt(Ph_3P)_4$ in 5.80 mL of toluene (0.10 M) with 1.5 mL of 1-(1-diazoethyl)-4-methylbenzene (0.643 mmol, 1.10 equiv) added as a 0.428 M solution in toluene. 2,2'-(1-(*p*-Tolyl)ethane-1,1-diyl)bis(4,4,5,5-

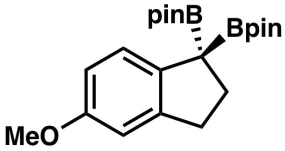
tetramethyl-1,3,2-dioxaborolane) was isolated as a clear crystalline solid (0.175 g, 80% yield, mp = 131.3 °C) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 2991 (w), 2933 (m), 2874 (w), 2812 (w), 1445 (w), 1339 (s), 1298 (s), 1274 (s), 1211 (w), 1125 (m), 966 (m), 847 (w), 765 (m), 702 (m), 564 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 2.28 (s, 3H), 1.43 (s, 3H), 1.23 (d, J = 1.2 Hz, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.14, 133.70, 128.80, 128.23, 83.43, 24.84, 21.14, 18.87, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{21}H_{35}B_2O_4^+$ $[M+H]^+$: 373.213 Found: 373.218.



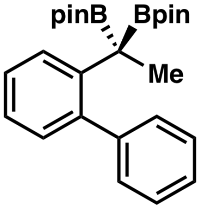
2,2'-(1-(4-(Trifluoromethyl)phenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.178 g (0.749 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.028 g (0.022 mmol, 0.03 equiv) $Pt(Ph_3P)_4$ in 7.50 mL of toluene (0.10 M) with 1.5 mL of 1-(1-diazoethyl)-4-methylbenzene (0.823 mmol, 1.10 equiv) added as a 0.549 M solution in toluene. 2,2'-(1-(4-(Trifluoromethyl)phenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a clear crystalline solid (0.217 g, 68% yield, mp = 115.4 °C) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 2996 (w), 2986 (m), 2922 (m), 2867 (w), 1467 (m), 1340 (m), 1319 (s), 1287 (m), 1142 (m), 1107 (w), 1010 (m), 972 (m), 862 (m), 687 (w). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48 (d, J = 15.4 Hz, 2H), 7.46 (d, J = 15.4 Hz, 2H), 1.47 (s, 3H), 1.22 (d, J = 3.2 Hz, 24H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.44, 130.51, 128.78, 128.30, 128.20, 126.75, 126.43, 126.30, 124.82, 124.78, 124.71, 123.60, 83.77, 24.81, 24.79, 17.67, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{21}H_{32}B_2F_3O_4^+$ [M+H]$^+$: 427.036 Found: 427.131.



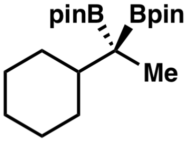
2,2'-(1-(4-Chlorophenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.051 g (0.215 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.008 g (0.006 mmol, 0.03 equiv) Pt(Ph$_3$P)$_4$ in 0.59 mL of toluene (0.40 M) with 1.0 mL of 1-(1-diazoethyl)-4-methylbenzene (0.237 mmol, 1.10 equiv) added as a 0.237 M solution in toluene. 2,2'-(1-(4-Chlorophenyl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a white solid (0.051 g, 61% yield, mp = 146.1 °C) after silica gel chromatography (TLC R$_f$ = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 2977 (m), 2933 (w), 2876 (w), 1491 (m), 1460 (m), 1371 (m), 1311 (s), 1268 (m), 1142 (s), 1087 (s), 1012 (m), 967 (m), 853 (s). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.28 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 1.43 (s, 3H), 1.21 (d, J = 3.3 Hz, 24H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 143.61, 130.21, 129.55, 127.99, 83.64, 24.81, 18.03, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{20}H_{32}B_2ClO_4^+$ [M+H]$^+$: 393.509 Found: 393.548.



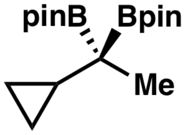
2,2'-(5-Methoxy-2,3-dihydro-1*H*-indene-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.038 g (0.162 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.006 g (0.005 mmol, 0.03 equiv) $Pt(Ph_3P)_4$ in 0.36 mL of toluene (0.50 M) with 4.0 mL of 1-diazo-5-methoxy-2,3-dihydro-1*H*-indene (0.180 mmol, 1.11 equiv) added as a 0.045 M solution in toluene. 2,2'-(5-Methoxy-2,3-dihydro-1*H*-indene-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a clear oil (0.049 g, 76% yield) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 3022 (w), 2987 (m), 2952 (w), 2887 (w), 1482 (m), 1450 (m), 1320 (m), 1218 (w), 1132 (m), 1067 (w), 973 (w), 859 (m), 862 (m), 687 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ (dd, J = 5.7, 3.3 Hz, 1H), 7.53 (dd, J = 5.7, 3.3 Hz, 1H), 4.35 – 4.08 (m, 2H), 1.69 (dt, J = 12.2, 6.1 Hz, 1H), 1.50 – 1.15 (m, 17H), 0.96 – 0.85 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.96, 132.68, 131.09, 129.02, 68.38, 38.96, 30.59, 29.15, 23.97, 23.21, 14.27, 11.19, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{21}H_{35}B_2O_5^+$ $[M+H]^+$: 389.237 Found: 389.244.



2,2'-(1-([1,1'-Biphenyl]-2-yl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.040 g (0.167 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.006 g (0.005 mmol, 0.03 equiv) $Pt(Ph_3P)_4$ in 0.36 mL of toluene (0.46 M) with 1.5 mL of 2-(1-diazoethyl)-1,1'-biphenyl (0.175 mmol, 1.05 equiv) added as a 0.117 M solution in toluene. 2,2'-(1-([1,1'-Biphenyl]-2-yl)ethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a clear oil (0.051 g, 71% yield) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 3054 (w), 2977 (m), 2930 (m), 2873 (w), 1478 (m), 1447 (m), 1378 (m), 1313 (s), 1265 (m), 1212 (w), 1140 (s), 1071 (m), 967 (m), 849 (s), 747 (m), 703 (m). ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.42 (m, 2H), 7.34 – 7.29 (m, 2H), 7.29 – 7.25 (m, 2H), 7.20 (ddd, J = 7.8, 7.2, 1.7 Hz, 1H), 7.12 (td, J = 7.4, 1.4 Hz, 1H), 7.06 – 7.03 (m, 1H), 1.32 (s, 3H), 1.15 (d, J = 5.8 Hz, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.51, 143.63, 142.91, 132.71, 131.40, 130.24, 127.93, 127.15, 126.73, 124.95, 83.49, 25.09, 25.06, 21.91, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{26}H_{37}B_2O_4^+$ $[M+H]^+$: 435.283 Found: 435.290.

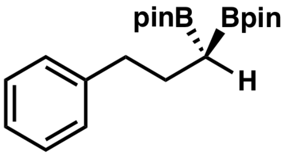


2,2'-(1-Cyclohexylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.026 g (0.108 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.005 g (0.004 mmol, 0.03 equiv) $Pt(Ph_3P)_4$ in 0.30 mL of toluene (0.36 M) with 2.0 mL of (1-diazoethyl)cyclohexane (0.128 mmol, 1.18 equiv) added as a 0.064 M solution in toluene. 2,2'-(1-Cyclohexylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a crystalline solid (0.032 g, 81% yield, mp = 81.9 °C) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 2979 (m), 2922 (m), 2859 (w), 1448 (m), 1382 (m), 1145 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (ddd, J = 11.6, 7.2, 3.1 Hz, 1H), 1.63 (dd, J = 26.7, 12.5 Hz, 3H), 1.49 (d, J = 12.6 Hz, 2H), 1.31 (ddd, J = 22.3, 16.3, 4.8 Hz, 3H), 1.21 (d, J = 2.8 Hz, 24H), 1.15 (dd, J = 12.5, 3.3 Hz, 1H), 1.10 – 1.00 (m, 1H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.06, 41.19, 30.89, 27.32, 26.73, 25.04, 24.91, 11.15, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{20}H_{39}B_2O_4^+$ $[M+H]^+$: 365.299 Found: 365.292.



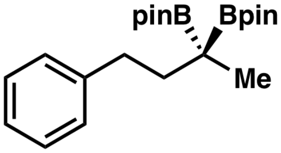
2,2'-(1-Cyclopropylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.006 g (0.025 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.001 g (0.0008 mmol, 0.03

equiv) $Pt(Ph_3P)_4$ in 0.25 mL of toluene (0.10 M) with 1.5 mL of (1-diazoethyl)cyclopropane (0.025 mmol, 1.00 equiv) added as a 0.016 M solution in toluene. 2,2'-(1-Cyclopropylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a crystalline solid (0.006 g, 75% yield, mp = 57.2 °C) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 2965 (w), 2936 (m), 2878 (w), 1449 (m), 1380 (m), 1146 (w), 1067 (w) 755 (w), 697 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (ddd, J = 11.6, 7.2, 3.1 Hz, 1H), 1.63 (dd, J = 26.7, 12.5 Hz, 3H), 1.49 (d, J = 12.6 Hz, 2H), 1.31 (ddd, J = 22.3, 16.3, 4.8 Hz, 3H), 1.21 (d, J = 2.8 Hz, 24H), 1.15 (dd, J = 12.5, 3.3 Hz, 1H), 1.10 – 1.00 (m, 1H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.02, 24.88, 24.87, 14.96, 14.70, 1.89, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{17}H_{33}B_2O_4^+$ $[M+H]^+$: 323.252 Found: 323.258.



2,2'-(3-Phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.049 g (0.209 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.007 g (0.006 mmol, 0.03 equiv) $Pt(Ph_3P)_4$ in 1.14 mL of toluene (0.18 M) with 1.0 mL of (3-diazopropyl)benzene (0.229 mmol, 1.10 equiv) added as a 0.23 M solution in toluene. 2,2'-(3-Phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a clear crystalline solid (0.054 g, 70% yield, mp = 87.5 °C) after silica gel chromatography (TLC R_f

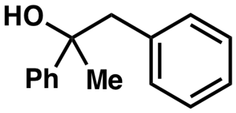
= 0.30 in 90:10 hexanes:diethyl ether). IR (thin film): 2976 (m), 2930 (m), 2862 (w), 1454 (w),1360 (s), 1309 (s), 1262 (m), 1137 (s), 968 (m), 849 (m), 747 (m), 699 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 2H), 7.27 – 7.18 (m, 3H), 2.72 – 2.61 (m, 2H), 1.93 (dd, J = 16.1, 8.0 Hz, 2H), 1.31 (d, J = 3.3 Hz, 24H), 0.89 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.16, 128.79, 128.31, 125.68, 83.18, 38.94, 28.21, 25.13, 24.74, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{21}H_{35}B_2O_4^+$ $[M+H]^+$: 373.272 Found: 373.271.



2,2'-(4-Phenylbutane-2,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared by the representative procedure given above from 0.023 g (0.100 mmol, 1.00 equiv) bis(pinacolato)diboron and 0.004 g (0.003 mmol, 0.03 equiv) $Pt(Ph_3P)_4$ in 0.25 mL of toluene (0.40 M) with 1.10 mL of (3-diazobutyl)benzene (0.110 mmol, 1.10 equiv) added as a 0.10 M solution in toluene. 2,2'-(4-Phenylbutane-2,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) was isolated as a clear crystalline solid (0.032 g, 84% yield, mp = 88.6 °C) after silica gel chromatography (TLC R_f = 0.30 in 92:8 hexanes:diethyl ether). IR (thin film): 2977 (s), 2931 (m), 2868 (w), 1457 (m),1379 (s), 1370 (s), 1345 (s), 1304 (s), 1257 (m), 1140 (s), 1087 (m), 967 (m), 850 (m), 699 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.23 (m, 4H), 7.18 (ddd, J = 6.2, 3.4, 1.7 Hz, 1H), 2.67 – 2.58 (m, 2H), 1.92 – 1.84 (m, 2H), 1.28 (s, 24H), 1.21 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 143.98, 128.75, 128.32, 125.57, 83.19, 36.95, 34.41, 24.98, 24.85, 16.21, (*C*B cannot be detected). HRMS (ESI+) Calcd for $C_{22}H_{37}B_2O_4^+$ [M+H]$^+$: 387.284 Found: 387.280.

Representative Procedure for the Alkylation/Oxidation Competition Experiment to Test Mechanism:



1,2-Diphenylpropan-2-ol. To a 10 mL round bottom flask was added 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (0.024 g, 0.068 mmol, 1.00 equiv) with a Teflon-coated stir bar and the reaction vessel was sealed with a rubber septa. The flask was evacuated and purged with N_2 atmosphere three times and the starting material was then dissolved with 0.68 mL tetrahydrofuran solvent. Then, at 23 °C, bromochloromethane was added (4.60 μL, 0.068 mmol, 1.00 equiv) and cooled to –78 °C while stirring. At –78 °C, the dropwise addition of *n*-butyllithium (28.2 μL, 0.069 mmol, 1.01 equiv) was administered down the sidewalls of the reaction flask to allow precooling of the base. Immediately following the first drop of the lithium reagent a noticeable color change occurred and the reaction mixture was allowed to stir for 10 min at –78 °C. After this reaction period benzyl bromide (8.20 μL, 0.068 mmol, 1.00 equiv) was added to the center of the reaction solution to avoid freezing of the electrophile. This addition was followed by a loss of color from the reaction mixture. The reaction was stirred at –78 °C for 2 h and then at 23 °C for 12 h. Then the reaction vessel was cooled to 0 °C for the addition of a 3 M solution of NaOH in H_2O (1.00 mL) followed by the addition H_2O_2 as a 30% solution in H_2O (0.50 mL) for 2 h of rapid stirring while slowly warming to 23 °C. At which point the reaction contents were poured into a separatory funnel for extraction of the crude organics with ethyl acetate. The combined ethyl acetate layers were washed with brine (3x), collected, dried with Na_2SO_4, and filtered. Following filtration, the solvent was removed under reduced pressure delivering the crude alcohol product as a yellow oil, which was further purified by silica gel chromatorgraphy (TLC R_f = 0.30 in 90:10 hexanes:ethyl acetate). These operations delivered 0.013 g (0.061 mmol, 91%) of 1,2-diphenylpropan-2-ol as a clear oil. Full characterization for this material has been previously reported in the literature.[205]

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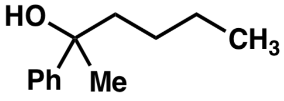
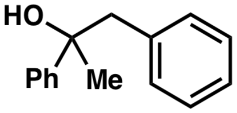
(205) "Formation of Chiral Tertiary Homoallylic Alcohols via Evans Aldol Reaction or Enzymatic Resolution and their Influence on the Sharpless Asymmetric Dihydroxylation," Theurer, M.; Fischer, P.; Baro, A.; Nguyen, G. S.; Kourist, R.; Bornscheuer, U.; Laschat, S. *Tetrahedron* **2010**, *66*, 3814–3823.

Representative Procedure for the Tandem Alkylation/Oxidation Sequence of a Disubstituted Geminal Bis(pinalocato)boronic Ester to access Tertiary Alcohols:



2-Phenylhexan-2-ol. To a 10 mL round bottom flask was added 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (0.017 g, 0.047 mmol, 1.00 equiv) with a Teflon-coated stir bar and the reaction vessel was sealed with a rubber septa. The flask was evacuated and purged with N_2 atmosphere three times and the starting material was then dissolved with 0.68 mL tetrahydrofuran solvent. Then, at –78 °C, the dropwise addition of methyllithium as a 2.60 M solution in dimethoxyethane (18.5 μL, 0.048 mmol, 1.01 equiv) was administered down the sidewalls of the reaction flask to allow precooling of the base. Immediately following the first drop of the lithium reagent a noticeable color change of the colorless solution occurred and the reaction mixture was allowed to stir for 30 min at –78 °C. After this reaction period, 1-bromobutane (5.05 μL, 0.047 mmol, 1.00 equiv) was added to the center of the yellow reaction solution. This addition was followed by a loss of color from the reaction mixture. The reaction was stirred at –78 °C for 2 h and then at 23 °C for 12 h. Then the reaction vessel was cooled to 0 °C for the addition of a 3 M solution of NaOH in H_2O (1.00 mL) followed by the addition H_2O_2 as a 30% solution in H_2O (0.50 mL) for 2 h of rapid stirring while slowly warming to 23 °C. At which point the reaction contents were poured into a separatory funnel for extraction of the crude organics with ethyl acetate. The combined ethyl acetate layers were washed with brine (3x), collected, dried with Na_2SO_4, and filtered. Following filtration, the solvent was removed under reduced pressure to deliver the crude alcohol product as a yellow oil, which was further purified by silica gel chromatorgraphy (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). These operations delivered 0.007 g (0.061 mmol, 88%) of 1,2-diphenylpropan-2-ol as a clear oil. Full characterization for this material has been previously reported in the literature.[206]



1,2-Diphenylpropan-2-ol. Prepared by the representative procedure given above from 0.022 g (0.061 mmol, 1.00 equiv) 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) and 23.6 μL (0.061 mmol, 1.01 equiv) methyllithium in 0.60 mL of tetrahydrofuran (0.10 M) with 7.31 μL of benzyl bromide (0.061 mmol, 1.01 equiv) added following the 10 min reaction period. 1,2-Diphenylpropan-2-ol was isolated as a colorless solid (0.012 g, 96% yield, mp = 49.6 °C) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). Full characterization for this material has

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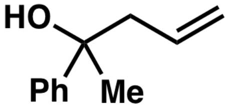
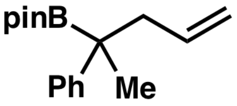
(206) "Reductive Retrofunctionalization of Single-Walled Carbon Nanotubes," Syrgiannis, Z.; Gebhardt, B.; Dotzer, C.; Hauke, F.; Graupner, R.; Hirsch, A. *Angew. Chem. Int. Ed*. **2010**, *49*, 3322–3325.

been previously reported in the literature.[207]



2-Phenylpent-4-en-2-ol. Prepared by the representative procedure given above from 0.028 g (0.078 mmol, 1.00 equiv) 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) and 30.5 μL (0.079 mmol, 1.01 equiv) methyllithium in 0.78 mL of tetrahydrofuran (0.10 M) with 6.88 μL of allyl bromide (0.079 mmol, 1.01 equiv) added following the 10 min reaction period. 2-Phenylpent-4-en-2-ol was isolated as a clear oil (0.012 g, 97% yield) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:ethyl acetate). Full characterization for this material has been previously reported in the literature.[207]

Representative Procedure for the Alkylation of Disubstituted Geminal Bis(pinalocato)boronic Ester to access Tertiary Boronic Esters:



4,4,5,5-Tetramethyl-2-(2-phenylpent-4-en-2-yl)-1,3,2-dioxaborolane. To a 2 dram vial was added 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (0.039 g, 0.109 mmol, 1.00 equiv) with a Teflon-coated stir bar and the reaction vessel was sealed with a rubber septa. The vial was evacuated and purged with N_2 atmosphere three times and the starting material was then dissolved with 1.09 mL tetrahydrofuran solvent. Then, at –78 °C, the dropwise addition of methyllithium as a 2.60 M solution in dimethoxyethane (42.3 μL, 0.110 mmol, 1.01 equiv) was administered down the sidewalls of the reaction vial to allow precooling of the base. Immediately following the first drop of the lithium reagent a noticeable color change of the colorless solution occurred and the reaction mixture was allowed to stir for 30 min at –78 °C. After this reaction period, allylbromide (9.50 μL, 0.110 mmol, 1.01 equiv) was added to the center of the yellow reaction solution. This addition was followed by a loss of color from the reaction mixture. The reaction was stirred at –78 °C for 1 h and then 0.50 mL of a 30% HCl solution in methanol was added to quench the reaction. Then the reaction vessel was warmed to 23 °C for the extraction of the crude organics with diethyl ether. The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3x), collected, dried with $MgSO_4$, and filtered. Following filtration, the solvent was removed under reduced pressure to deliver the crude product as a clear oil, which was further purified by a short silica gel plug (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). These operations delivered 0.027 g (0.100 mmol, 92%) of 4,4,5,5-tetramethyl-2-(2-phenylpent-4-en-2-yl)-1,3,2-dioxaborolane as a clear oil. Full characterization for this material has been previously reported in the literature.[208]

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[207] "Silver-Catalyzed, Manganese-Mediated Allylation and Benzylation Reactions of Aldehydes and Ketones," Barczak, N. T.; Jarvo, E. R. *Eur. J. Org. Chem.* **2008**, 5507-5510.

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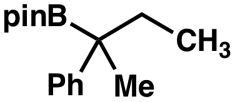
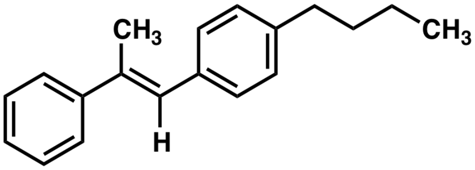
(208) "Improved Method for the Conversion of Pinacolboronic Esters into Trifluoroborate Salts. Facile Synthesis of Chiral Secondary and Tertiary Trifluoroborates," Bagutski, V.; Ros, A.; Aggarwal, V. K. *Tetrahedron* **2009**, *65*, 9956-9960.



4,4,5,5-Tetramethyl-2-(2-phenylbutan-2-yl)-1,3,2-dioxaborolane. Prepared by the representative procedure given above from 0.242 g (0.676 mmol, 1.00 equiv) 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) and 276.0 μL (0.682 mmol, 1.01 equiv) methyllithium (2.47 M in dimethoxymethane) in 6.76 mL of tetrahydrofuran (0.10 M) with 59.5 μL of ethyl bromide (0.743 mmol, 1.10 equiv) added following the 10 min reaction period. 4,4,5,5-Tetramethyl-2-(2-phenylbutan-2-yl)-1,3,2-dioxaborolane was isolated as a clear oil (0.158 g, 90% yield) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). Full characterization for this material has been previously reported in the literature.[208]

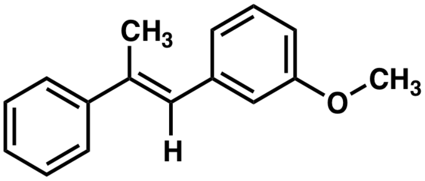
Representative Procedure for the Lithiation of Disubstituted Geminal Bis(pinalocato)boronic Ester to access Trisubstituted Alkenes:



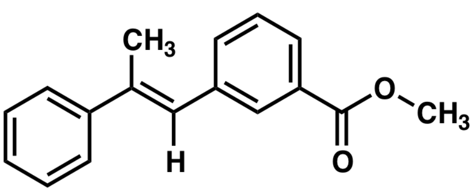
(*E*)-1-Butyl-4-(2-phenylprop-1-en-1-yl)benzene. To a 2 dram vial was added 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (20.1 mg, 0.056 mmol, 1.00 equiv) with a Teflon-coated stir bar and the reaction vessel was sealed with a rubber septa. The vial was evacuated and purged with N_2 atmosphere three times and the starting material was then dissolved with

1.09 mL tetrahydrofuran solvent. Then, at –78 °C, the dropwise addition of methyllithium as a 2.42 M solution in dimethoxyethane (23.4 μL, 0.057 mmol, 1.01 equiv) was administered down the sidewalls of the reaction vial to allow precooling of the base. Immediately following the first drop of the lithium reagent a noticeable color change of the colorless solution occurred and the reaction mixture was allowed to stir for 10 min at –78 °C. After this reaction period, 4-butylbenzaldehyde (9.49 μL, 0.057 mmol, 1.01 equiv) was added to the center of the yellow reaction solution. This addition was followed by a loss of color from the reaction mixture. The reaction was stirred for 3 h while warming to 23 °C and then the reaction contents were poured into a separatory funnel for extraction of the crude organics with ethyl acetate. The organic layer was washed with brine (3x), collected, dried with $MgSO_4$, and filtered. Following filtration, the solvent was removed under reduced pressure to deliver the crude product as a clear oil (5.25:1 *E*:*Z*), which was further purified by a silica gel chromatography (TLC R_f = 0.30 in 100 % hexanes). These operations delivered 10.8 mg (0.043 mmol, 77%) of (*E*)-1-Butyl-4-(2-phenylprop-1-en-1-yl)benzene as a clear oil. IR (thin film): 3020 (w), 2955 (w), 2926 (w), 2856 (w), 1509 (w), 1444 (w), 1377 (w), 1259 (w), 1067 (w), 1026 (w), 872 (w), 754 (m), 694 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 7.2 Hz, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.28 (t, J = 6.4 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 6.81 (s, 1H), 2.67 – 2.58 (m, 2H), 2.29 (d, J = 1.3 Hz, 3H), 1.69 – 1.56 (m, 2H), 1.38 (dd, J = 14.9, 7.6 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C

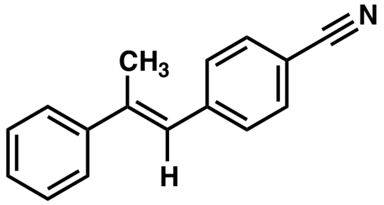
NMR (100 MHz, $CDCl_3$): δ 144.40, 141.47, 136.90, 135.87, 129.27, 128.51, 128.45, 127.91, 127.24, 126.20, 35.62, 33.84, 22.62, 17.75, 14.20. HRMS (ESI+) Calcd for $C_{19}H_{23}^+$ $[M+H]^+$: 251.378 Found: 251.381.



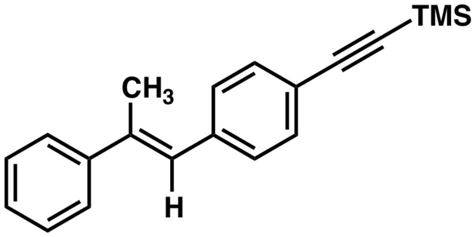
(*E*)-1-Methoxy-3-(2-phenylprop-1-en-1-yl)benzene. Prepared by the representative procedure given above from 26.3 mg (0.073 mmol, 1.00 equiv) 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) and 30.6 μL (0.074 mmol, 1.01 equiv) methyllithium (2.42 M in dimethoxymethane) in 0.73 mL of tetrahydrofuran (0.10 M) with 9.04 μL of *m*-anisaldehyde (0.074 mmol, 1.01 equiv) added following the 10 min reaction period. (*E*)-1-Methoxy-3-(2-phenylprop-1-en-1-yl)benzene was isolated as a clear oil (11.8 mg, 72% yield) after silica gel chromatography (TLC R_f = 0.30 in 90:10 hexanes:diethyl ether). IR (thin film): 2997 (w), 2937 (w), 2833 (w), 1597 (w), 1576 (w), 1491 (w), 1444 (w), 1268 (w), 1156 (w), 1048 (w), 873 (w), 760 (m), 694 (m). ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.49 (m, 2H), 7.38 (ddd, J = 7.8, 4.5, 1.2 Hz, 2H), 7.32 – 7.27 (m, 2H), 6.96 (dd, J = 7.6, 0.7 Hz, 1H), 6.91 (s, 1H), 6.81 (t, J = 5.4 Hz, 2H), 3.84 (s, 3H), 2.29 (d, J = 1.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.64, 144.12, 139.97, 137.95, 129.34, 128.54, 127.80, 127.43, 126.23, 121.92, 114.92, 112.25, 55.46, 17.81. HRMS (ESI+) Calcd for $C_{16}H_{17}O^+$ $[M+H]^+$: 225.133 Found: 225.127.



