Stereoselective Transition-Metal-Free Diboration of Alkenes

Author: Robert Leon

Boston College

The Morrissey College of Arts and Sciences

Chemistry Department

STEREOSELECTIVE, TRANSITION-METAL-FREE DIBORATION OF ALKENES

A thesis

by

ROBERT M. LEON

Submitted in partial fulfillment of the requirements for

CHEM660101/CHEM660201: Senior Thesis Research in Chemistry

and the degree of

BACHELOR OF SCIENCE

May 2016

Abstract

Robert M. Leon

Stereoselective, Transition-Metal-Free Diboration of Alkenes

(Under the direction of Professor James P. Morken)

Boronates are extremely useful in synthesis due to the ability of carbon-boron bonds to be transformed into carbon-oxygen, carbon-nitrogen, or carbon-carbon bonds stereospecifically. This makes the stereoselective construction of carbon-boron bonds especially useful. The development of transition-metal catalyzed diboration of alkenes gave synthetic organic chemists a way to quickly make not one, but two carbon-boron bonds in a stereoselective fashion. However, there are many drawbacks to transition-metal catalysis, such as high cost of catalysts and chiral ligands, and air and moisture sensitivity of catalysts. These issues, in addition to difficulties in removing trace amounts of metal contaminants from reaction products have prevented transition-metal-catalysis from being used on the industrial scale. Discussed in this thesis are two different methods for stereoselective, transition-metal-free diboration of alkenes developed by the Morken group. Also discussed is the pioneering work in the area of transition-metal-free diboration done by the Fernández group, which inspired these methodologies.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my research advisor Prof. James P. Morken who has been so willingly helpful with everything over the past two and a half years, as well as being an amazing teacher and a wealth of chemistry knowledge. I would also like to acknowledge Prof. Lawrence T. Scott as well as Prof. Christine M. Goldman for everything they did for the Honors Chemistry Program at BC during my freshman and sophomore years, which really fostered my budding excitement about chemistry.

The Morken Lab has been a great environment to learn about chemistry and working here has truly solidified my desire to become a scientist. Specifically, in the Morken Lab, I would like to acknowledge my mentors Tom Caya, Dr. Tom Blaisdell, Dr. Lichao Fang, and Lu Yan. These people have all been sources of countless pieces of advice. Tom Blaisdell, with whom I worked for the longest has been and continues to be a true role model for me. Though I never worked specifically with her on a project, I would also like to acknowledge Meredith Eno for always being available to answer questions. Also, I thank my internship supervisor Dr. Dan Robbins for all his help and his providing me with new perspective on how to do chemistry. Another thanks goes out to Tom Blaisdell and Lu Yan for proofreading this thesis and helping me with the writing process.

Finally, I'd like to thank all my friends and family for being there for me over the years: my parents Bob and Maureen, my close friends and roommates Ajay and Andrew, the friends I've made here Amanda, Christina, Jesse, Rachel, and Tucker, and my longtime friends Billy, Gabbie, Josh, and Paul. I would not have made it this far without them.

LIST OF ABBREVIATIONS USED

d = doublet (spectral)

dba = dibenzylideneacetone

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM = dichloromethane

DG = directing group

DIAD = diisopropyl azodicarboxylate

DIPA = diisopropylamine

dr = diasteromer ratio

ee = enantiomeric excess

equiv. = equivalents

er = enantiomer ratio

Et_3N = triethylamine

EtOAc = ethyl acetate

EtOH = ethanol

GC = gas chromatography

mCPBA = *meta*-chloroperoxybenzoic acid

MeOH = methanol

neo = neopentyl glycol

NMR = nuclear magnetic resonance

Ph = phenyl

pin = pinacol

RT = room temperature

SFC = supercritical fluid chromatography

t = triplet (spectral)

TBAF = tetrabutylammonium fluoride

TBS = *tert*-butyl dimethylsilyl

THF = tetrahydrofuran

Ts = *para*-toluenesulfonyl

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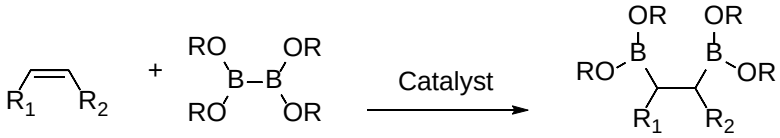
I. Introduction

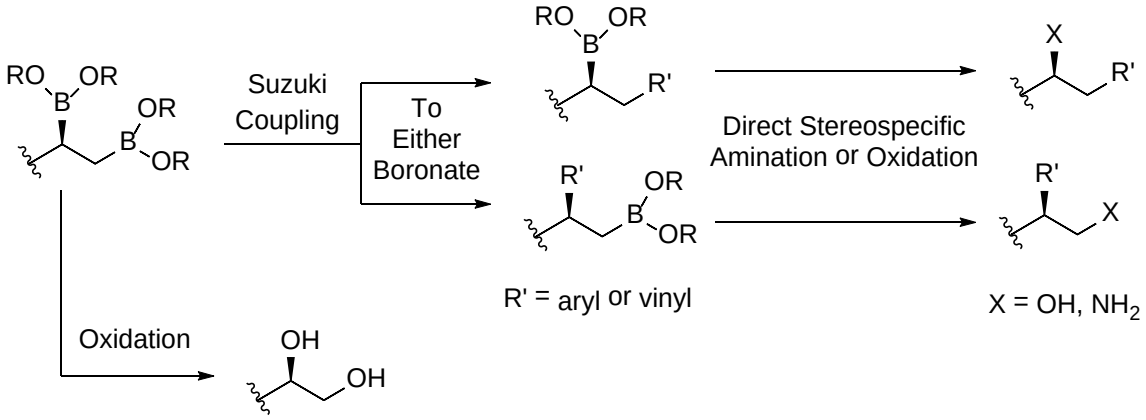
Diboration is a process by which two boron atoms are added across an unsaturated bond, installing two boron atoms within the molecule. Alkenes are an excellent substrate class for diboration due to the availability of simple alkenes as feedstock chemicals, and the vast number of ways to build alkene functionality into more complex molecules. In the case of alkene diboration, the two new bonds that are formed are carbon-boron bonds (Scheme 1), which can be manipulated in a number of useful ways. They can be transformed into carbon-oxygen bonds by oxidation, carbon-nitrogen bonds by amination[1], or carbon-carbon bonds by metal catalyzed cross-coupling (Scheme 2). There are a number of ways for differentiation[2] between the two boryl groups in 1,2-bis(boronates), and transformations of the formed C-B bonds are often stereospecific. This makes these bis(boronate) products very useful, and with new reactivity involving carbon-boron bonds still being discovered[3], their importance in organic synthesis is only growing.

Scheme 1: Diboration of alkenes



[1] Mlynarski, S. N.; Karns, A. S.; Morken, J. P. J. *Am. Chem. Soc.*, **2012**, 134 (40), pp 16449–16451
[2] Blaisdell, T. P.; Morken, J. P. *J. Am. Chem. Soc.*, **2015**, 137 (27), pp 8712–8715
[3] Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science*, **2016** 351 (6268) 70-74

Scheme 2: Utility of 1,2-bis(boronates)



Transition-metal catalysis is extremely powerful in organic synthesis, as it allows for reactivity that would not be possible otherwise. Diboration in particular has historically been an area in which transition-metal catalysis has played a large role. There have been methods for rhodium[4], platinum[5], palladium[6], copper[7], silver[8], and gold[9] catalyzed alkene diboration, with each new development solving problems left unaddressed by previous ones. Though these methods proved to be reliable ways to generate useful bis(boronates), there are serious drawbacks to the use of transition metals in synthesis. As previously alluded to, catalysts and ligands for transition-metal catalysis can be very expensive and difficult or impossible to recycle in a practical way.

[4] (a) Baker, T. R.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem. Int. Ed.* **1995**, *34*, 1336-1338. (b) Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B. *Chem. Commun.* **1998**, 1983-1984. (c) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702-8703. (d) Toribatake, K.; Nishiyama, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 11011-11015. (e) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.* **2005**, *70*, 9538-9544.

[5](a) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134-9135. (b) Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 11222-11231. (c) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689-690. (d) Iverson, C. N.; Smith III, M. R. *Organometallics* **1997**, *16*, 2757-2759. (e) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210-13211 (f) Marder, T. B.; Norman, N. C.; Rice, C. R. *Tetrahedron Lett.* **1998**, *39*, 155-158

[6] Lillo, V.; Mas-Marzá, E.; Segarra, A. M.; Carbó, J. J.; Bo, C.; Peris, E.; Fernandez, E. *Chem. Commun.* **2007**, 3380-3382

[7] Lillo, V.; Fructos, M. R.; Ramírez, J.; Braga, A. A. C.; Maseras, F.; Díaz-Requejo, M. M.; Pérez, P. J.; Fernández, E. *Chem. Eur. J.* **2007**, *13*, 2614-2621

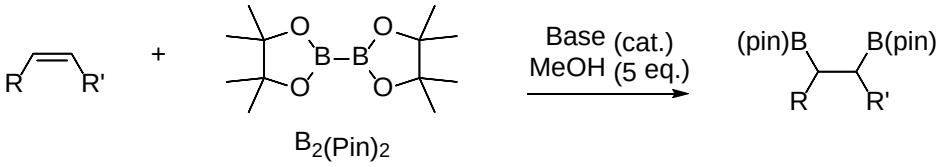
[8] Ramírez, J.; Corberán, R.; Sanaú, M.; Peris, E.; Fernandez, E. *Chem. Commun.* **2005**, 3056-3058

[9] Ramírez, J.; Sanaú, M.; Fernández, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 5194-5197.

Also, they must be handled in an inert atmosphere making reaction set-up operationally difficult. Transition metal waste can also be toxic, and on the industrial scale, having even trace impurities of transition metals in products can present problems.

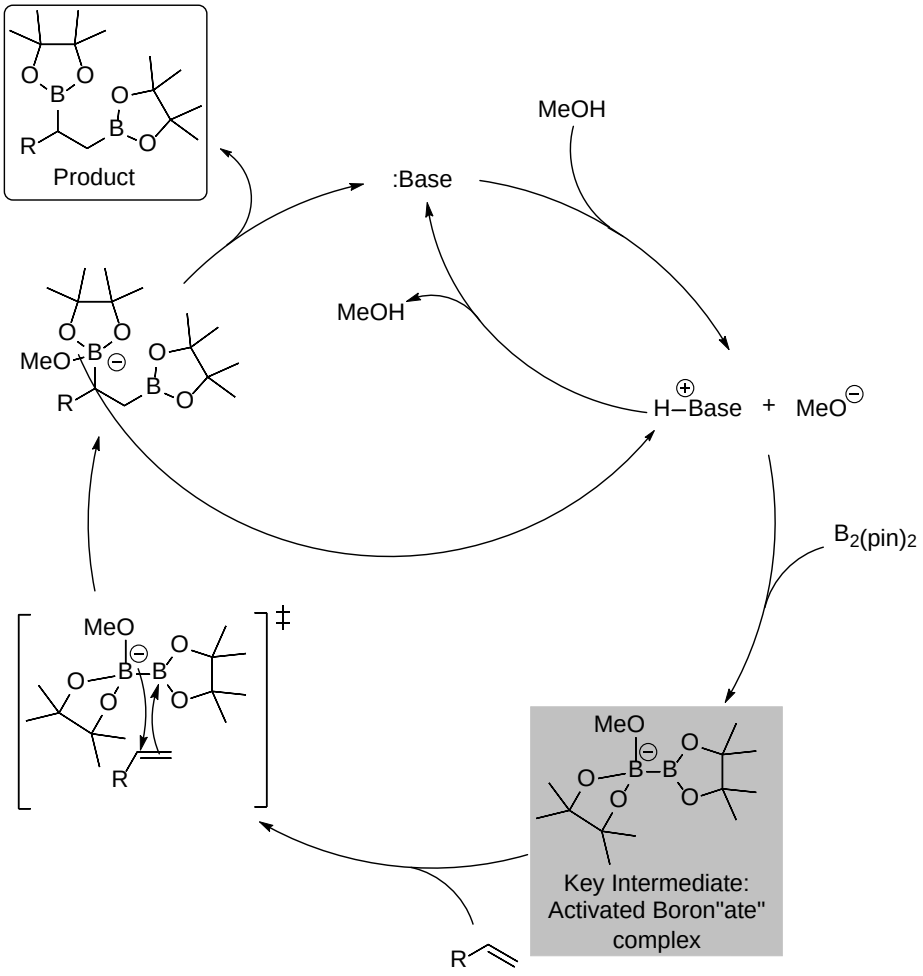
To address these shortcomings, the Fernández group recently disclosed that a simple alkoxide generated by mixing an alcohol and a carbonate base was sufficient to activate the diboron reagent $B_2(Pin)_2$ for addition across an alkene[10] (Scheme 3). This was a major breakthrough in diboration chemistry, as it represented the first modern practical method for transition-metal-free diboration. Their proposed mechanism and catalytic cycle is depicted in Scheme 4.

Scheme 3: Transition-metal-free diboration



[10] Bonet, A.; Pubil-Ulldemolins, C.; Bo, C.; Gulyas, H,; Fernandez, E. *Angew. Chem. Int. Ed.* **2011**, 50, 7158

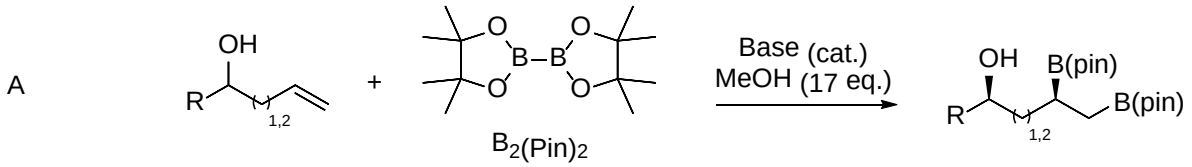
Scheme 4: Proposed mechanism for transition-metal-free diboration



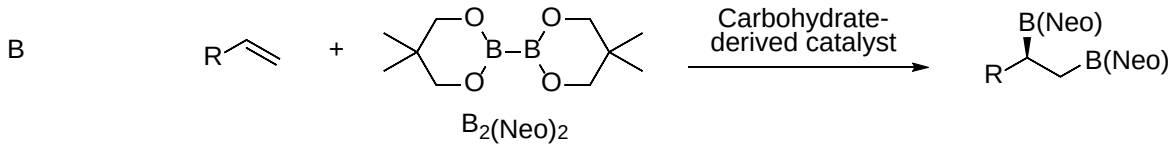
Based on DFT calculations, they proposed that the alkoxide of methanol generated by a catalytic amount of base would add to one of the empty *p*-orbitals on a boron atom of the diboron reagent, creating an activated Lewis acid-base adduct in which the boron atom now bearing the methoxide group is sp^3 hybridized. This complex, with a now polarized B-B bond is able to carry out a nucleophilic attack on a substrate molecule, and the resulting buildup of electron density on the substrate is used in an attack on the other boron atom of the diboron. Abstraction of a proton from a protonated base molecule by the methoxide releases the 1,2-bis(boronate) product, as well as the base which is free to catalyze another cycle.

This method was shown to be applicable to a wide range of substrates, simple to perform, able to be set up in the open atmosphere, and furnished the 1,2-bis(boronates) in high yield. Despite these benefits, this method was not stereoselective. The Morken lab has since been able to build upon this and invent stereoselective methods for transition-metal-free diboration, in the form of a hydroxyl-directed diastereoselective diboration[11] (Scheme 5A), and a carbohydrate-catalyzed enantioselective diboration[12] (Scheme 5B).

Scheme 5: Stereoselective fransition-metal-free diboration reactions



Hydroxyl-Directed Diastereoselective Diboration - Morken 2014



Carbohydrate-Catalyzed Enantioselective Diboration - Morken 2016

Further studies conducted on these methodologies will be discussed in the following chapters.

[11] Blaisdell, T. P.; Caya, T. C.; Zhang, L.; Sanz-Marco, A.; Morken, J. P. *J. Am. Chem. Soc.*, **2014**, 136 (26), 9264–9267

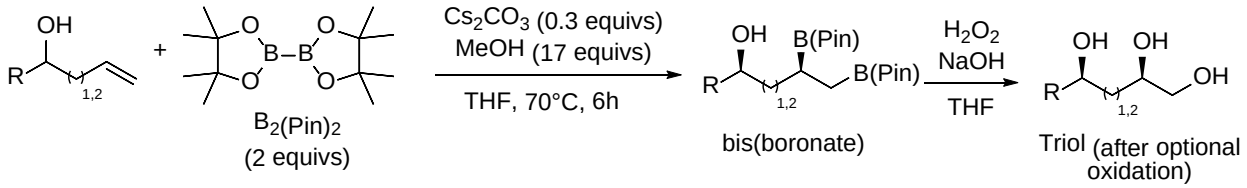
[12] Fang, L.; Yan, L.; Haeffner, F.; Morken, J. P *J. Am. Chem. Soc.*, **2016**, 138 (8), 2508–2511

II. Directed Diastereoselective Diboration of Alkenes

A. Hydroxyl-Directed Diboration

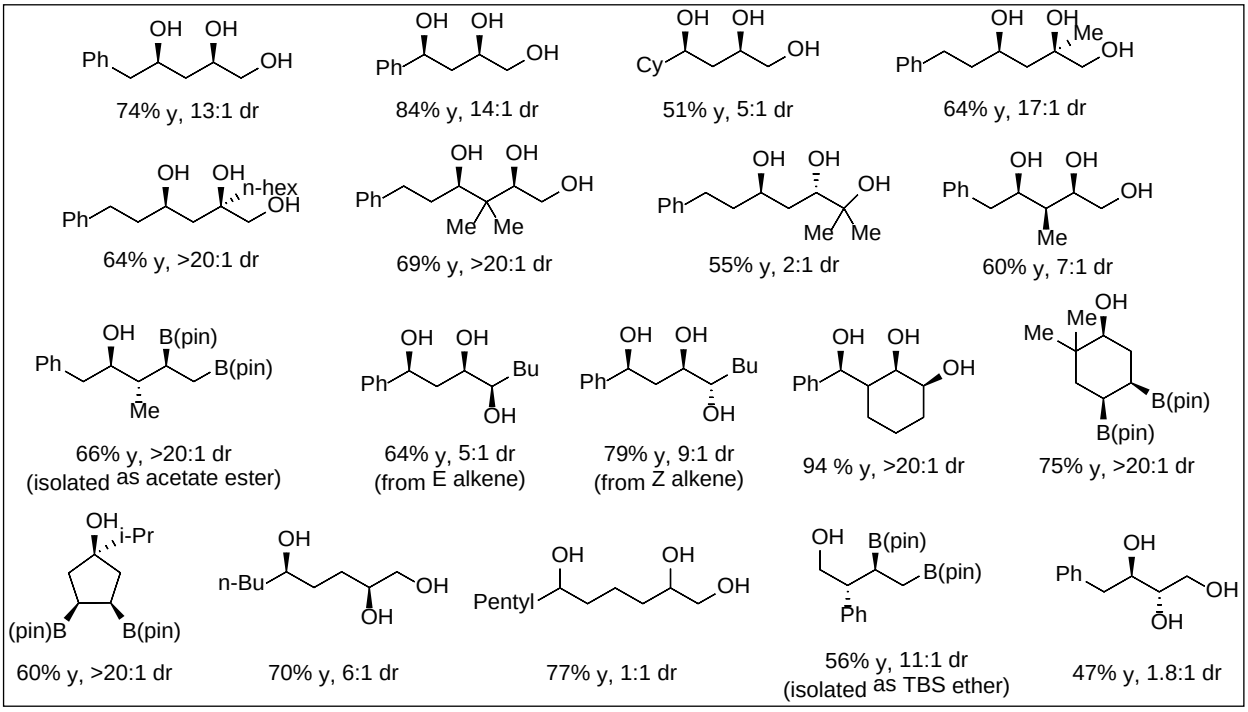
The observation that the Fernández diboration required the use of an alcohol additive inspired the Morken group to test whether a hydroxyl group in the alkene substrate molecule could be a suitable replacement for the additive. Although it was found that an excess of a hydroxyl-containing additive was still necessary for the reaction to proceed, diastereoselectivity was observed in the case of homoallylic and bishomoallylic alcohol substrates, with diastereoselectivities reaching up to >20:1, favoring the *syn* stereoisomer.

Scheme 6: Directed diboration scheme[13]



[13] Bis(boronate) products were usually oxidized to their corresponding triols for ease of characterization

Table 1: Hydroxyl-directed diboration substrate scope

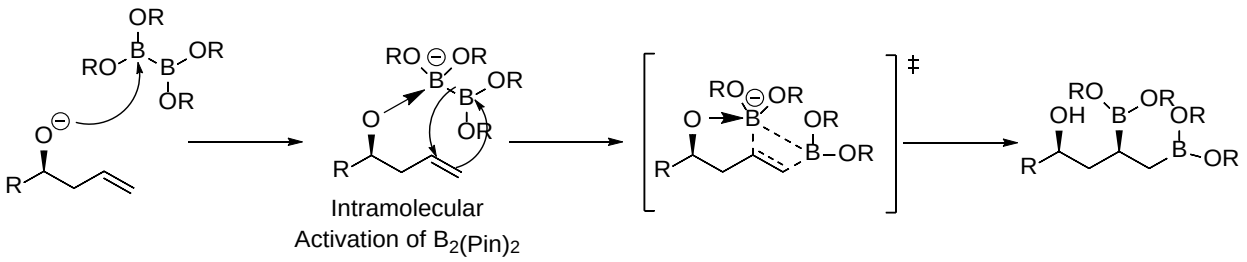


The rationale for stereoselectivity is that the hydroxyl group within the substrate coordinates to a boron atom on the diboron reagent and aligns it in such a way that it adds to the same face of the alkene that the hydroxyl group is on (Scheme 7). The first structure shown in Scheme 7 is reminiscent of the key intermediate proposed by the Fernández group. The positioning of the hydroxyl group in relation to the olefin is key: homoallylic alcohols give the best selectivity, with bishomoallylic alcohols also providing some directing function. Trishomoallylic alcohols however do not show any selectivity in the reaction. Presumably, this is due to the hydroxyl group being too distant to provide any organizational benefit. Allylic alcohols also do not participate in the directed reaction in any predictable[14] manner. The transition state depicted in Scheme 7 provides an explanation for why this might occur: in the case of homoallylic alcohols, a 5-

[14] High stereoselectivity was only observed with one *cis* disubstituted allylic alcohol substrate, and it required the use of 4 equivalents of the pyrophoric reagent n-BuLi

membered ring transition state can be accessed in which the hydroxyl directing group can maintain coordination to the diboron reagent as it adds across the alkene. In the case of bishomoallylic alcohols, an analogous 6-membered ring transition state can be imagined. This would not be possible in the cases of either allylic or trishomoallylic alcohols; their respective 4 and 7-membered ring transition states likely present too large an energy barrier, and thus no selectivity is observed for those substrates. Finally, when the methyl ether of a homoallylic alcohol was subjected to the reaction conditions, no selectivity was observed, indicating that an adequately positioned free hydroxyl group is required for any directing effect.