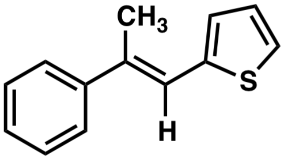
(*E*)-Methyl 3-(2-phenylprop-1-en-1-yl)benzoate. Prepared by the representative procedure given above from 25.5 mg (0.071 mmol, 1.00 equiv) 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) and 29.7 μL (0.072 mmol, 1.01 equiv) methyllithium (2.42 M in dimethoxymethane) in 0.71 mL of tetrahydrofuran (0.10 M) with 9.04 mg of methyl 2-formylbenzoate (0.072 mmol, 1.01 equiv) added following the 10 min reaction period. (*E*)-Methyl 3-(2-phenylprop-1-en-1-yl)benzoate was isolated as a clear oil (14.2 mg, 79% yield) after silica gel chromatography (TLC R_f = 0.30 in 90:10 hexanes:diethyl ether). IR (thin film): 3056 (w), 3028 (w), 2991 (w), 2950 (w), 2921 (w), 2854 (w), 1720 (s), 1599 (w), 1580 (w), 1494 (w), 1437 (m), 1379 (w), 1285 (s), 1241 (m), 1202 (m), 1107 (m), 1084 (m), 758 (m), 744 (m), 696 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.54 (dd, J = 8.6, 7.2 Hz, 3H), 7.45 (t, J = 7.7 Hz, 1H), 7.38 (dd, J = 8.2, 6.7 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 6.84 (s, 1H), 3.94 (s, 3H), 2.28 (d, J = 1.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.38, 143.85, 138.88, 138.83, 133.75, 130.44, 130.35, 128.60, 128.48, 127.78, 127.64, 126.84, 126.24, 52.39, 17.74. HRMS (ESI+) Calcd for $C_{17}H_{17}O_2^+$ $[M+H]^+$: 253.058 Found: 253.122.



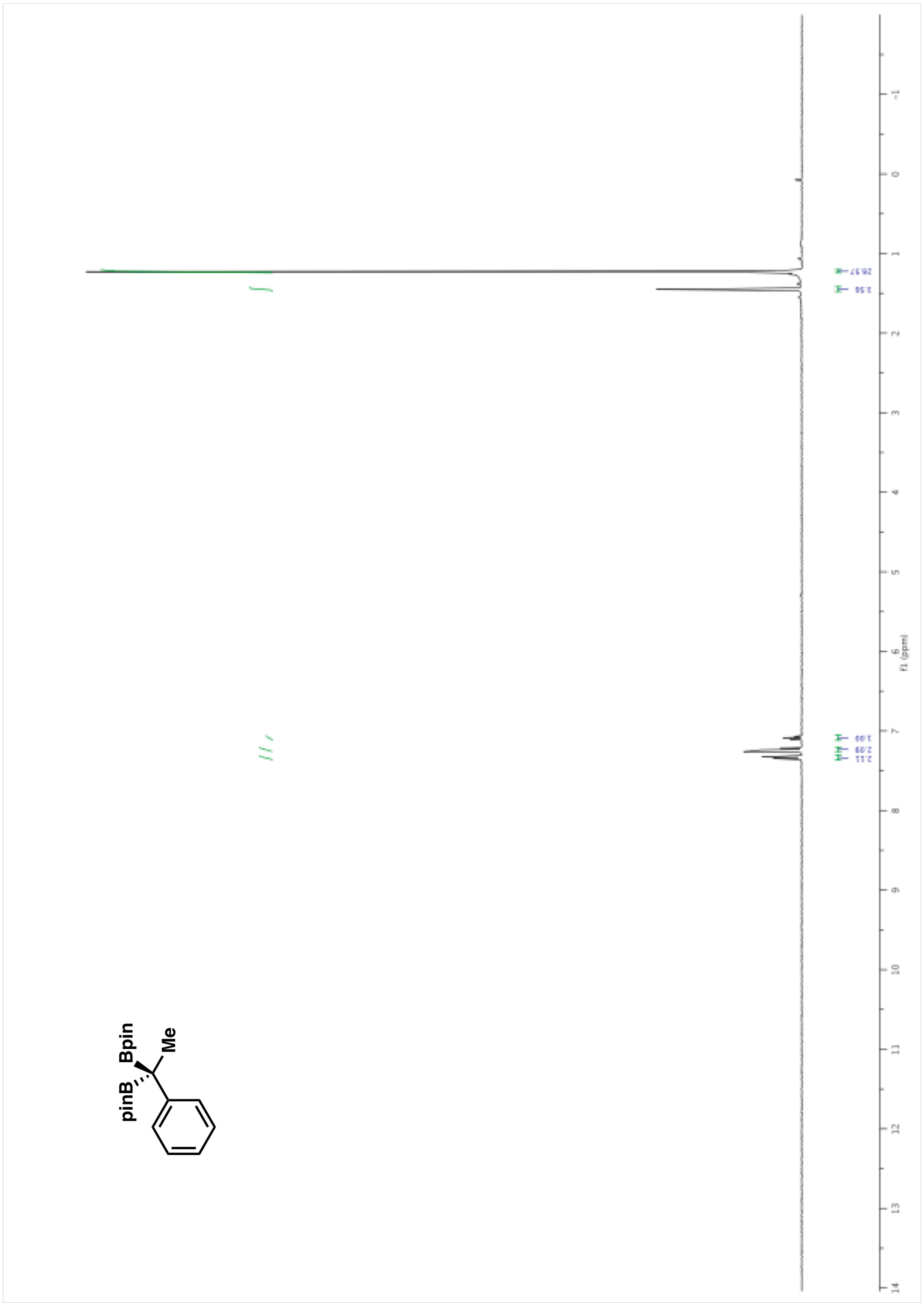
(*E*)-4-(2-Phenylprop-1-en-1-yl)benzonitrile. Prepared by the representative procedure given above from 24.8 mg (0.069 mmol, 1.00 equiv) 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) and 28.9 μL (0.070 mmol, 1.01 equiv) methyllithium (2.42 M in dimethoxymethane) in 0.69 mL of tetrahydrofuran (0.10 M) with 9.17 mg of 4-cyanobenzaldehyde (0.070 mmol, 1.01 equiv) added following the 10 min reaction period. (*E*)-4-(2-Phenylprop-1-en-1-yl)benzonitrile was isolated as a white crystalline solid (12.3 mg, 81% yield, mp = 87.6 °C) after silica gel chromatography (TLC R_f = 0.30 in 90:10 hexanes:diethyl ether). IR (thin film): 3063 (w), 2984 (m), 2926 (w), 2855 (w), 2223 (m), 1597 (m), 1498 (m), 1446 (m), 1378 (w), 1027 (w), 880 (m), 827 (w), 764 (m), 700 (m), 555 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.63 (m, 2H), 7.52 (dd, J = 5.3, 3.2 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.33 (dd, J = 10.1, 4.3 Hz, 1H), 6.80 (s, 1H), 2.29 (d, J = 1.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.40, 143.27, 140.98, 132.22, 129.91, 128.71, 128.71, 128.10, 126.28, 126.26, 119.31, 17.96. HRMS (ESI+) Calcd for $C_{16}H_{14}N^+$ $[M+H]^+$: 220.122 Found: 220.114.



(*E*)-Trimethyl((4-(2-phenylprop-1-en-1-yl)phenyl)ethynyl)silane. Prepared by the representative procedure given above from 19.8 mg (0.055 mmol, 1.00 equiv) 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) and 23.0 μL (0.056 mmol, 1.01 equiv) methyllithium (2.42 M in dimethoxymethane) in 0.55 mL of tetrahydrofuran (0.10 M) with 11.3 mg of 4-((trimethylsilyl)ethynyl)benzaldehyde (0.056 mmol, 1.01 equiv) added following the 10 min reaction period. (*E*)-Trimethyl((4-(2-phenylprop-1-en-1-yl)phenyl)ethynyl)silane was isolated as a clear oil (12.0 mg, 75% yield) after silica gel chromatography (TLC R_f = 0.30 in 100% hexanes). IR (thin film): 3028 (w), 2958 (w), 2925 (w), 2854 (w), 2156 (m), 1600 (w), 1496 (w), 1444 (w), 1249 (m), 863 (m), 842 (m), 757 (m) 696 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.43 (m, 4H), 7.41 – 7.34 (m, 2H), 7.34 – 7.27 (m, 3H), 6.79 (s, 1H), 2.28 (d, J = 1.4 Hz, 3H), 0.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.80, 138.62, 131.99, 129.19, 128.59, 128.58, 127.57, 127.37, 126.23, 126.23, 105.46, 17.88, 0.23. HRMS (ESI+) Calcd for $C_{20}H_{23}Si^+$ $[M+H]^+$: 291.160 Found: 291.154.



(*E*)-2-(2-Phenylprop-1-en-1-yl)thiophene. Prepared by the representative procedure given above from 18.9 mg (0.052 mmol, 1.00 equiv) 2,2'-(1-phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) and 22.0 μL (0.053 mmol, 1.01 equiv) methyllithium (2.42 M in dimethoxymethane) in 0.52 mL of tetrahydrofuran (0.10 M) with 4.90 μL of 2-thiophenecarbaldehyde (0.053 mmol, 1.01 equiv) added following the 10 min reaction period. (*E*)-2-(2-Phenylprop-1-en-1-yl)thiophene was isolated as a yellow oil (6.76 mg, 64% yield) after silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes:diethyl ether). IR (thin film): 3056 (w), 3025 (w), 2955 (w), 2924 (m), 2852 (w), 1596 (w), 1492 (w), 1444 (w), 1378 (w), 1263 (w), 1077 (w), 1026 (w), 853 (w), 815 (w), 760 (m), 693 (s), 507 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, J = 8.2, 1.0 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.31 (d, J = 5.3 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 3.2 Hz, 1H), 7.08 – 7.05 (m,1H), 6.95 (s, 1H), 2.42 (d, J = 1.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.75, 135.93, 128.58, 128.58, 127.82, 127.31, 127.17, 126.23, 125.33, 121.21, 18.64. HRMS (ESI+) Calcd for $C_{13}H_{13}S^+$ $[M+H]^+$: 201.071 Found: 201.074.



pinB
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3.56
1.00
2.09
2.11
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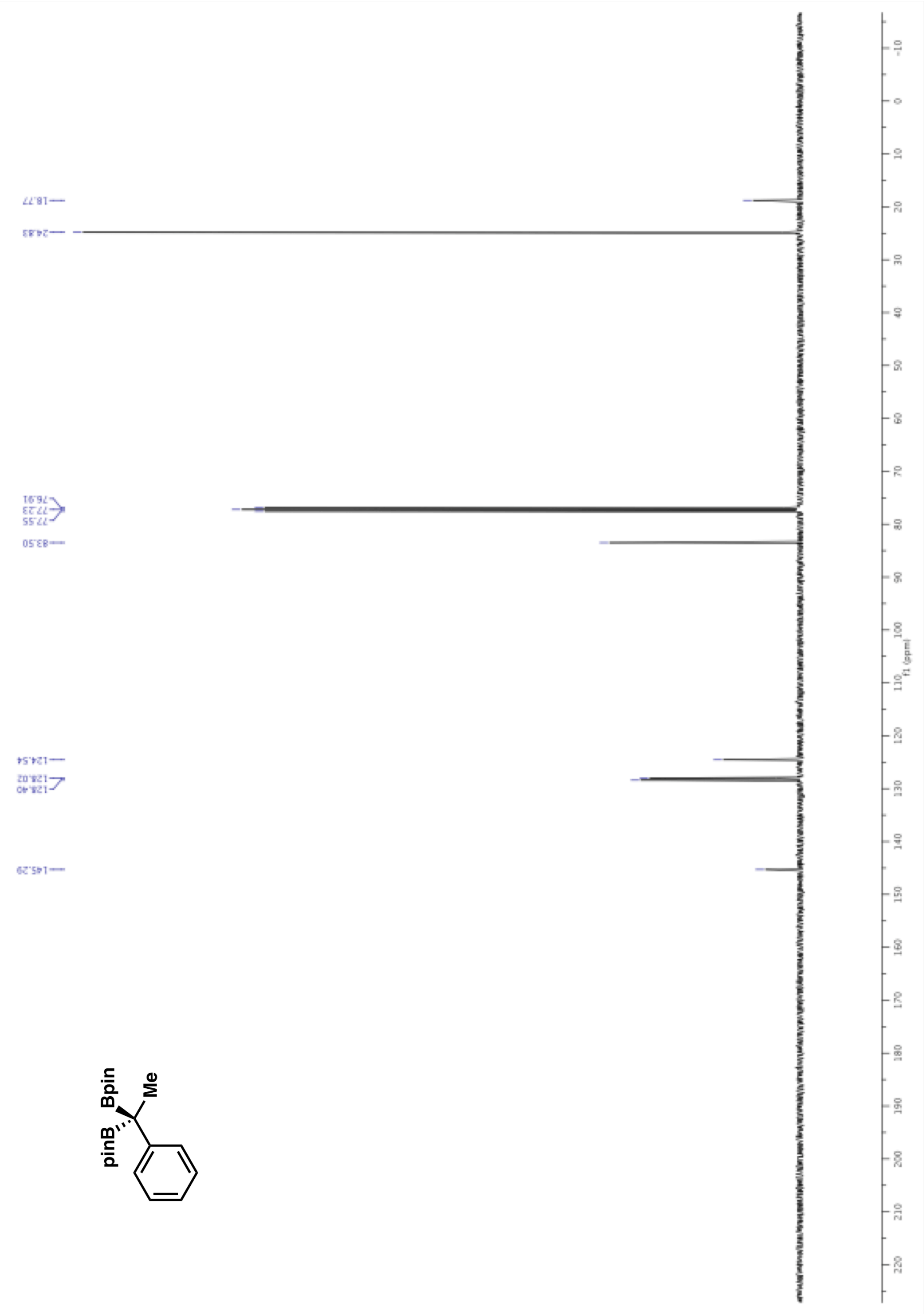
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145.29
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130
140
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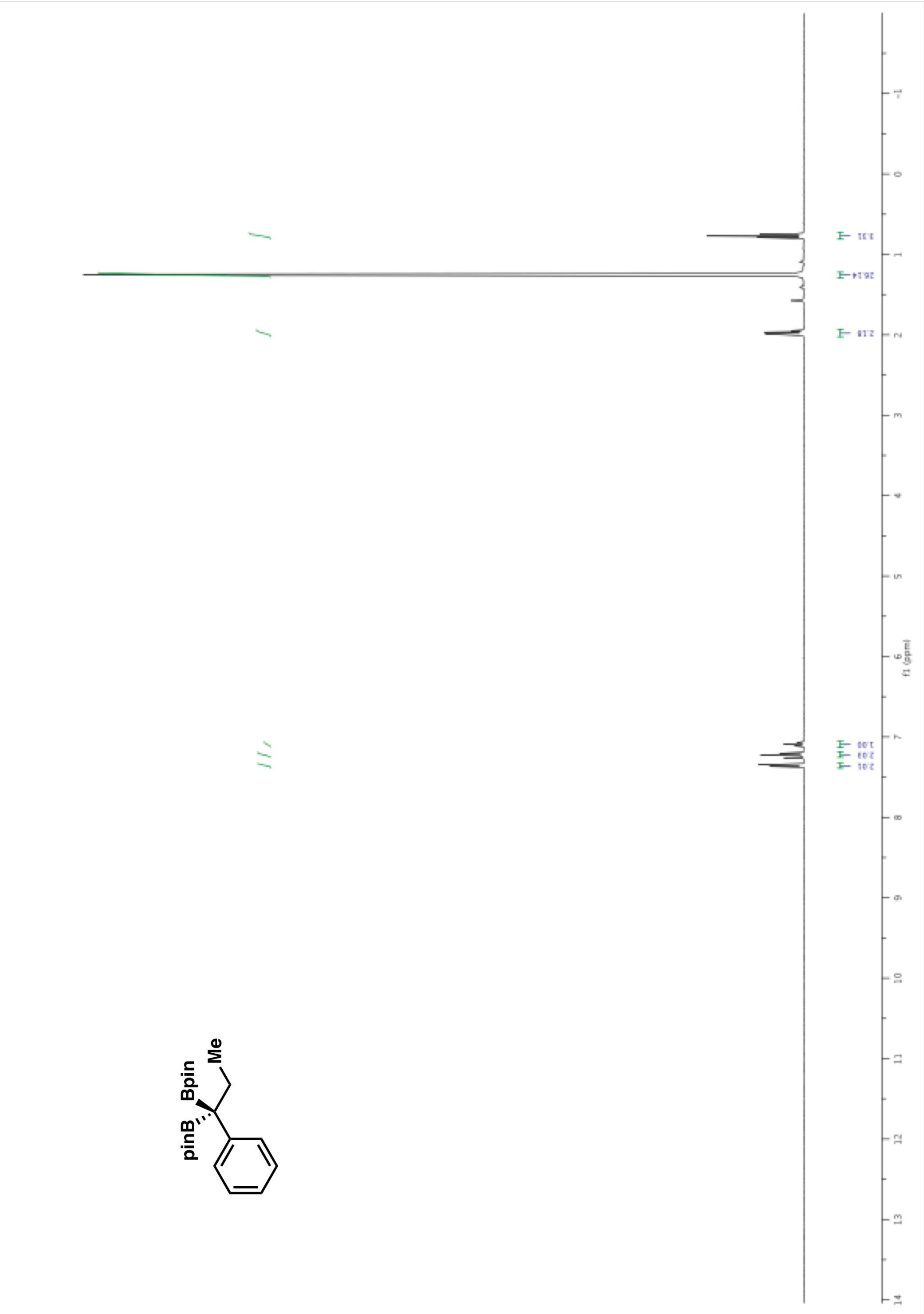
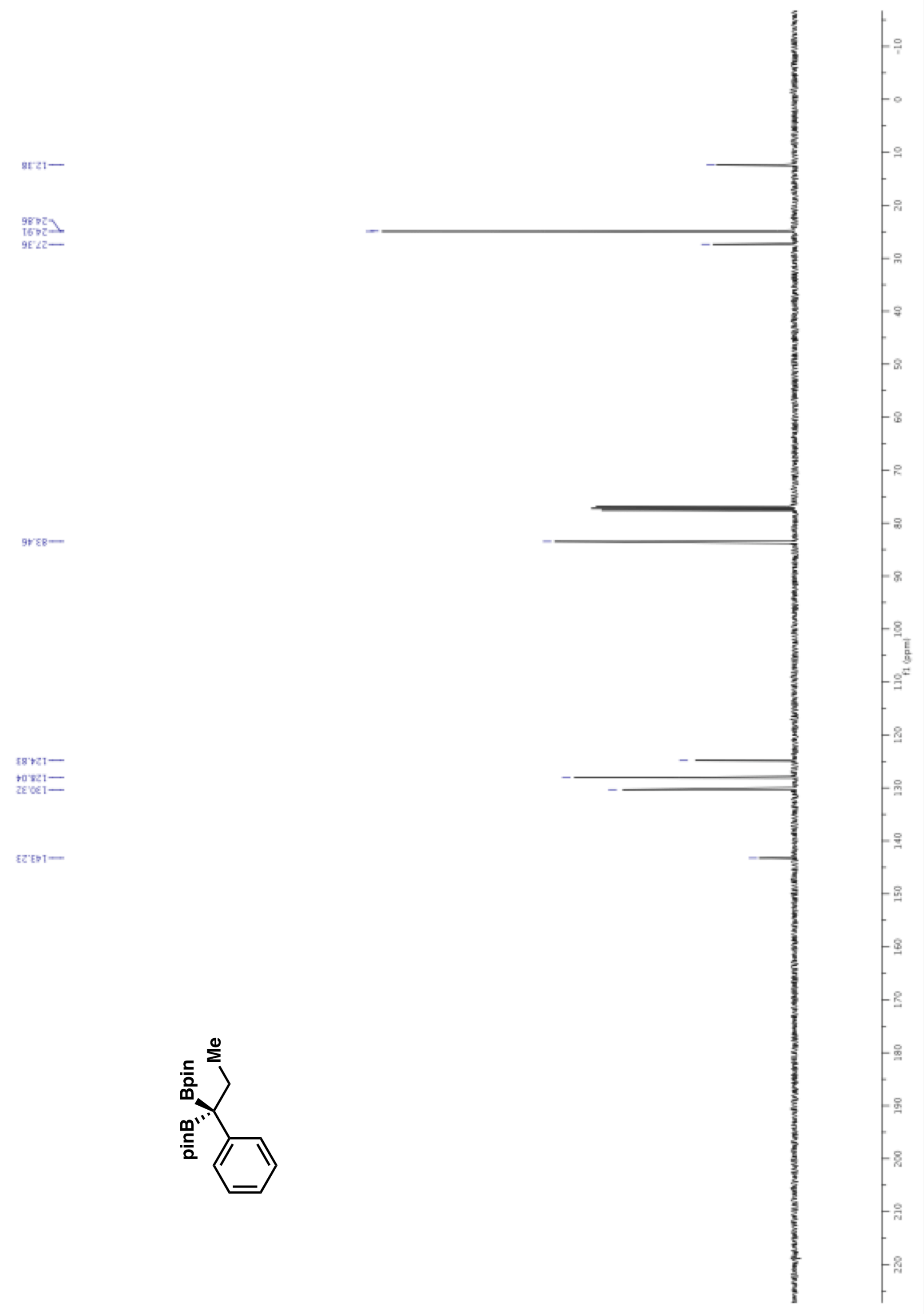
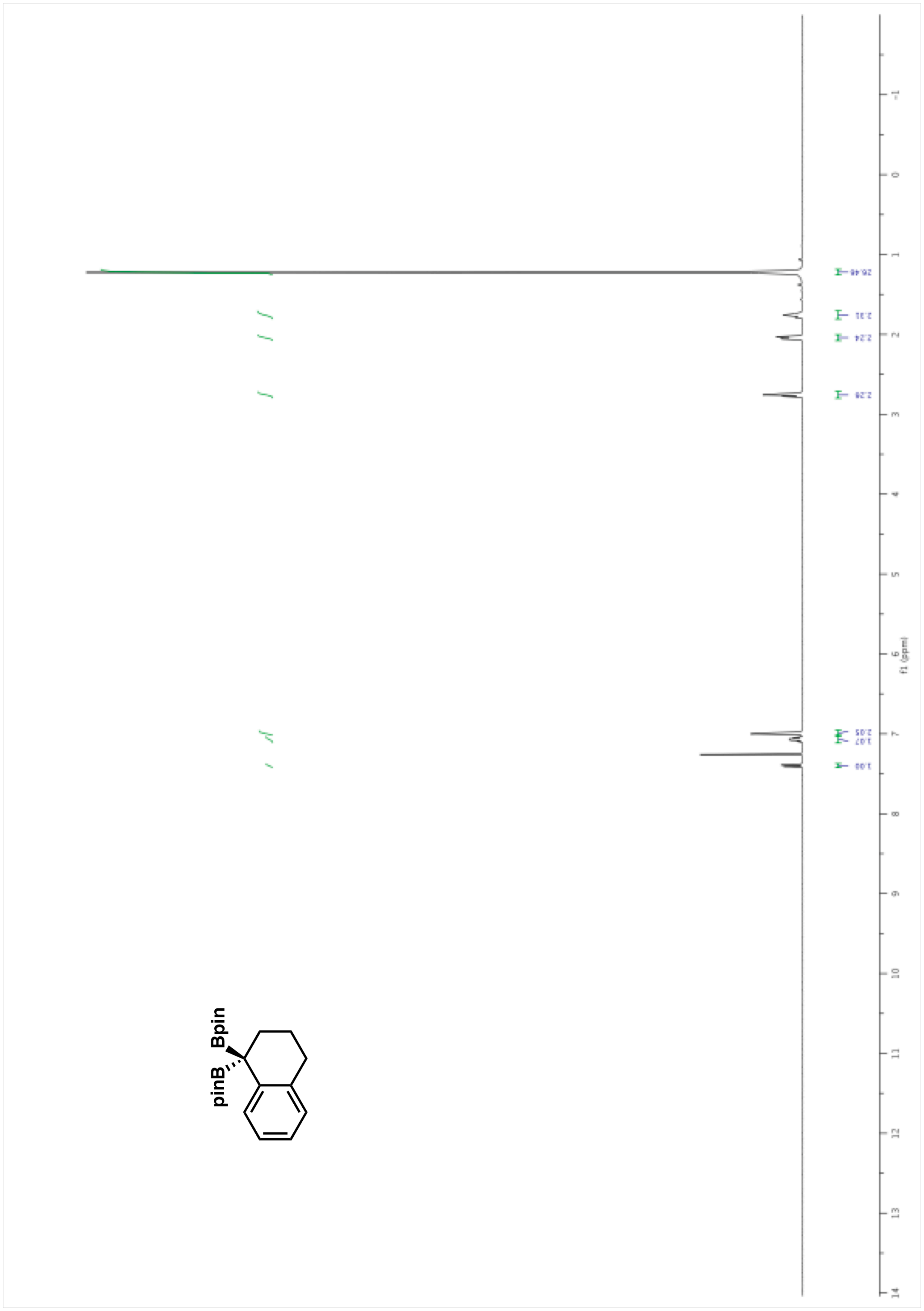
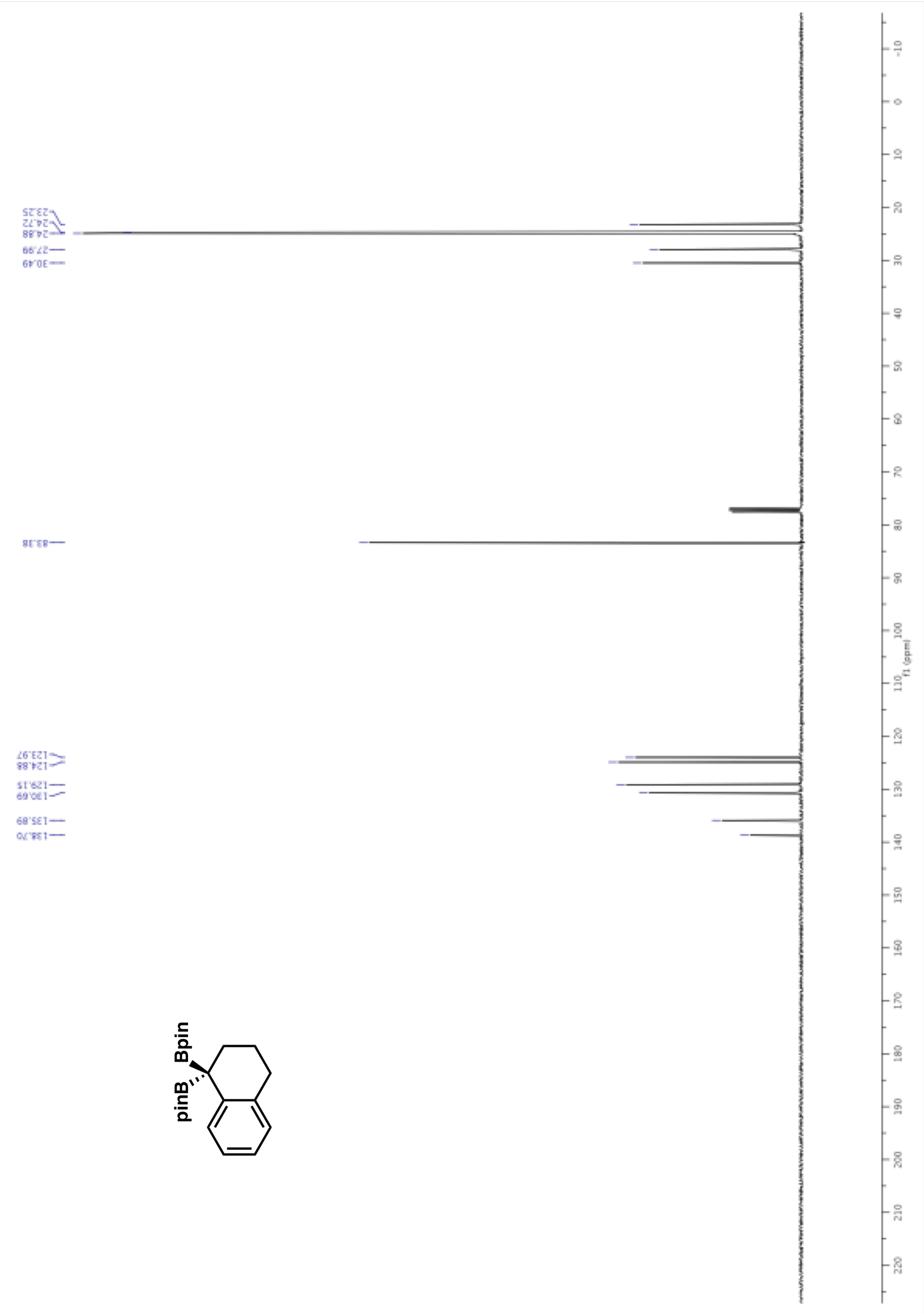
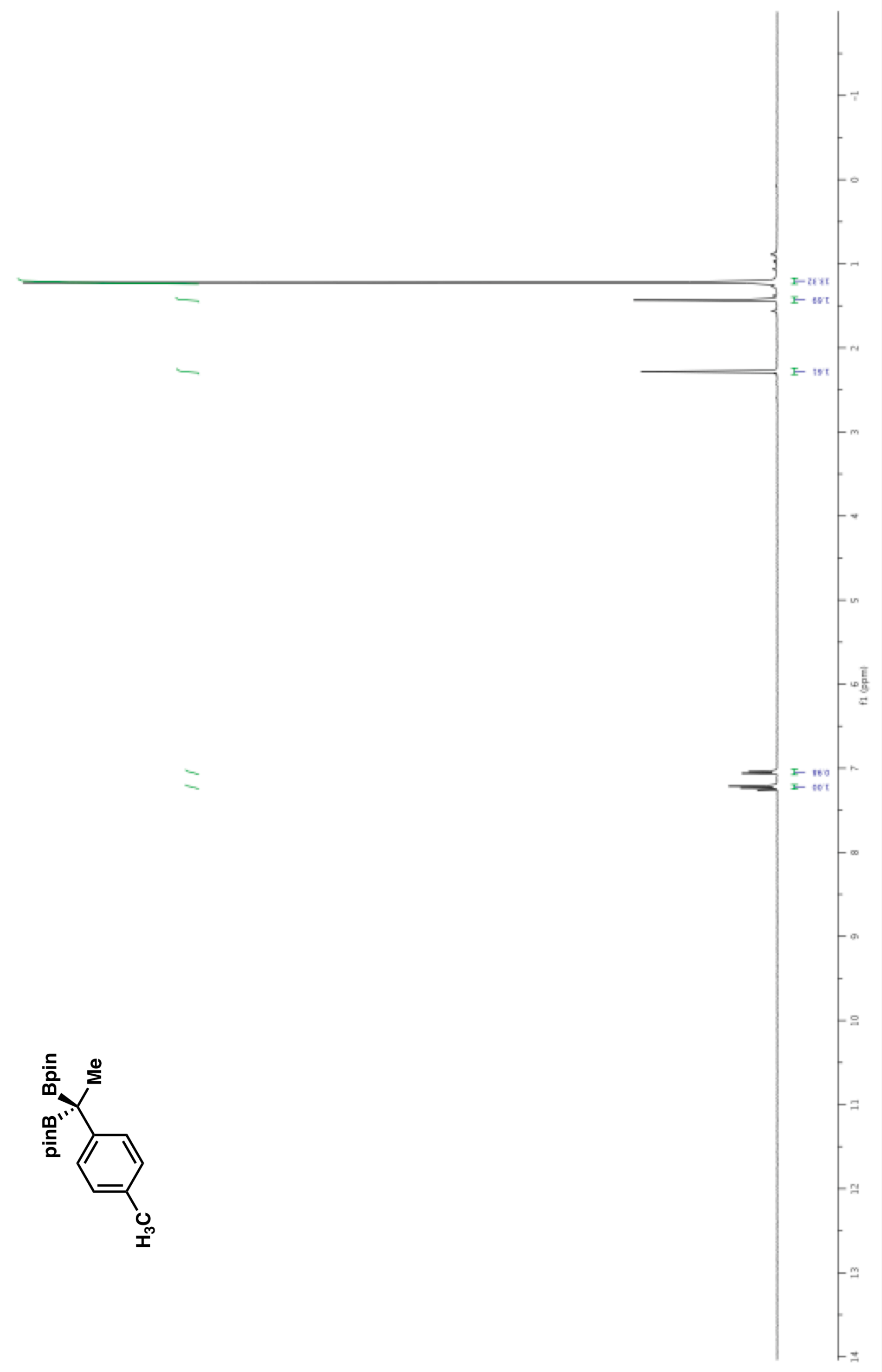
200
210
220
f1 (ppm)