Scheme 7: Stereochemical model for directed diboration

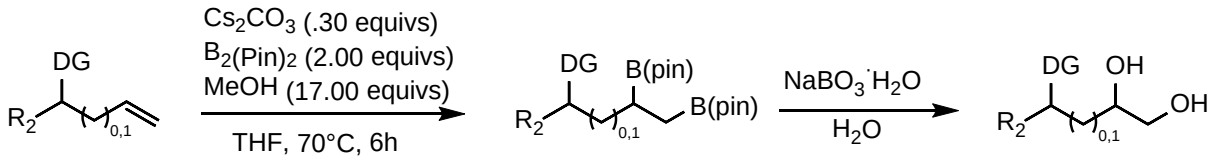


The strangely specific optimal amount of methanol employed in these reactions (17 equivalents) makes one wonder what the role of the methanol really is in the reaction. The proposed mechanism (Scheme 4) seems to suggest that methanol should be catalytic, as it is regenerated at the end of the cycle just as the base is. The use of 17 equivalents however was found to be ideal for both reactivity and stereoselectivity. Using more, or less methanol results in erosion of diastereoselectivity. A simple explanation could be that methanol serves to help dissolve the cesium carbonate allowing the reaction to proceed. Another could be that it stabilizes the stereochemistry-determining transition state through hydrogen-bonding interactions. Too much methanol however, and it will out-compete the substrate's hydroxyl group for coordination to the diboron reagent and the reaction will be less selective.

B. Examination of Other Functional Groups as Directing Groups

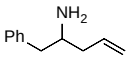
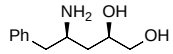
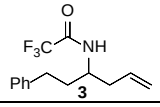
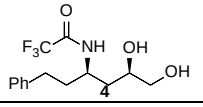
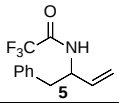
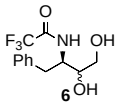
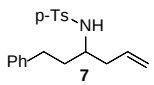
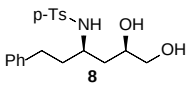
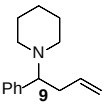
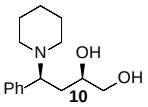
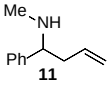
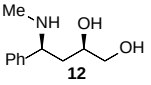
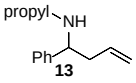
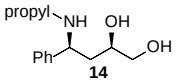
The excellent levels of stereoselectivity observed with homoallylic alcohols make it reasonable to think that other functional groups at the homoallylic position could direct for a diastereoselective addition of $B_2(Pin)_2$. Potentially, Lewis basic groups other than hydroxyl could coordinate to boron and proceed through the same sort of Lewis acid-base adduct intermediate leading to diastereoselectivity. To probe the possibility of other functional groups potentially being able to direct the reaction, a number of substrates were prepared and subjected to the directed diboration conditions (Table 2).

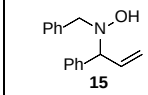
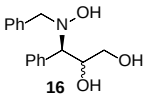
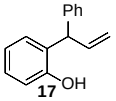
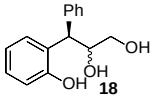
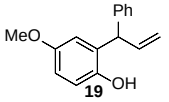
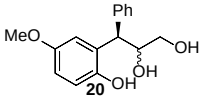
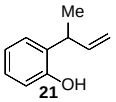
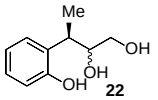
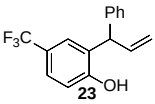
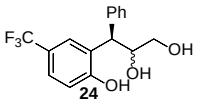
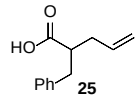
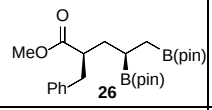
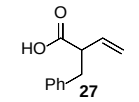
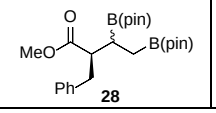
Scheme 8: Attempted directed diboration of other substrates[15]



[15] The oxidizing agent was switched from hydrogen peroxide to the milder reagent sodium perborate due to the susceptibility of amines to undergo oxidation to the N-oxide.

Table 2: Substrates with other potential directing groups examined

Entry	Substrate	Desired Product	Yield	dr
1	 **1**	 **2**	No Desired Product	--
2	 **3**	 **4**	65%	1.8:1[b]
3	 **5**	 **6**	25%	2.0:1[a]
4	 **7**	 **8**	60%	1.9:1[b]
5[d]	 **9**	 **10**	93%	1.4:4[c]
6	 **11**	 **12**	(63%)	1.3:1[a]
7	 **13**	 **14**	(74%)	1.2:1[a]

Entry	Substrate	Desired Product	Yield	dr
8	 **15**	 **16**	No Desired Product	--
9	 **17**	 **18**	75%	2.4:1[a]
10	 **19**	 **20**	76%	2.0:1[a]
11	 **21**	 **22**	78%	1.8:1[a]
12	 **23**	 **24**	No Desired Product	--
13[e]	 **25**	 **26**	43%	1.2:1[b]
14[e]	 **27**	 **28**	51%	2.7:1[a]

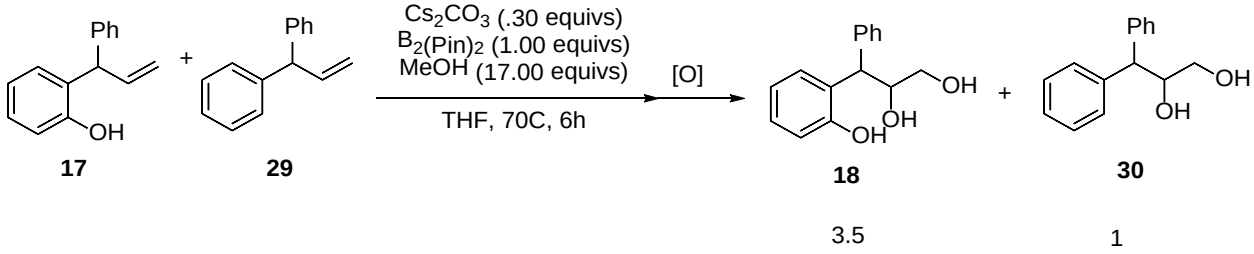
Yields in parentheses refer to conversion as determined by crude ^{1}H NMR [a]dr determined by ^{1}H NMR [b]dr determined by ^{13}C NMR [c]dr determined by SFC [d]H_2O_2/NaOH used as oxidant [e]reaction performed with 1.3 equivalents of base, and instead of oxidation, the acid was converted to the methyl ester before isolation

Unfortunately, no substrates containing groups other than an aliphatic hydroxyl group gave the same level of selectivity that had been seen with homoallylic alcohols, though most of their functional groups were tolerated by the reaction conditions. A homoallylic free amine (Entry 1) did not give any conversion to the desired product. Both allylic and homoallylic amides (Entries 2, 3, and 4) participated in the diboration, but with low levels of selectivity. N-alkyl amines (Entries 5, 6, and 7) did also participate in the reaction, but again with little to no diastrereoselectivity. An allylic hydroxylamine (Entry 8) was tested, but did not undergo diboration and only decomposed under the reaction conditions. Phenol-containing substrates underwent diboration relatively

cleanly but still no significant amounts of diastereoselectivity were observed. In the case of carboxylate-containing substrates, catalytic amount of base gave no reaction (likely due to the acid group neutralizing the 30 mol % base preventing the reaction from proceeding) so for these reactions, 1.3 equivalents of base were used. Any small amount of diastereoselectivity in these reactions was attributed to steric bias of the particular substrate rather than a directing effect. The major diastereomer in these reactions was not determined.

In the hydroxyl-directed diboration, a rate increase in the diboration of homoallylic alcohols relative to simple aliphatic alkenes was observed. A competition experiment revealed that there may be some directing effect happening in the case of phenol-containing substrates due to an increase in rate of diboration of **17** relative to an analogous substrate without a hydroxyl group (Scheme 9). The fact that no stereoselectivity was observed with these substrates however diminishes the synthetic utility of this finding. This phenomenon was not observed in the case of carboxylic acid-containing substrates.

Scheme 9: Phenol-containing substrate competition experiment[16]



C. Examination of Other Catalyst Systems

During the hydroxyl-directed diboration studies, it was found that amine bases, along with an equivalent amount of a salt additive were suitable for the activation of $B_2(pin)_2$ addition across an alkene (Scheme 10).

[16] Conversion determined by ^{1}H NMR

Scheme 10: Amine Bases with Salt Additives in the Directed Diboration

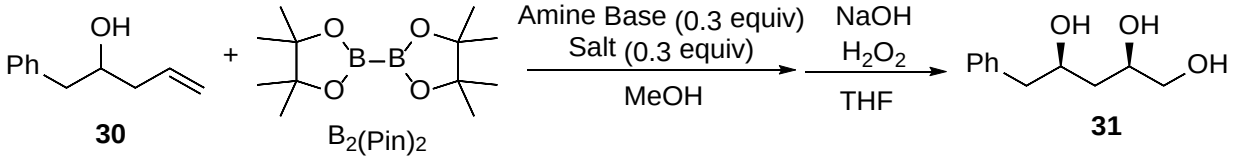


Table 3: Amine bases with salt additives in the directed diboration

Entry	Base	Salt	Conversion	dr
1	DBU	NaCl	79%	8:1
2	DBU	None	26%	2.3:1
3	DBU	LiCl	75%	5:1
4	DBU	CsCl	>99%	6:1
5	DBU	Na_2SO_4	30%	5.7:1
6	DBU	NaH_2PO_4	<5%	--
7	Et_3N	NaCl	>99%	8.3:1
8	Et_2N	NaCl	20%	5.3:1
9	Pyridine	NaCl	<5%	--
10	Ph_3N	NaCl	<5%	--
11	Et_2PhN	NaCl	<5%	--
12	None	NaCl	<5%	--

Conversion and dr were both determined by SFC analysis of crude reaction mixture

Though the diasatereoselectivity and yields were generally lower than what had been observed with cesium carbonate, it was interesting to see that amine bases could catalyze the reaction. Having a salt additive present in the reaction is thought to stabilize the protonated amine which helps the reaction to progress (as seen by greater conversion in Entry 1 than 2), and also seems to diminish the amount of background reaction (as seen by better selectivity in Entry 1 than 2). When a series of salts were screened using DBU as the base, it was found that CsCl gave the highest conversion, indicating that the Cs^+ cation could have some non-innocent effect in the reaction as a counterion (since Cs_2CO_3 was initially found to be the ideal base for the reaction by the Fernández and later the Morken groups).

D. Conclusions

Homoallylic alcohols seem to be a special case in which excellent levels of diastereoselectivity can be observed in the directed diboration reaction. Many other substrates containing proximal Lewis-basic groups were tested, but none were able to give stereoselective reactions as in the case of homoallylic alcohols. Studies showed that the reaction, though optimally catalyzed by the inorganic base cesium carbonate could be catalyzed by organic amine bases.

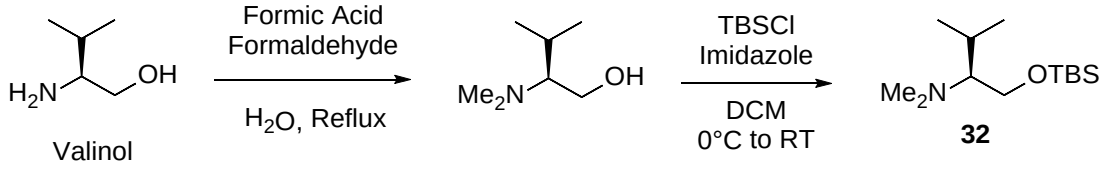
III. Enantioselective Transition-Metal-Free Diboration

A. Attempt to Design an Enatioselective Organocatalytic Reaction

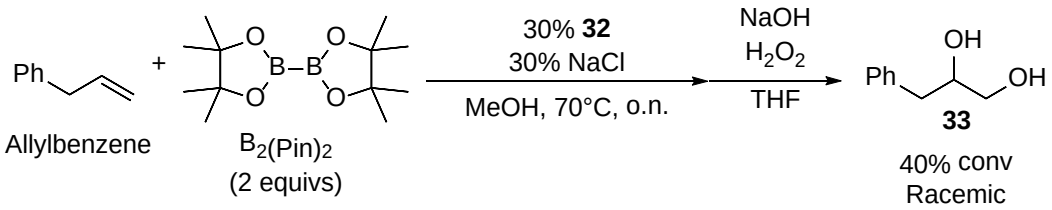
A benefit to the use of transition metal catalysts is that the use of a chiral ligand in sub-stoichiometric amounts can result in catalytic transfer of chirality to the reaction products, generating a large amount of chiral product from racemic or achiral starting materials. This is one of the primary methods for catalytic chirality transfer in organic synthesis today. In reactions that do not employ a transition metal catalyst, chirality must be imparted in some other way.

With the knowledge that a simple trialkyl amine, such as triethylamine with the addition of a salt additive could be used to catalyze the directed diboration reaction (Table 2, Entry 7) the door was opened for the possibility of asymmetric catalysis with a catalytic amount of a chiral amine acting as the base, and the reaction could be extended to substrates without directing groups. To test whether using a chiral amine could have any effect on stereoselectivity, a chiral trialkyl amine was synthesized from the commercially available L-Valinol (Scheme 11). The protected amino alcohol **32** was then employed as a catalyst in the diboration reaction with a simple achiral alkene, allylbenzene, while holding all other conditions constant. (Scheme 12)

Scheme 11: Synthesis of a potential catalyst



Scheme 12: Attempt at designing an asymmetric organocatalytic reaction

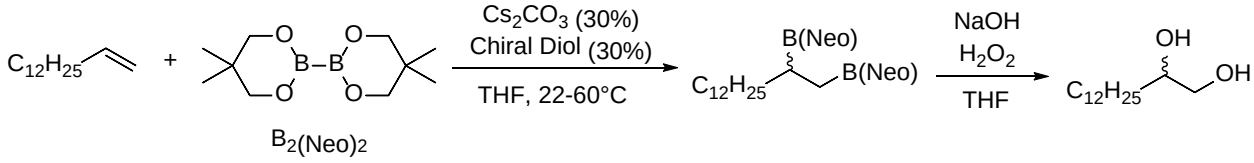


Unfortunately, although the chiral amine was able to catalyze the addition of $B_2(Pin)_2$, it gave racemic product. This result seemed to suggest that the base employed is not involved in the transition state in which the diboron reagent is actually added to the alkene, but rather that the base deprotonates a solvent molecule and the resultant alkoxide coordinating to the boron is what activates it for addition. This is again in concordance with the mechanism proposed by Fernández. There would have to be some other chiral species in the reaction if there was to be hope of developing an enantioselective transition-metal-free diboration.

B. Carbohydrate Catalyzed Enantioselective Diboration

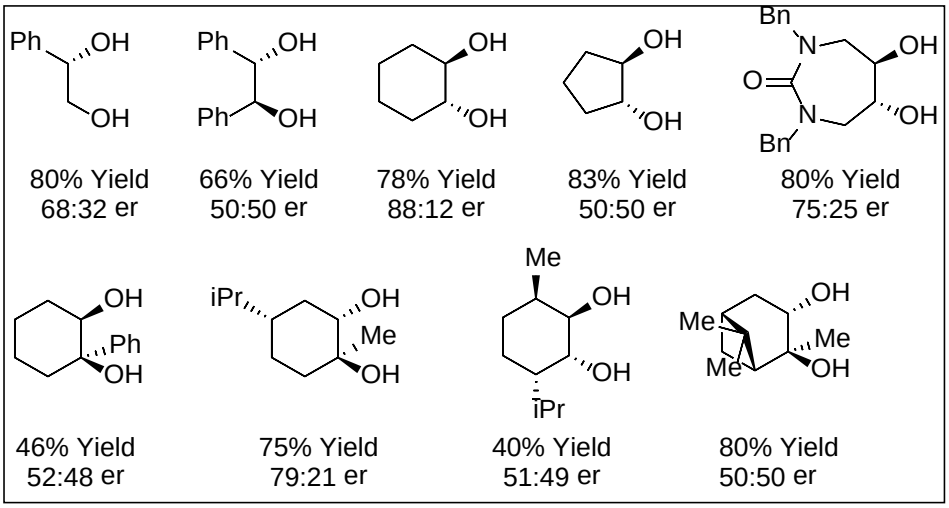
Again taking inspiration from the Fernández group, who demonstrated that enantioselectivity in their transition-metal-free diboration could be achieved using super-stoichiometric chiral alcohol additives[17], the Morken group wondered whether the use of a chiral diol, rather than a mono-alcohol could improve enantioselectivity in the diboration. A number of chiral diols were screened with $B_2(Neo)_2$ now as the diboron reagent, (Scheme 13) and of the screened diols (Table 3), it was found that some of them, in catalytic amounts were able to deliver diboration product in good yield and enantioselectivity.

Scheme 13: Screening of chiral diols



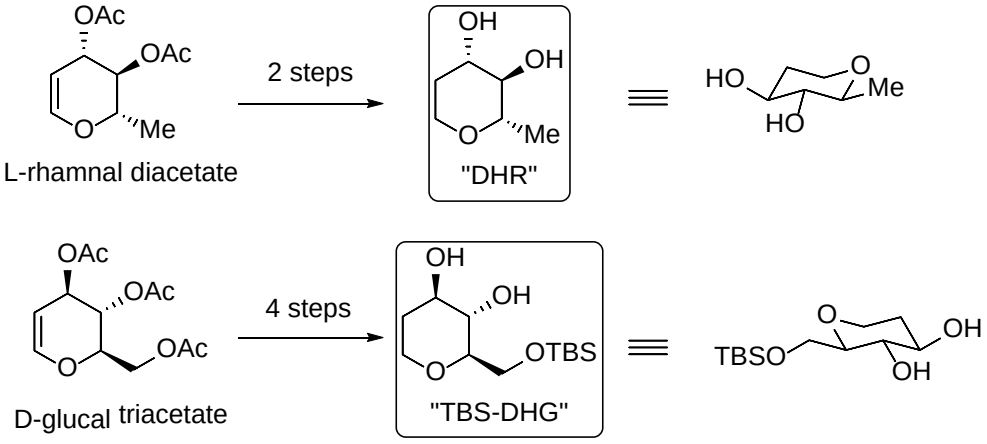
[17] Bonet, A.; Sole, C.; Gulyas, H.; Fernandez, E**.** *Org. Biomol. Chem.***, 2012,**10, 6621-6623

Table 4: Chiral diols screened



The screen revealed that *trans*-1,2 cyclohexane diol was the best for enantioselectivity, and still gave very good yield. *Trans*-1,2 diols were thought to work better because this conformation would allow both substituent groups to be equatorial, making the overall molecule, and eventual complex with boron more stable. *Trans*-1,2-cyclopentanediol gave racemic product, likely due to the angle between the two adjacent hydroxyl groups being too wide to both coordinate to one central boron atom. In the case of 6-memebered rings, the hydroxyl groups' being substituents on a 6-memebered ring means significantly less torsional strain will be introduced by coordination to a central boron atom. With this knowledge, catalysts were prepared from the cheap and commercially available chiral carbohydrates L-rhamnal diacetate and D-glucal triacetate (Scheme 14).

Scheme 14: Preparation of catalysts from carbohydrates



These pseudoenantiomeric catalysts, after some further optimization, were able to catalyze enantioselective addition of $B_2(Neo)_2$ across a number of unactivated simple alkenes (Scheme 15, Table 4). The TBS-DHG catalyst proved to be slightly better for yield and enantioselectivity in most cases, but use of the DHR catalyst would usually provide the other enantiomer of product in as good yield and enantioselectivity as TBS-DHG (though double the amount of catalyst was needed).

Scheme 15: Optimized carbohydrate catalyzed diboration

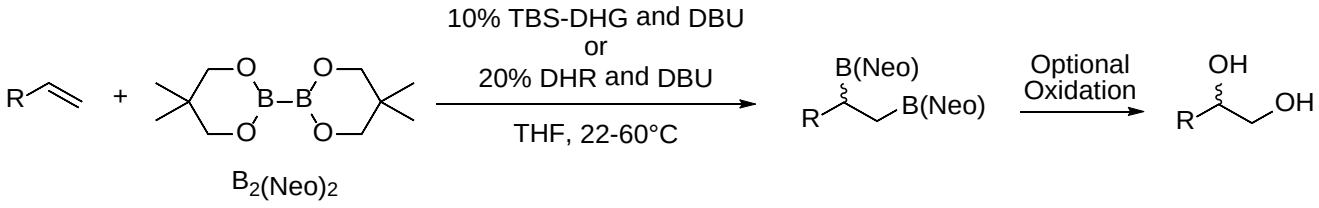
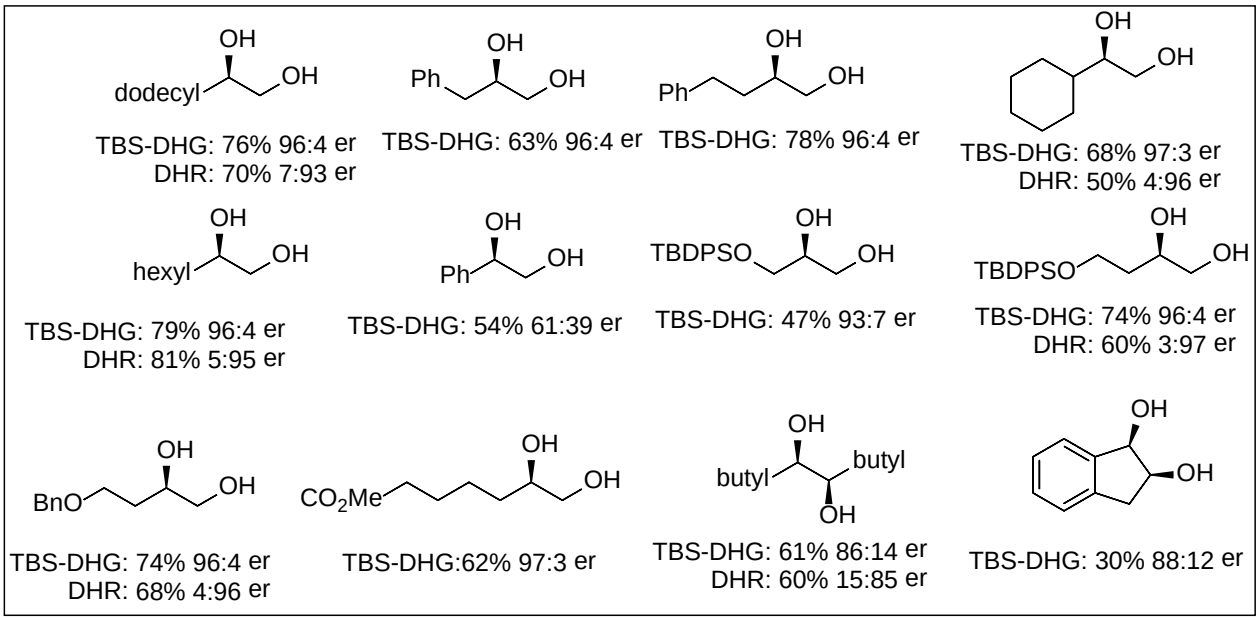


Table 5: Carbohydrate catalyzed diboration substrate scope



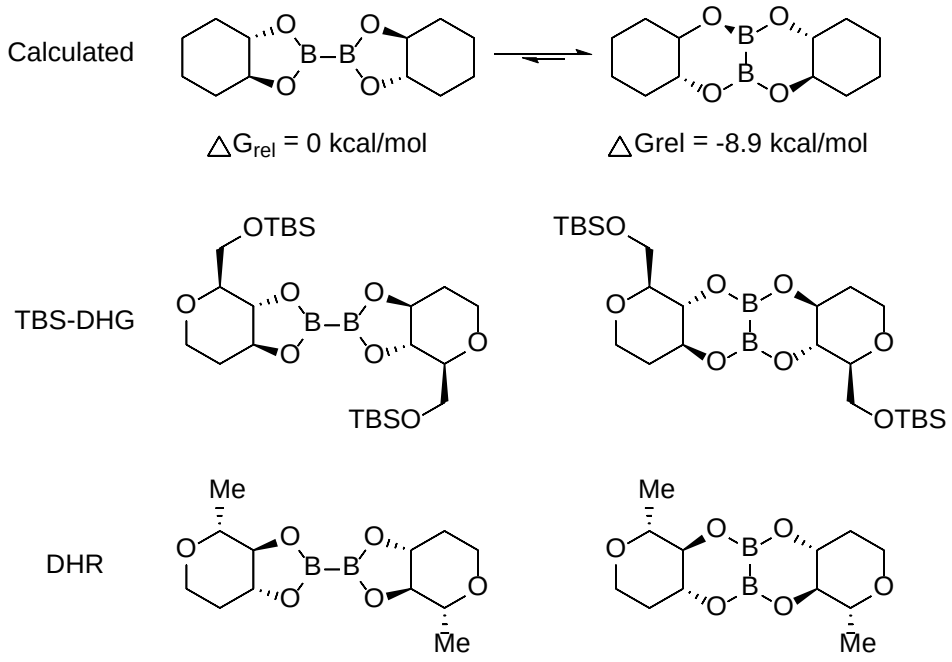
The reaction showed decent functional group tolerance, although styrenes suffered from low yield and selectivity. Internal alkenes, although suffering from somewhat lower levels of enantioselectivity, did undergo asymmetric diboration under these conditions. Interestingly, under previously developed platinum-catalyzed conditions, internal olefins had been found to be completely unreactive[5(b)].

C. Attempts at rational design of a new catalyst

Next, attempts were made to elucidate the structure of the active diboron species that actually participates in the enantioselective diboration. Perhaps knowing more about the structure of the active species would help design a catalyst that would work for more challenging substrates. Mass spectroscopy experiments with $B_2(Neo)_2$ and *trans*-1, 2-cyclohexanediol showed that a complete double exchange occurred, in which both neopentyl glycol ligands were replaced by cyclohexanediol ligands, while there was no observed exchange of only one neopentyl glycol ligand for a cyclohexanediol ligand. This allowed for computational models to be constructed, in which it was found that in the case of *trans*-1, 2-cyclohexanediol, 1, 2-bonding gave a more stable

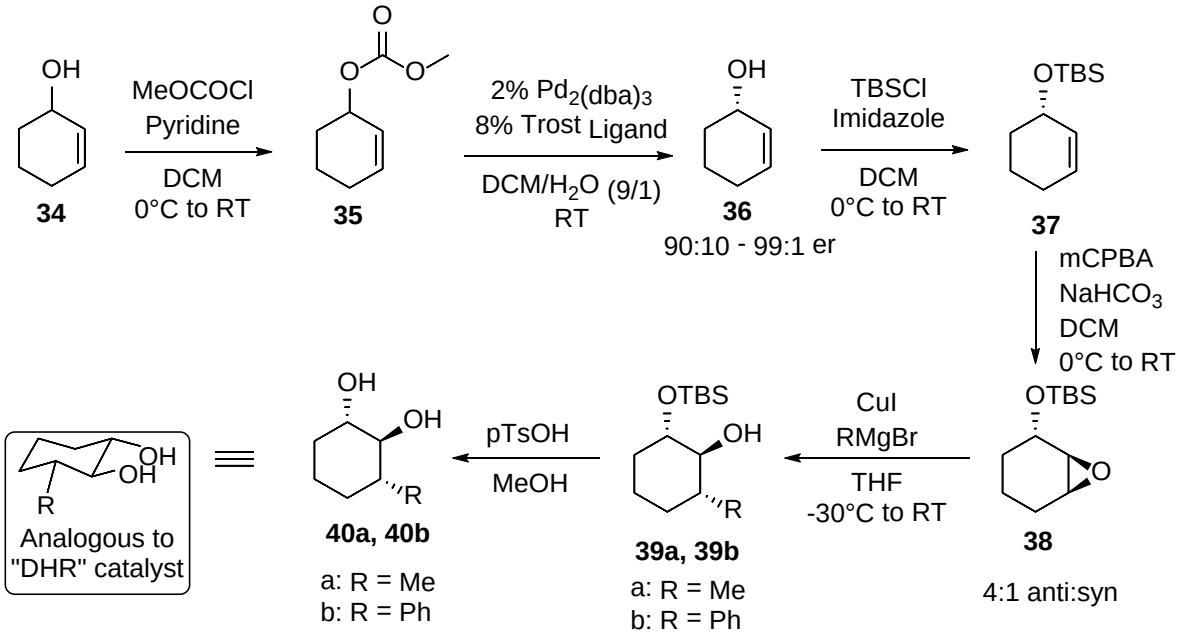
complex than 1,1-bonding (Scheme 16, Note: analogous 1, 2-bonded structures for the TBS-DHG and DHR catalysts are also shown). This suggests that it is more likely that this 1, 2-bonded chiral diboron complex is what gets activated to form the activated boron "ate" complex proposed by Fernández.

Scheme 16: Calculated and possible bonding modes for diboron reagents

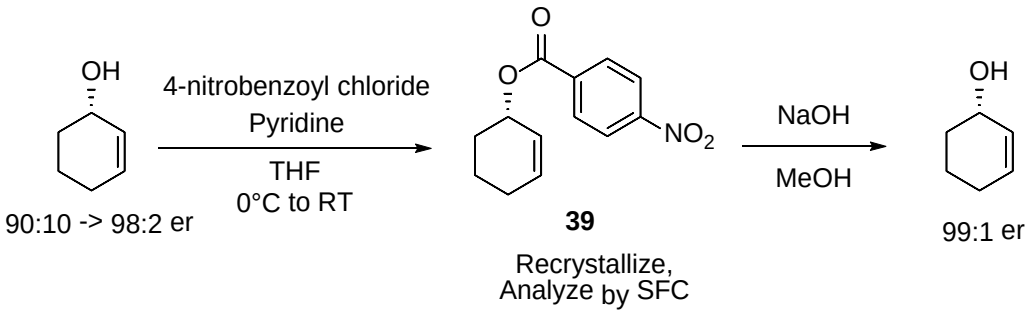


Since the DHR and TBS-DHG catalysts are derived from natural carbohydrate sources, they contain an oxygen in their core 6-membered ring. In order to probe whether or not the oxygen was having any effect on the progress of the reaction, analogues of the DHR catalyst were prepared (Scheme 17) in which the 6-membered ring was comprised of all carbon atoms. This synthetic route was decided on because of the utility of the epoxide intermediate **38** which could be opened with a number of different nucleophiles to potentially generate a library of catalyst candidates. Also, the ability to convert chiral alcohol intermediate **36** to the *para*-nitrobenzoyl ester for SFC analysis and if desired, recrystallization to improve optical purity (Scheme 18) made this synthetic route desirable.

Scheme 17: Synthesis of catalyst analogues



Scheme 18: Recrystallization to improve optical purity



Diborations with the prepared catalyst derivatives were performed (Scheme 19) and the results are displayed in the table below (Table 5).

Scheme 19: Diborations with catalyst analogues

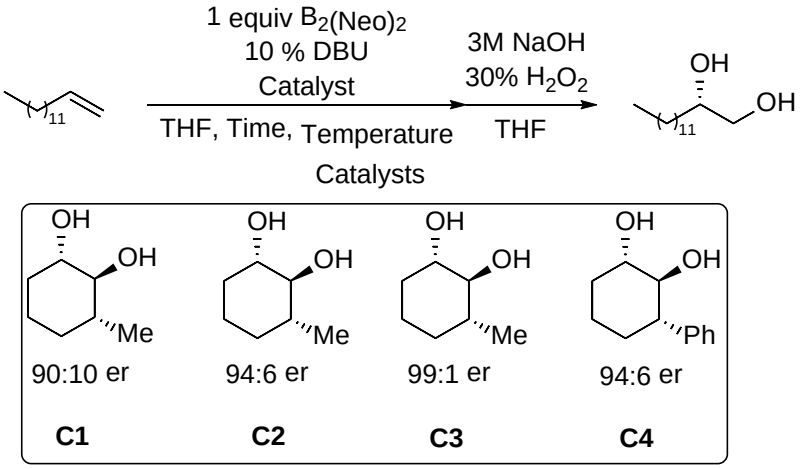


Table 6: Results of diborations with catalyst analogues

Entry	Catalyst	Temperature	Time	Conversion[a]	er[b]
1	10% C**1**	RT	24 h	45%	90:10
2	10% C**1**	35°C	24 h	48%	89:11
3	10% C**1**	RT	48 h	50%	90:10
4	10% C**1**	35°C	48 h	53%	86:14
5	10% C**1**	60°C	48 h	49%	85:5
6	20% C**1**[c]	35°C	48 h	60%	91:1
7	10% C**1**[d]	RT	24 h	20%	--
8	10% C**2**	RT	24 h	46%	94:6
9	10% C**2**[e]	RT	48 h	trace	--
10	10% C**3**	RT	24 h	50%	93:7
11	10% C**3**[f]	RT	24 h	65%	93:7
12	10% C**4**	RT	24 h	30%	93:7

[a]conversion determined by ^{1}H NMR with reference to a 1,1,2,2-tetrachloroethane internal standard [b]ER determined by GC after conversion to acetonide according to the method described in the literature[12] [c]20% DBU instead of 10% [d]10% Cs_2CO_3 instead of DBU [e]2 equiv. $B_2(neo)_2$ instead of 1 [f]1-octene used as substrate instead of 1-tetradecene

No significant improvement in yield was seen by running the reaction for twice as long (24 hours to 48) nor did running the reaction at elevated temperatures (which actually eroded enantioselectivity). An interesting feature of this reaction is that it seems to be very sensitive to the solubility of either the catalyst or the diboron reagent. When 2 equivalents of $B_2(Neo)_2$ were used, there was surprisingly only trace formation of the product. Though this reaction was stirred vigorously for 48 hours at room temperature, it appeared that the diboron reagent never fully

dissolved in the solvent; perhaps preventing any of the catalyst from getting into solution which is what caused the reaction to not occur. Also, higher conversion was seen when the substrate was changed from 1-tetradecene to 1-octene. An explanation for this could be that the longer alkyl chain of tetradecene makes the overall solvent environment less polar causing a decrease in catalyst solubility.

D. Non-linear Effect

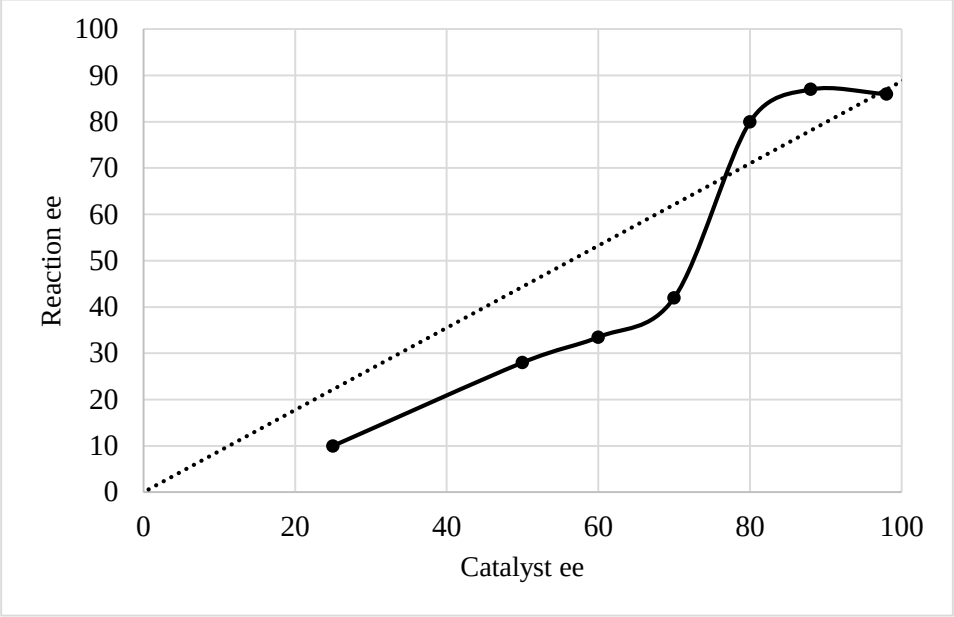
It was also found that there was a substantial non-linear effect with methyl-substituted catalyst derivative **40a**. The enantioselectivity observed in the reaction when the catalyst was a 90:10 ratio of enantiomers matched, being 90:10 (Table 6, Entries 1 and 3). Then when the catalyst was slightly more optically pure the enantioselectivity of the reaction rose accordingly (Table 6, Entry 8). Enantioselectivity for the reaction topped out at 94:6 however, even when catalyst of 99:1 er was used (Entry 10). This non-linear behavior was further examined by preparing a series of catalyst mixtures with different relative amounts of enantiomers and seeing how they performed in the reaction (Table 6, Figure 20).

Table 7: Non-linear effect data[18]

Entry	Catalyst ee	Reaction Product ee
1	98%	86%
2	88%	87%
3	80%	80%
4	70%	42%
5	60%	33%
6	50%	28%
7	25%	10%

[18] Ee reported instead of er for ease of data presentation. Reported ee values represent the average of at least two experiments.

Figure 20: Plot of reaction product ee vs. catalyst ee



A plot of ee of the reaction vs. ee of the used catalyst reveals the interesting non-linear behavior of this catalyst system. The most common examples of non-linear effects are either positive or negative non-linear effects, where the experimental data traces a curve either above or below the straight theoretical line. In this case however, it seems that with catalyst of lower optical purity there is a negative non-linear effect, while with catalyst of higher optical purity there is a positive non-linear effect. Inflection points in plots like these usually indicate some kind of aggregation phenomenon occurring in which the catalyst molecules can cause the active species to form clusters containing multiple catalyst molecules. The inflection point that is seen between 70% and 80% catalyst ee suggests that once a certain concentration of one enantiomer of catalyst is reached, non-catalytically active racemic complexes will form and leave comparatively more enantiopure catalyst molecules free in solution to catalyze the reaction. This type of reservoir effect

in which some of the catalyst is sequestered in an inactive form off the catalytic cycle is known to occur in situations where aggregation of the reactive species can occur[19].

E. Conclusions

A carbohydrate-catalyzed diboration of alkenes was developed. Though high yielding and highly stereoselective, changes to the catalyst used or a better understanding of how the catalyst works in the reaction could allow for improved reactivity and selectivity, especially in the case of certain problematic substrates. Mechanistic experiments suggest that the active species in the reaction consists of a complex of more than one catalyst molecule with a diboron reagent, making design of a new catalyst challenging.

[19] Gillaneux, D.; Zhao, S.; Samuel, O.; Rainford, D.; Kagan, H. J. Am. Chem. Soc. **1994**, 116, 9430-9439

IV. Experimental

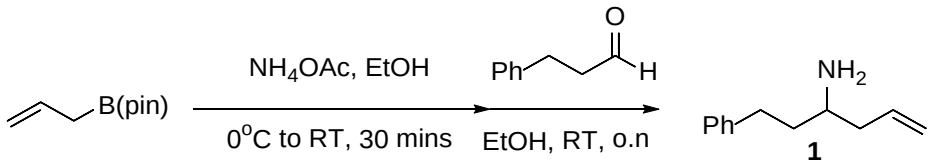
A. General Experimental Information

^{1}H NMR spectra were measured using a Varian Gemini 600 MHz, a Varian Unity Inova 500 MHz or a Varian Gemini 400 MHz spectrometer. Chemical shifts are reported in ppm with the $CDCl_3$ =7.24 ppm solvent resonance as the internal standard unless otherwise stated. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. $^{13}C\{^{1}H\}$NMR spectra were recorded on Varian Unity Inova 500 MHz (125 MHz) or a Varian Gemini 400 MHz (100 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.00 ppm). High resolution mass spectrometry (HRMS) was performed at Boston College, Chestnut Hill, MA. Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO2, 230 x 450 Mesh) purchased from Silicycle, or using a Biotage ® Automated Liquid Chromatography System Isolera One ® using Biotage ® SNAP KP-Sil 25-50g silica gel cartridges. Thin layer chromatography was performed on 25 μm silica gel glass or aluminum backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), cerium ammonium molybdate (CAM), or potassium permanganate (KMnO4). Analytical chiral gas-liquid chromatography (GLC) was performed on an Agilent Technologies 6850 Series chromatograph with a flame ionization detector, and a Supelco β-Dex 120 column with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Chromatograph equipped with an auto sampler and a Waters photoiodide array detector with isopropanol or methanol as the modifier. Tetrahydrofuran, dichloromethane, and diethyl ether were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina

columns after being purged with argon. Commercially available reagents were used as received, with the exception of bis(neopentyl glycolato) diboron which was recrystallized before use.

B. Experimental Procedures and Characterization

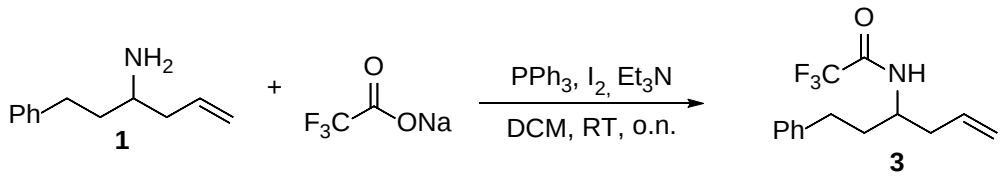
Synthesis of 1: 1-phenylhex-5-en-3-amine



To a flame dried round bottom flask in the glovebox was added allyl B(pin) (1.10 equiv, 0.59 mL, 3.13 mmol). The flask was sealed and brought out of the glovebox. Under nitrogen, EtOH (2.6 mL) was added and the reaction mixture was cooled to 0°C in an ice bath and NH_4OAc (1.10 equivs, 241 mg, 3.13 mmol) was added. This mixture was stirred for 30 minutes and then an additional portion of EtOH (2.6 mL) and aldehyde (1.00 equiv, 0.38 mL, 2.85 mmol) were added. This mixture was stirred overnight at room temperature. To the reaction was added 1M HCl, and ether. The ether layer was put aside and the aqueous layer was basicified with 3M NaOH, and extracted 5x with DCM. DCM extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5-10% DIPA in hexanes) to afford the product as a pale yellow oil (221 mg, 44%). Spectral data are in agreement with the literature[20].