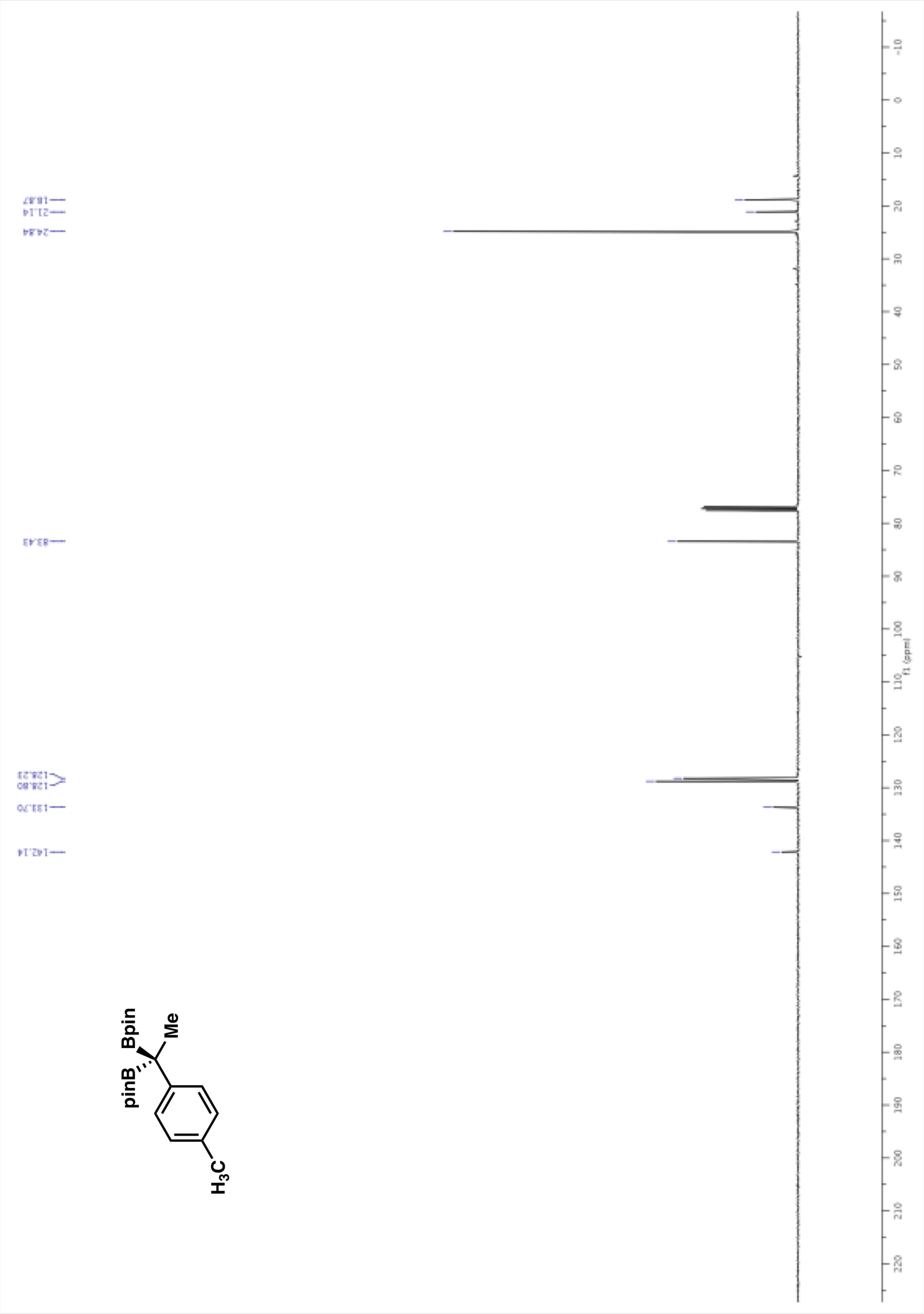

pinB
Bpin
Me
2.01
2.03
1.00
2.18
26.14
3.31
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

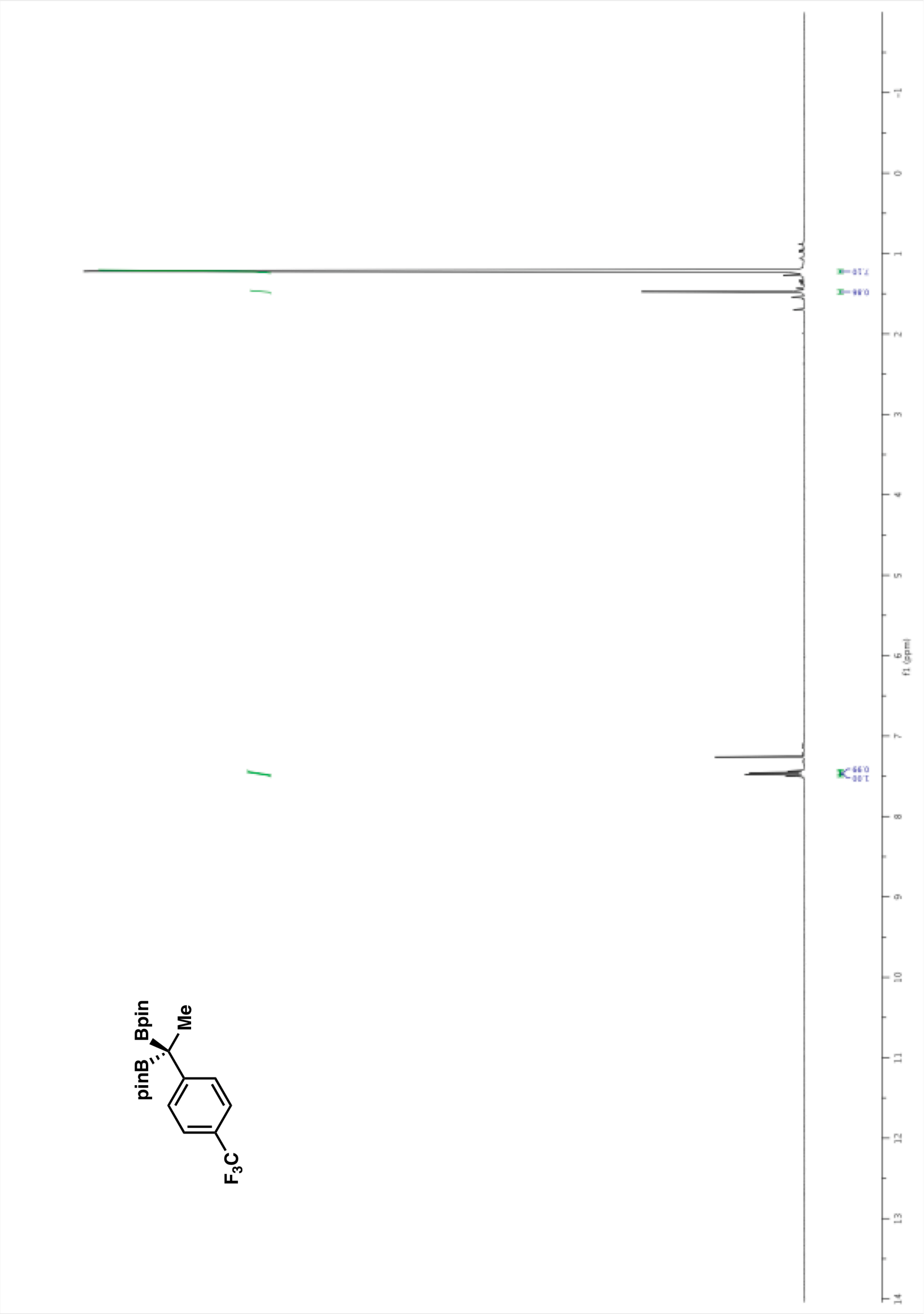

12.38
24.86
24.91
27.36
83.46
124.83
128.04
130.32
143.23
pinB
Bpin
Me
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

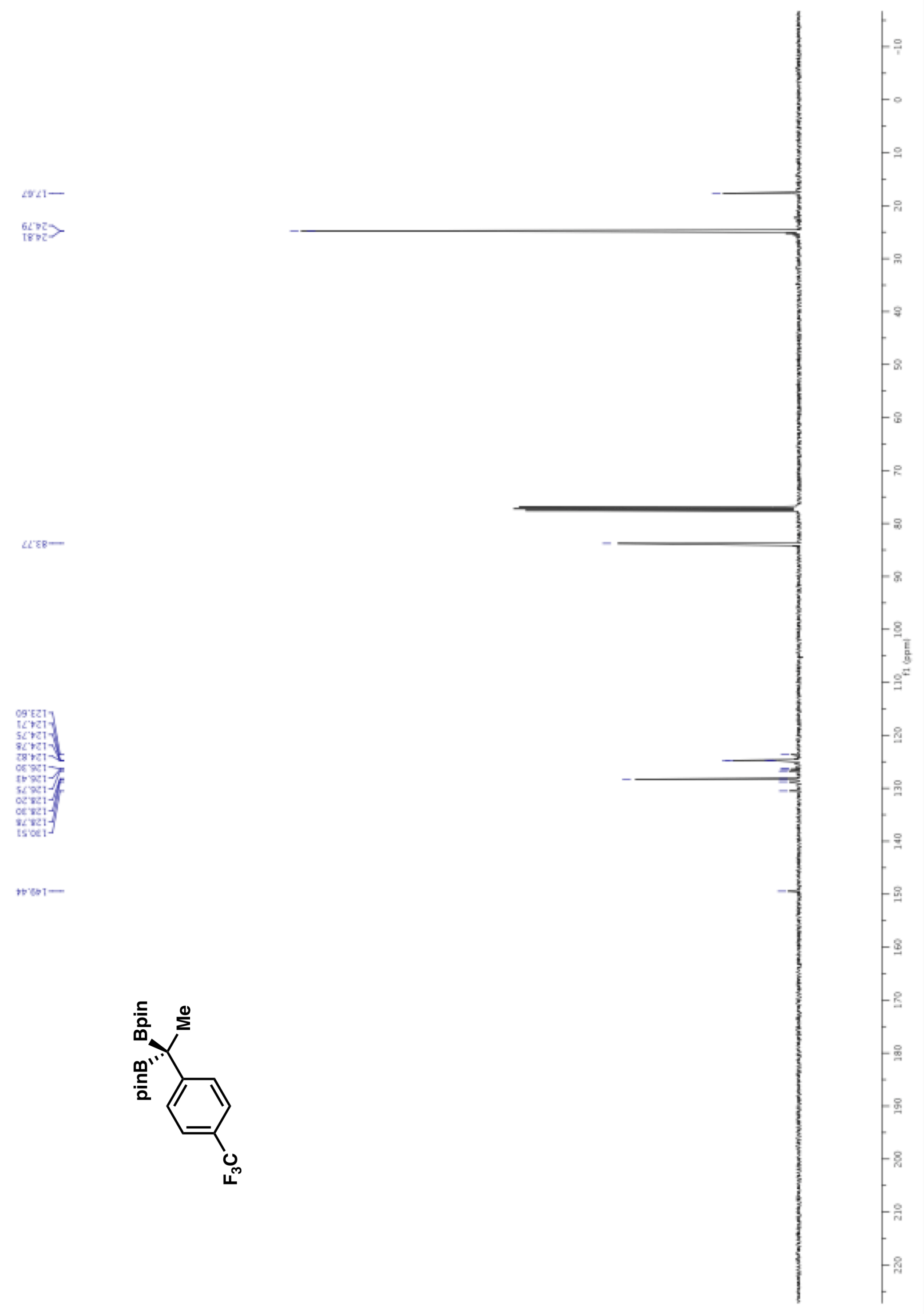

pinB
Bpin
1.00
1.07
2.05
2.28
2.24
2.31
26.48
14
13
12
11
10
9
8
7
6
f1 (ppm)
5
4
3
2
1
0
-1

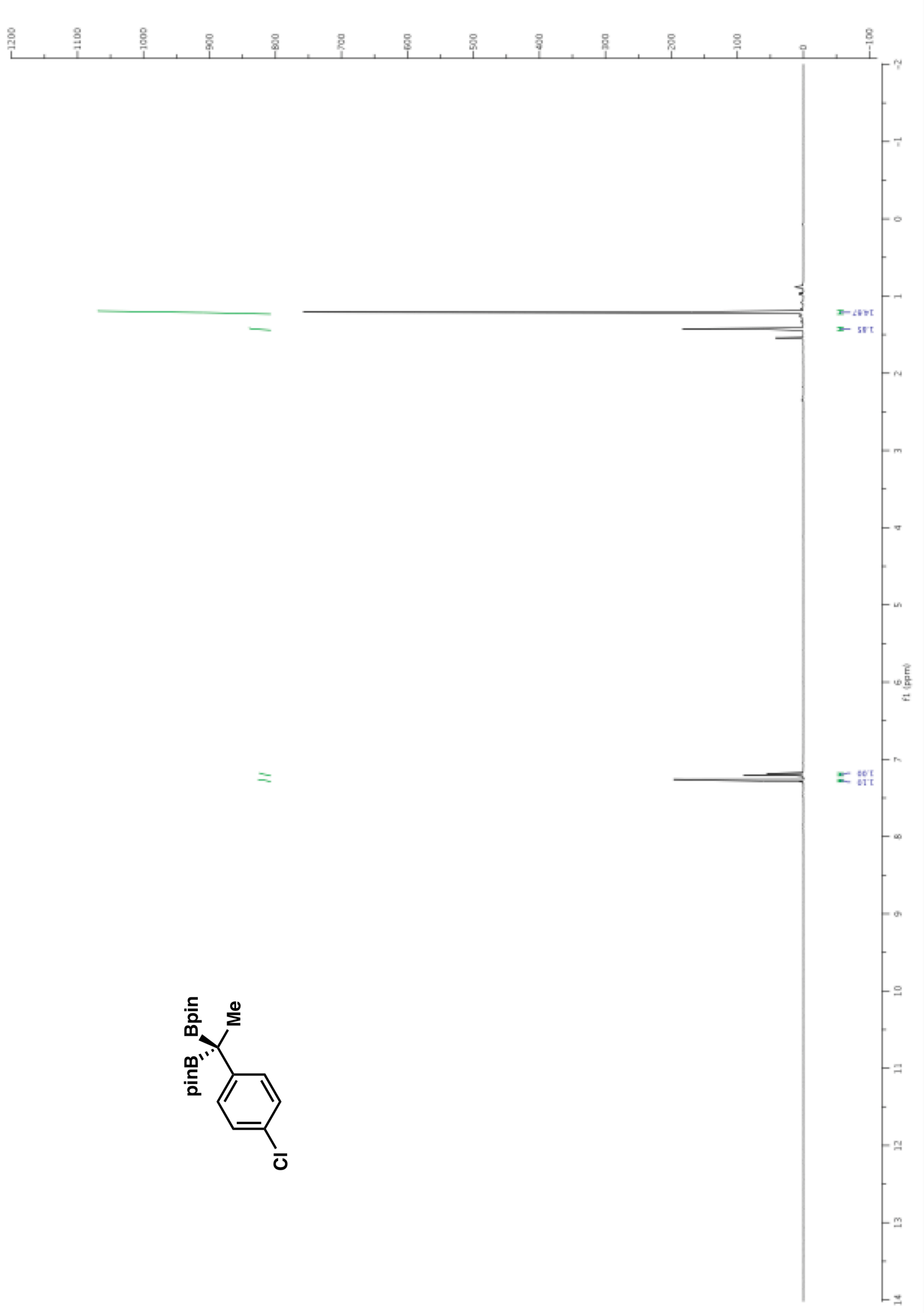

23.25
24.72
24.88
27.99
30.49
83.38
123.97
124.88
129.15
130.69
135.89
138.70
pinB
Bpin
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

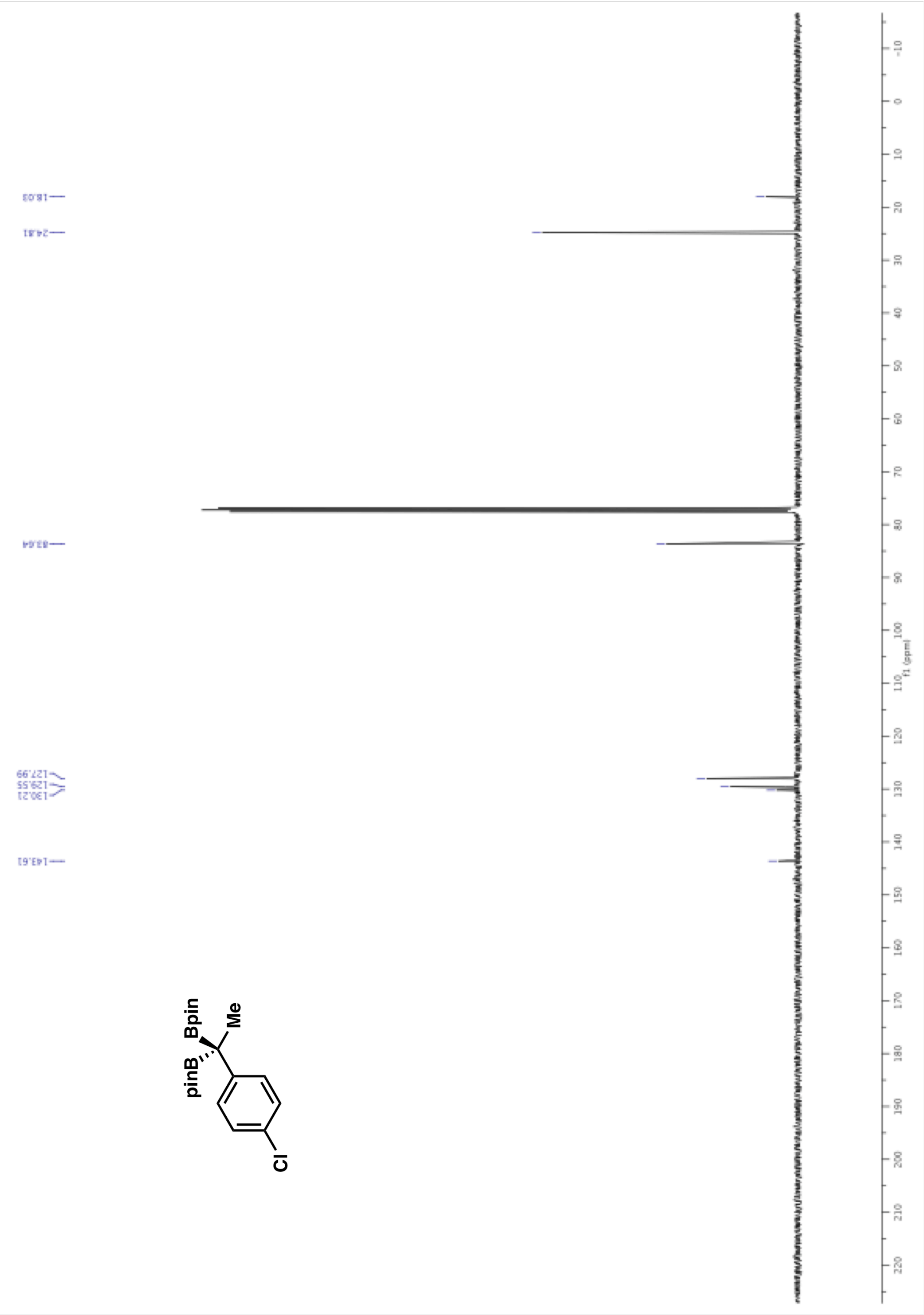

pinB
Bpin
Me
H_3C
12.92
1.69
1.61
0.98
1.00
-1
0
1
2
3
4
5
6
f1 (ppm)
7
8
9
10
11
12
13
14