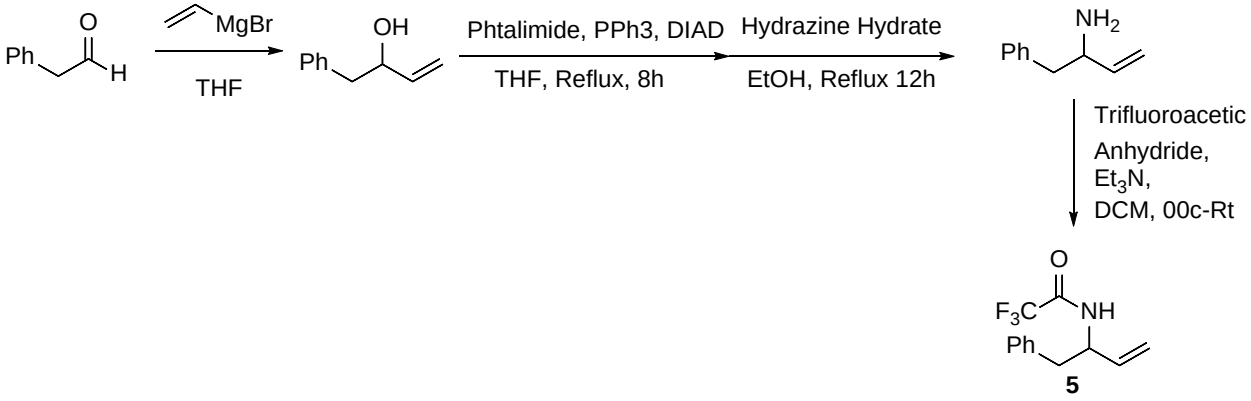
[20] Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, 126 (23), 7182-7183

Synthesis of 3: 2,2,2-trifluoro-N-(1-phenylhex-5-en-3-yl)acetamide



To a solution of PPh_3 (1.00 equiv, 449 mg, 1.71 mmol) in dry DCM (43 mL) under nitrogen, I_2 (1.00 equiv., 434 mg, 1.71 mmol) was added, followed by sodium trifluoroacetate (1.00 equiv, 233 mg, 1.71 mmol). The solution was stirred for 45 minutes and amine **1** (1.00 equiv, 299 mg, 1.71 mmol) was added followed by Et_3N (1.0 equiv, 0.24 mL, 1.7 mmol). The mixture was allowed to stir at room temperature overnight, then was quenched with sat. aq. sodium thiosulfate and 10% aqueous HCl. The mixture was diluted with water and additional DCM. The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford the product (134 mg, 29%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.79-1.85 (m, 1H), 1.88-1.93 (m, 1H), 2.26-2.30 (m, 1H), 2.34-2.38 (m, 1H), 2.66 (t, 2H, J = 8.25 Hz), 4.06-4.11 (m, 1H), 5.08-5.14 (m, 2H), 5.68-5.75 (m, 1H) 5.88-6.03 (s, br, 1H) 7.14-7.20 (m, 3H), 7.26-7.29 (m, 2H)

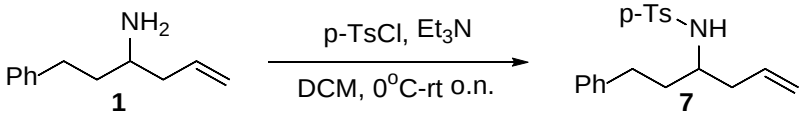
Synthesis of 5: 2,2,2-trifluoro-N-(1-phenylbut-3-en-2-yl)acetamide



To a stirred solution of PPh_3 (1.00 equiv., 1.73g, 6.61 mmol) and phthalimide (1.00 equiv., 972 mg, 6.61 mmol) in dry THF (22 mL) under nitrogen was added allylic alcohol (1.00 equiv., 979 mg, 6.6 mmol) that had been prepared by the same method as compound **30**. DIAD (1.00 equiv., 1.30 mL, 6.61 mmol) was added dropwise, and the reaction was refluxed for 8 hours. The solvent was removed *in vacuo,* and the residue was taken up in ether. Precipitated solids were filtered off, and the filtrate was concentrated *in vacuo* to a yellow oil which was purified by flash chromatography on silica gel (5-20% EtOAc in hexanes) to afford the pure product (1.41g, 77%). This material was taken up in EtOH and hydrazine monohydrate (3.00 equiv., 0.74 mL, 15.25 mmol) was added. the mixture was refluxed for 12 hours then quenched with 1M HCl. EtOH was removed *in vacuo,* and 2 M NaOH and water were added until the mixture was at a pH of ~10. The aqueous layer was extracted 3x with EtOAc, and organic extracts were washed with brine and dried over $MgSO_4$. The organic extracts were concentrated *in vacuo* to afford the pure product (450 mg, 60%). This material was taken up in DCM (15 mL) and Et_3N (3.0 equiv, 0.63 mL, 4.5 mmol) was added. After stirring at 0°C for 5 minutes, trifluoroacetic anhydride (1.5 equiv., 0.32 mL, 2.3 mmol) was added, and the reaction was stirred for overnight while warming to room temperature. The reaction was then cooled back down to 0°C and quenched with water. Additional DCM was added and the layers were separated. The organic layer was washed 2x with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (10-15% EtOAc in hexanes) to afford the product as a yellow-white solid (308 mg, 79%). Spectral data are in agreement with the literature[21].

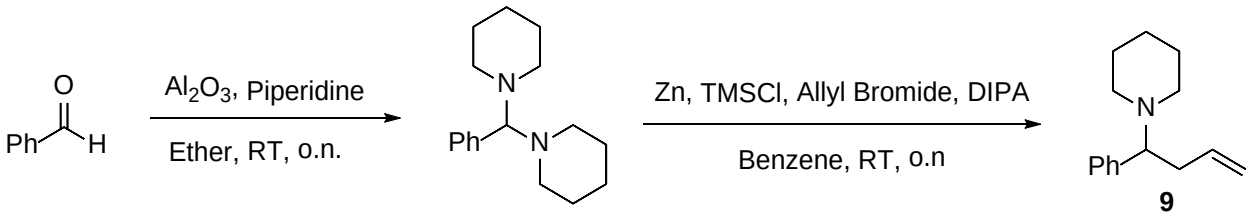
[21] Fässler, A.; Bold, G.; Capraro, H.; Cozens, R.; Mestan, J.; Poncioni, B.; Rösel, J.; Tintelnot-Blomley, M.; Lang, M. *J. Med. Chem.*, **1996**, 39 (16), 3203–3216

Synthesis of 7: 4-methyl-N-(1-phenylhex-5-en-3-yl)benzenesulfonamide



To a flame dried round bottom flask with a stirbar was added tosyl chloride (1.05 equiv., 571 mg, 2.99 mmol). The flask was purged with nitrogen, cooled to 0°C and dry DCM (2.85 mL) was added. Amine (1.00 equiv., 500mg, 2.85 mmol), and Et_3N (3.00 equiv., 1.19 mL, 8.55 mmol) were added and the reaction was stirred overnight while warming to room temperature. The reaction was then diluted with water and Et_2O. The layers were separated and the aqueous layer was extracted 3x with ether. Combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (2-10% EtOAc in hexanes) to afford the pure product (143 mg, 15%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63-1.78 (m, 2H), 2.11 (t, 2H, *J* = 6.5 Hz), 2.42 (s, 3H), 2.47-2.62 (m, 2H), 3.30-3.34 (m, 1H), 4.31 (d, 1H, *J* = 7.00 Hz), 4.95 (d, 1H, *J* = 15.0 Hz), 5.03 (d, 1H, *J* = 10.5 Hz), 5.49-5.55 (m, 1H), 7.04 (d, 2H, *J* = 6.50 Hz), 7.16 (t, 1H, *J* = 7.25 Hz), 7.22-7.28 (m, 4H), 7.71 (d, 2H, *J* = 8.00 Hz)

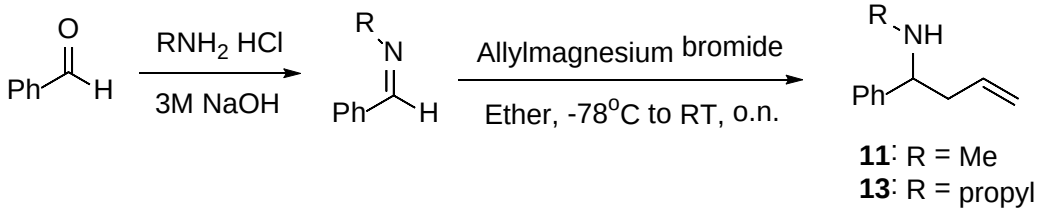
Synthesis of 9: 1-(1-phenylbut-3-en-1-yl)piperidine



To a flame dried round bottom flask with a stirbar was added oven dried basic alumina (1.5 g). The flask was flame dried again and allowed to cool under vacuum, then backfilled with nitrogen. Dry Et_2O (3 mL) and aldehyde (1.00 equiv., 0.39 mL, 3.87 mmol) were added, and the

reaction was cooled to 0°C in an ice bath. Piperidine (2.50 equiv., 0.96 mL, 9.69 mmol) was added and the ice bath was removed. The reaction was allowed to stir overnight at room temperature. The slurry was then filtered through a fritted glass funnel and washed with Et_2O. The resultant white solid was recrystallized from hexanes to afford the pure product as a white solid (280 mg, 28%). Spectral data are in agreement with the literature[22].

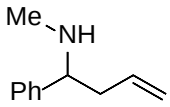
General procedure for synthesis of N-alkyl homallylic amines 11 and 13:



To a round bottom flask with a stirbar was added amine (1.50 equiv.) and 3 M aqueous NaOH (2.0 M with respect to amine). The flask was cooled to 0°C in an ice bath and aldehyde (1.00 equiv.) was added. The reaction was allowed to stir while warming to room temperature overnight. Then, DCM was added, the layers were separated, and the aqueous layer was extracted 3x with DCM. Combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the pure imine product. Without further purification, a portion of the imine was taken up in dry ether in a flame dried round bottom flask with a stirbar and cooled to -78°C. Under nitrogen, allylmagnesium bromide solution (1.0 M in ether, 2.00 equiv.) was added, and the reaction was allowed to stir overnight while warming to room temperature. The reaction was then quenched with sat. aq. NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous

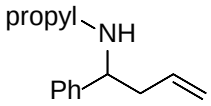
[22] Hatano, B.; Nagahashi, K.; Kijima, T. *J. Org. Chem*. **2008**, 73, 9188-9191

layer was extracted 3x with EtOAc. Combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (5-10% DIPA in hexanes) to afford the products.



11

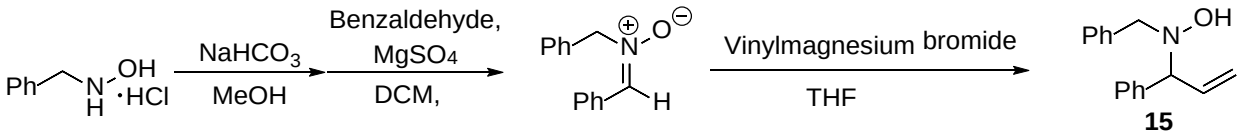
Compound 11: N-methyl-1-phenylbut-3-en-1-amine was prepared according to the general procedure for synthesis of N-alkyl homoallylic amines. (514 mg, 51% over 2 steps). Spectral data are in agreement with the literature[23].



13

Compound 13: 1-phenyl-N-propylbut-3-en-1-amine was prepared according to the general procedure for synthesis of N-alkyl homallyilic amines (956 mg, 60% over 2 steps). Spectral data are in agreement with the literature[14].

Synthesis of 15: N-benzyl-N-(1-phenylallyl)hydroxylamine

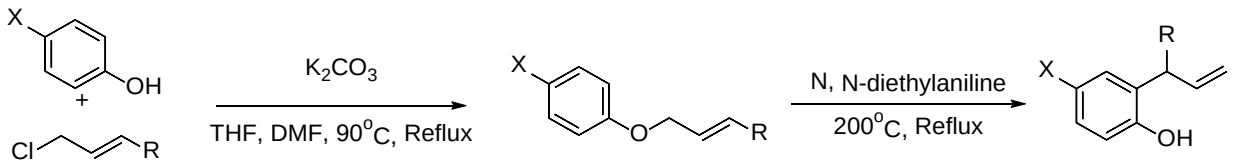


15

[23] Shibata, I.; Nose, K.; Sakamoto, K.; Yasuda, M.; Baba, A. *J. Org. Chem.*, **2004**, 69 (6), 2185–2187

N-hydroxybenzylamine hydrochloride (1.00 equiv., 200 mg, 1.25 mmol) was taken up in methanol (10 mL) and $NaHCO_3$ (1.00 equiv., 105 mg, 1.25 mmol) was added. The mixture was stirred for 30 minutes to ensure freebasing had occurred, and the mixture was concentrated *in vacuo*. The residue was then taken up in DCM (10 mL) and benzaldehyde (1.10 equiv., 0.15 mL, 1.38 mmol) and $MgSO_4$ (2.0 equiv., 300 mg, 2.50 mmol)) were added. The mixture was allowed to stir at room temperature overnight and was filtered and concentrated *in vacuo*. This crude residue was taken up in dry THF (6.25 mL) in a flame dried 20 mL vial with a stirbar, and under nitrogen at 0°C, vinylmagnesium bromide solution (1M in THF, 2.00 equiv., 2.50 mL, 2.50 mmol) was added. The reaction was allowed to stir for 1 hour while warming to room temperature and was then quenched with sat. aq. NH_4Cl and diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted 3x with EtOAc. Combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was triturated with hexane to give the pure product as a white solid (100 mg, 48%). Spectral data are in agreement with the literature[24].

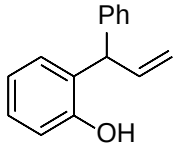
General procedure for synthesis of allylic phenol substrates 17, 19, 21, and 23



17: R = Ph, X = H
19: R = Ph, X = MeO
21: R = Me, X = H
23: R = Ph, X = CF_3

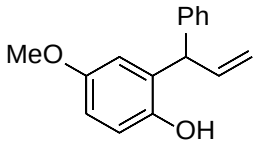
[24] Ishikawa, T.; Kawakami, M.; Fukui, M.; Yamashita, A.; Urano, J.; Saito, S. *J. Am. Chem. Soc.*, **2001**, 123 (31), 7734–7735

A solution of the allyl chloride (1.00 equiv.) in DMF (0.18 M with respect to allyl chloride) was added to a solution of the phenol (1.45 equiv.) and K_2CO_3 in THF (0.18 M with respect to allyl chloride) which was stirring in a round bottom flask equipped with a reflux condenser. The mixture was heated to 90°C and stirred for 4 hours. After 4 hours, the mixture was diluted with ethyl acetate and water. The aqueous layer was extracted 2x with ethyl acetate, and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford the aryl-allyl ether. (reference) This allyl-aryl ether was then taken up in N, N – diethylaniline (1.1 M with respect to allyl-aryl ether) and refluxed at 200°C. After cooling to room temperature, Et_2O was added to the reaction mixture and the organic layer was washed 6x with 1M HCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel to afford the product.



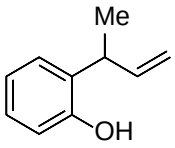
17

Compound 17: 2-(1-phenylallyl)phenol was prepared according to the general procedure for preparation of allylic phenol substrates (685 mg, 52% over 2 steps) ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.82-4.83 (m, 1H), 4.94-5.02 (m, 2H), 5.227(d, 1H, *J* = 9.50 Hz), 6.28-6.35 (1H, m), 6.79 (d, 1H, *J* = 9.50 Hz), 6.89 (t, 1H, *J* = 7.50 Hz), 7.05-7.07 (m, 1H), 7.12-7.15 (m, 1H), 7.12-7.24 (m, 3H), 7.29-7.32 (m, 2H)



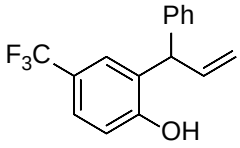
19

Compound 19: 4-methoxy-2-(1-phenylallyl)phenol was prepared according to the general procedure for preparation of allylic phenol substrates (906 mg, 37% over 2 steps) ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (s, 3H), 4.49 (s, 1H,), 4.91 (d, 1H, *J* = 6.00 Hz), 4.98-5.02 (m, 2H), 5.26-5.29 (m, 1H), 6.26-6.32 (m, 1H), 6.64-6.74 (m, 4H), 7.20-7.24 (m, 2H), 7.28-7.31 (m, 2H)



21

Compound 21: 2-(but-3-en-2-yl)phenol was prepared according to the general procedure for preparation of allylic phenol substrates (755 mg, 40% over 2 steps). Spectral data are in agreement with the literature[25].



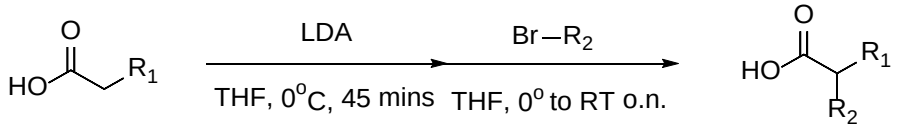
23

Compound 23: 2-(1-phenylallyl)-4-(trifluoromethyl)phenol was prepared according to the general procedure for preparation of allylic phenol substrates (38 mg, 18% over 2 steps) ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (d, 1H, *J* = 7.00 Hz), 5.01 (d, 1H, *J* = 17.5 Hz), 5.13 (s, 1H), 6.26-6.33

[25] Vekariya, R. H.; Liu, R.; Aubé, J. *Org. Lett.*, **2014**, 16 (7), 1844–1847

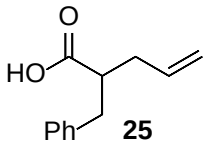
(m, 1H), 6.86 (d, 1H, *J* = 8.00 Hz), 7.18 (d, 2H, *J* = 7.50 Hz), 7.26 (d, 1H, *J* = 7.00 Hz), 7.31-7.36 (m, 3H), 7.40 (d, 1H, *J* = 8.00 Hz)

Synthesis of alkenyl carboxylic acid substrates 25 and 27:



25: R_1 = Bn, R_2 = allyl
27: R_1 = vinyl, R_2 = Bn

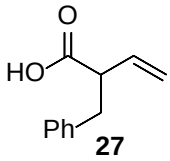
To a solution of DIPA (2.04 equiv.) in THF (2.41 M with respect to DIPA) under nitrogen at 0°C was added n-BuLi (2.5 M in hexanes, 2.04 equiv.). Carboxylic acid (1.00 equiv.) and the mixture was allowed to stir at 0°C for 45 minutes. Then, bromide (1.02 equiv) was added and the mixture was allowd to stir overnight while slowly warming to room temperature. The reaction was quenched and purified by flash chromatography on silica gel (10-50% EtOAc in hexanes) to afford the products as pale yellow oils.



25

Compound 25: 2-benzylpent-4-enoic acid was prepared according to the general procedure for synthesis of carboxylic acid substrates (1.48 g, 78%). Spectral data are in agreement with the literature[26].

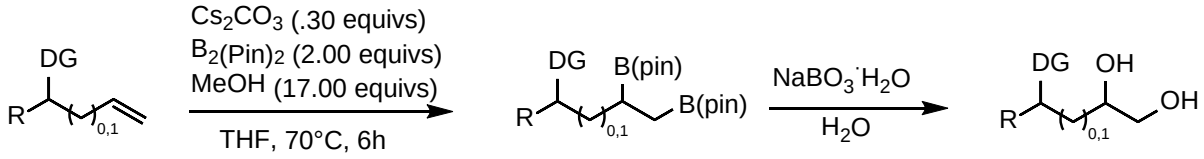
[26] Wang, L.; Thai, K.; Gravel, M. *Org. Lett.*, **2009**, 11 (4), 891–893



27

Compound 27: 2-benzylbut-3-enoic acid was prepared according to the general procedure for synthesis of carboxylic acid substrates (500 mg, 24%) Spectral data are in agreement with the literature[27].

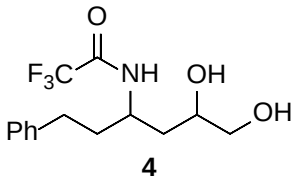
General procedure for directed diboration/oxidation of alkenyl amides, amines, and phenols



To an oven dried 2-dram vial with a stirbar was added substrate (1.0 equiv., 0.50 mmol), $B_2(pin)_2$ (2.00 equiv., 254 mg, 1.00 mmol), THF (1 mL, 0.5 M with respect to substrate) and cesium carbonate (0.3 equivs, 49 mg, 0.15 mmol). Methanol (17 equiv., 0.34 mL, 8.5 mmol) was added, and the vial was sealed and heated at 70°C in an oil bath while stirring for 6-18 hours. After 6-18 hours, the reaction mixture was transferred to a 20 mL vial with ~1 mL THF and placed into an ice bath. ~ 1 mL of water was added, and sodium perborate (5.00 equiv., 500 mg, 2.50 mmol) was added. After stirring for an additional hour, the reaction was quenched with sat. aq. sodium thiosulfate and diluted with water and EtOAc. The aqueous layer was acidified to pH ≈ 1 with 1M HCl. The aqueous layer was extracted 3x with EtOAc. The combined organic extracts were

[27] Nodwell, M.; Pereira, A.; Riffell, J. L.; Zimmerman, C.; Patrick, B. O.; Roberge, M,; Andersen, R. J. *J. Org. Chem.*, **2009**, 74 (3), 995–1006

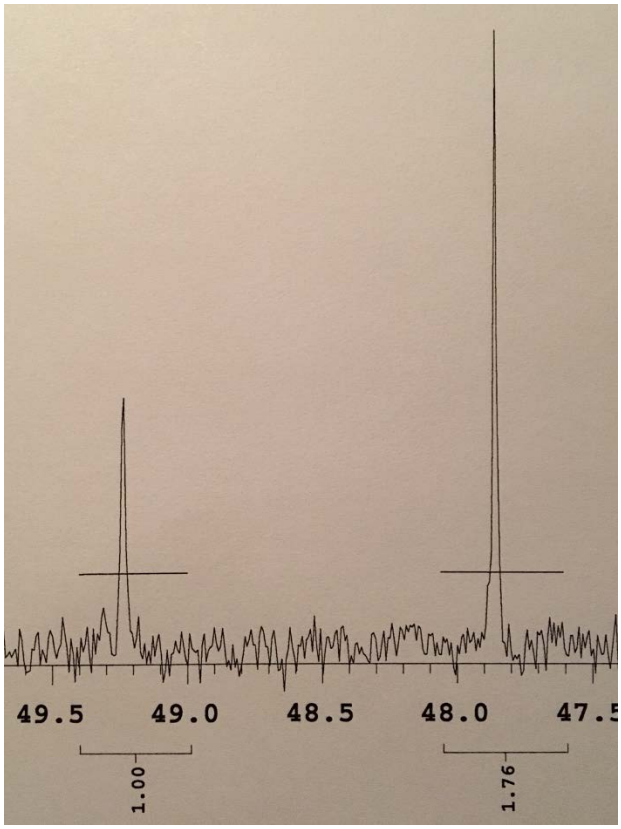
concentrated *in vacuo* and purified by flash chromatography on silica gel (15-100% EtOAc in hexanes) to afford the product.

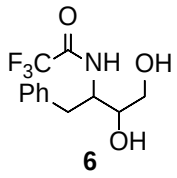


4

Compound 4: N-(5,6-dihydroxy-1-phenylhexan-3-yl)-2,2,2-trifluoroacetamide was prepared according to the general procedure for directed diboration of alkenyl amides, amines, and phenols, and was isolated as a mixture of diastereomers (98 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53-1.76 (m, 2H), 1.89-2.07 (m, 2H), 2.63-2.68 (m, 2H), 3.19 (s, br, 1H) 3.42-3.46 (m, 1H), 3.59-3.65 (m, 1H), 3.78-3.82 (m, 1H), 4.08-4.23 (m, 1H), 6.77 (s, br, 1H), 6.98 (s, br, 1H), 7.14-7.20 (m, 3H), 7.26-7.29 (m, 2H)

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{13}C NMR signals corresponding to the carbinol carbon atoms. Diastereomer ratio was determined to be approximately 1.8:1. The major diastereomer was not determined.