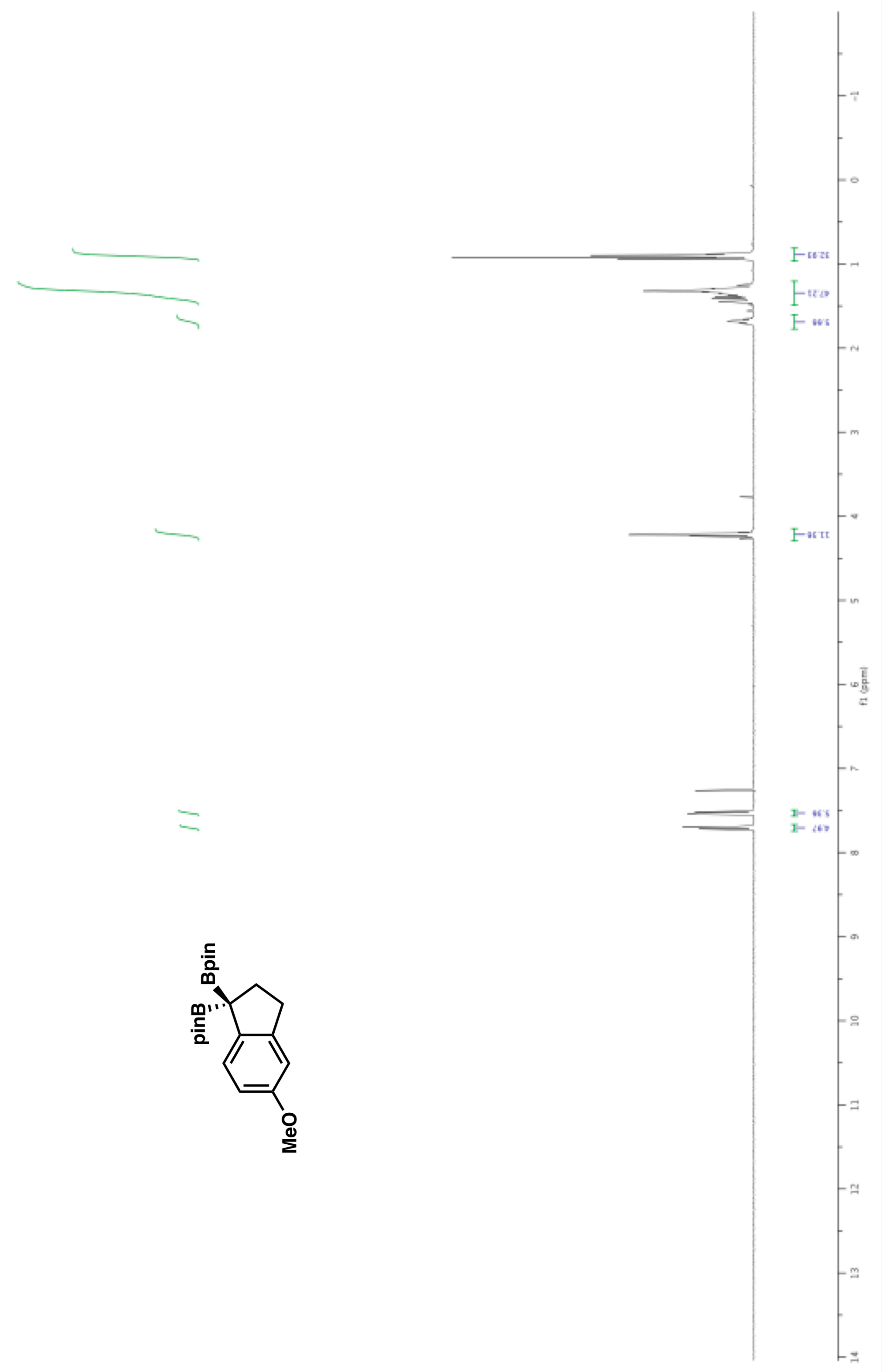

18.87
21.14
24.84
83.43
128.23
128.80
133.70
142.14
pinB
Bpin
Me
H3C
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

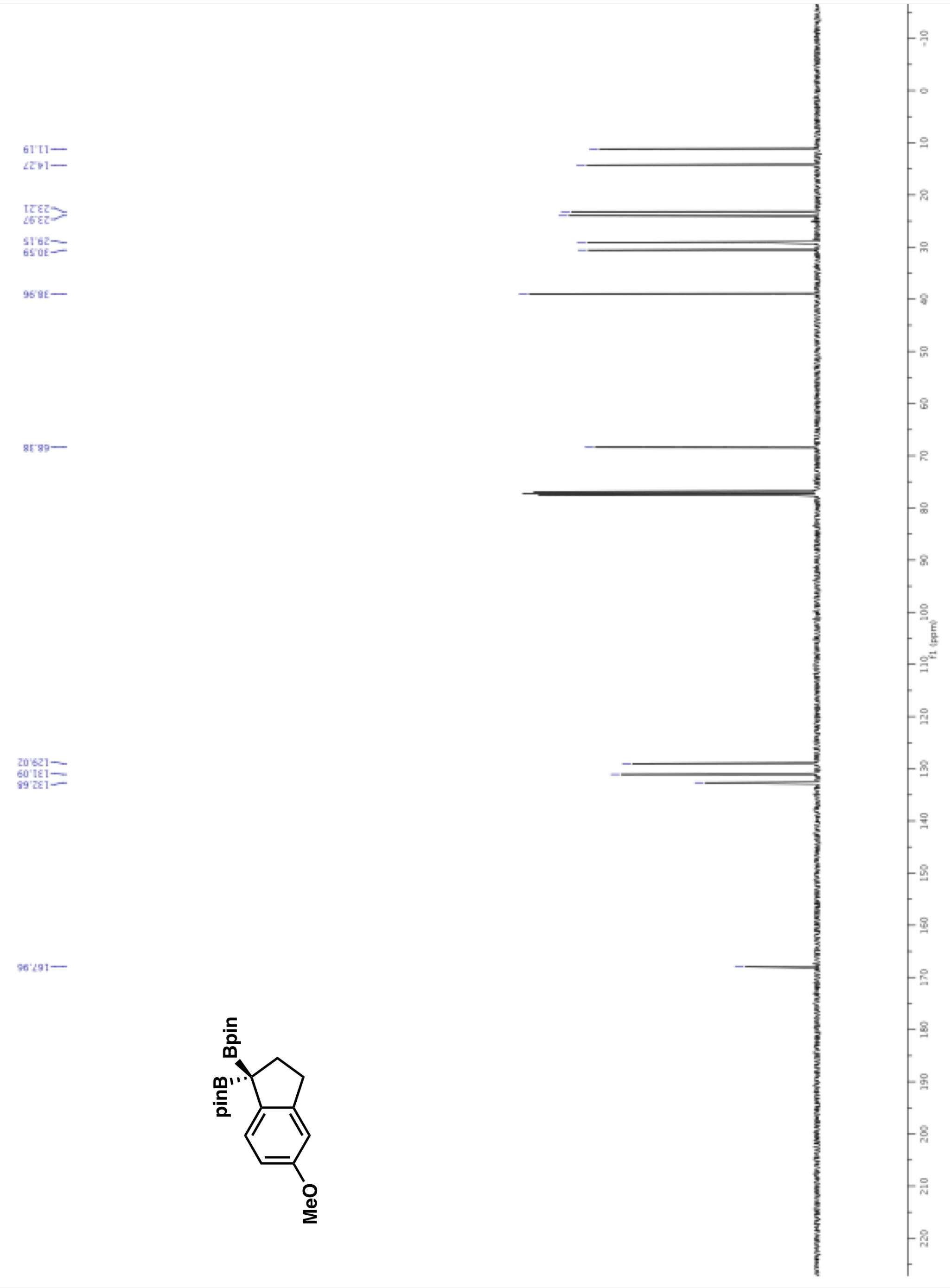

pinB
Bpin
Me
F3C
7.10
0.88
0.99
1.00
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)

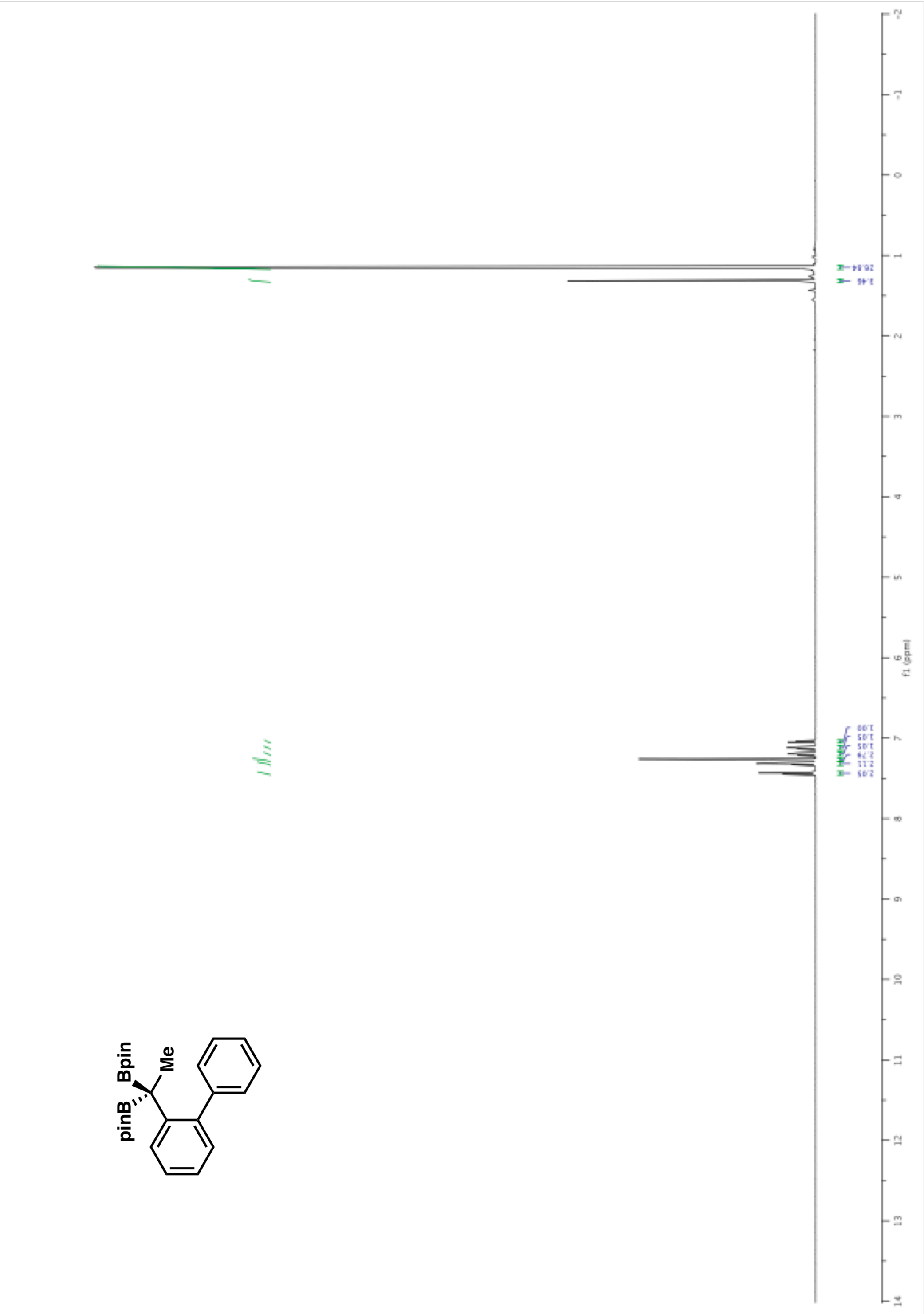

17.67
24.79
24.81
83.77
123.60
124.71
124.75
124.78
124.82
126.30
126.43
126.75
128.20
128.30
128.78
130.51
149.44
pinB
Bpin
Me
F3C
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

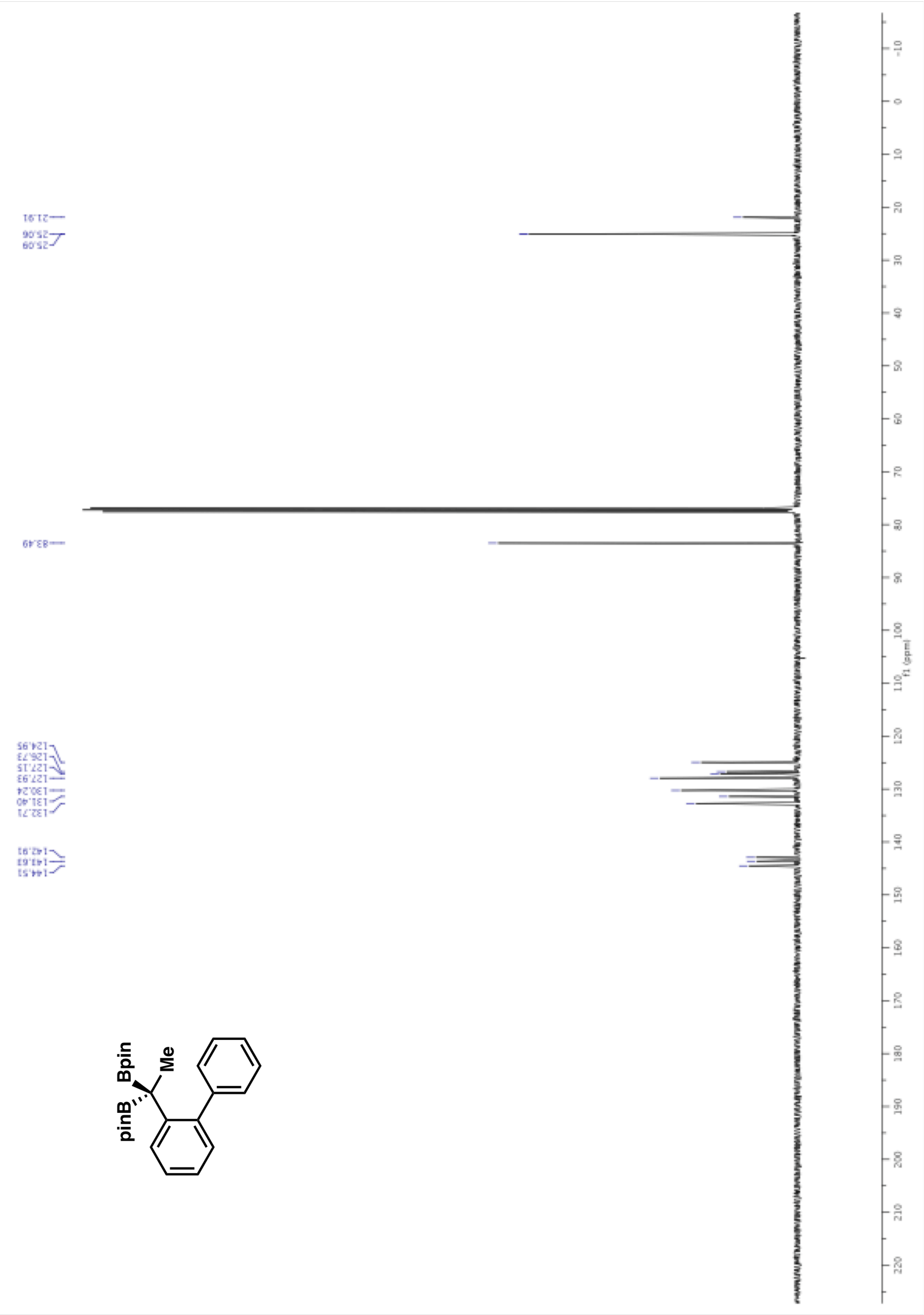

pinB
Bpin
Me
Cl
14.97
1.85
1.00
1.10
f1 (ppm)
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

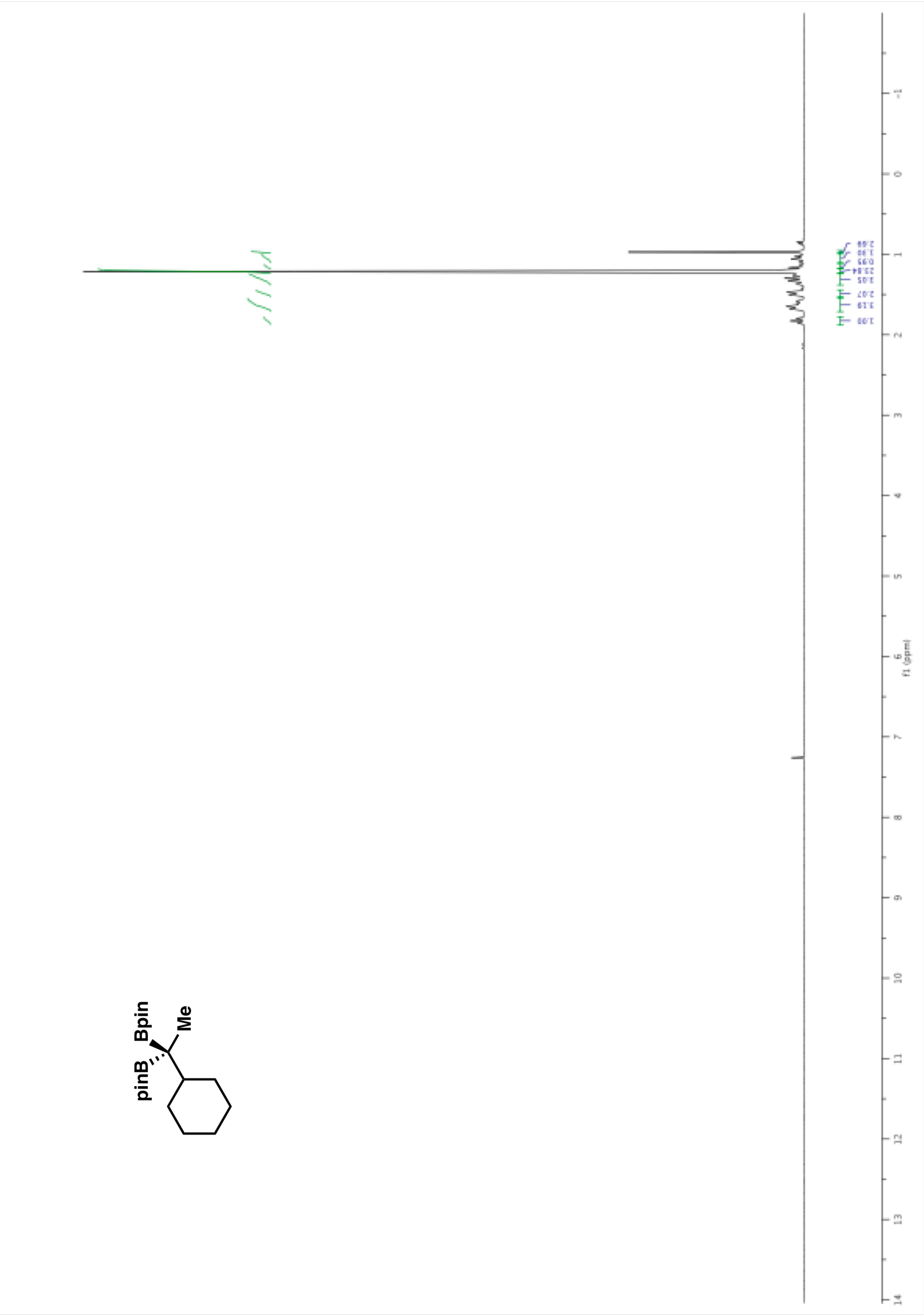

143.61
130.21
129.55
127.99
83.64
24.81
18.03
pinB
Bpin
Me
Cl
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

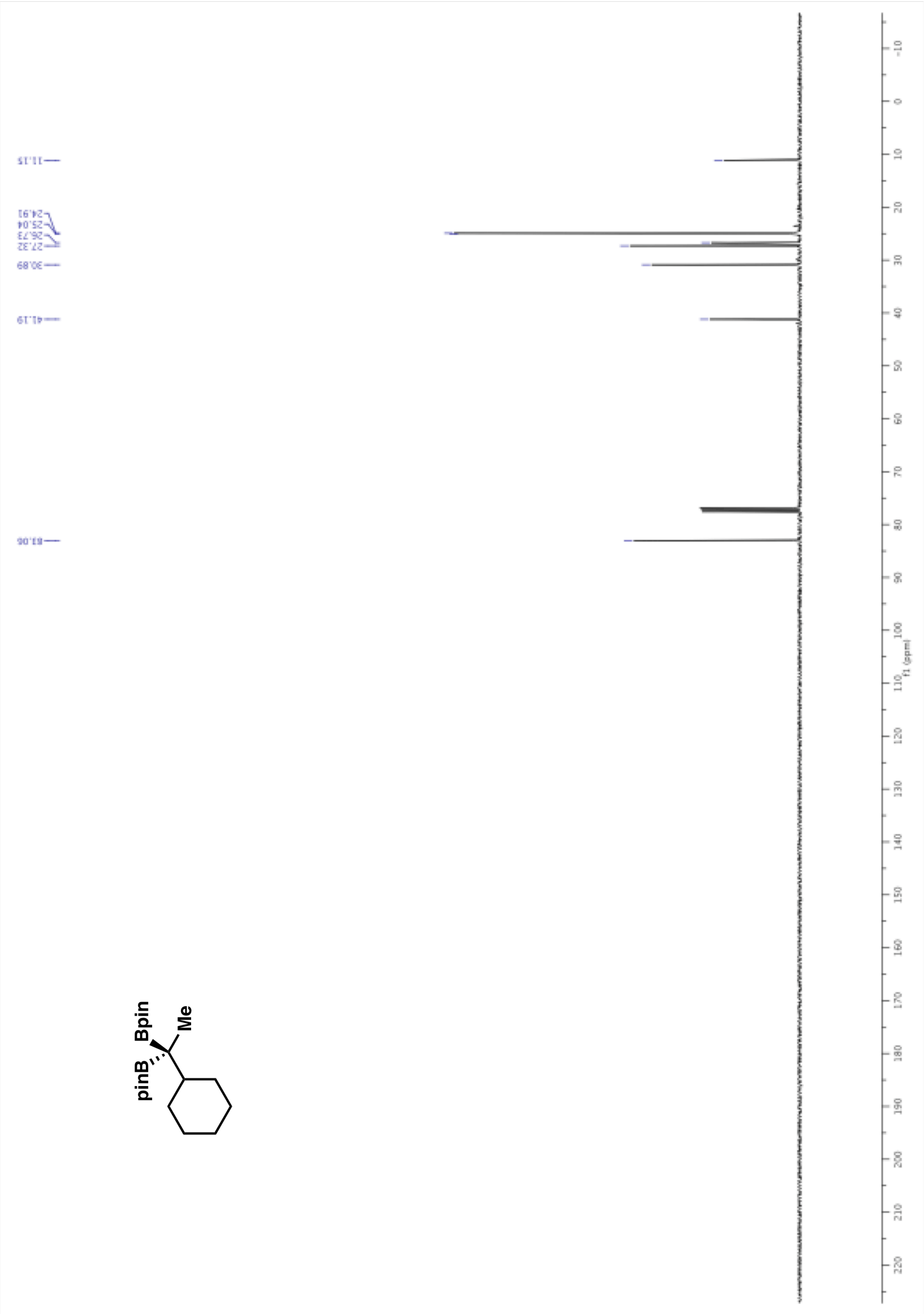

pinB
Bpin
MeO
32.93
47.21
5.99
11.56
5.96
4.97
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)


11.19
14.27
23.21
23.97
29.15
30.59
38.96
68.38
129.02
131.09
132.68
167.96
pinB
Bpin
MeO
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

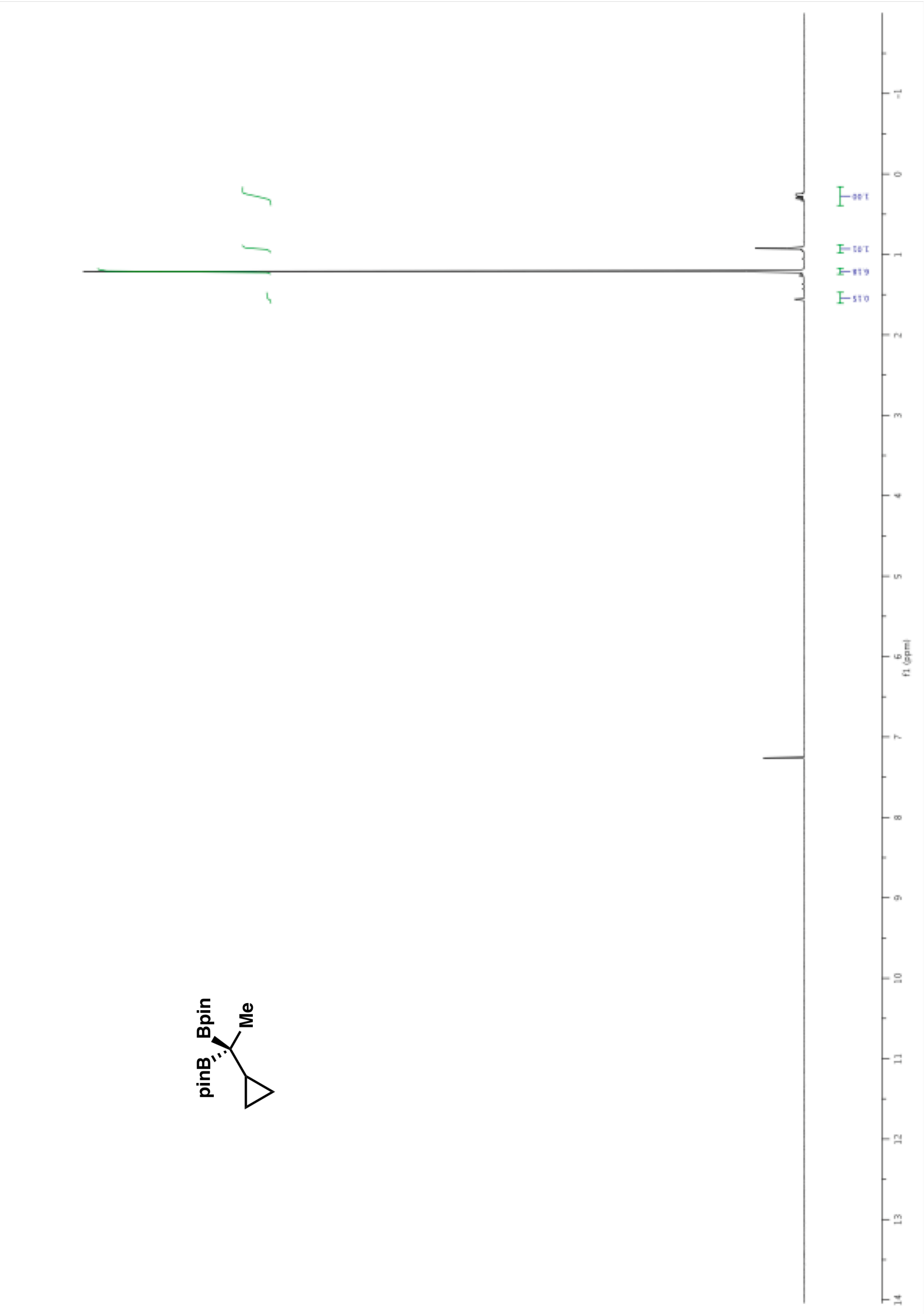

pinB
Bpin
Me
f1 (ppm)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

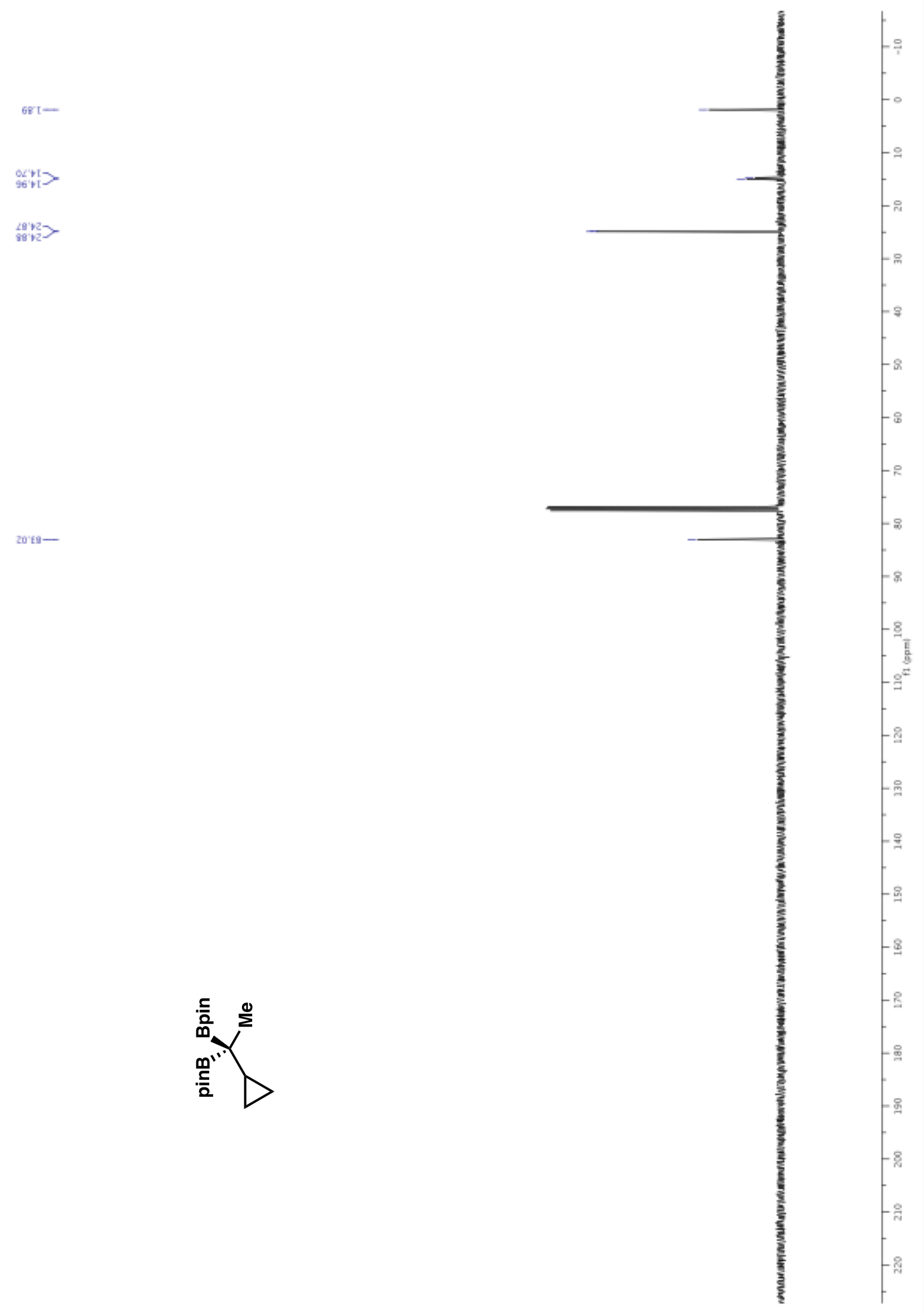

pinB
Bpin
Me
21.91
25.06
25.09
83.49
124.95
126.73
127.15
127.93
130.24
131.40
132.71
142.91
143.63
144.51
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