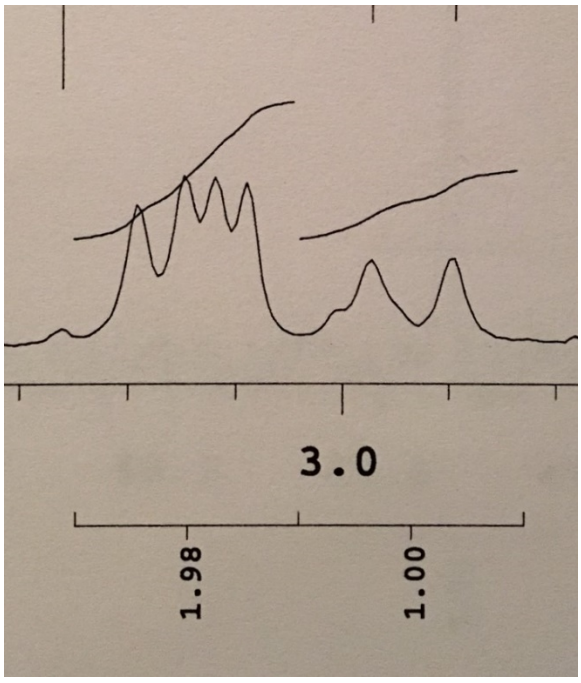


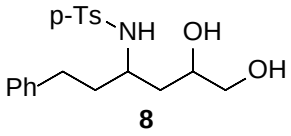
6

Compound 6: N-(3,4-dihydroxy-1-phenylbutan-2-yl)-2,2,2-trifluoroacetamide was prepared according to the general procedure for directed diboration of alkenyl amides, amines, and phenols, and was isolated as a mixture of diastereomers (17 mg, 25%). ^{1}H NMR (500 MHz, $CDCl_3$): 2.98-3.00 (m, 1H, minor), 3.03-3.06 (m, 1H, major), 3.35 (s, 1H), 3.40-3.54 (m, 1H), 3.60-3.63 (m, 1H,

major), 3.70-3.76 (m, 2H), 3.80-3.82 (m, 1H, minor), 4.21-4.22 (m, 1H, minor), 4.27-4.30 (m, 1H, major), 5.11 (s, 1H), 6.77 (s, br, 1H), 7.20-7.26 (m, 2H), 7.27-7.34 (m, 3H)

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{1}H NMR signals corresponding to the carbinol protons. Diastereomer ratio was determined to be approximately 2:1. The major diastereomer was not determined.



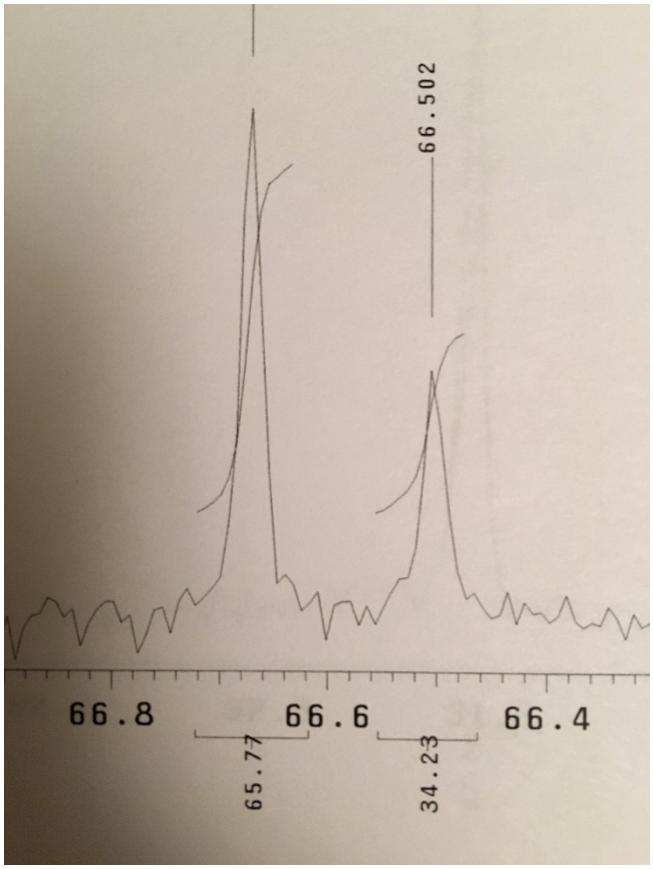


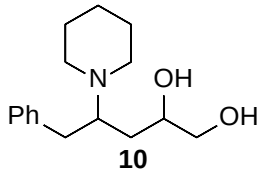
8

Compound 8: N-(5,6-dihydroxy-1-phenylhexan-3-yl)-4-methylbenzenesulfonamide was prepared according to the general procedure for directed diboration of alkenyl amides, amines, and phenols, and was isolated as a mixture of diastsereomers (94 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (t, 1H, *J* = 12.0 Hz), 1.54-1.74 (3H, m), 2.31-2.42 (m, 5H), 3.33-3.57 (m, 3H), 3.74

(s, br, 1H), 4.04-4.07 (m, 1H), 5.38 (d, 1H, *J* = 9.00 Hz), 5.65 (d, 1H, *J* = 7.00 Hz), 6.93 (d, 1H, *J* = 7.00 Hz), 7.12 (d, 1H, *J* = 7.50 Hz), 7.14-7.26 (m, 5H), 7.71 (d, 2H, *J* = 8.00 Hz)

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{13}C NMR signals corresponding to the carbinol carbon atoms. Diastereomer ratio was determined to be approximately 1.9:1. The major diastereomer was not determined.



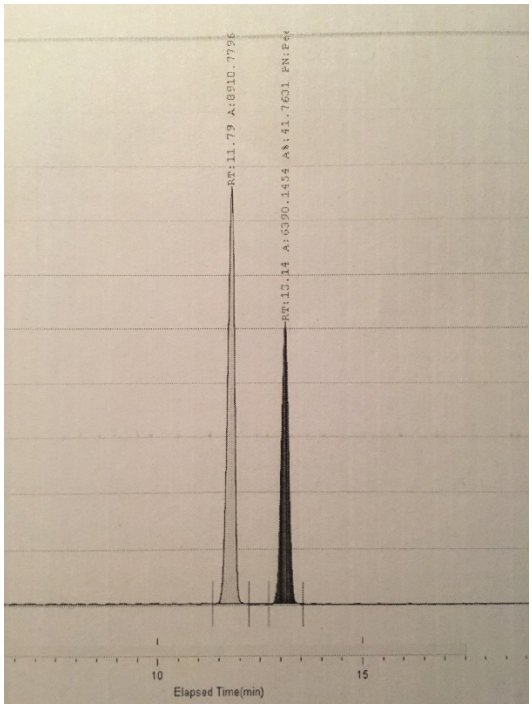


10

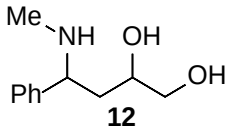
Compound 10: 5-phenyl-4-(piperidin-1-yl)pentane-1,2-diol was prepared according to the general procedure for directed diboration of alkenyl amides, amines, and phenols, and was isolated

as a mixture of diastereomers. (116 mg, 93%) (Note: since H_2O_2 was used as the oxidant in the reaction, it was possibly isolated as the N-oxide) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (t, 1H, *J* = 11.3 Hz), 1.54-1.89 (m, 4H), 2.11-2.12 (m, 1H), 2.61-2.73 (m, 2H), 3.43-3.47 (m, 1H), 3.53-3.57 (m, 1H), 3.59-3.68 (m, 1H, minor), 3.78-3.79 (m, 1H, major), 3.89-3.90 (m, 1H, minor), 3.90-3.95 (m, 1H, major), 4.00 (d, 1H, minor, *J* = 2.00 Hz), 4.65 (d, 1H, *J* = 9.00 Hz, minor), 4.79 (d, br, 1H), 5.09-5.11 (m, 2H), 7.11-7.18 (m, 2H), 7.31-7.38 (m, 3H)

Proof of Stereochemistry: Diastereomer ratio was determined by SFC analysis. Diastereomer ratio was determined to be approximately 1.9:1. The major diastereomer was not determined.



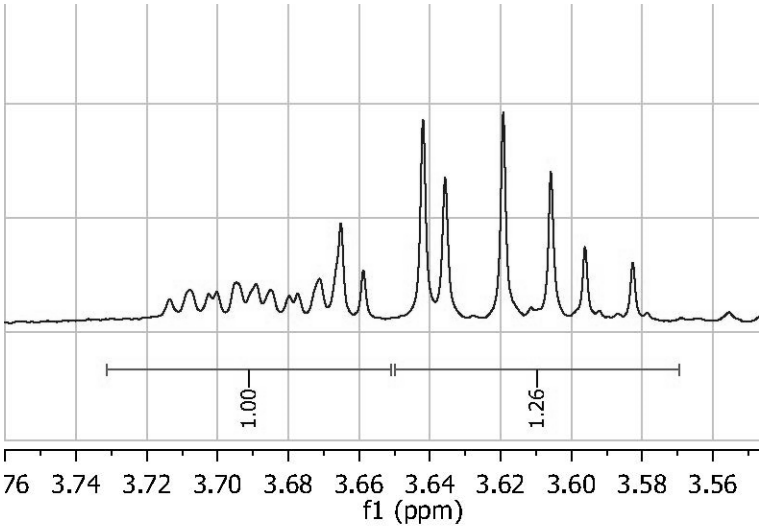
Peak Info			
Peak No	% Area	Area	RT (min)
1	58.2369	8910.7796	11.79
2	41.7631	6390.1454	13.14
Total:	100	15300.925	

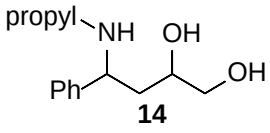


12

Compound 12: 4-(methylamino)-4-phenylbutane-1,2-diol was prepared according to the general procedure for directed diboration of alkenyl amides, amines, and phenols. Due to its polarity, it was not isolated, but dr was determined by analysis of the reaction crude ^{1}H NMR.

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{1}H NMR signals corresponding to the carbinol protons. Diastereomer ratio was determined to be approximately 1.3:1. The major diastereomer was not determined.

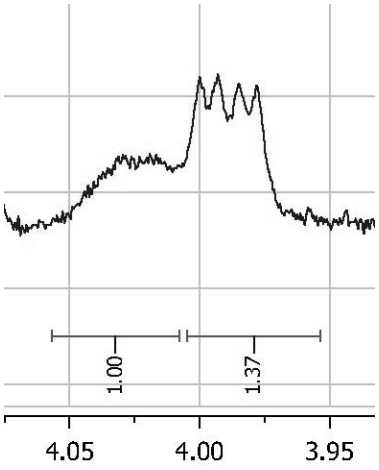


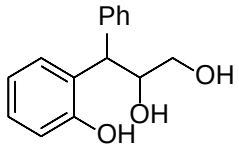


14

Compound 14: 4-phenyl-4-(propylamino)butane-1,2-diol was prepared according to the general procedure for directed diboration of alkenyl amides, amines, and phenols. Due to its polarity, it was not isolated, but dr was determined by analysis of the reaction crude ^{1}H NMR.

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{1}H NMR signals corresponding to the carbinol protons. Diastereomer ratio was determined to be approximately 1.2:1. The major diasteromer was not determined.

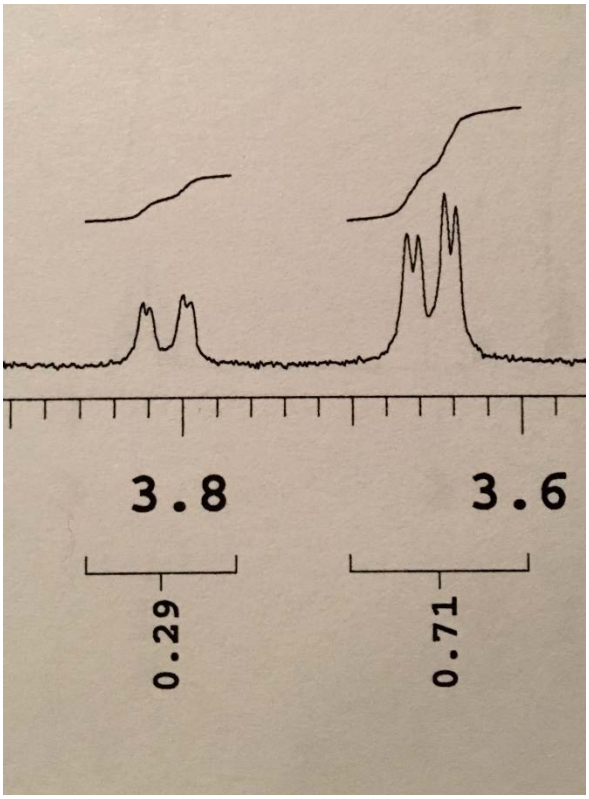


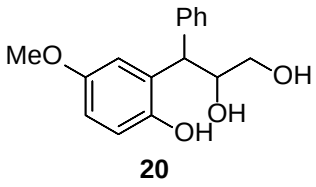


18

Compound 18: 3-(2-hydroxyphenyl)-3-phenylpropane-1,2-diol was prepared according to the general procedure for directed diboration of alkenyl amides, amines, and phenols, and isolated as a mixture of diastereomers. (91 mg, 75%) ^{1}H NMR (500 MHz, D_2O): δ 3.45-3.51 (m, 1H), 3.66 (d, 1H, *J* = 11.0 Hz, major), 3.81 (d, 1H, *J* = 12.0 Hz, minor), 4.27 (d, 1H, *J* = 5.50 Hz, major), 4.41 (d, 1H, J = 4.00 Hz, minor), 4.51-4.57 (m, 1H), 4.69 (s, br, 1H), 6.76-6.98 (m, 4H), 7.05-7.93 (m, 5H)

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{1}H NMR signals corresponding to the carbinol protons. Diastereomer ratio was determined to be approximately 2.4:1. The major diastereomer was not determined.

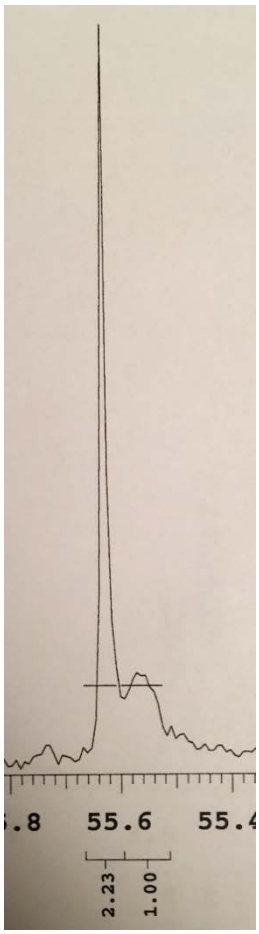


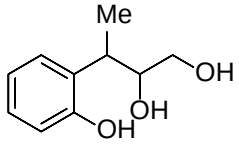


20

Compound 20: 3-(2-hydroxy-5-methoxyphenyl)-3-phenylpropane-1,2-diol was prepared according to the general procedure for directed diboration of alkenyl amides, amines, and phenols, and was isolated as a mixture of diastereomers (103 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.47-3.53 (m, 1H), 3.70 (s, 3H), 4.24 (d, 1H, *J* = 6.5 Hz), 5.36-5.40 (m, 1H), 4.52-4.54 (m, 1H), 6.61-6.64 (m, 1H), 6.70-6.75 (m, 1H), 6.83-6.85 (m, 1H), 7.21-7.38 (m, 5H)

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{13}C NMR signals corresponding to the aryl methoxy group carbon atoms. Diastereomer ratio was determined to be approximately 2.4:1. The major diastereomer was not determined.



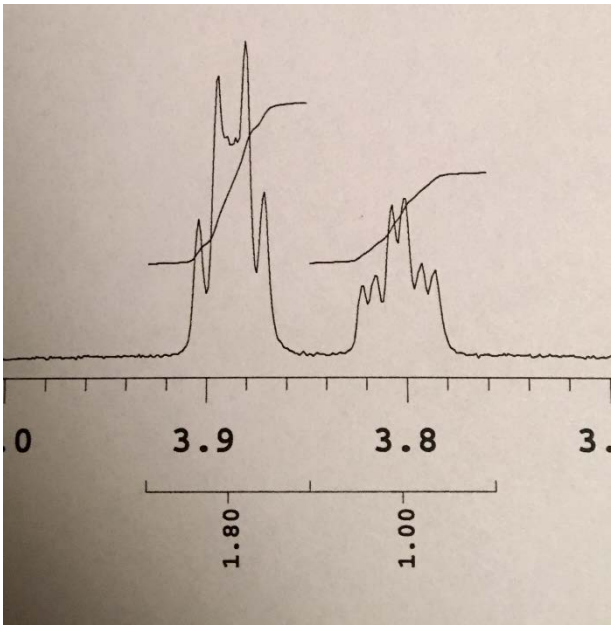


22

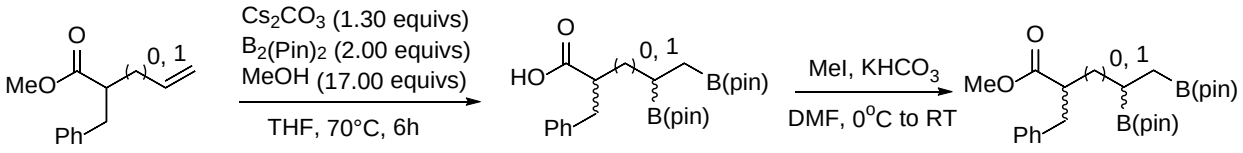
Compound 22: 3-(2-hydroxyphenyl)butane-1,2-diol was prepared according to the general procedure for directed diboration of alkenyl amides, amines, and phenols, and was isolated as a

mixture of diastereomers (71 mg, 78%). ^{1}H NMR (500 MHz, CD_3OD): δ 1.33 (d, 3H, *J* = 7.00 Hz), 3.17-3.26 (m, 1H), 3.33-3.49 (m, 2H), 3.79-3.82 (m, 1H, minor), 3.87-3.90 (m, 1H, major), 6.77-6.81 (m, 2H), 7.01-7.06 (m, 1H), 7.14 (t, 1H, *J* = 4.00 Hz)

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{1}H NMR signals corresponding to the carbinol protons. Diastereomer ratio was determined to be approximately 1.8:1. The major diastereomer was not determined.

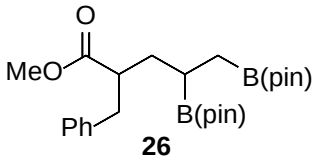


General procedure for directed diboration/oxidation of alkenyl carboxylic acids:



To an oven dried 2-dram vial with a stirbar was added (1 equiv., 0.50 mmol), $B_2(pin)_2$ (2 equiv., 254 mg, 1.00 mmol), THF (1 mL, 0.5 M with respect to substrate) and cesium carbonate (0.3 equiv., 49 mg, 0.15 mmol). Methanol (17 equiv., 0.34 mL, 8.5 mmol) was added, and the vial was sealed and heated at 70°C in an oil bath while stirring for 6-18 hours. After 6-18 hours, the

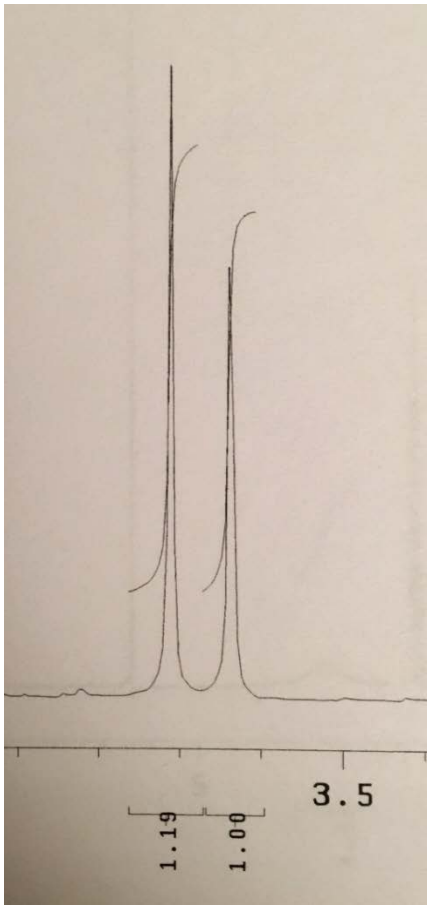
solvent was removed and the residue was taken up in DMF (0.4 M with respect to starting material) and cooled to 0°C. $KHCO_3$ (1.10 equiv.) and methyl iodide (2.00 equiv.) were added and the mixture was allowed to stir overnight while warming to room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ and diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted 3x with EtOAc. Combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford the product.

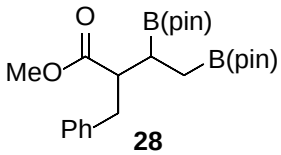


26

Compound 26: methyl 2-benzyl-4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate was prepared according to the general procedure for directed diboration of alkenyl carboxylic acids, and was isolated as a mixture of diastereomers (49 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82-0.87 (m, 2H), 1.14-1.26 (m, 25H), 1.54 (m, 1H, major), 1.64-1.70 (m, 1H), 1.88 (m, 1H, minor), 2.71-2.89 (m, 3H), 3.53 (s, 3H, minor), 3.54 (s, 3H, major), 7.14-7.17 (m, 3H), 7.22-7.26 (m, 2H)

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{1}H NMR signals corresponding to the ester methyl group protons. Diastereomer ratio was determined to be approximately 1.2:1. The major diastereomer was not determined.



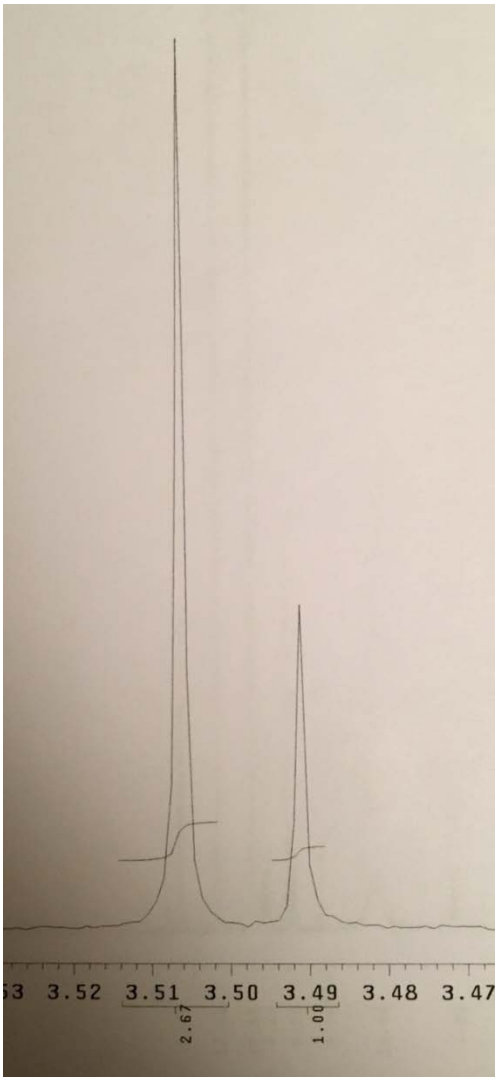


28

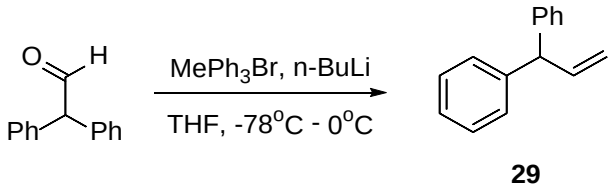
Compound 28: methyl 2-benzyl-3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate was prepared according to the general procedure for directed diboration of alkenyl carboxylic acids and was isolated as a mixture of diastereomers (57 mg, 51%) ^{1}H NMR (500 MHz,

$CDCl_3$): δ 0.77-0.84 (m, 2H), 0.92-1.03 (m, 1H), 2.72-2.80 (m, 1H, minor), 2.81-2.86 (m, 1H, major), 2.91-3.00 (m, 1H), 3.09-3.16 (m, 1H, minor), 3.23-3.30 (m, 1H, major), 3.49 (s, 3H, minor), 3.51 (s, 3H, major), 7.02-7.09 (m, 1H,), 7.10-7.25 (m, 3H), 7.29-7.32 (m, 1H)

Proof of Stereochemistry: Diastereomer ratio was determined by analysis of the relative strengths of ^{1}H NMR signals corresponding to the ester methyl group protons. Diastereomer ratio was determined to be approximately 2.7:1. The major diastereomer was not determined.



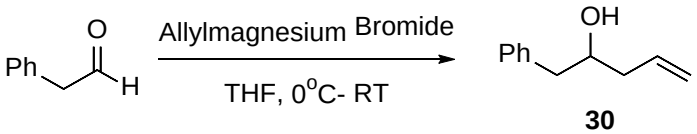
Preparation of competition experiment substrate 29: prop-2-ene-1,1-diyldibenzene



29

To an oven dried round bottom flask with a stirbar in a glovebox was added $MePPh_3Br$ (1.00 equiv, 714 mg, 2.00 mmol). The flask was sealed and removed from the glovebox, and under nitrogen dry THF (8.8 mL was added.) This solution was cooled to -78°C, and n-BuLi was added (2.5 M in hexane, 1.1 equivs, 0.85 mL, 2.1 mmol). The solution was allowed to stir for 2 hours while warming to room temperature slowly. The reaction was cooled back down to -78°C, and, a solution of aldehyde (1.0 equiv, 0.35 mL, 2.0 mmol) in THF (1.8 mL) was added dropwise. The reaction mixture was then allowed to stir for 24 hours while slowly warming to room temperature. After 24 hours, Et_2O was added to the reaction mixture and precipitates were filtered out. The ethereal filtrate was washed 3x with water, 1x with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford the product (265 mg, 68%). Spectral data were in agreement with the literature[28].

Synthesis of 30: 1-phenylpent-4-en-2-ol

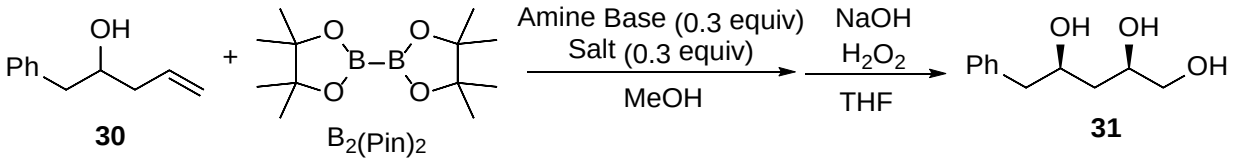


30

[28] López-Pérez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.*, **2009**, 11 (23), 5514–5517

To a flame dried round bottom flask with a stirbar was added allylmagnesium bromide solution (1.0 M in ether, 1.50 equivs, 18.5 mL, 18.492 mmol) under nitrogen. The flask was cooled to 0°C and a solution of aldehyde (1.00 equiv, 1.4 mL, 12.328 mmol) in THF (16.4 mL) was added dropwise. The reaction was allowed to stir overnight while slowly warming to room temperature. The reaction was quenched with sat. aq. NH_4Cl and diluted with water and EtOAc. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on Silica gel (5-15% EtOAc in hexanes) to afford the product as a pale yellow oil (1.042 g, 52%). Spectral data were in agreement with the literature[29].

General procedure for amine base/salt additive screen:

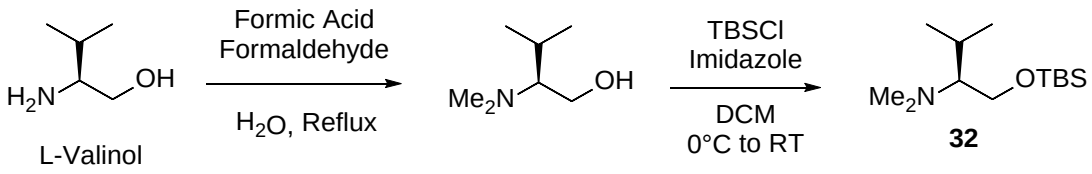


To an oven dried 2-dram vial with a stirbar was added substrate (1 equiv, 0.50 mmol), $B_2(pin)_2$ (2 equiv, 254 mg, 1.00 mmol), MeOH (1 mL, 0.5 M with respect to substrate) salt (0.3 equiv., 0.015 mmol), and base (0.3 equiv., 0.015 mmol). The vial was sealed and heated at 70°C in an oil bath while stirring for 6-18 hours. After 6-18 hours, the reaction mixture was transferred to a 20 mL vial with ~1 mL THF and placed into an ice bath. ~ 1 mL of 3M NaOH was added, and ~1 mL of 30% aq. H_2O_2 was added. After stirring for another 4 hours while warming to room temperature the reaction was quenched with sat. aq. sodium thiosulfate and diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted 3x with EtOAc. The

[29] Tan, X.; Shen, B.; Deng, W.; Zhao, H.; Liu, L.; Guo, Q. *Org. Lett.* **2003**, *5*, 1833-1835.

combined oganic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Reaction crude product mixture was analyzed by SFC to determine conversion and dr according to the method described in the literature[11].

Synthesis of 32: (S)-1-((tert-butyldimethylsilyl)oxy)-N,N,3-trimethylbutan-2-amine

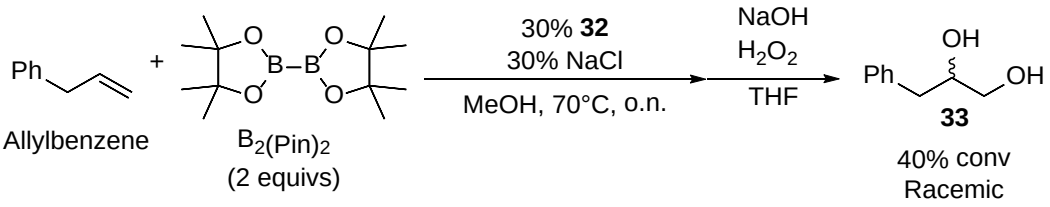


L-Valinol **32**

L-valinol (1.00 equiv., 2.23 mL, 20.0 mmol), water (6.7 mL), and formic acid (4.00 equiv., 3.06 mL, 80.0 mmol) were allowed to stir in a round bottom flask equipped with a reflux condenser and come to a reflux. Formaldehyde solution (37% in water, 1.50 equiv., 5.95 mL, 30.0 mmol) was added dropwise and the reaction was allowed to stir for 6 hours. After cooling to room temperature, the pH was adjusted to >11 with 2M NaOH. The aqueous mixture was extracted with DCM. Organic extracts were dried over MgSO4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (5-20% MeOH in DCM) to afford the amino alcohol product. (1.29 g, 49%). A portion (1.00 equiv., 197 mg, 1.50 mmol) of this material was taken up in DCM (7 mL) and imidazole (9 equiv., 919 mg, 13.5 mmol) was added. The reaction mixture was cooled to 0°C and a solution of TBSCl (3.00 equiv., 678 mg, 4.5 mmol) in toluene (1.5 mL) was added to the mixture. The reaction was allowed to stir overnight while slowly warming to room temperature and quenched with sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted 3x with DCM. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (2% Et_3N in hexanes) to afford the product. (75 mg, 38%) ^1H NMR (500 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.87 (s, 9H), 0.89 (d, 3H, *J* = 6.00 Hz), 0.94 (d, 3H, *J* = 7.00 Hz), 1.83-1.87 (m, 1H), 1.99-

2.03 (m, 1H), 2.32 (s, 6H), 3.64 (dd, 1H, *J* = 10.5 Hz, 5.50 Hz), 3.77 (dd, 1H, *J* = 10.8 Hz, 3.25 Hz)

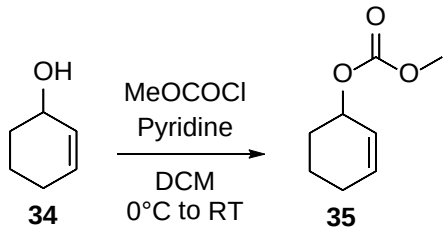
Chiral Amine Catalyzed Diboration of Allylbenzene



Diboration/oxidation was performed according to the general procedure for amine base/salt additive screen. Reaction crude product mixture was analyzed by SFC according to the method described in the literature[5(b)] to determine er.

Synthesis of carbohydrate catalyst derivatives 40a and 40b:

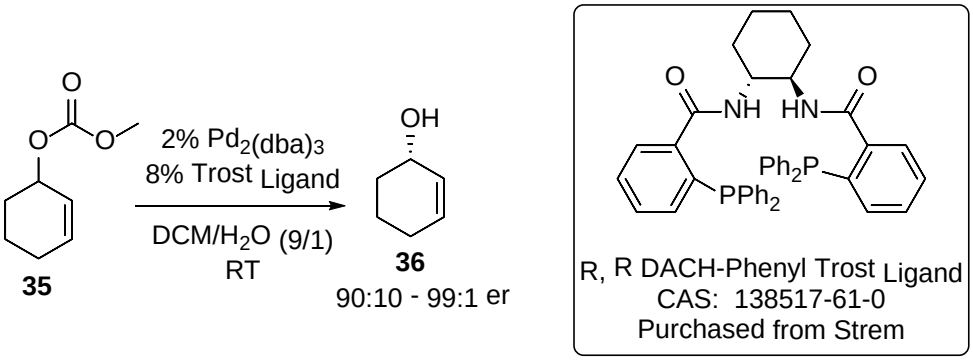
Synthesis of intermediate 35 [cyclohex-2-en-1-yl methyl carbonate]:



To a solution of alcohol **34** (1.00 equiv, 294 mg, 3.00 mmol) in DCM (9.25 mL, 0.325M with respect to alcohol 34) that had been cooled to 0°C in an ice bath was added methyl chloroformate (2.5 equivs, 0.580 mL, 7.50 mmol). The mixture was allowed to stir while warming to room temperature overnight. The reaction mixture was washed with 1M HCl twice, and then sat. aq. $NaHCO_3$. The aqueous layer was extracted an additional time with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was

purified by flash chromatography on silica gel (15% EtOAc in hexane) to afford carbonate **35** as a clear oil. (403 mg, 86%). Spectral data are in agreement with the literature[30].

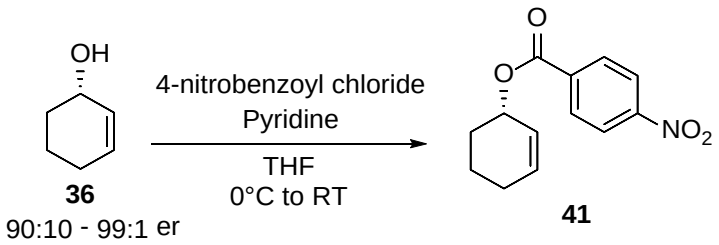
Synthesis of intermediate 36: (S)-cyclohex-2-en-1-ol



In the glovebox, to an oven dried round bottom flask with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (0.02 equivs, 130 mg, 0.12 mmol), and Trost Ligand (0.08 equivs, 330 mg, 0.48 mmol). The flask was sealed and removed from the glovebox. DCM (35 mL) and deoxygenated water (5.0 mL) were added to the flask under nitrogen and the catalyst mixture was allowed to stir. Then a solution of carbonate **35** (1.00 equiv, 936 mg, 6.00 mmol) in DCM (10 mL) was slowly added to the mixture. The reaction was allowed to stir at room temperature overnight, and was then filtered through a short pad of silica, washing with DCM and ether. The filtrate was concentrated *in vacuo* and the crude residue was purified by flash chromatography on silica gel (1:1 Et_2O:pentane) to afford the enantiomerically enriched alcohol **36** as a colorless oil (588 mg, 63%). Spectral data were in agreement with the literature[23]. Enantiomeric purity was determined after conversion to nitrobenzoyl ester **41**.

[30] Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.*, **2006**, 128 (51), 16438–16439

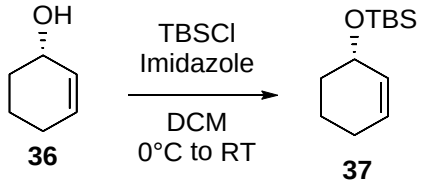
Synthesis of intermediate 41: (S)-cyclohex-2-en-1-yl 4-nitrobenzoate



To a solution of alcohol **36** (1.0 equiv., 31 mg, 0.31 mmol) in THF (0.40 mL) and pyridine (0.075 mL0) that had been cooled to 0°C in an ice bath was added 4-nitrobenzoyl chloride (1.0 equiv., 58 mg, 0.31 mmol). The reaction was allowed to stir while warming to room temperature overnight. THF was removed *in vacuo*, and the crude residue was directly loaded onto a column of silica gel and flash chromatography (DCM) was performed to afford the product as a green-white solid (50 mg, 65%). Spectral data are in agreement with the literature[31].

Proof of stereochemistry: Nitrobenzoyl ester 41 was analyzed by SFC according to the method described in the literature[23]. If the enantiopurity was found to be lower than desired, the ester could be recrystallized from hot hexanes to improve ee to up to 99%.

Synthesis of intermediate 37: (S)-tert-butyl(cyclohex-2-en-1-yloxy)dimethylsilane)

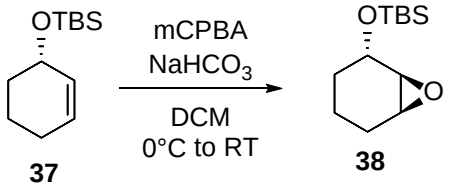


In a round bottom flask with a stirbar, alcohol **36** (1.00 equiv, 294 mg, 3.00 mmol) was taken up in DCM (13.7 mL) and imidazole (9.00 equivs, 1.83 g, 27.0 mmol) was added. The

[31] Shi, E.; Shao, Y.; Chen, S.; Hu, H.; Liu, Z.; Zhang, J.; Wan, X. *Org. Lett.*, **2012**, 14 (13), 3384–3387

reaction was cooled to 0°C in an ice bath and a solution of TBSCl (3.00 equivs, 1.35 g, 9.00 mmol) in toluene (3 mL) was added. The reaction was allowed to stir overnight while slowly warming to room temperature. The reaction was quenched with sat. aq. NH_4Cl, diluted with additional DCM and water, and the aqueous and organic layers were separated. The aqueous layer was extracted 3x with DCM and the combined organic extracts were concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (3% EtOAc in hexanes) to afford silyl ether **37** as a colorless oil (565 mg, 89%). Spectral data are in agreement with the literature[32].

Synthesis of intermediate 38: (((1S,2S,6S)-7-oxabicyclo[4.1.0]heptan-2-yl)oxy)(tert-butyl)dimethylsilane:

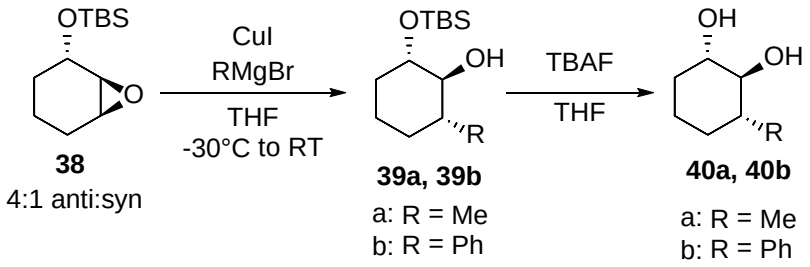


In a round bottom flask with a stirbar, silyl ether **37** (1.00 equiv., 1.64g, 7.73 mmol) was taken up in DCM (40 mL) and $NaHCO_3$ (1.50 equiv., 973 mg, 11.59 mmol) was added. The reaction mixture was cooled to 0°C in an ice bath and mCPBA (50% by weight in water/benzoic acid, 1.50 equiv., 4.13g, 11.59 mmol) was added. 10 mL additional DCM was added and the solution was stirred vigorously for 8 hours. The reaction then filtered through neutral alumina washing with DCM and EtOAc. The filtrate was concentrated *in vacuo* to afford a crude residue that was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford epoxide **38** as a white solid/clear oil (1.587g, 90%). This 4:1 mixture of diastereomers as determined by ^1H

[32] Renaud, P.; Ollivier, C.; Wever, V. *J. Org. Chem.*, **2003**, 68 (14), 5769–5772

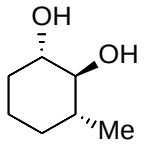
NMR was taken on to the next step. (Note: The major diastereomer was assumed to be the *trans* isomer due to the steric bulk of the OTBS group.) ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.89 (s, 9H), 1.15-1.24 (m, 2H) 1.41-1.48 (m, 1H), 1.69-1.76 (m, 2H), 1.95 (dt, 1H, *J* = 15.0 Hz, 4.60 Hz), 2.99 (d, 1H, *J* = 4.80 Hz, major), 3.12 (d, 1H, *J* = 4.20 Hz, minor) 3.19-3.21 (m, 1H), 3.94-3.96 (m, 1H, major), 3.98-4.02 (m, 1H, minor).

General procedure for opening of epoxide 38:



In the glovebox, to a flame dried vial with a stirbar was added copper iodide. The flask was sealed with a septum and removed from the glovebox. Under nitrogen, THF (1.5 M with respect to Grignard reagent) was added, followed by the addition of the Grignard reagent solution (1.4M in THF/Toluene, 1.5 equiv). The reaction mixture was stirred for 5 minutes, then cooled down to -30°C. A solution of epoxide **38** as a mixture of diastereomers in THF (0.33 M with respect to epoxide) was added dropwise. The reaction was then allowed to slowly warm to room temperature while stirring overnight. The reaction was quenched with sat. aq. NH_4Cl and diluted with ether and water. The aqueous and organic layers were separated and the aqueous layer was extracted 3x with ether. The combined organic extracts were concentrated *in vacuo* and the crude residue was taken up in THF (0. 2 M with respect to starting material) in a round bottom flask, and tetrabutylammonium fluoride hydrate (2 equivs.) was added and the reaction was allowed to stir

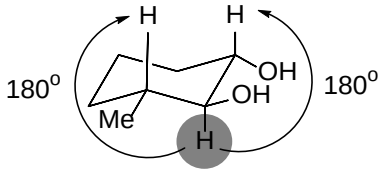
overnight. The reaction was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel (15-100% EtOAc in Hexanes) to afford the product as a white solid.



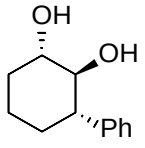
40a

Compound 40a: (1S,2S,3R)-3-methylcyclohexane-1,2-diol was prepared according to the general procedure for opening/deprotection of epoxide **38** (117 mg, 41% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (d, 3H, *J* = 6.00 Hz), 1.05-1.32 (m, 2H), 1.37-1.43 (m, 1H), 1.54-1.66 (m, 2H), 2.14 (m, 2H), 2.93 (t, 1H, *J* = 9.50 Hz), 3.35-3.40 (m, 1H)

Proof of Stereochemistry:



Analysis of the coupling constant for the proton at the 2 position (*J* = 9.50 Hz) was characteristic for vicinal proton-proton coupling with a dihedral angle of 180°.