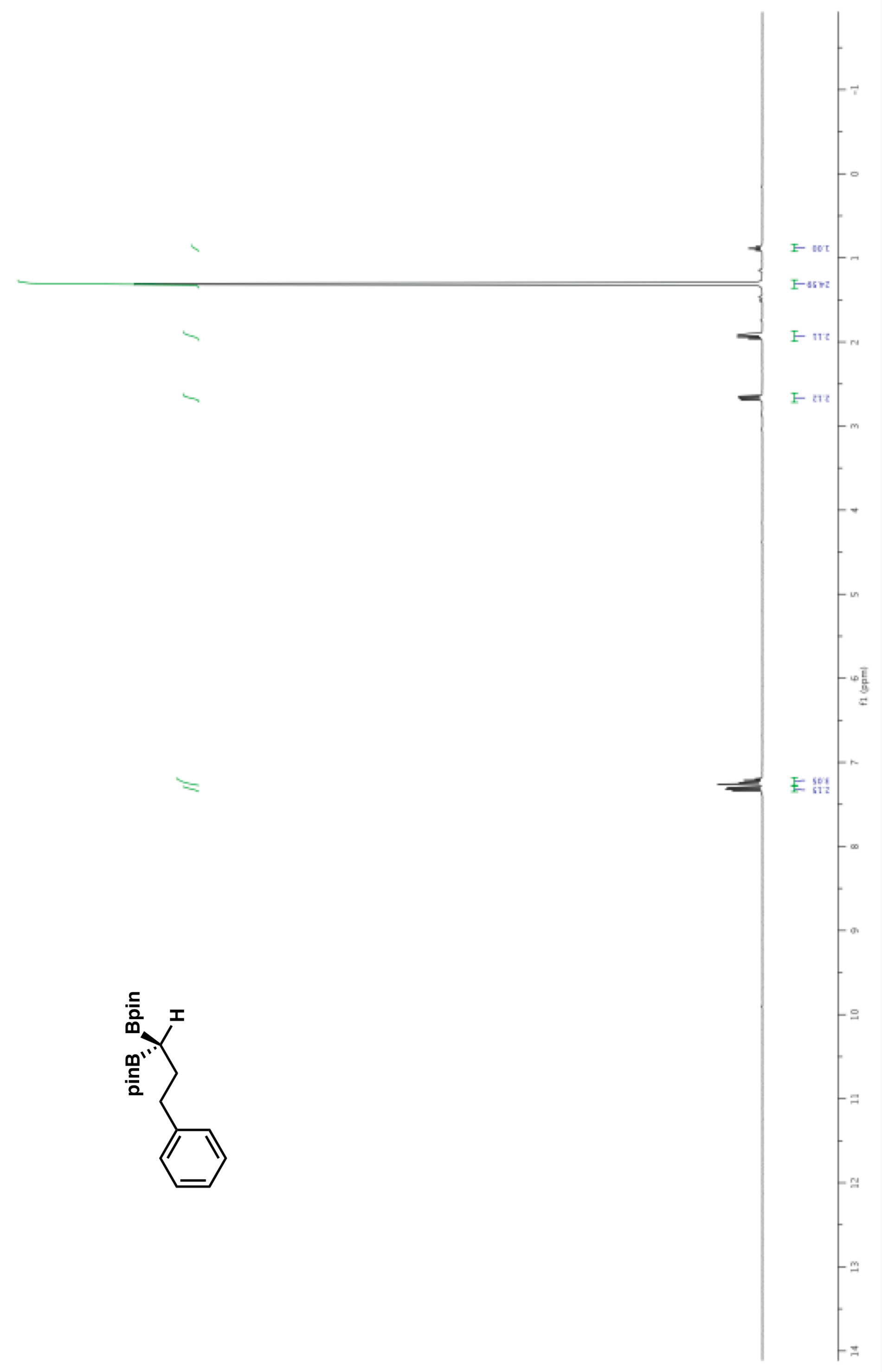

pinB
Bpin
Me
2.68
1.90
0.95
23.84
3.05
2.07
3.10
1.00
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)



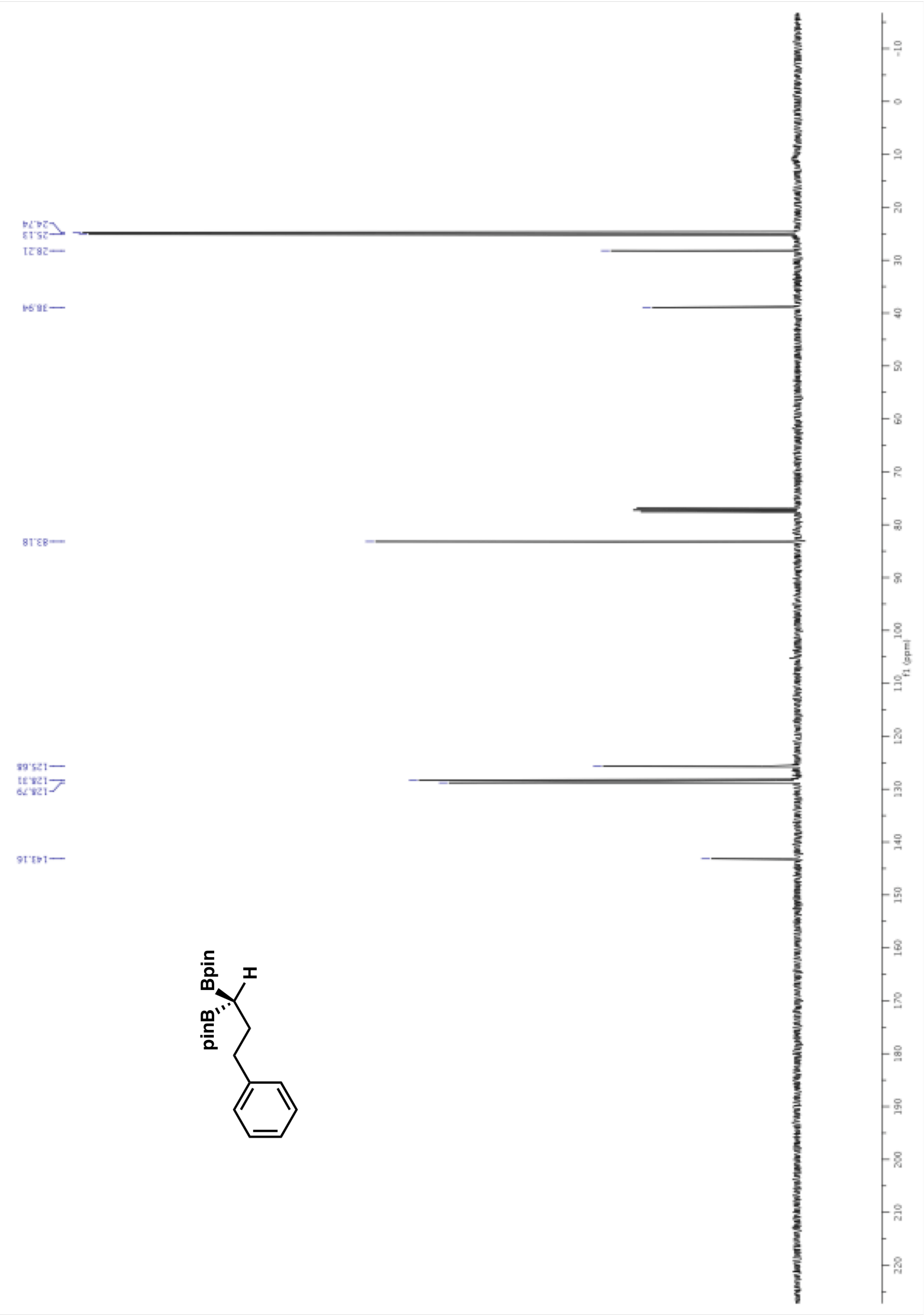
83.06
41.19
30.89
27.32
26.73
25.04
24.91
11.15
pinB
Bpin
Me
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

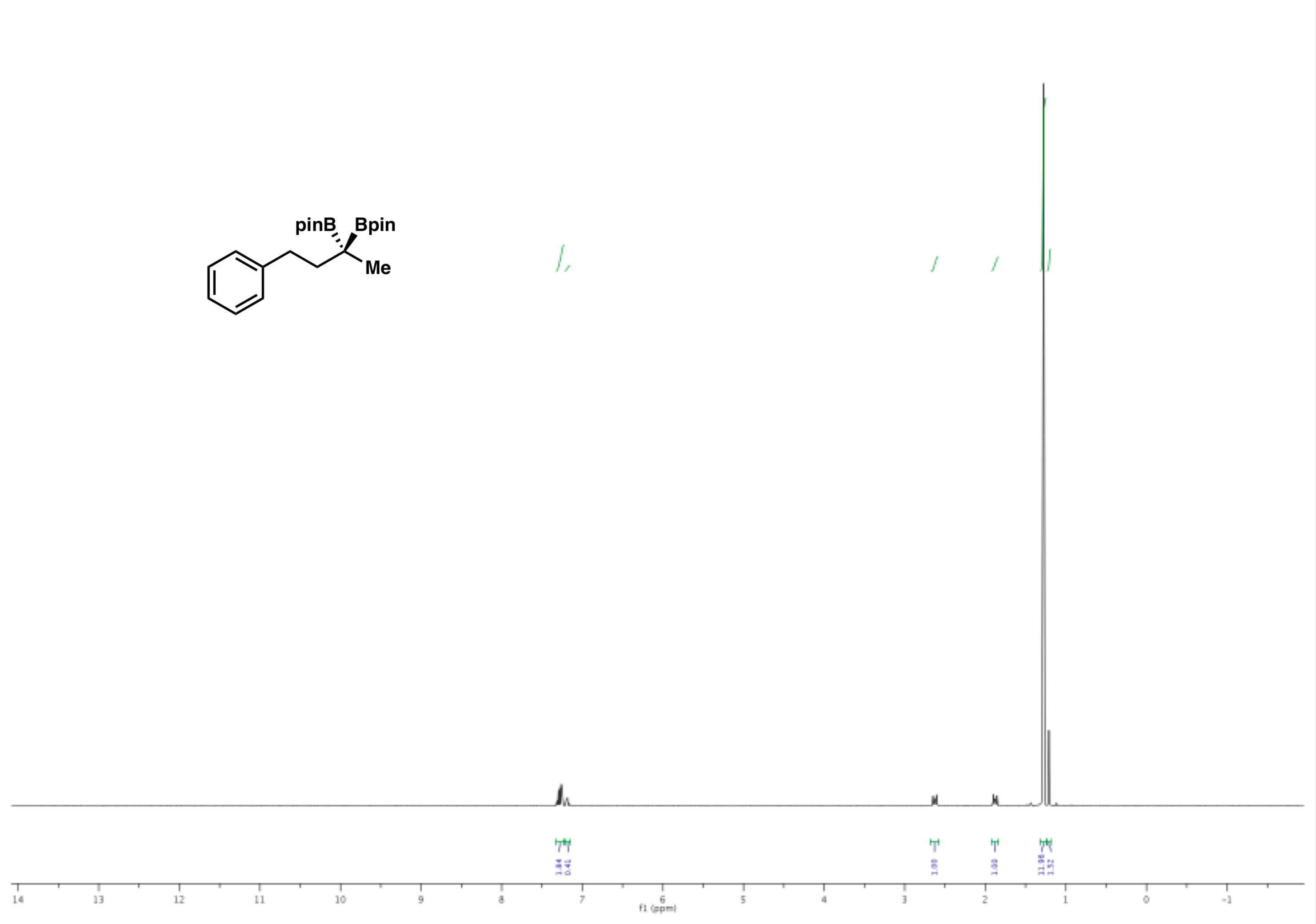

pinB
Bpin
Me
1.00
1.03
6.18
0.15
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)

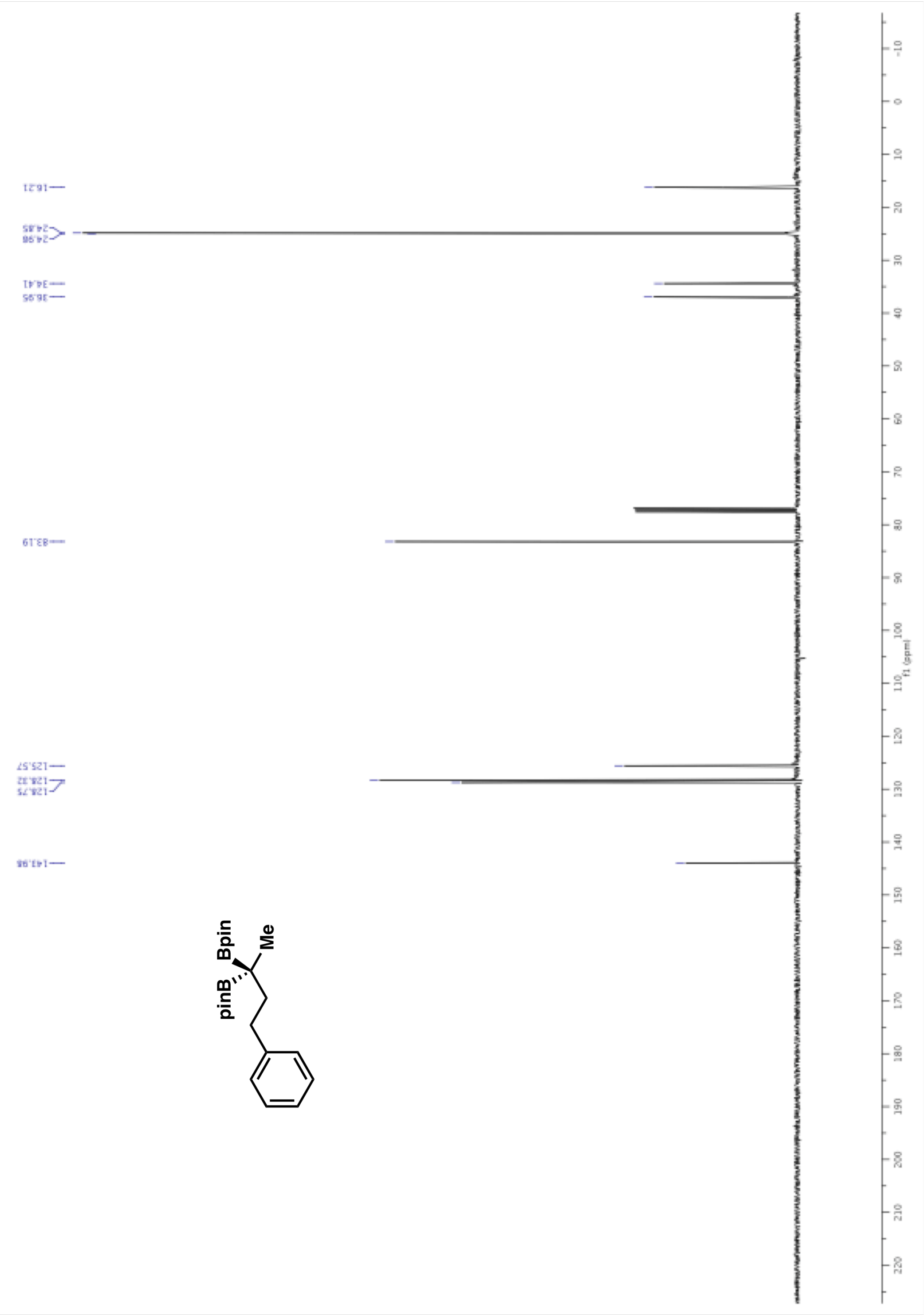

1.89
14.70
14.96
24.87
24.88
83.02
pinB
Bpin
Me
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

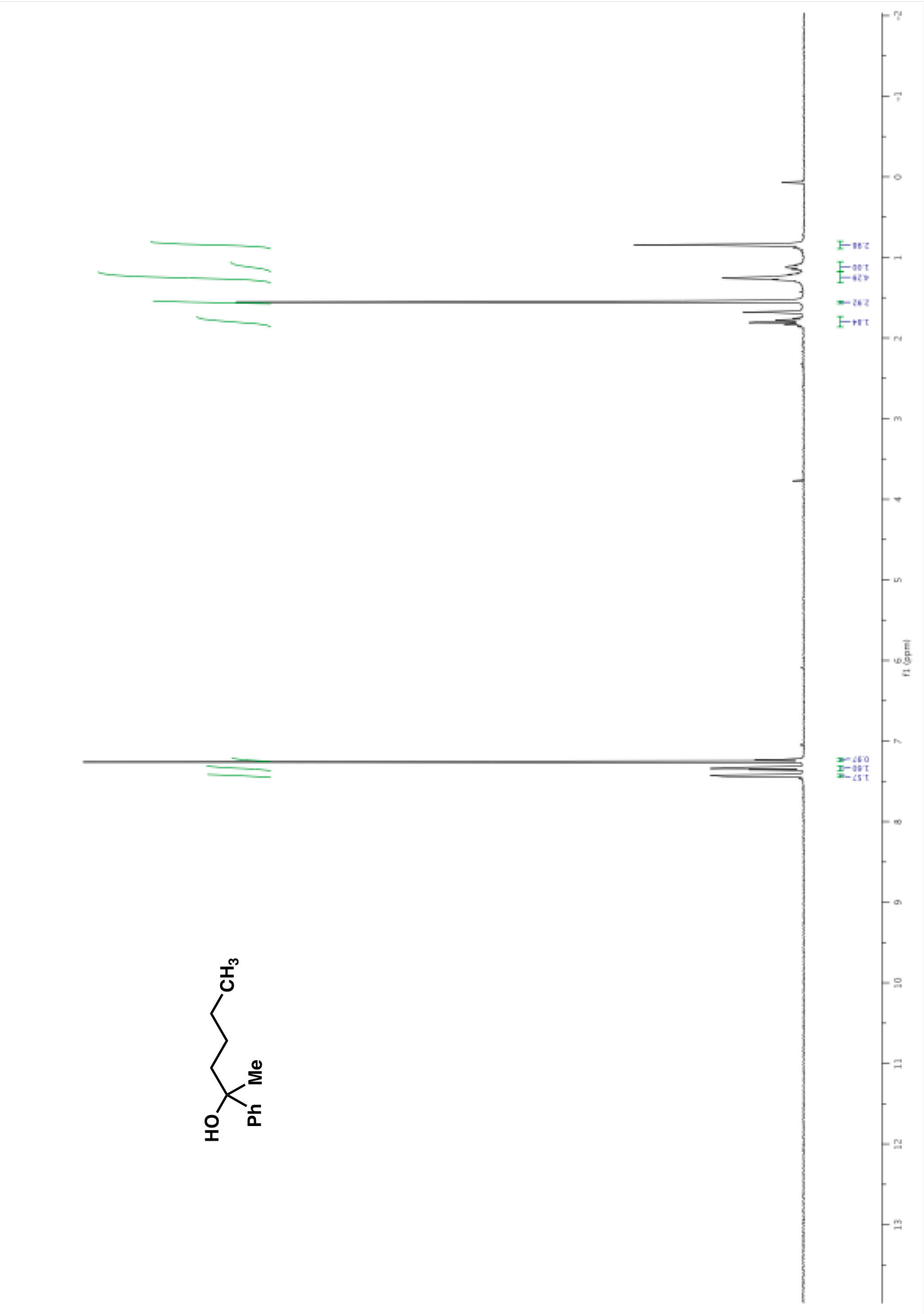


pinB
Bpin
H
1.00
24.59
2.11
2.12
3.05
2.15
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)

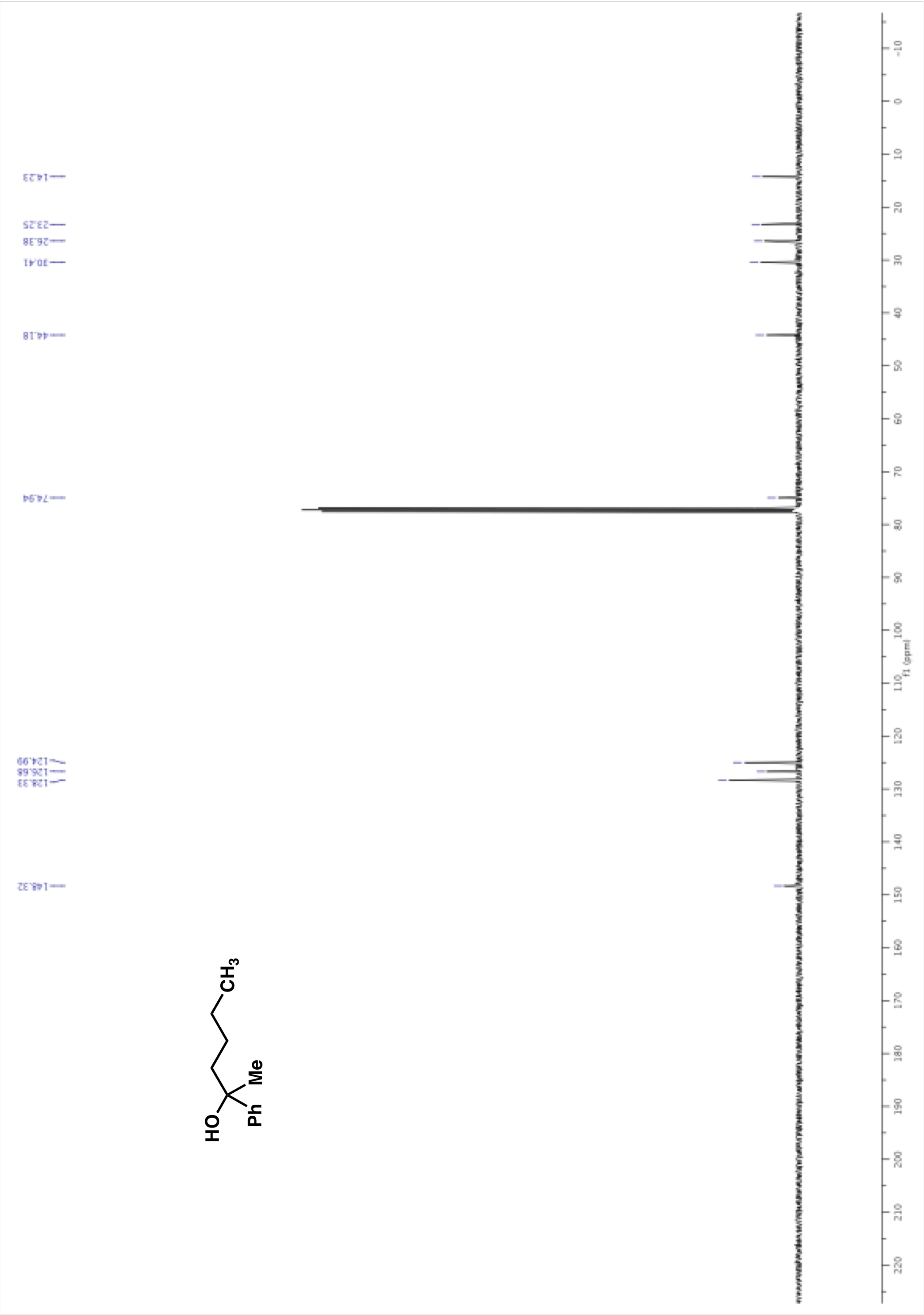

24.74
25.13
28.21
38.94
83.18
125.68
128.31
128.79
143.16
pinB
Bpin
H
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)


pinB
Bpin
Me
3.84
0.41
1.00
1.00
11.98
1.52
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