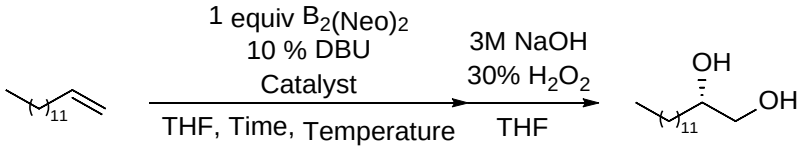


40b

Compound 40b: (1S,2S,3S)-3-phenylcyclohexane-1,2-diol was prepared according to the general procedure for opening/deprotection of epoxide **38** (21 mg, 7% yield over 2 steps). Stereochemistry was assigned by analogy to **40a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41-1.57 (m,

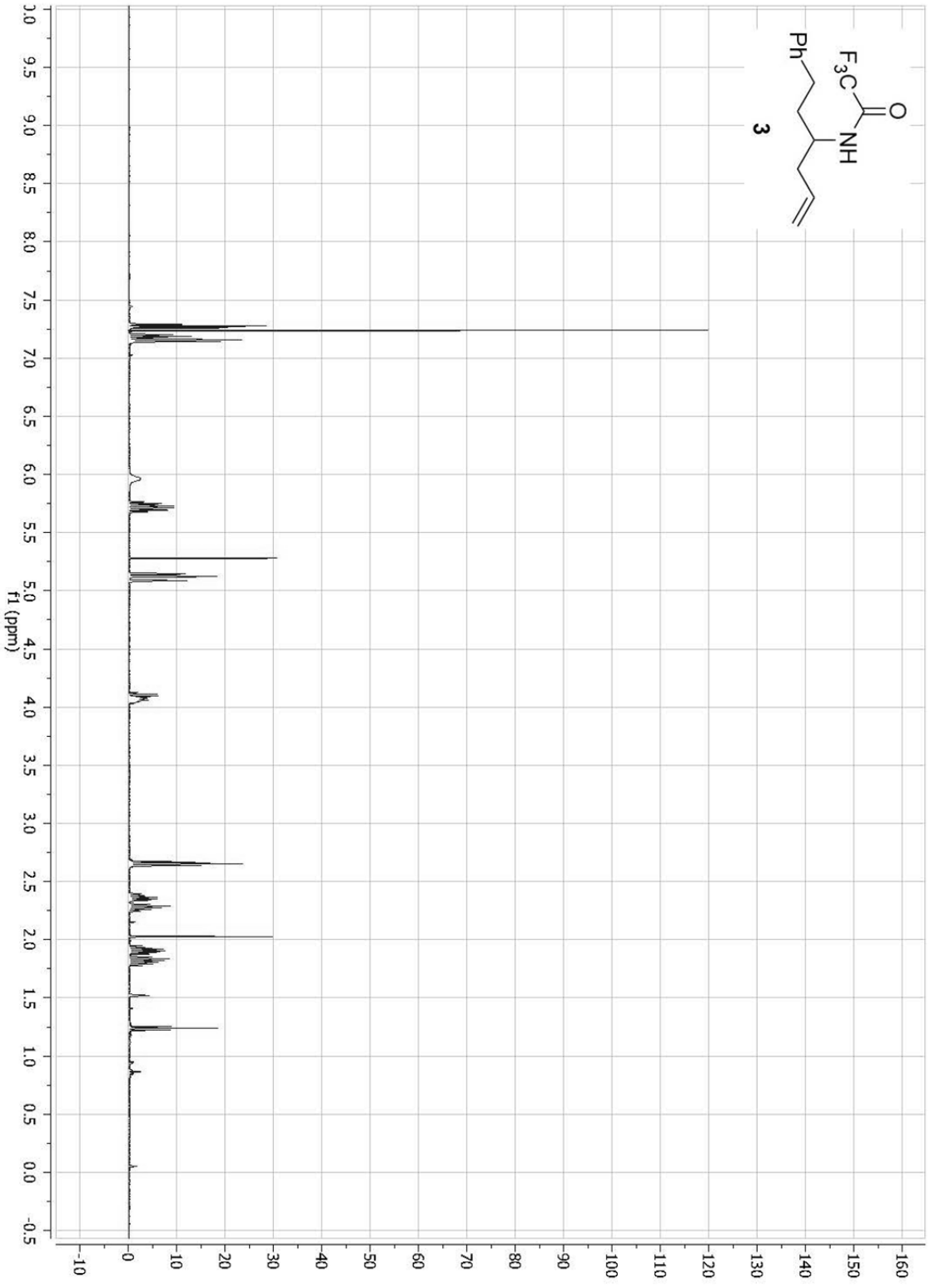
3H), 1.79-1.83 (m, 3H), 2.07 (m, 1H, *J* = 4.75 Hz), 2.48-2.55 (m, 2H), 3.51 (td, 1H, *J* = 9.38 Hz, 2.50 Hz), 3.59-3.60 (1H, m), 7.23-7.25 (m, 3H), 7.31-7.35 (m, 2H)

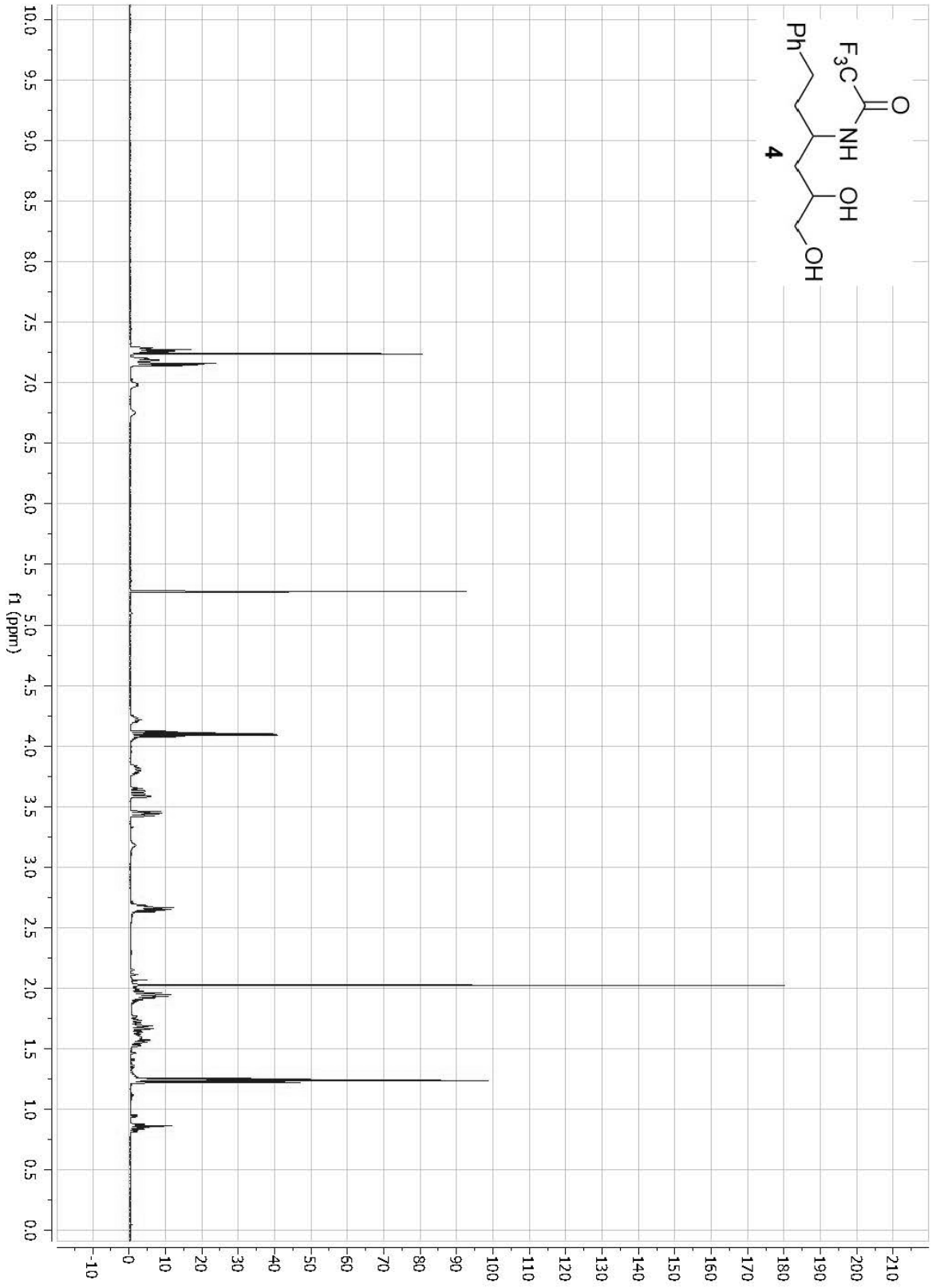
General Procedure for diborations with catalyst analogues and examination of nonlinear effect:



In the glovebox, an oven dried 2-dram vial with a stirbar was charged with catalyst (0.1 equiv. 0.05 mmol) $B_2(Neo)_2$ (1 equiv., 0.5 mmol), THF (0.5M with respect to substrate, 1 mL), 1-tetradecene (1 equiv., 0.5 equiv.) and DBU (0.1 equiv., 0.05 mmol). The vial was sealed, removed from the glovebox and allowed to stir for 24 hours at room temperature. The reaction mixture was then cooled to 0°C in an ice bath and additional THF (1 mL) 3M aqueous sodium hydroxide (2 mL) and 30% aqueous hydrogen peroxide (1 mL) were added. The reaction was allowed to stir for an additional 4 hours while slowly warming to room temperature and then sat. aq. sodium thiosulfate was added. The reaction mixture was diluted with EtOAc and water and the layers were separated. The aqueous layer was extracted 3x with EtOAc and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude reaction mixture. Conversion was determined by crude ^{1}H NMR analysis with reference to a 1,1,2,2-tetrachloroethane internal standard. Er was determined by GC according to the method described in the literature[12].

C. Spectral Data

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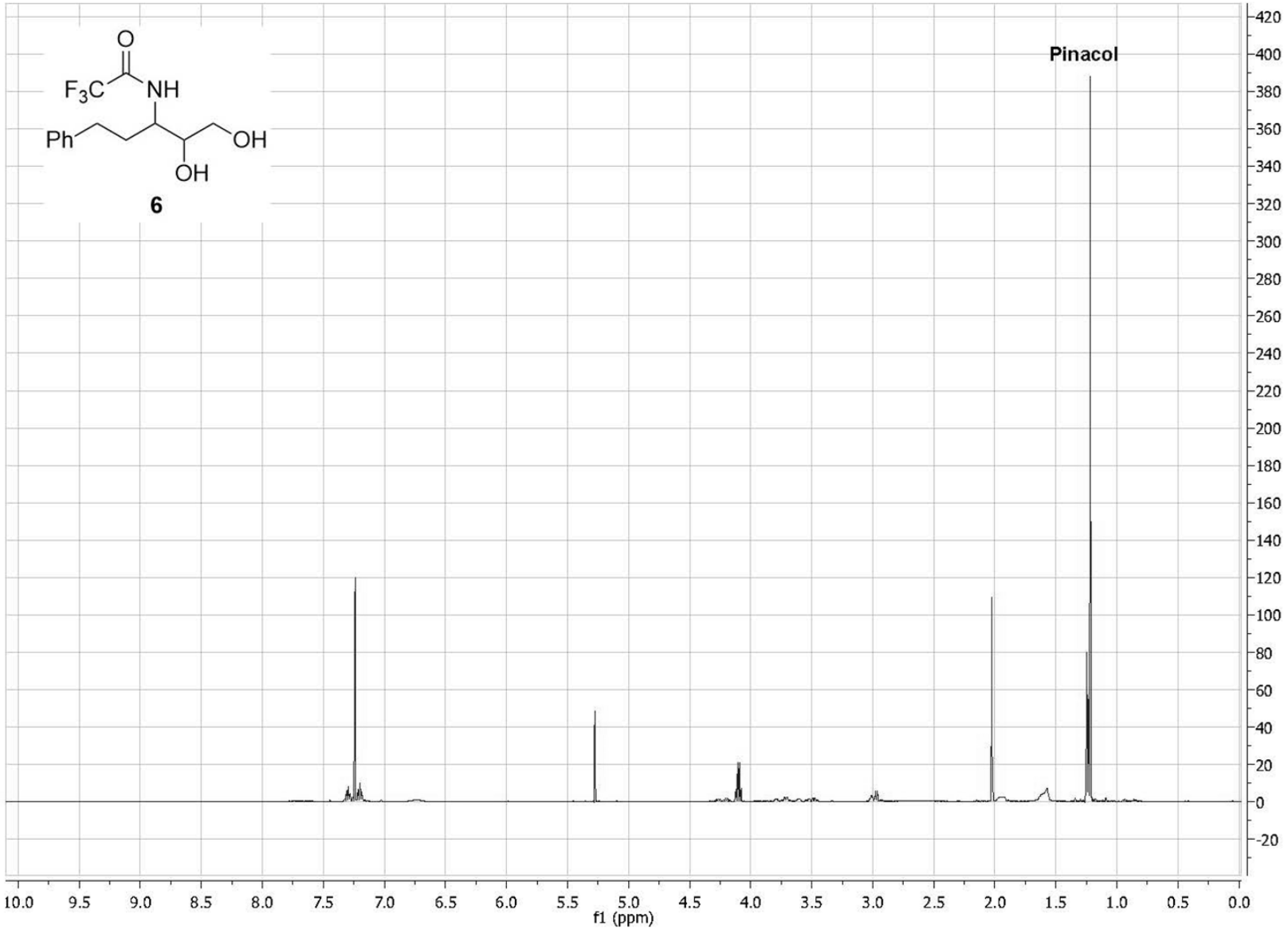
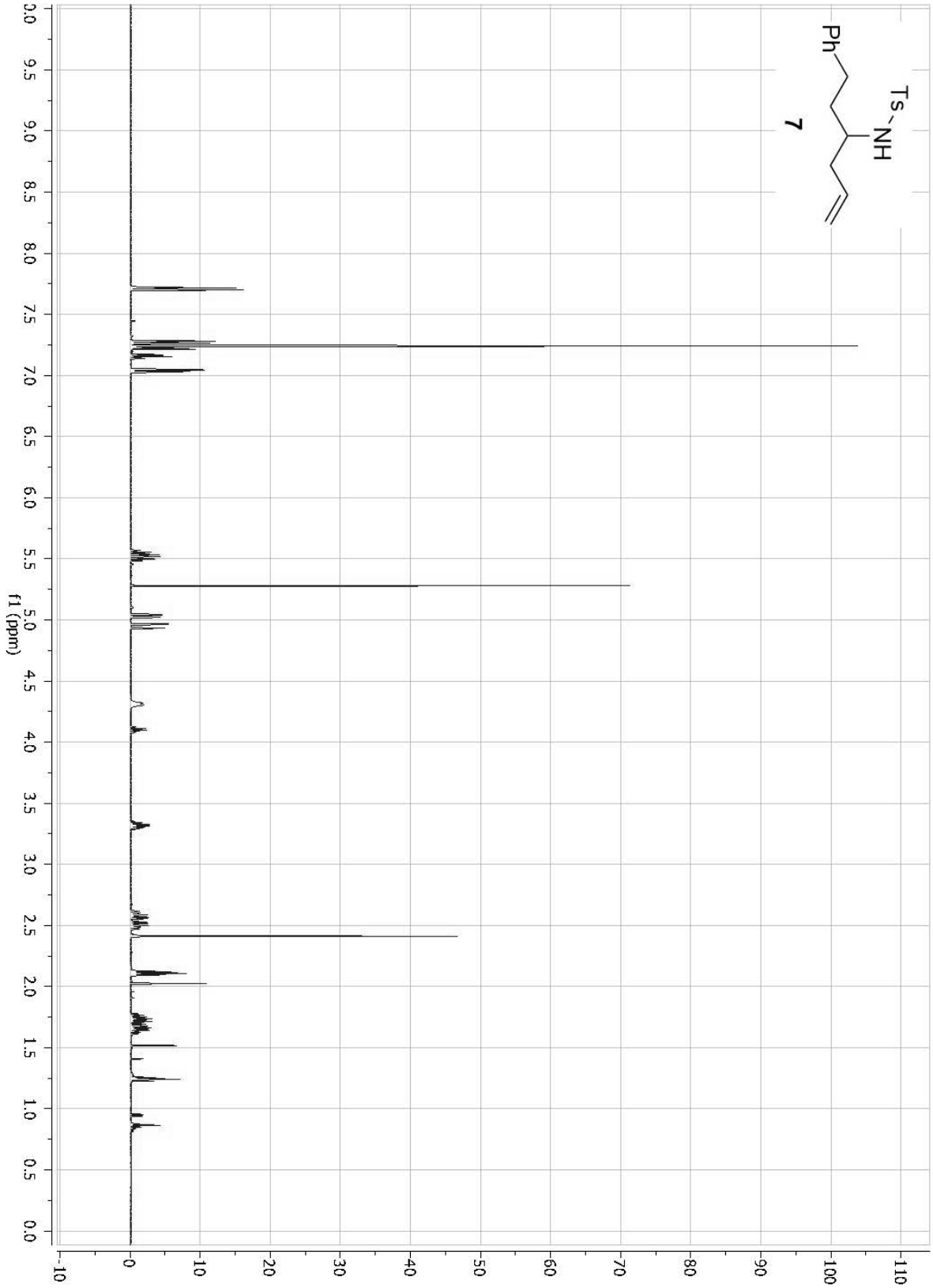
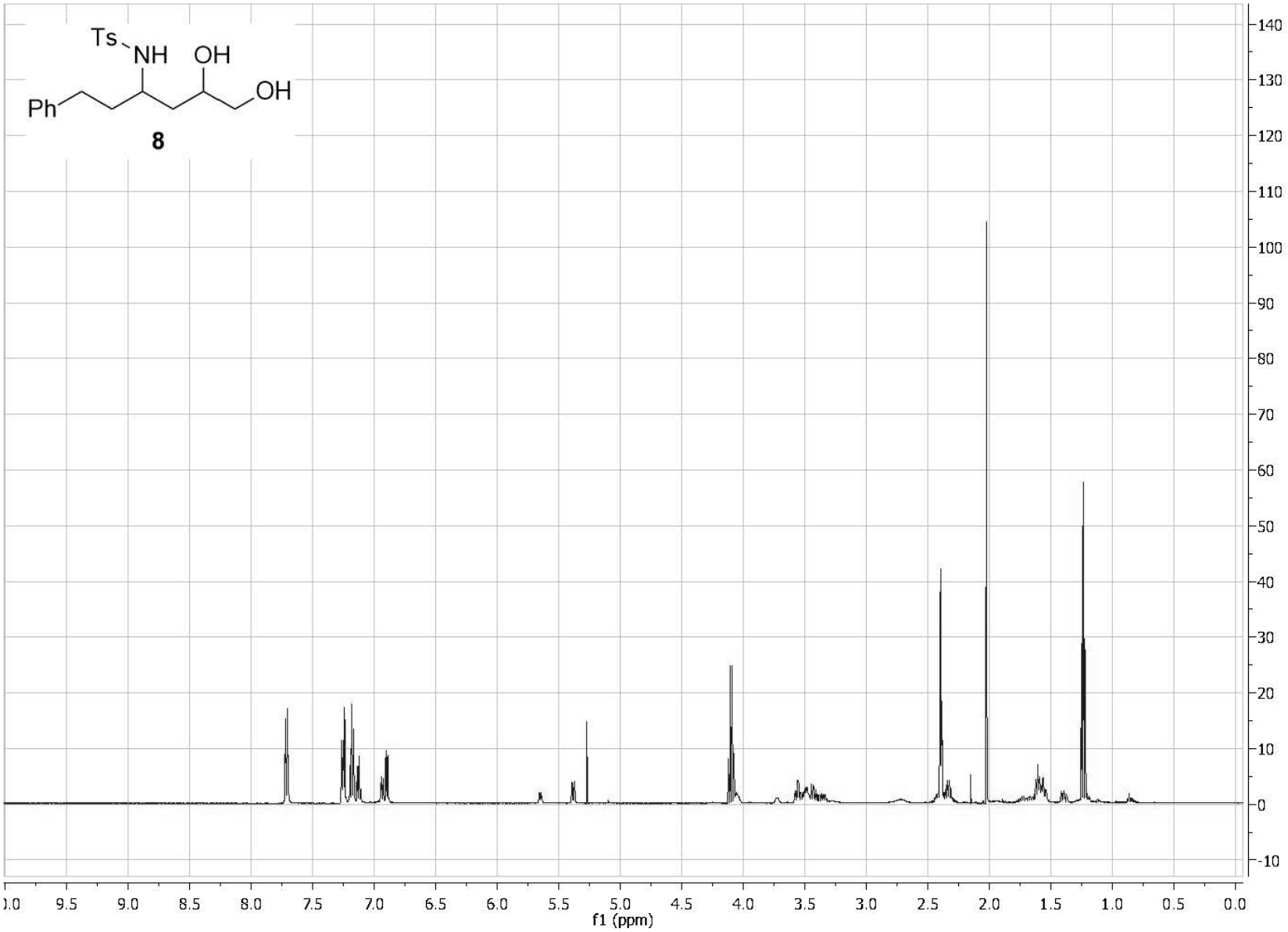
NH
OH
Ph
OH
4
f1 (ppm)


O
F3C
NH
Ph
OH
OH
6
Pinacol
420
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
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)


Ts
NH
Ph
7
f1 (ppm)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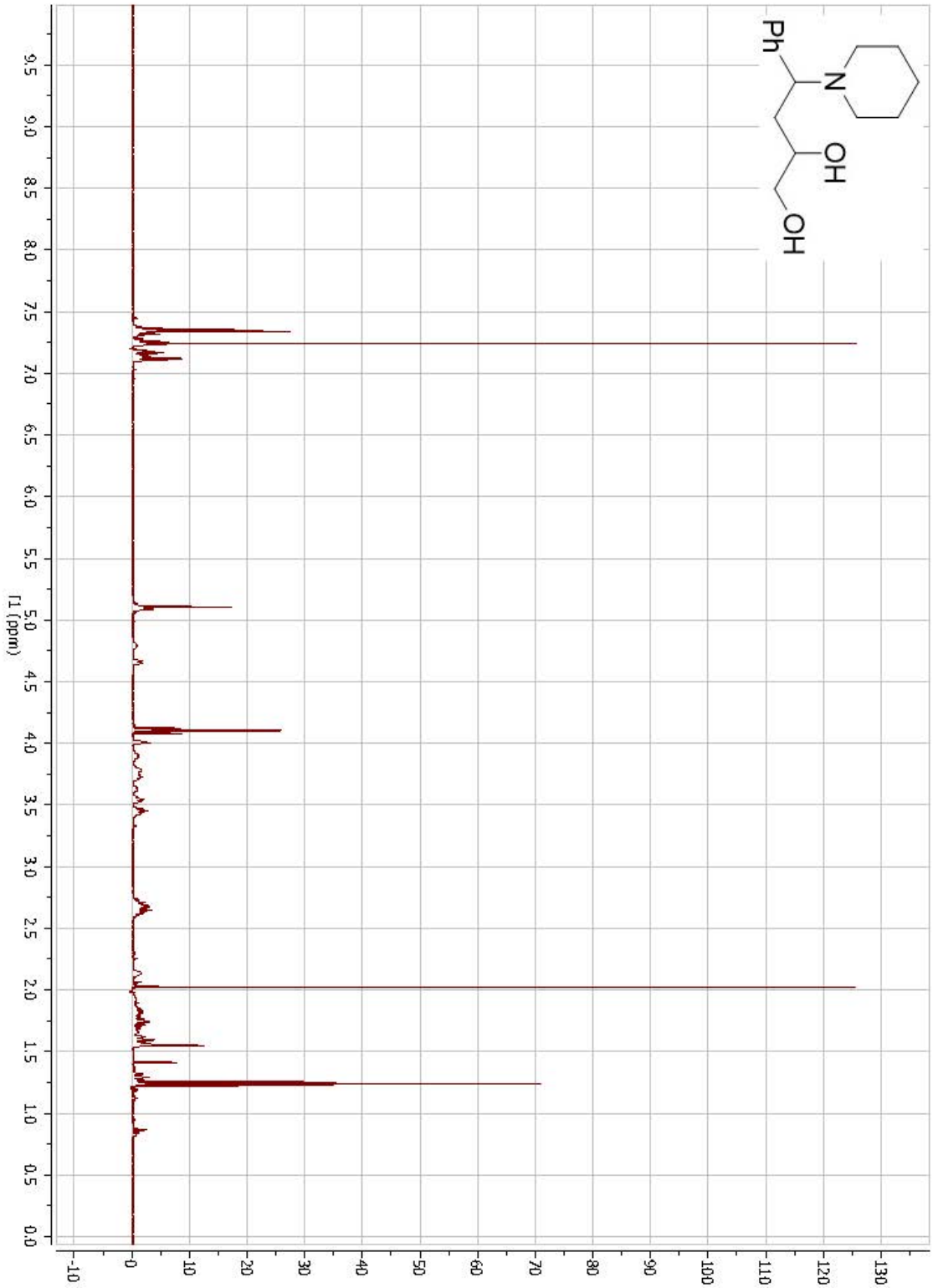
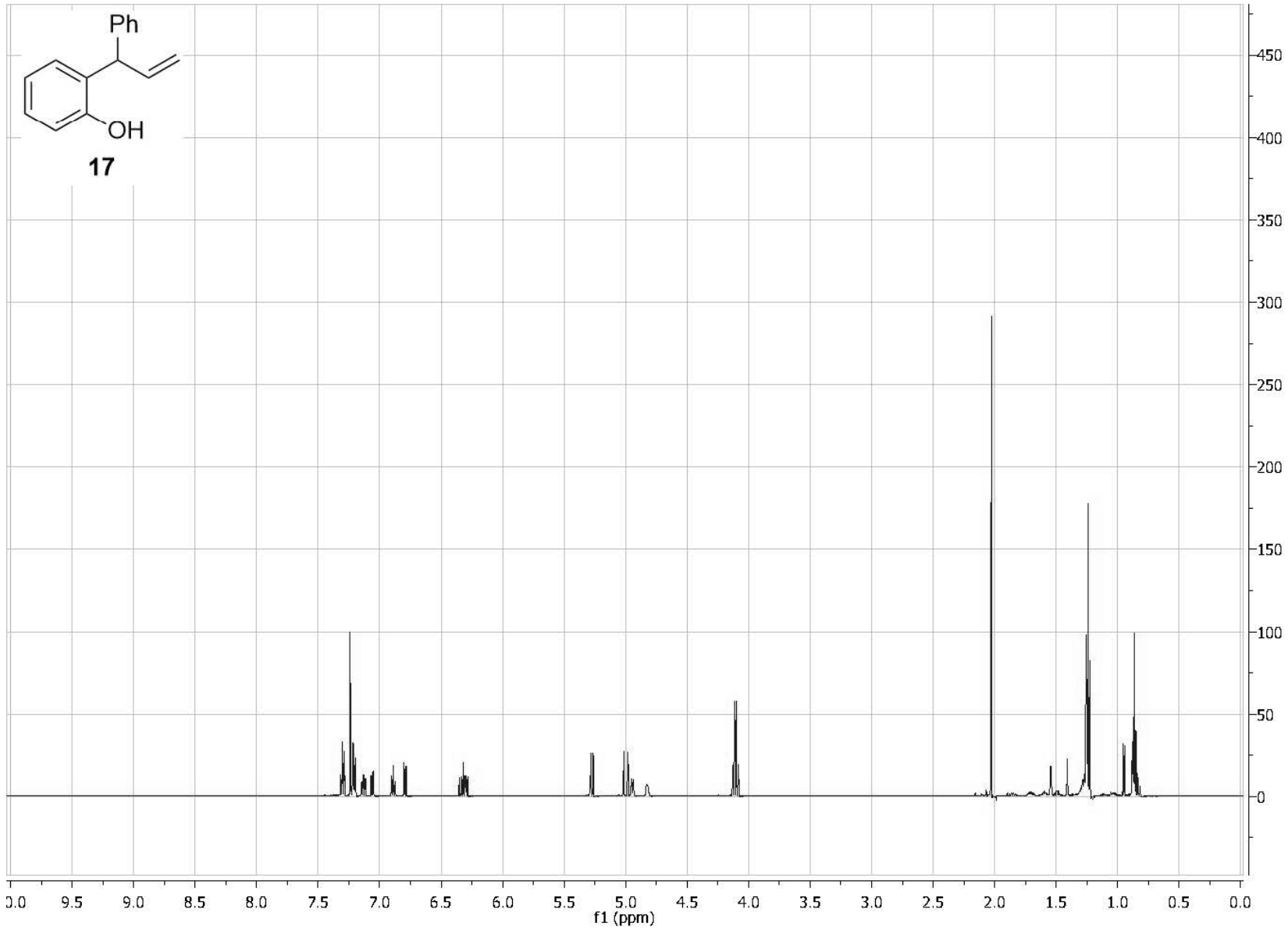
OH
OH
Ph
8
f1 (ppm)