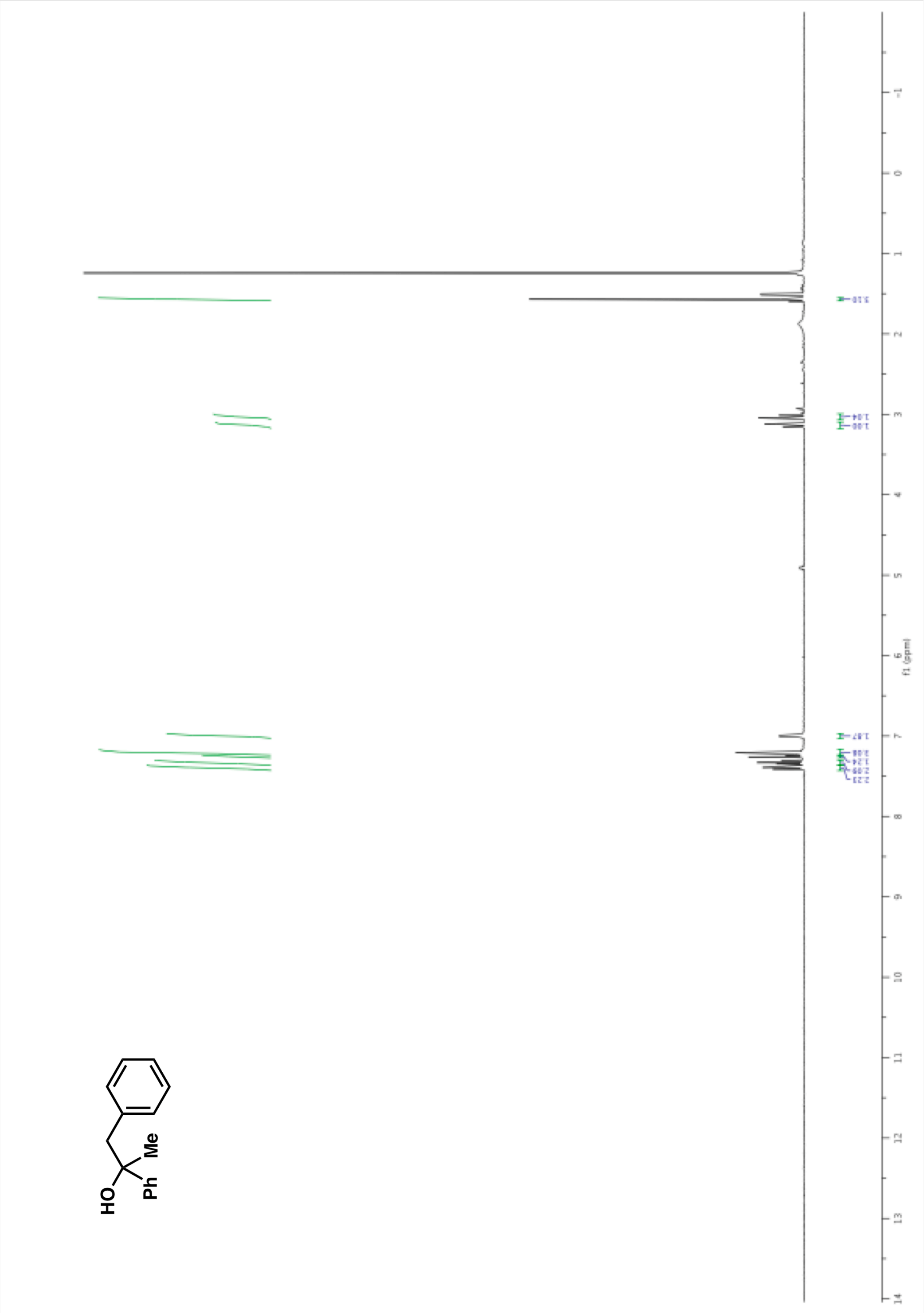

16.21
24.85
24.98
34.41
36.95
83.19
125.57
128.32
128.75
143.98
pinB
Bpin
Me
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220



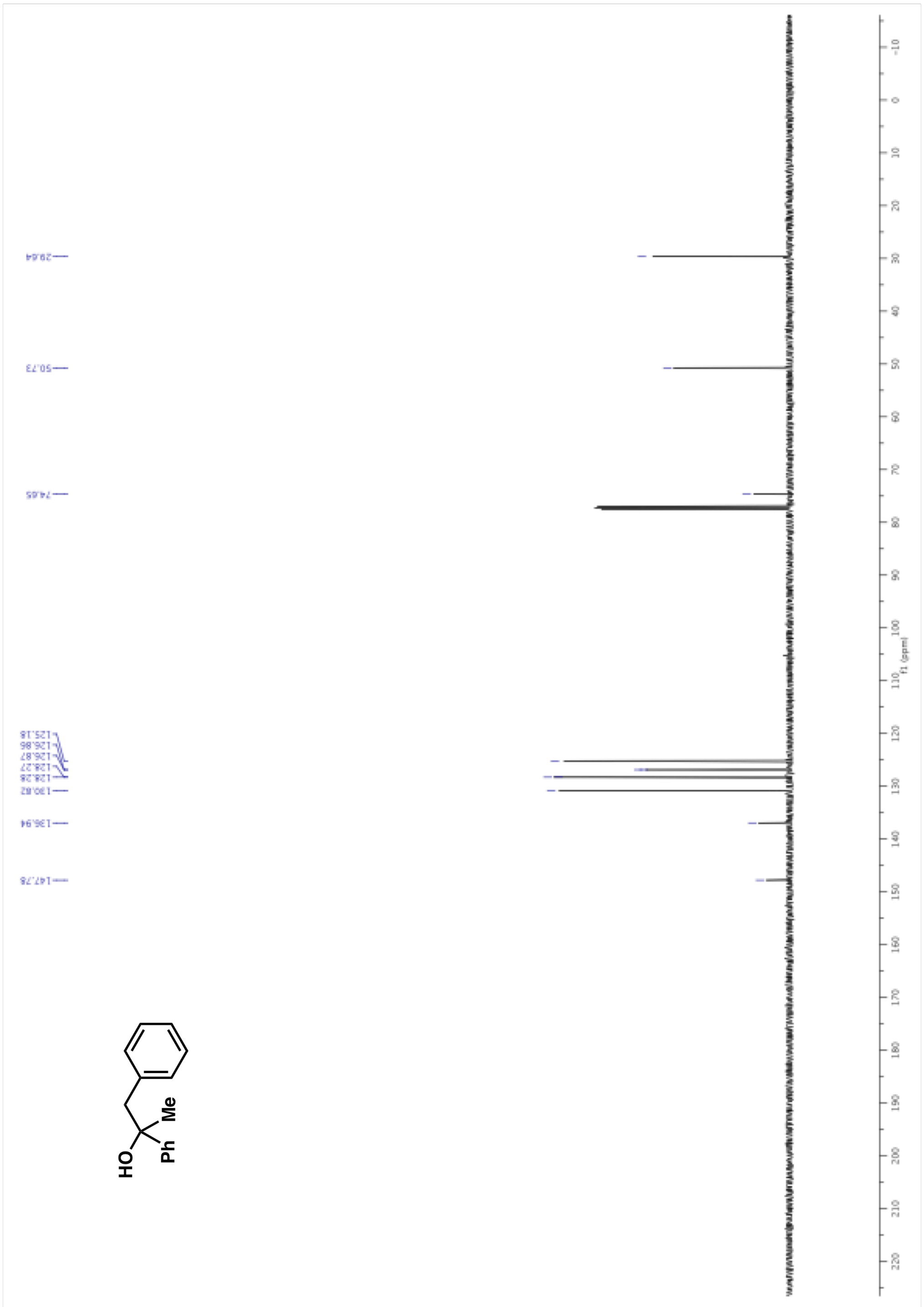
HO
Ph
Me
CH3
2.98
1.00
4.29
2.92
1.84
0.97
1.60
1.57
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)



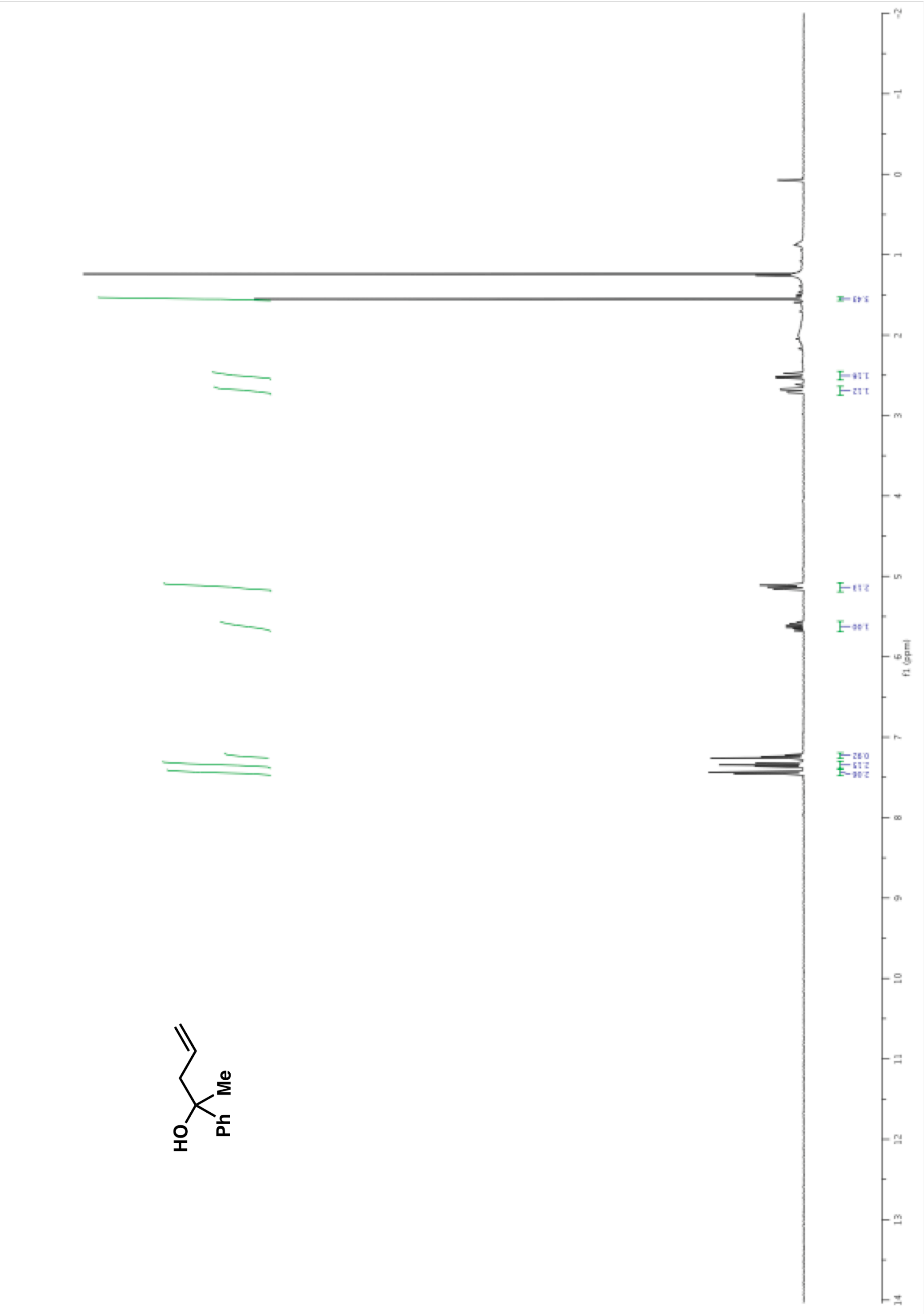
14.23
23.25
26.38
30.41
44.18
74.94
124.90
126.68
128.33
148.32
HO
Ph
Me
CH_3
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

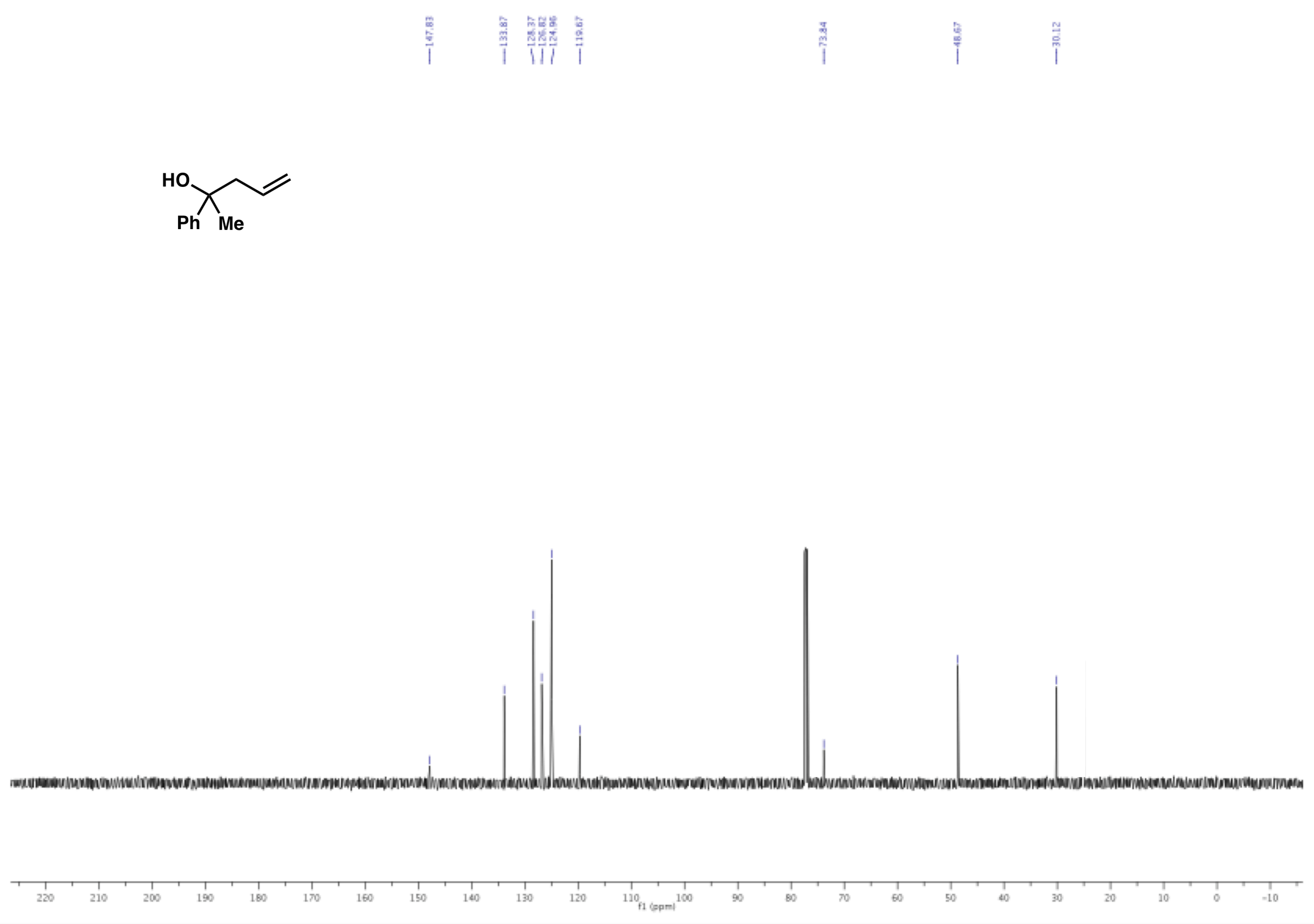


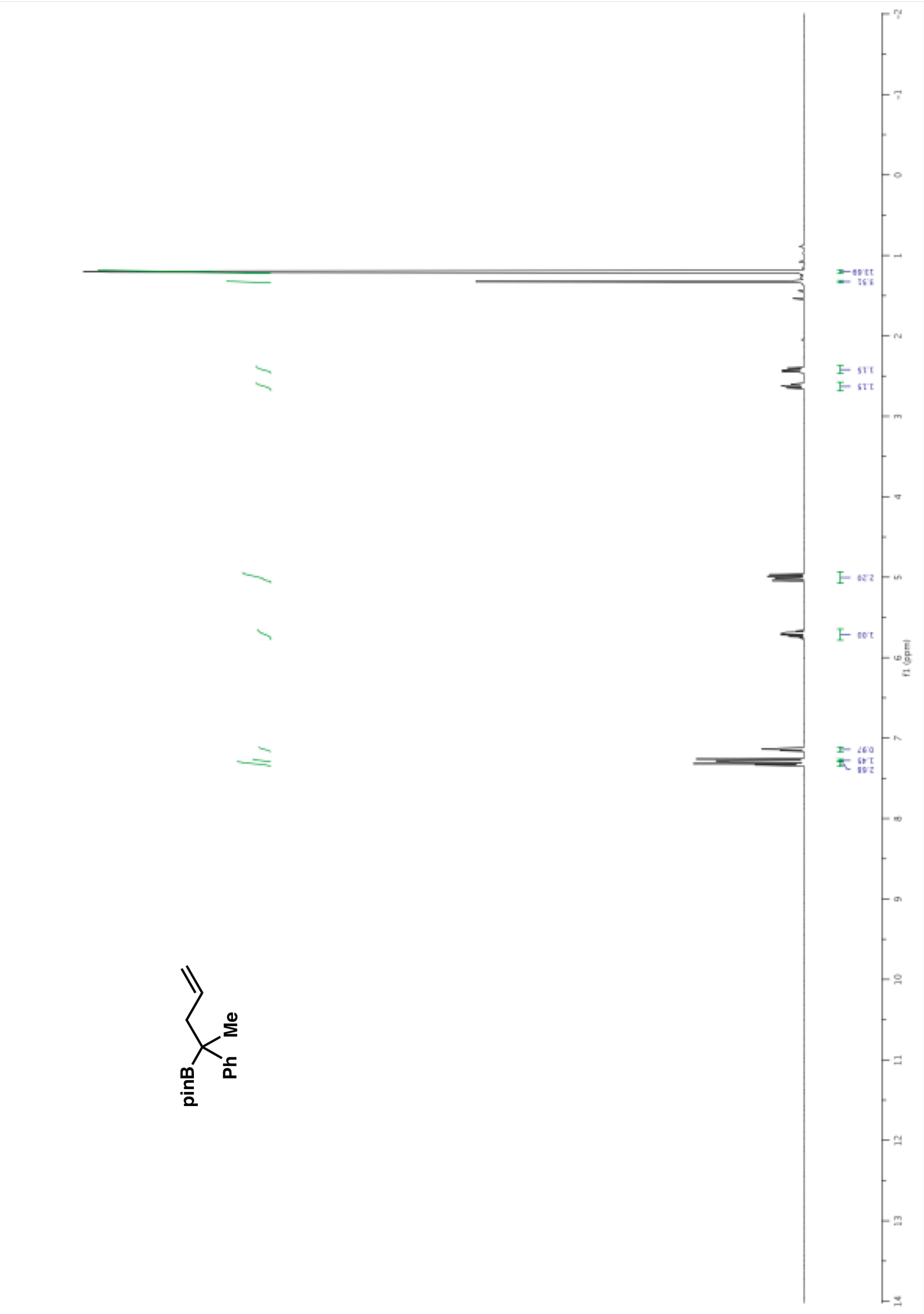
HO
Ph
Me
3.10
1.04
1.00
1.87
3.08
1.04
2.08
2.23
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)



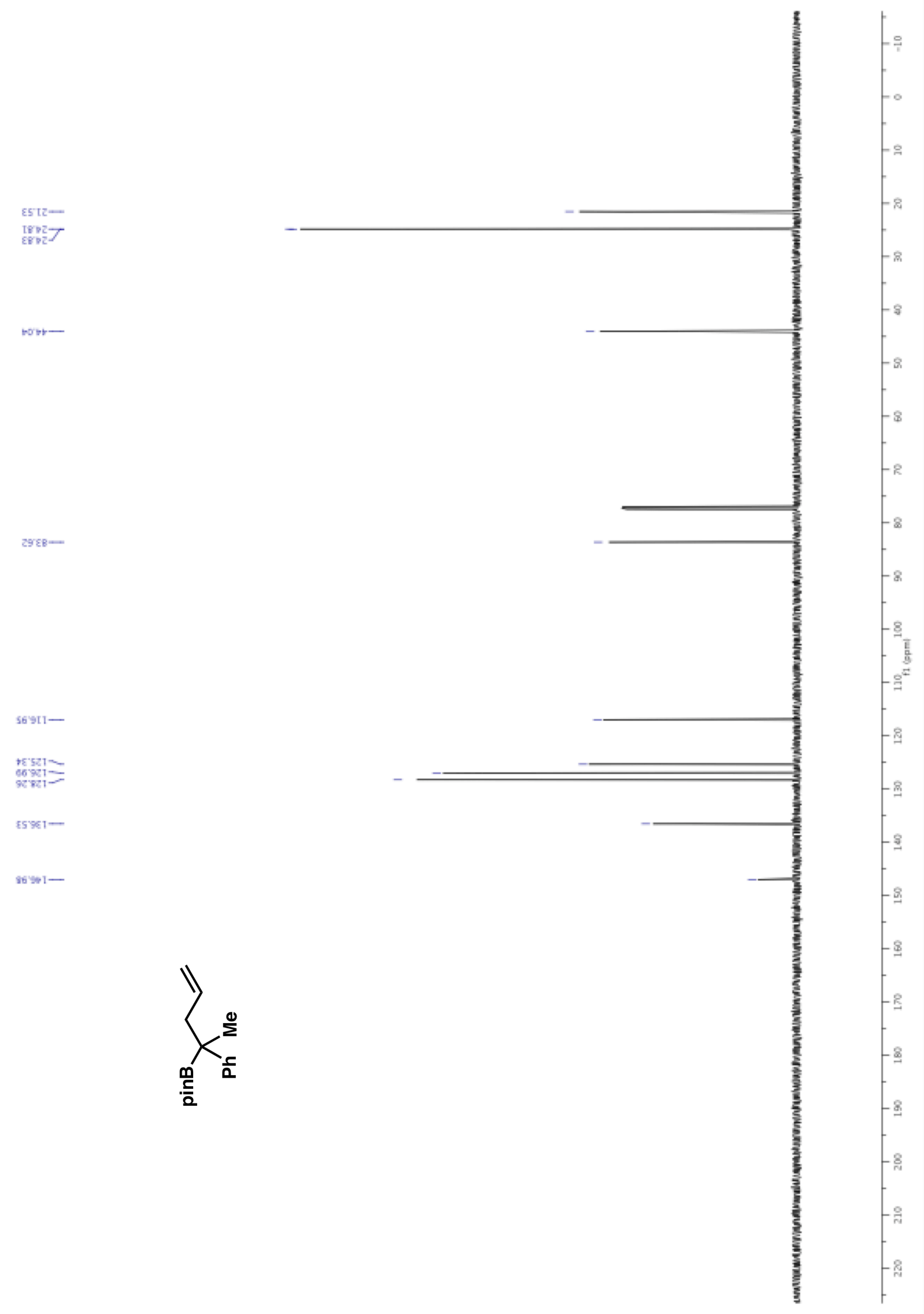
29.64
50.73
74.65
125.18
126.86
126.87
128.27
128.28
130.82
136.94
147.78
HO
Ph
Me
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

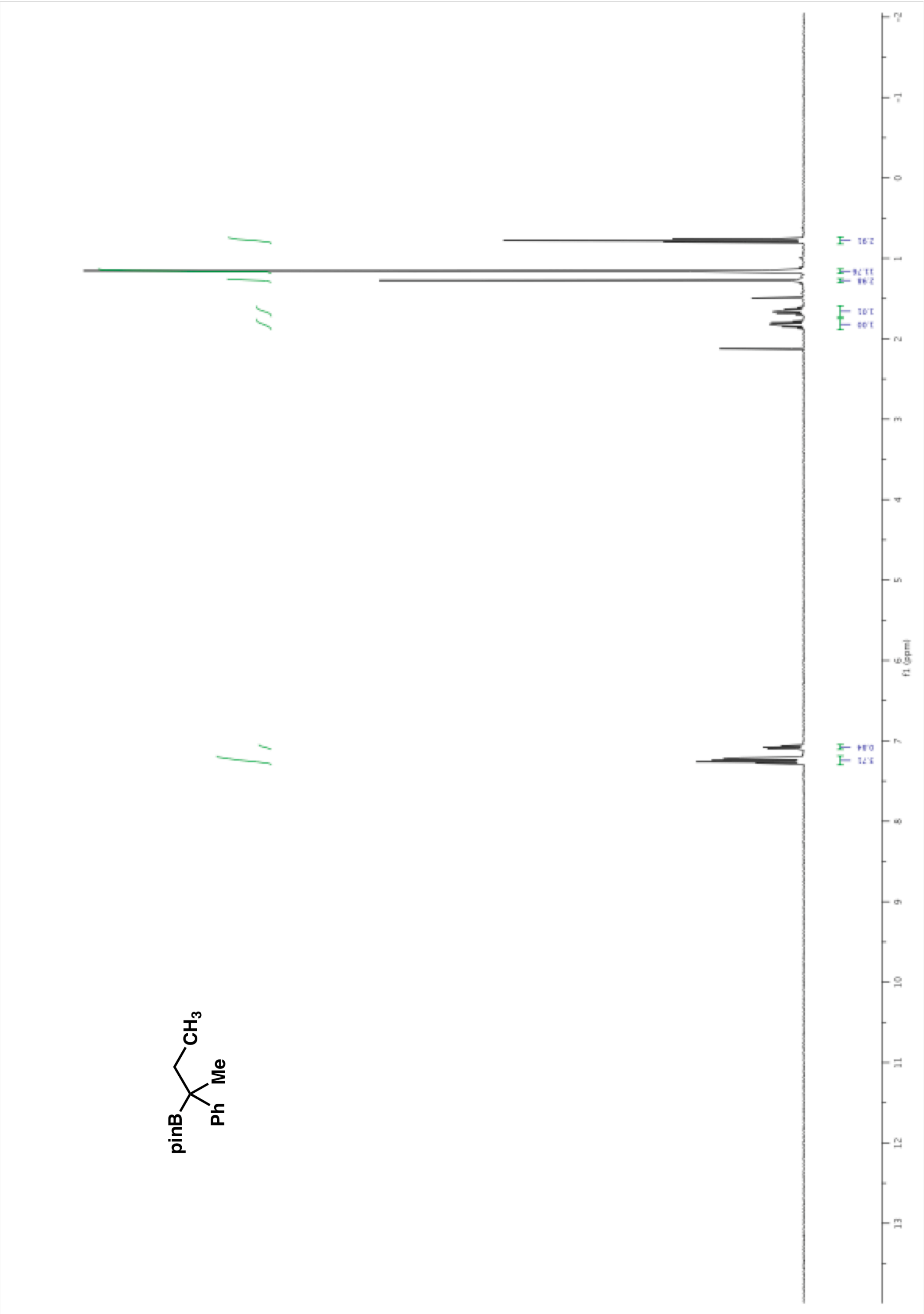

HO
Ph
Me
5.43
1.18
1.12
2.13
1.00
0.82
2.15
2.08
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)


147.83
133.87
128.37
126.82
124.96
119.67
73.84
48.67
30.12
HO
Ph
Me
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

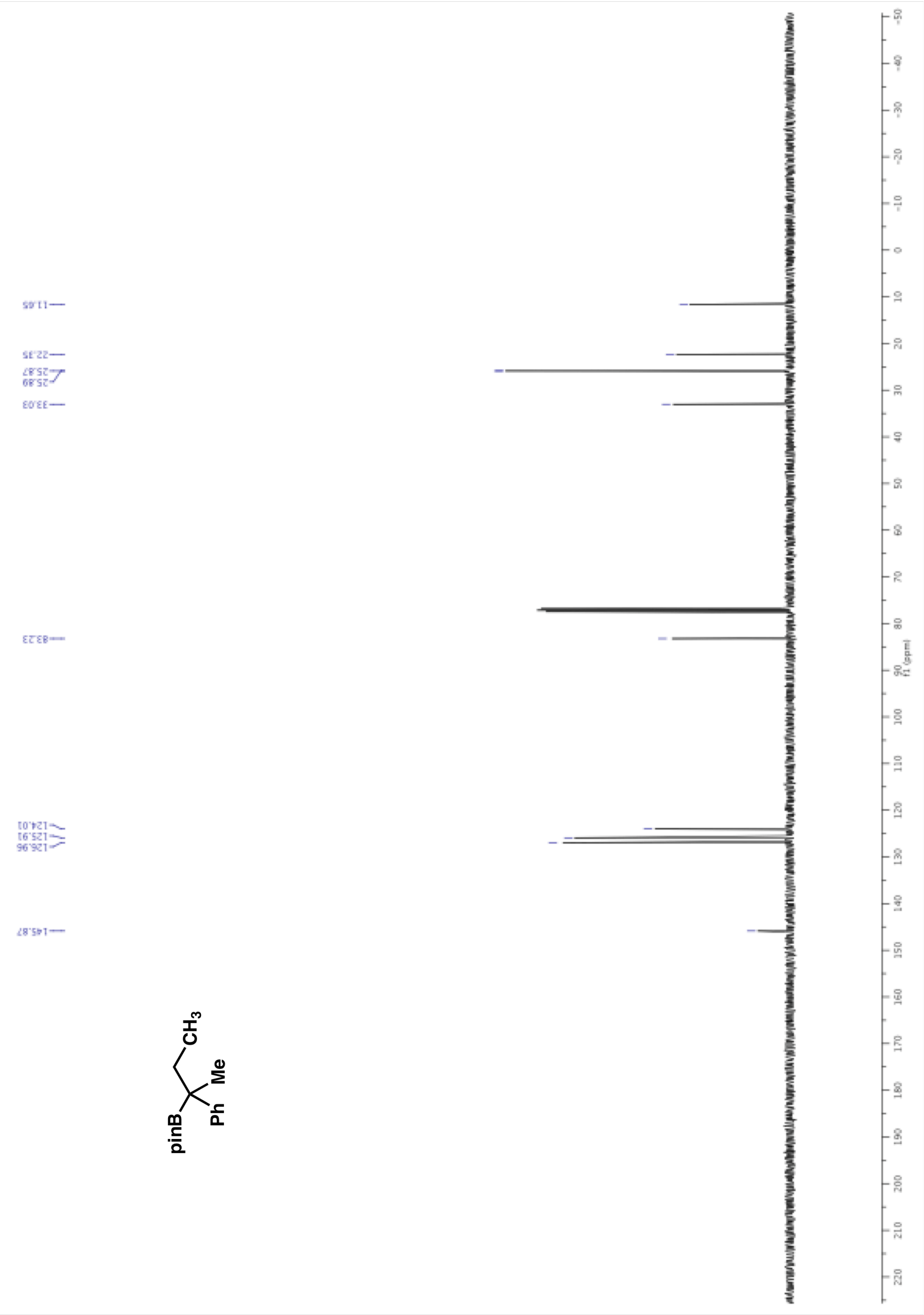


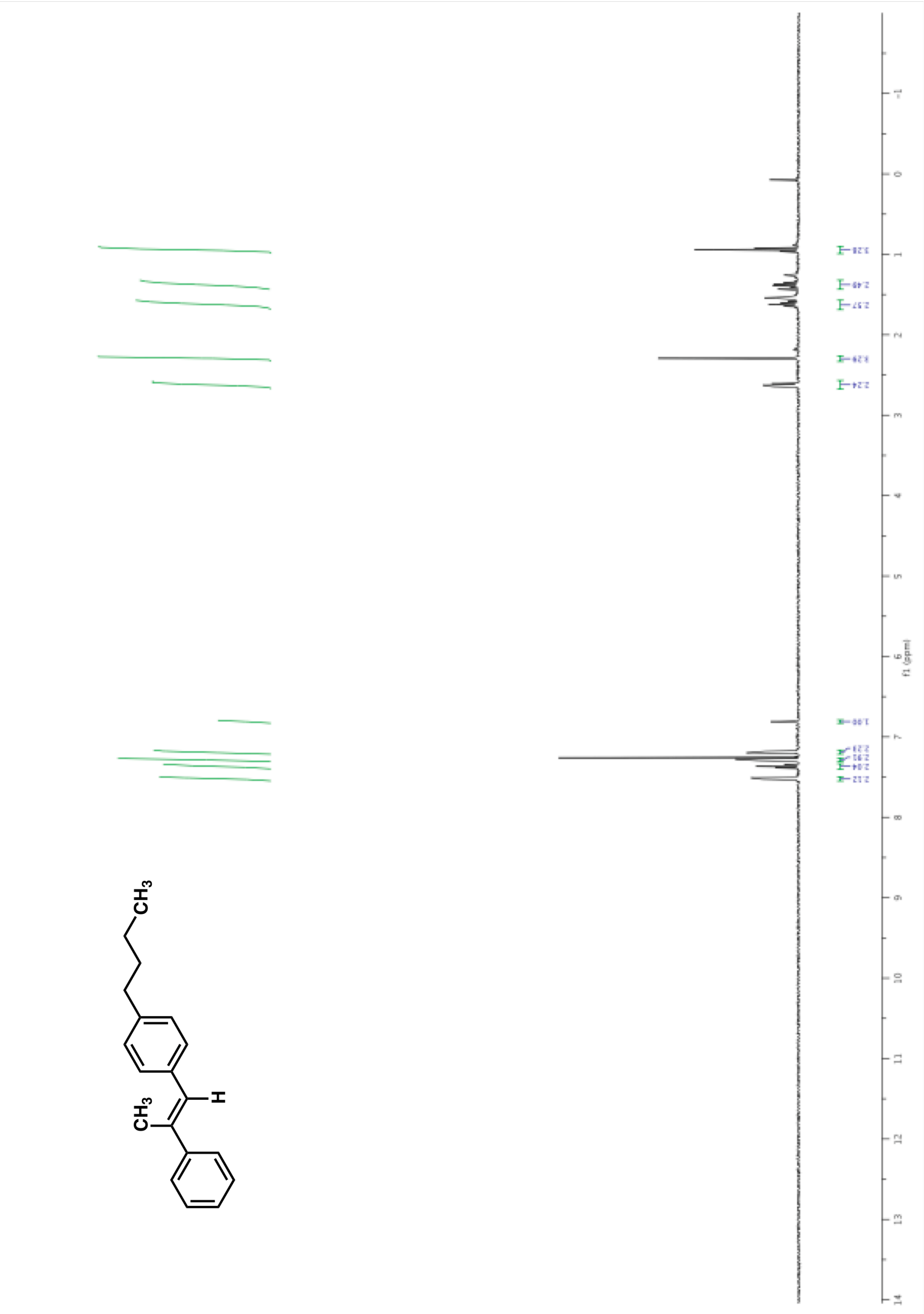
pinB
Ph
Me
13.68
9.51
1.15
1.15
2.20
1.00
0.97
1.45
2.88
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


21.53
24.81
24.83
44.04
83.62
116.95
125.34
126.90
128.26
136.53
146.98
pinB
Ph
Me
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

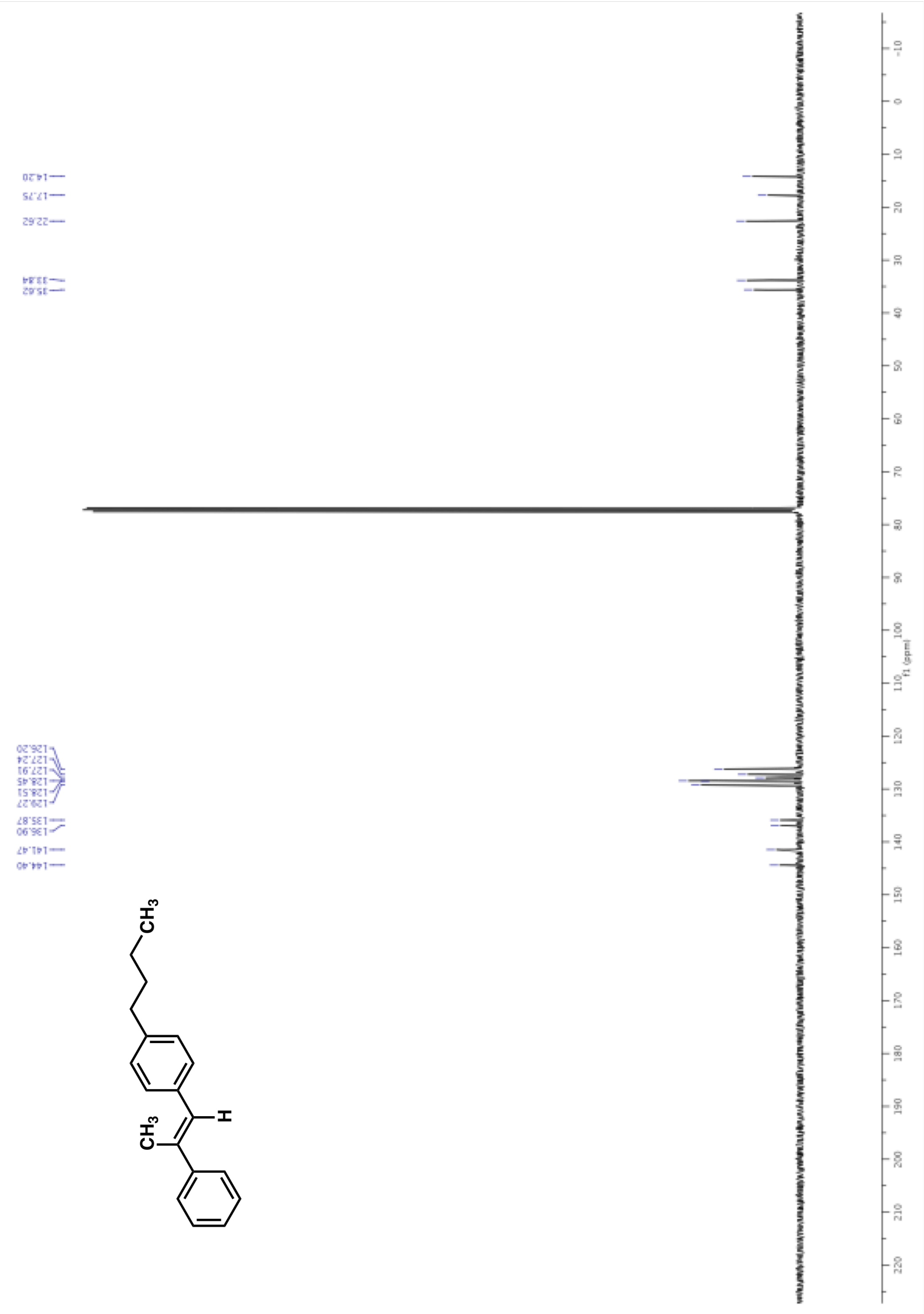


pinB
Ph
Me
CH3
2.91
11.76
2.98
1.01
1.00
0.84
3.71
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)

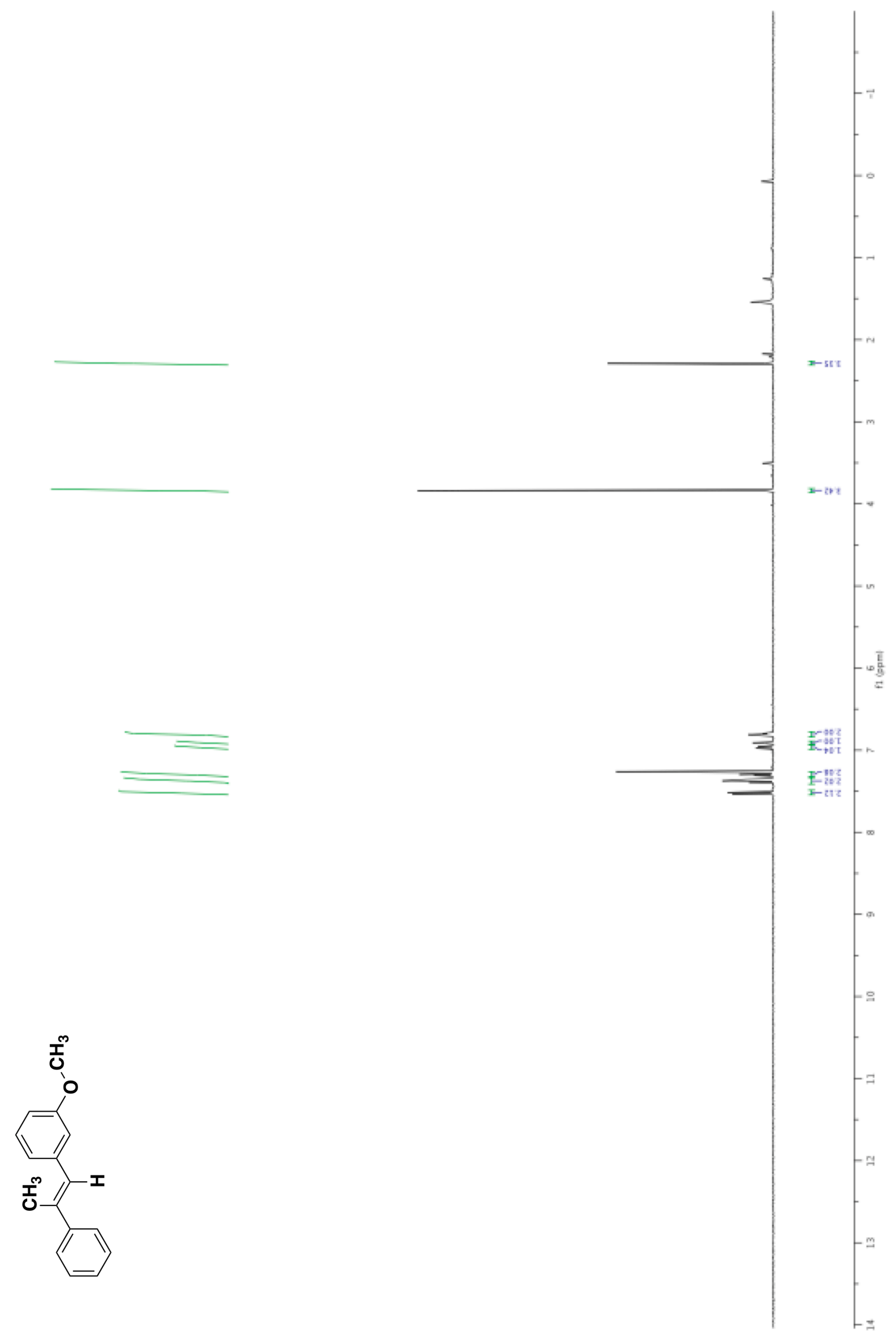

11.65
22.35
25.87
25.89
33.03
83.23
124.01
125.91
126.96
145.87
f1 (ppm)
pinB
Ph
Me
CH3

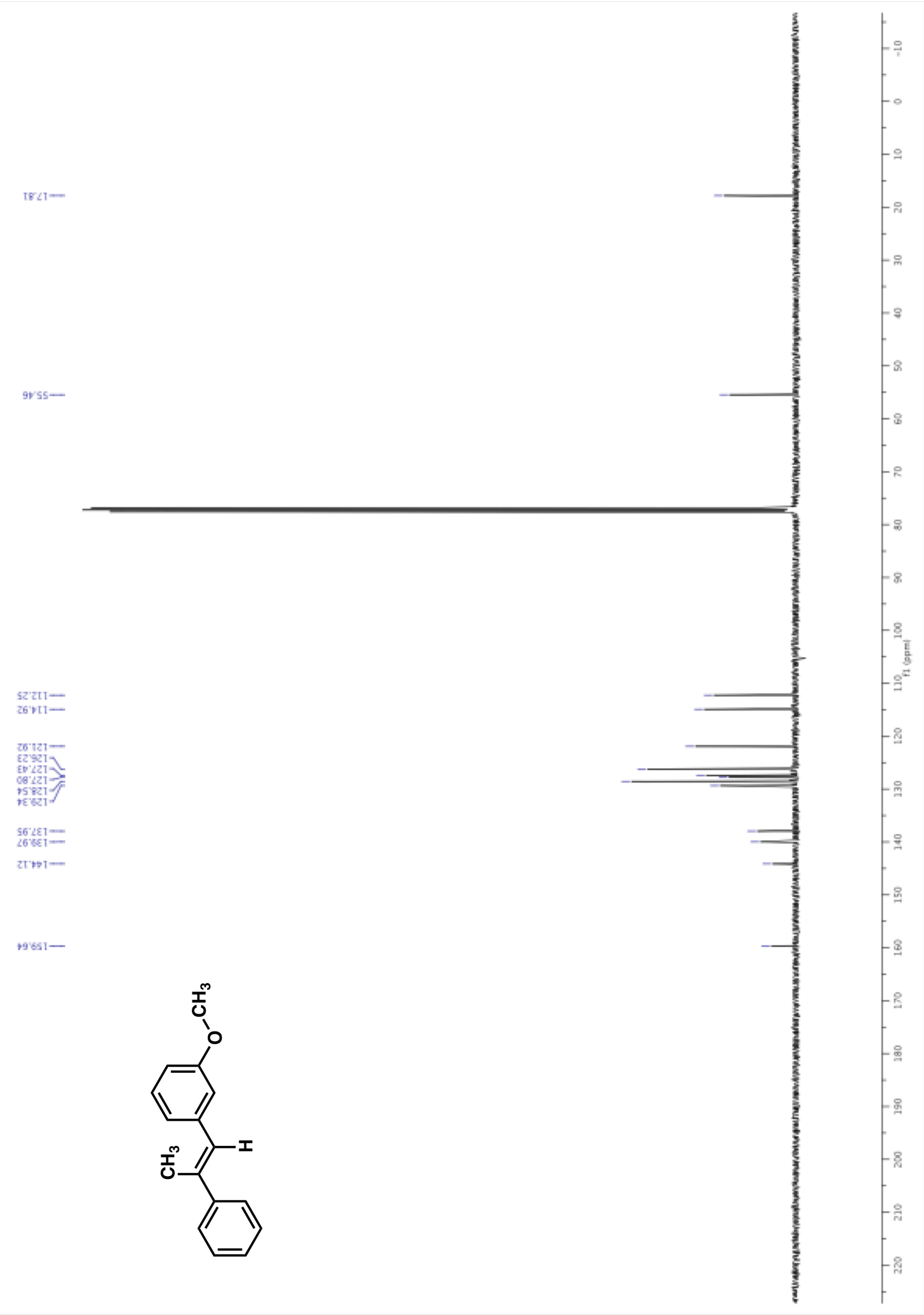


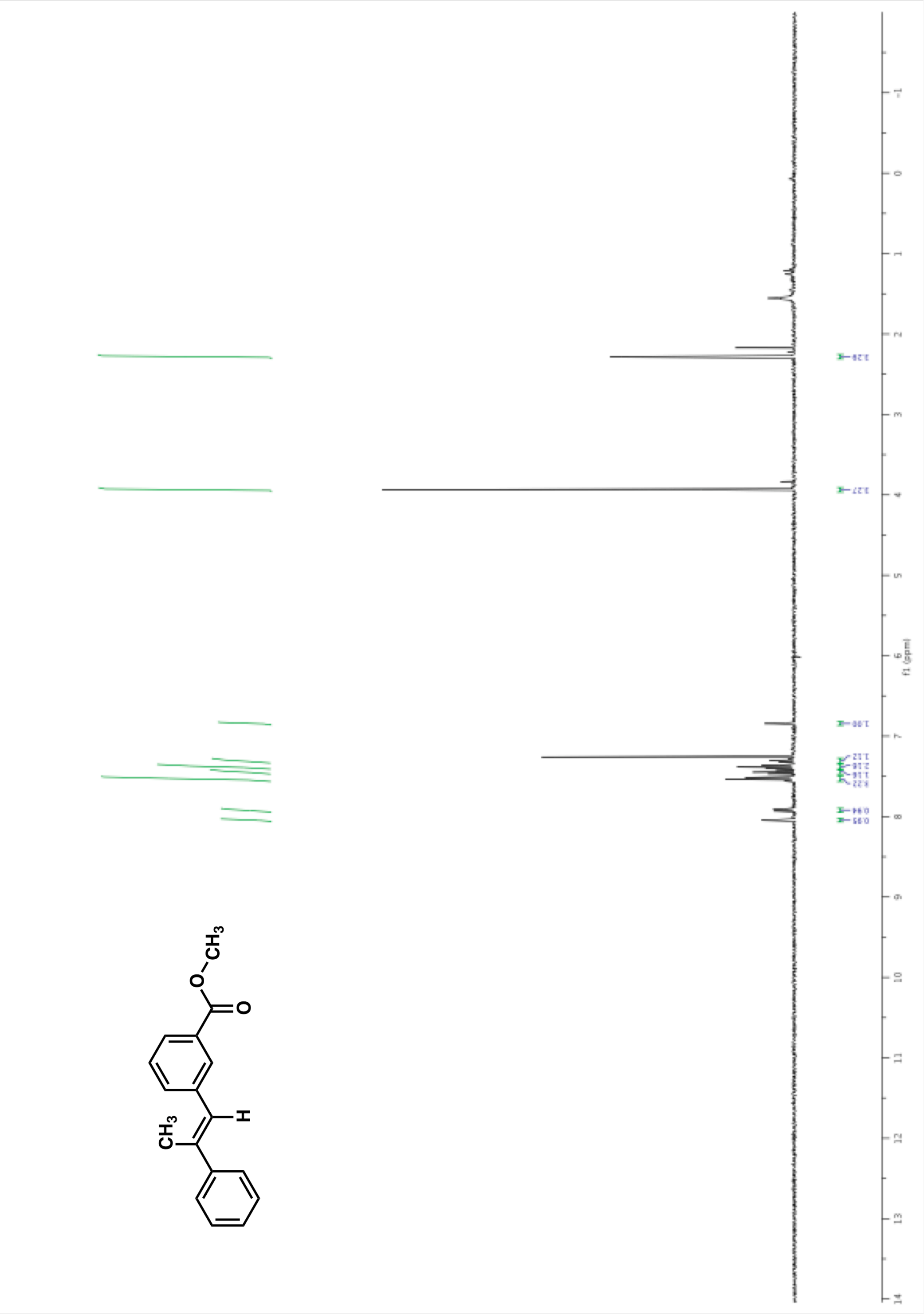
CH3
CH3
H
3.28
2.49
2.57
3.29
2.24
1.00
2.23
2.92
2.04
2.12
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)

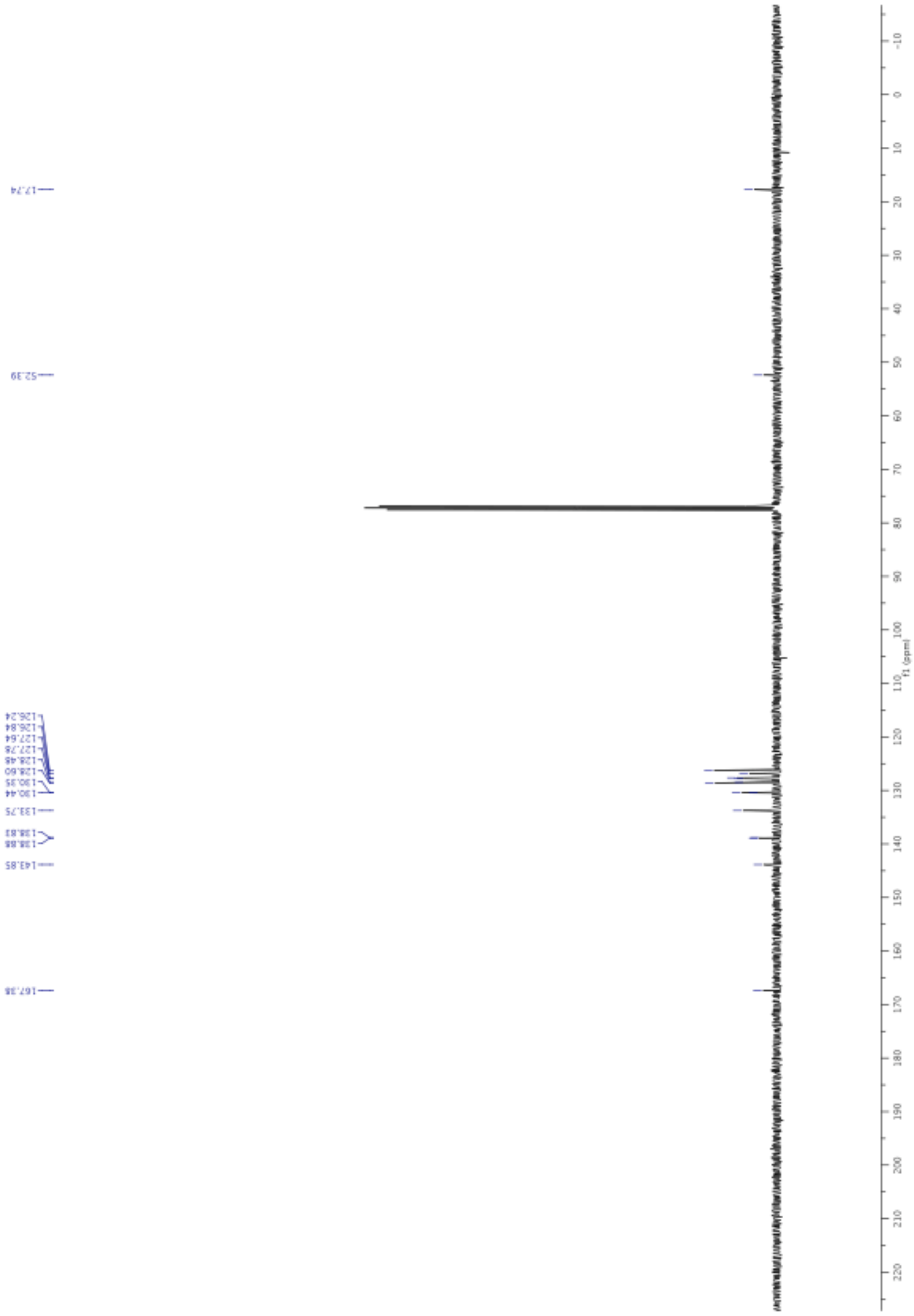


144.40
141.47
136.90
135.87
129.27
128.51
128.45
127.91
127.24
126.20
35.62
33.84
22.62
17.75
14.20
CH3
CH3
H
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

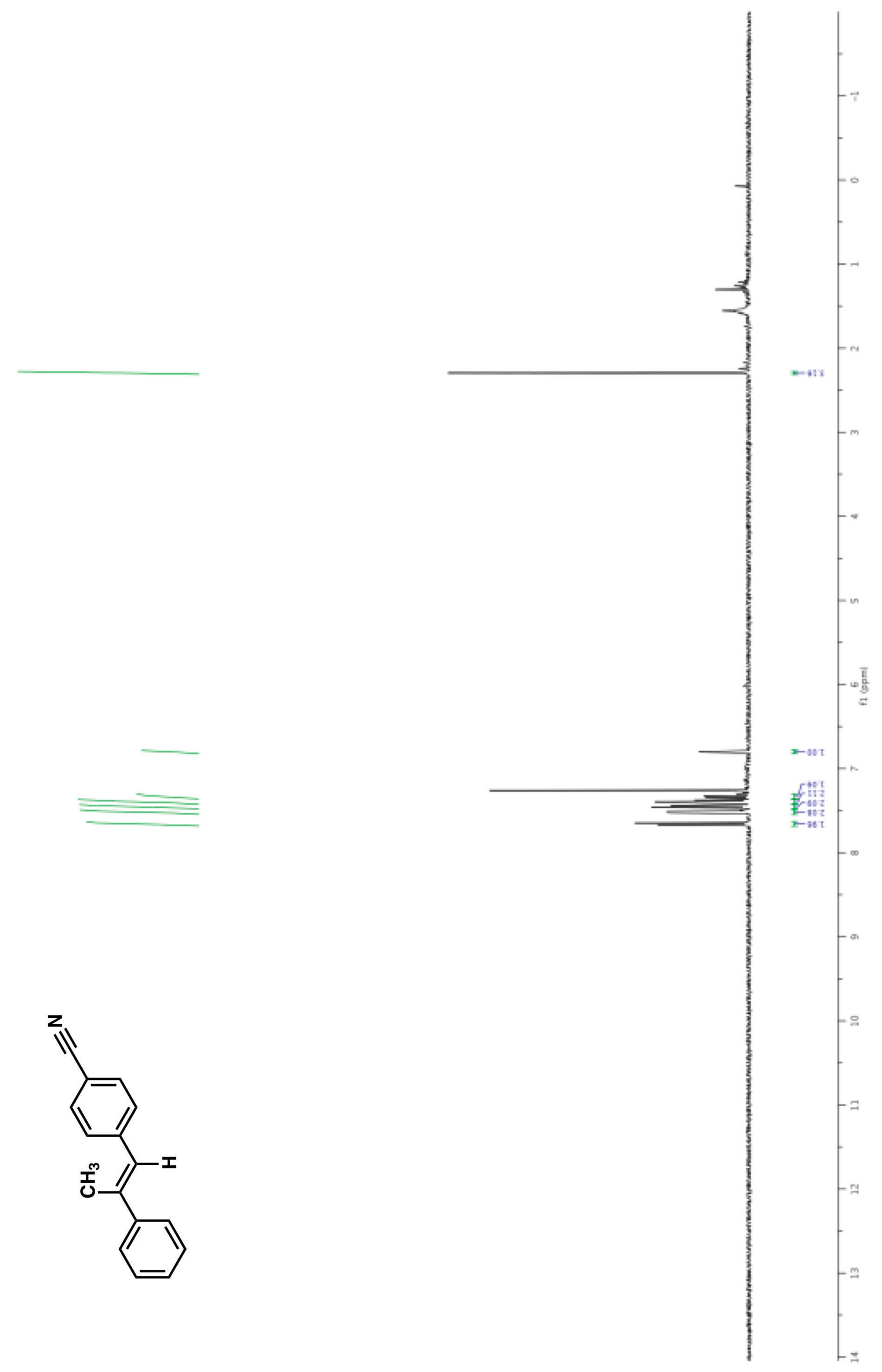

CH3
O
CH3
H
3.35
3.42
2.00
1.00
1.04
2.08
2.02
2.12
-1
0
1
2
3
4
5
6
f1 (ppm)
7
8
9
10
11
12
13
14

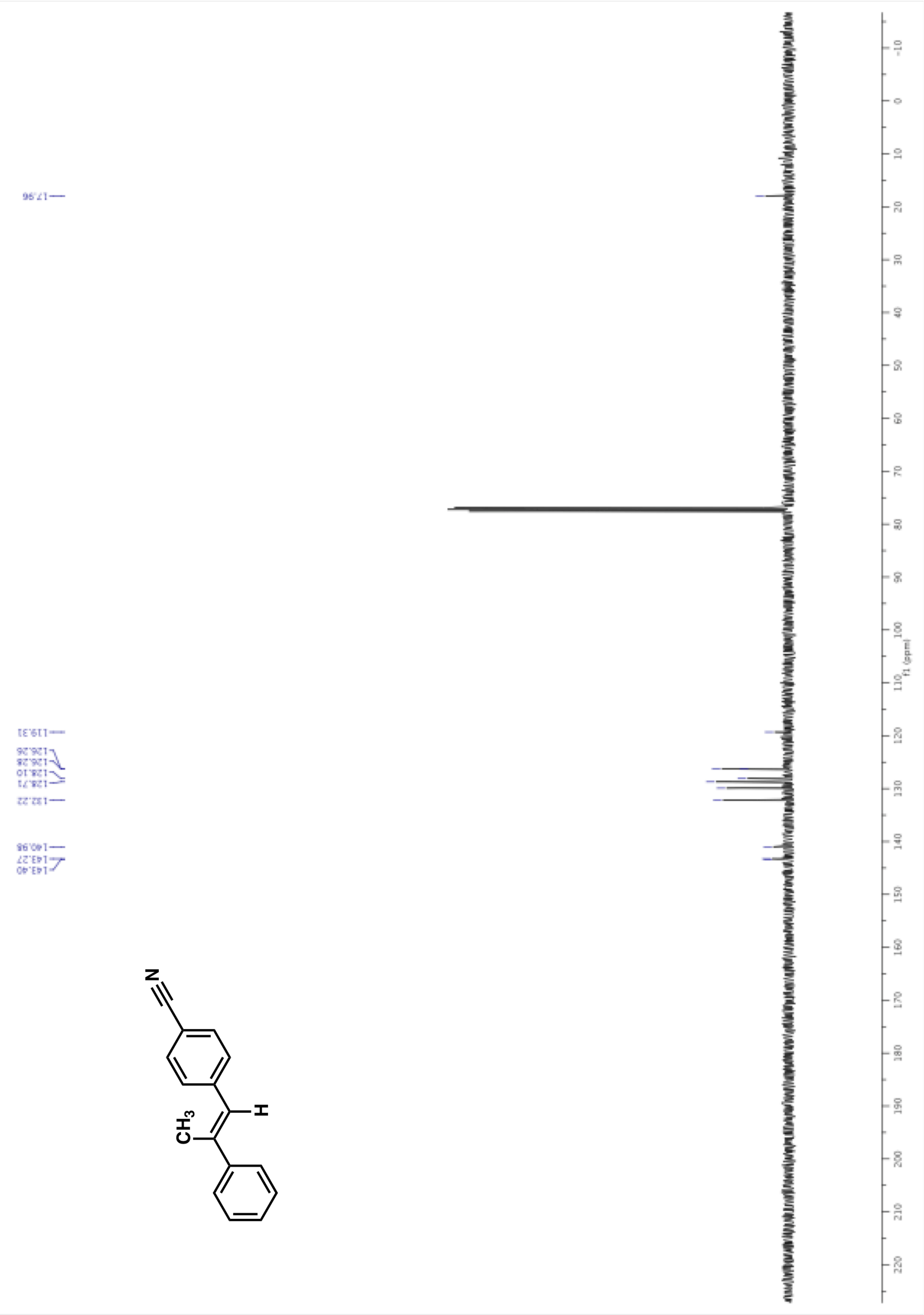

159.64
144.12
139.97
137.95
129.34
128.54
127.80
127.43
126.23
121.92
114.92
112.25
55.46
17.81
CH3
O
CH3
H
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

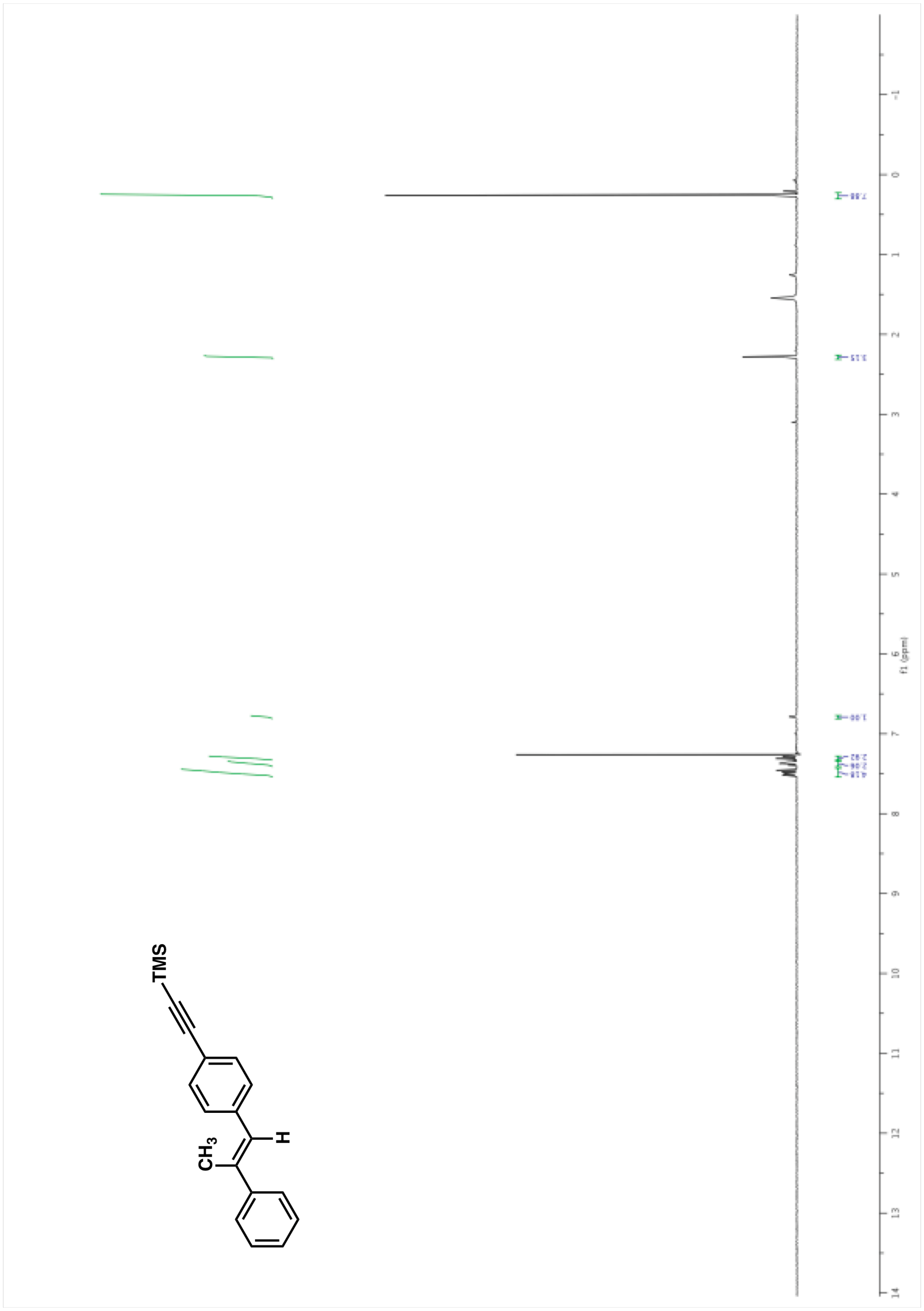
CH3
H
O
O
CH3
3.28
3.27
1.00
1.12
2.16
1.16
6.22
0.94
0.95
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

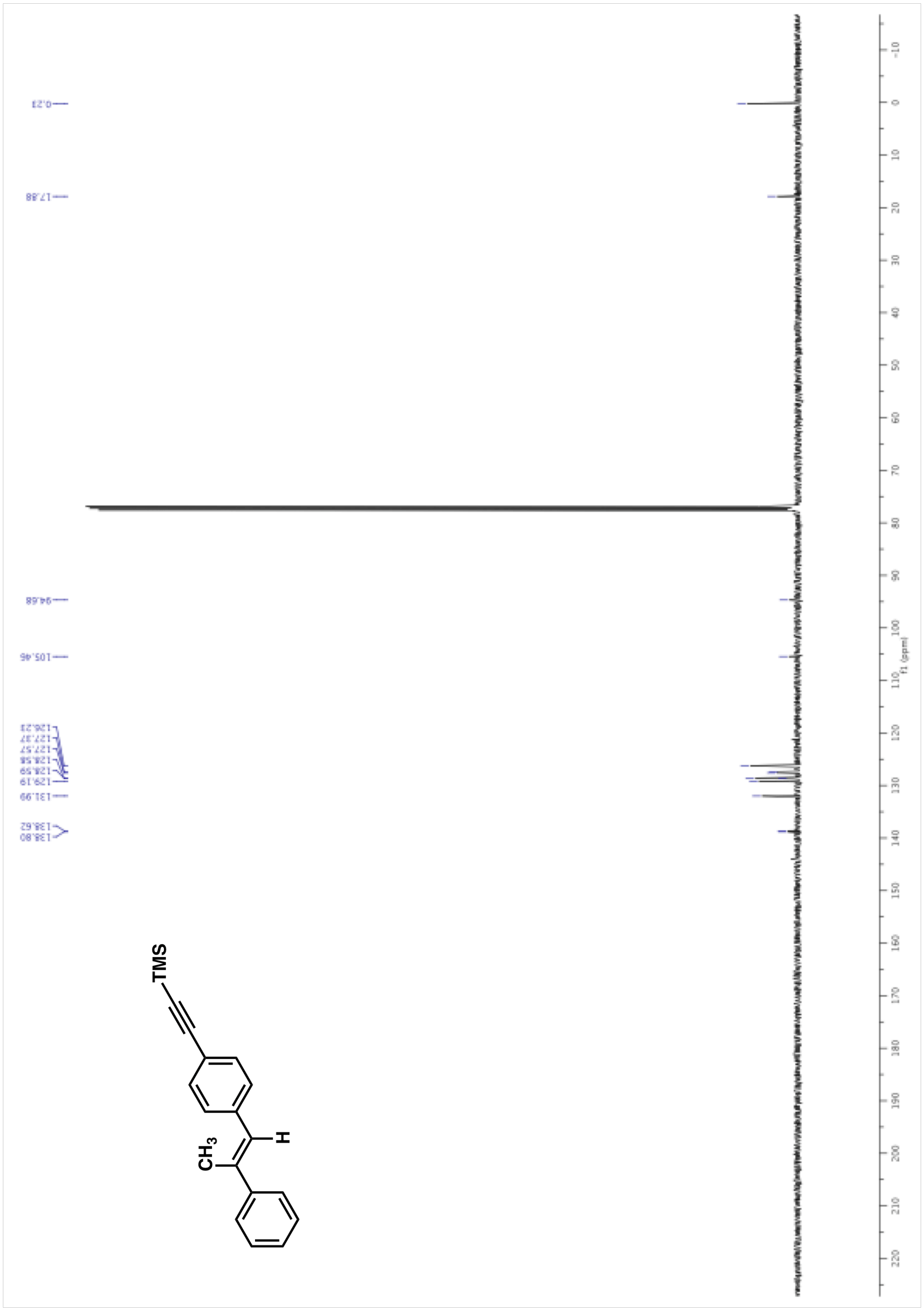


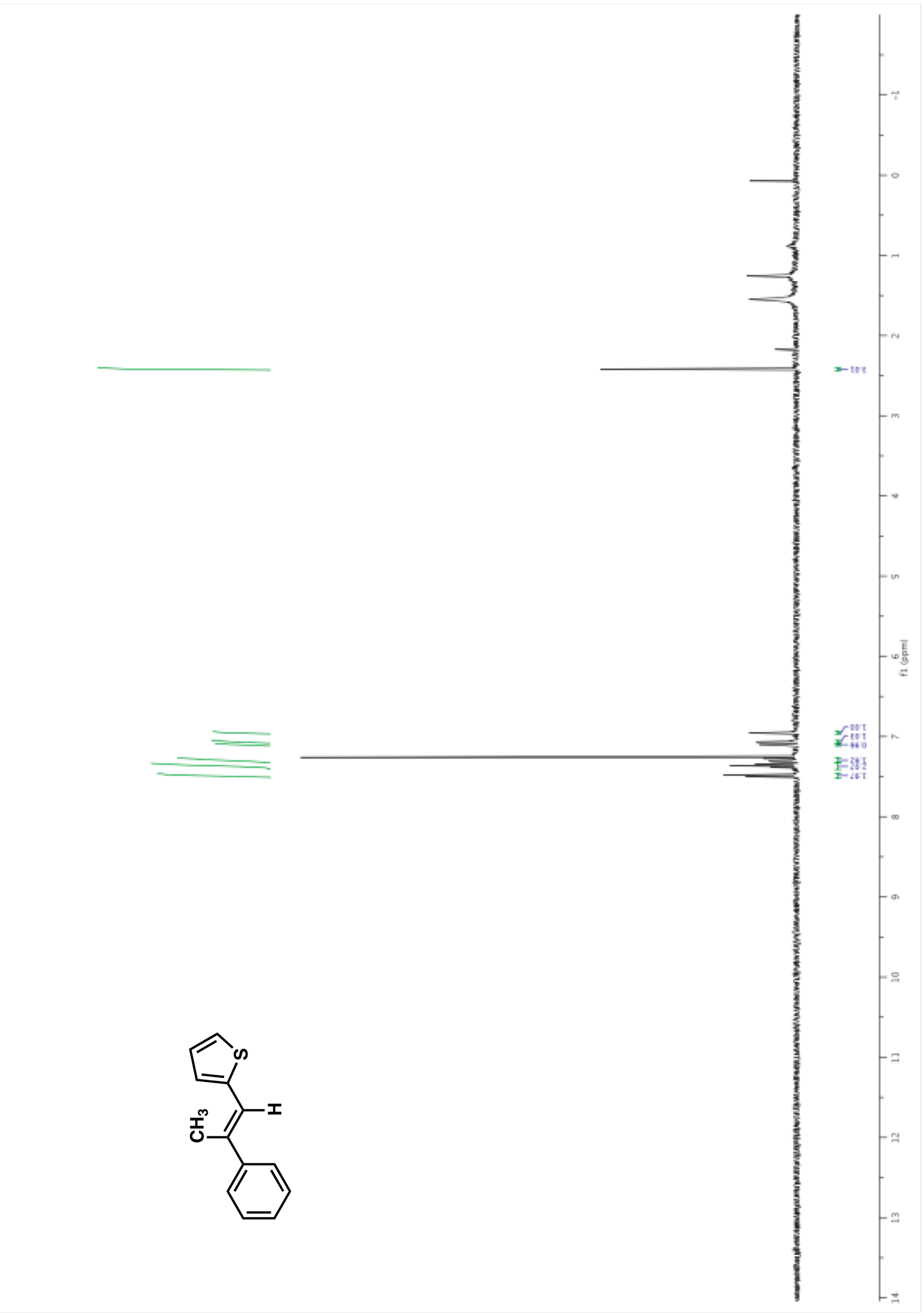
17.74
52.39
126.24
126.84
127.64
127.78
128.48
128.60
130.35
130.44
133.75
138.83
138.88
143.85
167.38
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)


N
CH$_3$
H
1.98
2.08
2.09
2.11
1.09
1.00
3.18
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

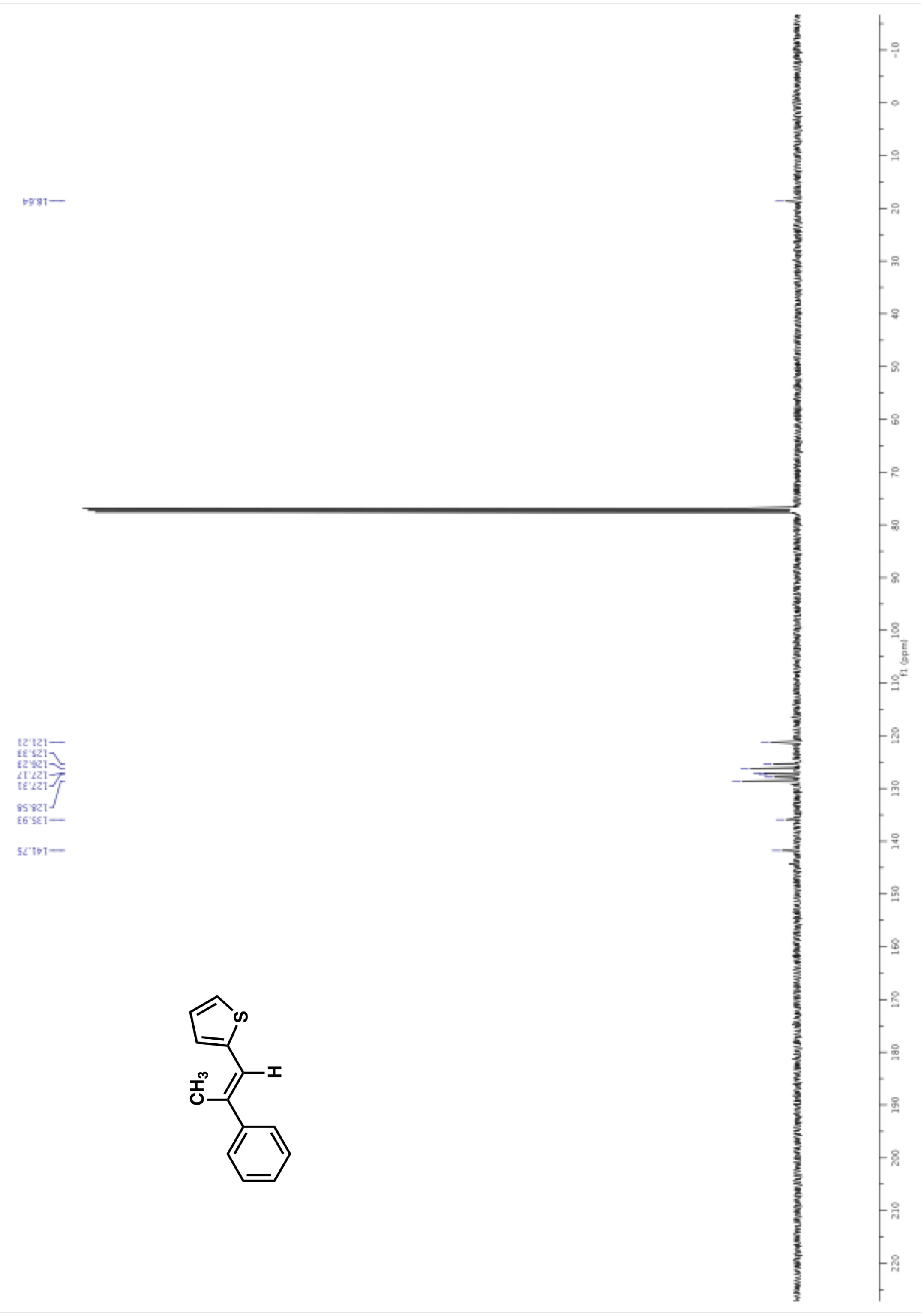

17.96
119.31
126.26
126.28
128.10
128.71
132.22
140.98
143.27
143.40
N
CH3
H
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)


TMS
CH3
H
7.88
3.15
1.00
2.02
2.06
4.18
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
f1 (ppm)

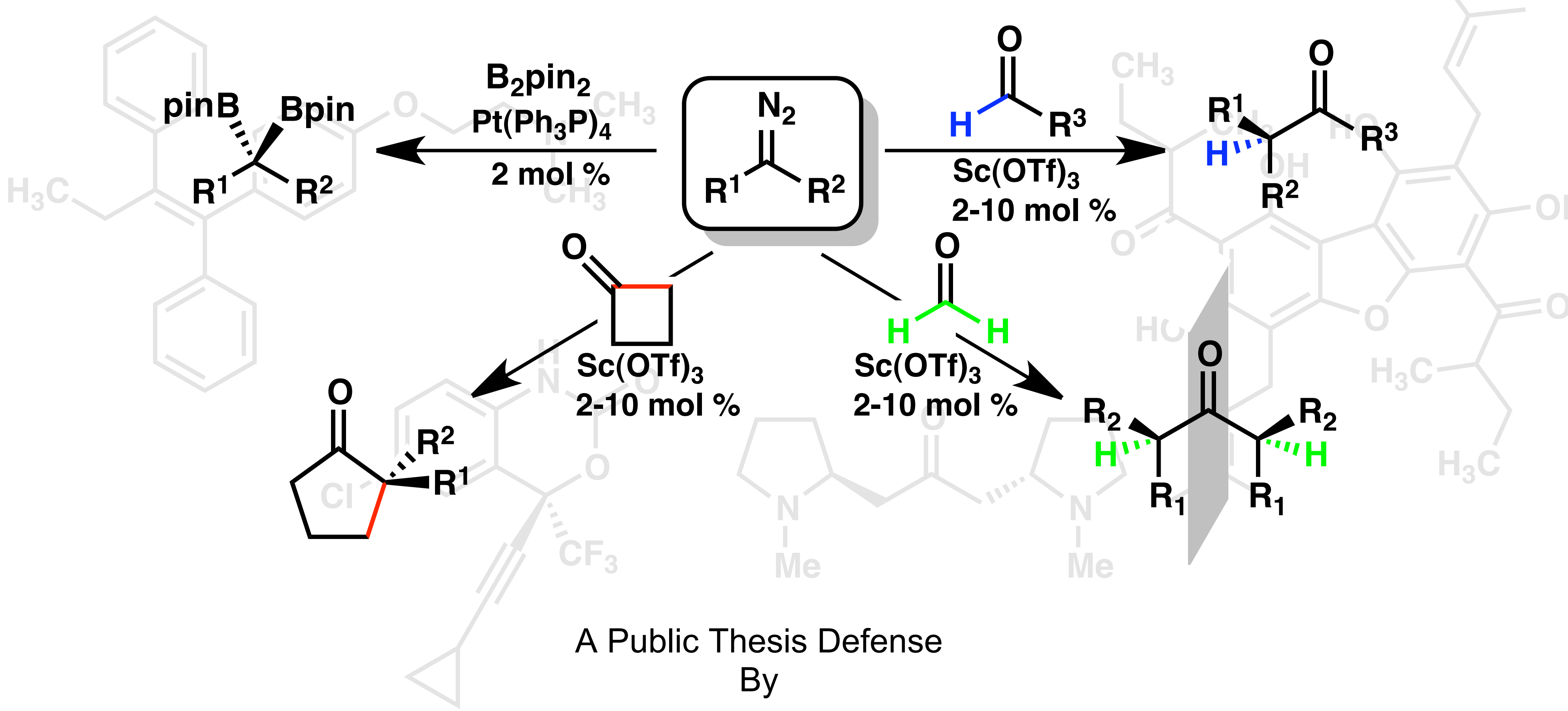

0.23
17.88
94.68
105.46
126.23
127.37
127.57
128.58
128.59
129.19
131.99
138.62
138.80
TMS
CH3
H
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220



S
CH3
H
3.03
1.00
1.03
0.96
1.92
2.02
1.97
f1 (ppm)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1


18.64
121.23
125.33
126.23
127.17
127.31
128.58
135.93
141.75
CH3
H
S
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

A MODULAR SYNTHESIS OF KETONES AND *GEM*-DIBORYLALKANES BY CATALYTIC CARBON INSERTION WITH NON-STABILIZED DIAZOALKANES



N_2
R^1
R^2
pinB
Bpin
B_2pin_2
$Pt(Ph_3P)_4$
2 mol %
O
H
R^3
$Sc(OTf)_3$
2-10 mol %
O
R^1
H
R^3
R^2
O
$Sc(OTf)_3$
2-10 mol %
O
R^2
R^1
O
H
H
$Sc(OTf)_3$
2-10 mol %
O
R_2
H
R_1
R_2
H
R_1

A Public Thesis Defense
By

Andrew J. Wommack

Wednesday, July 20th, 2011
1 pm
Merkert 127