Ph
N
OH
OH
f1 (ppm)


Ph
OH
17
450
400
350
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200
150
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9.5
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8.0
7.5
7.0
6.5
6.0
5.5
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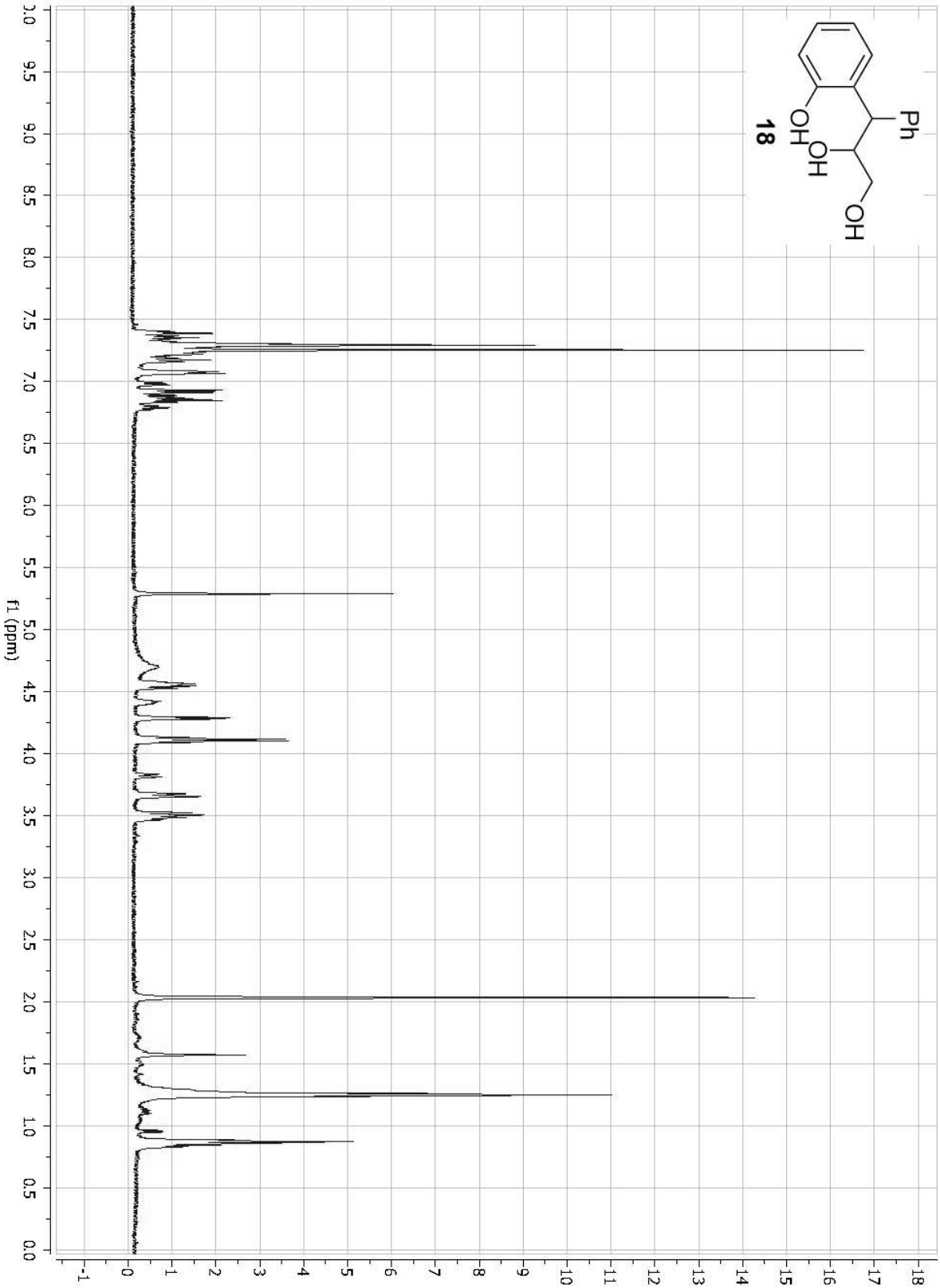
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Ph
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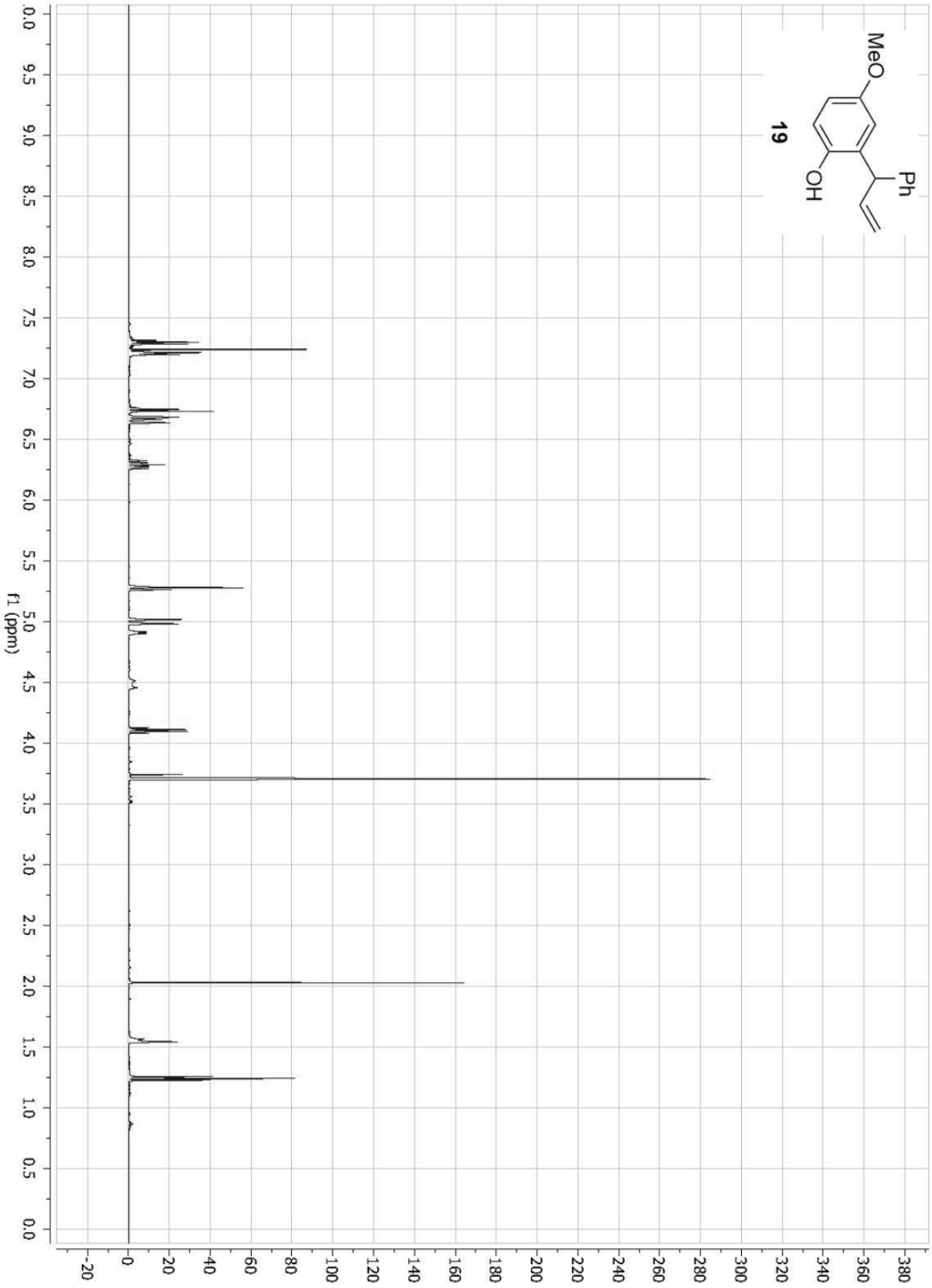
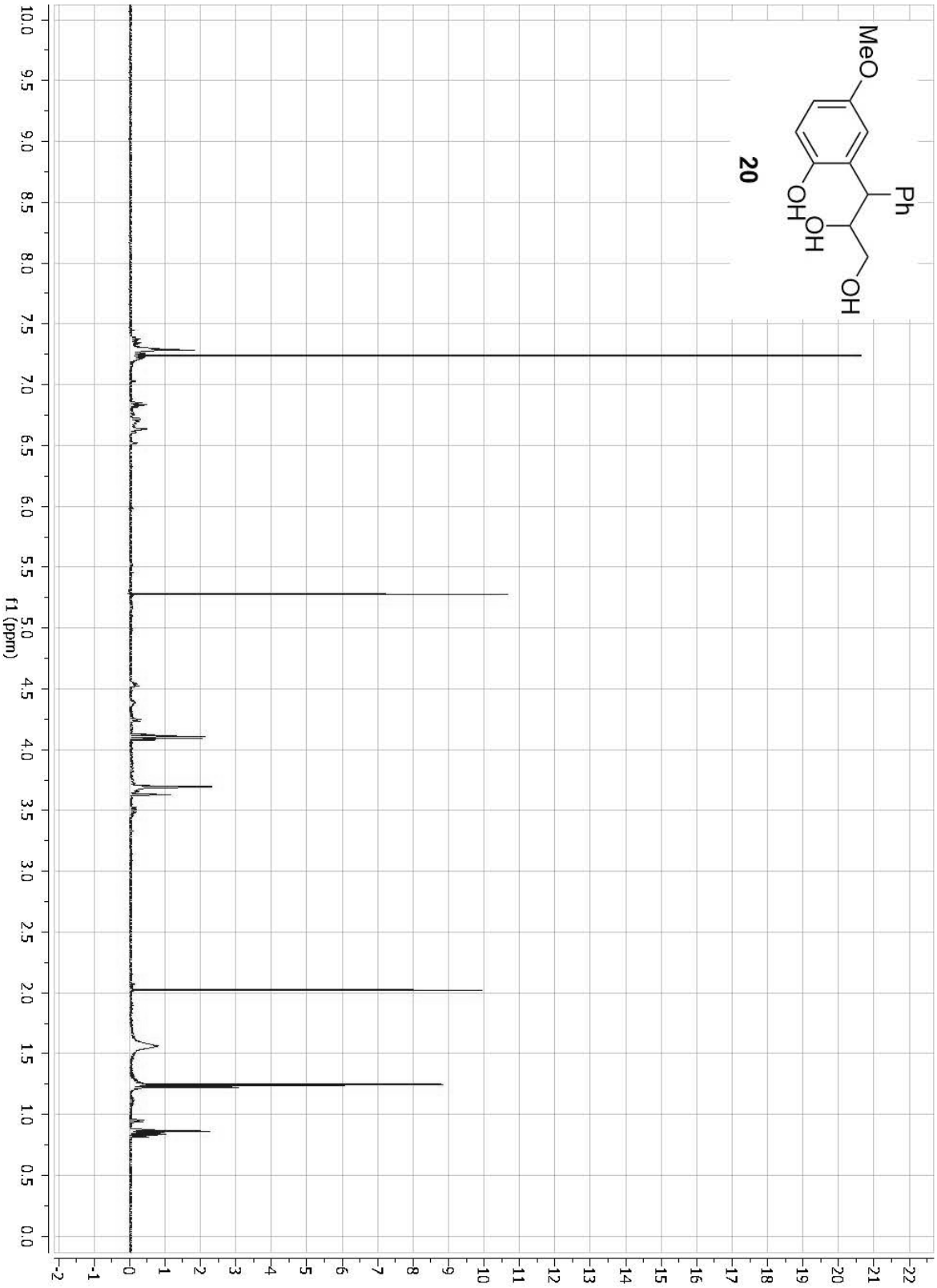
OH
OH
18
f1 (ppm)


MeO
Ph
OH
19
f1 (ppm)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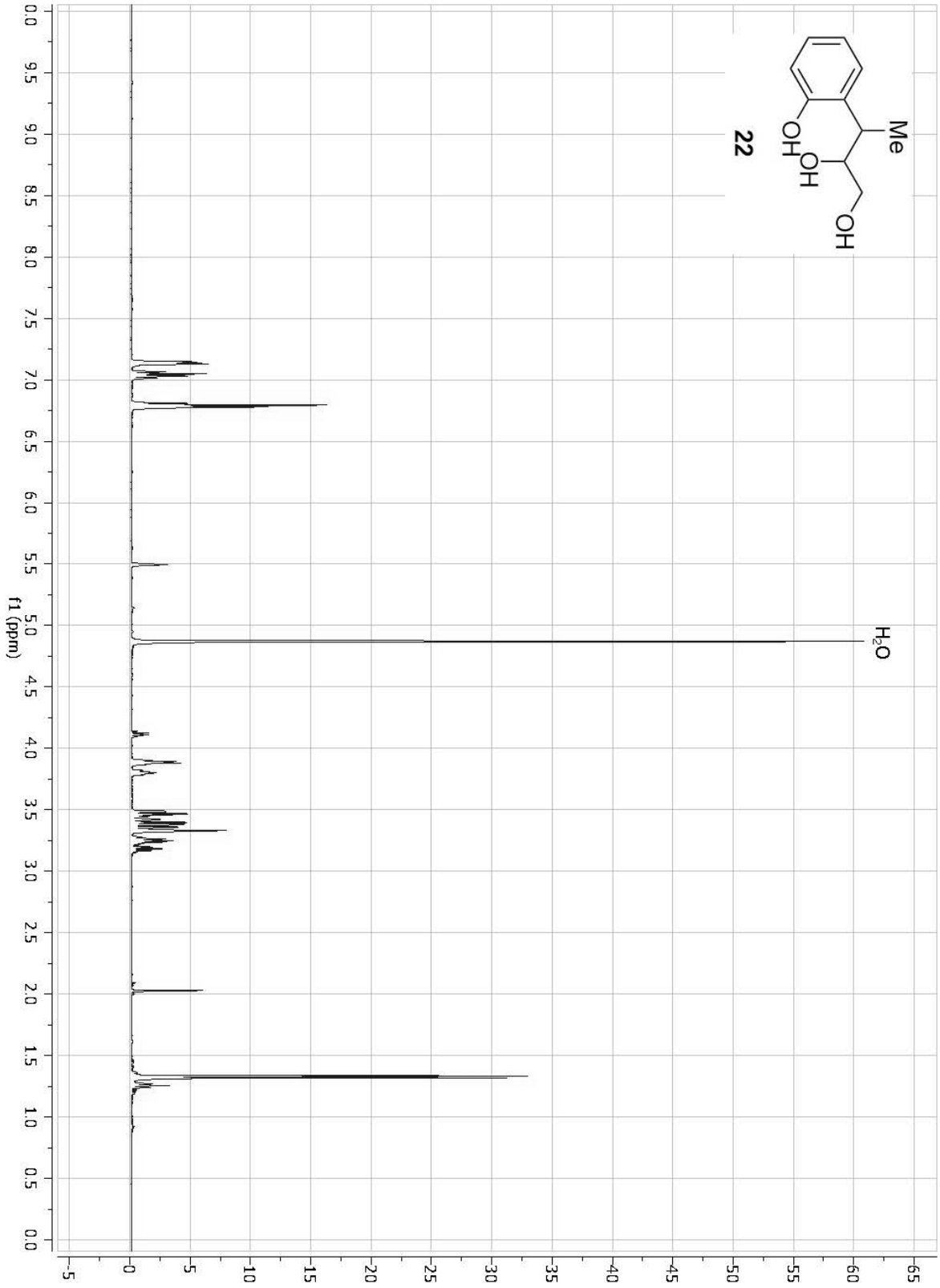
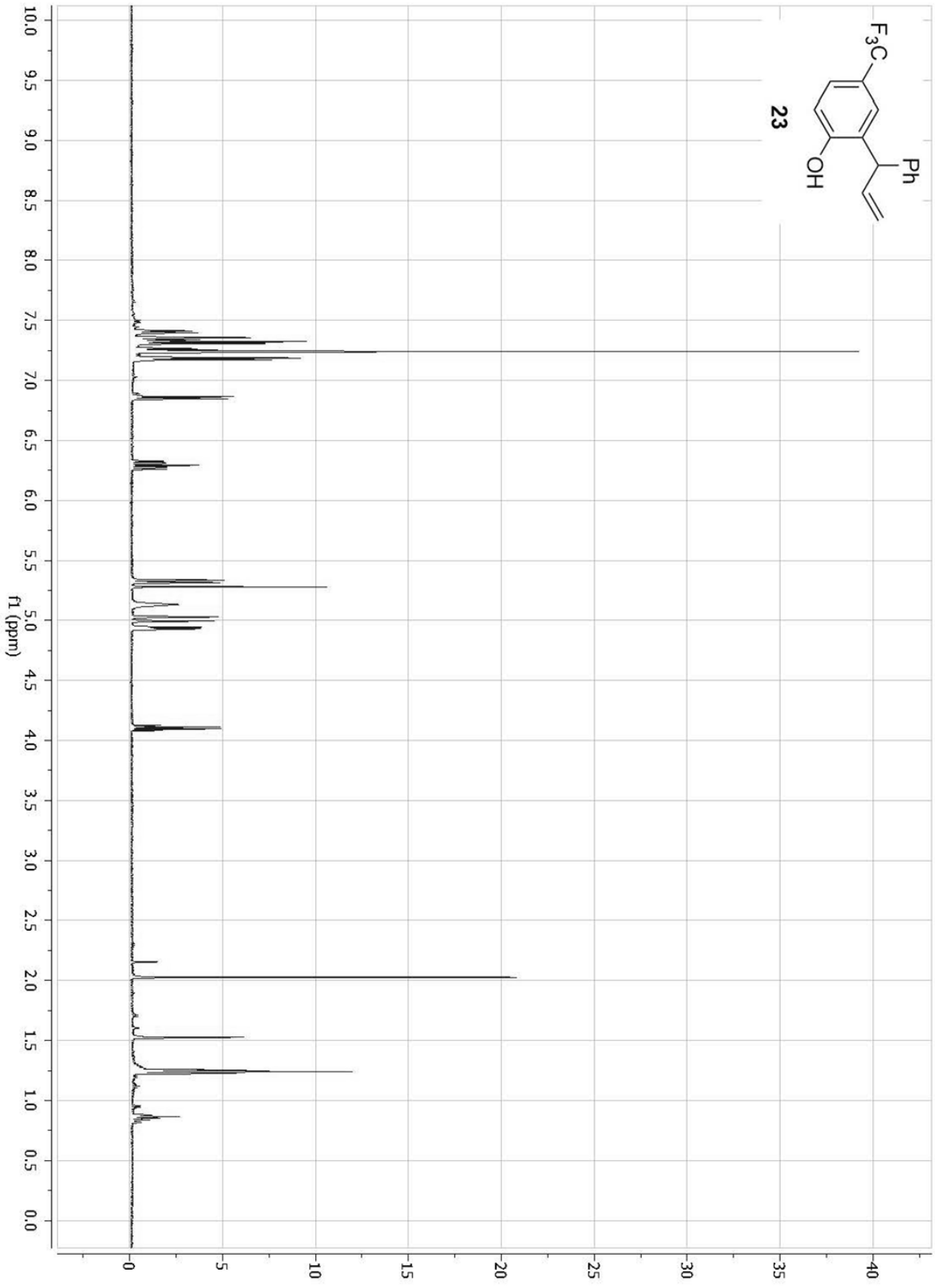
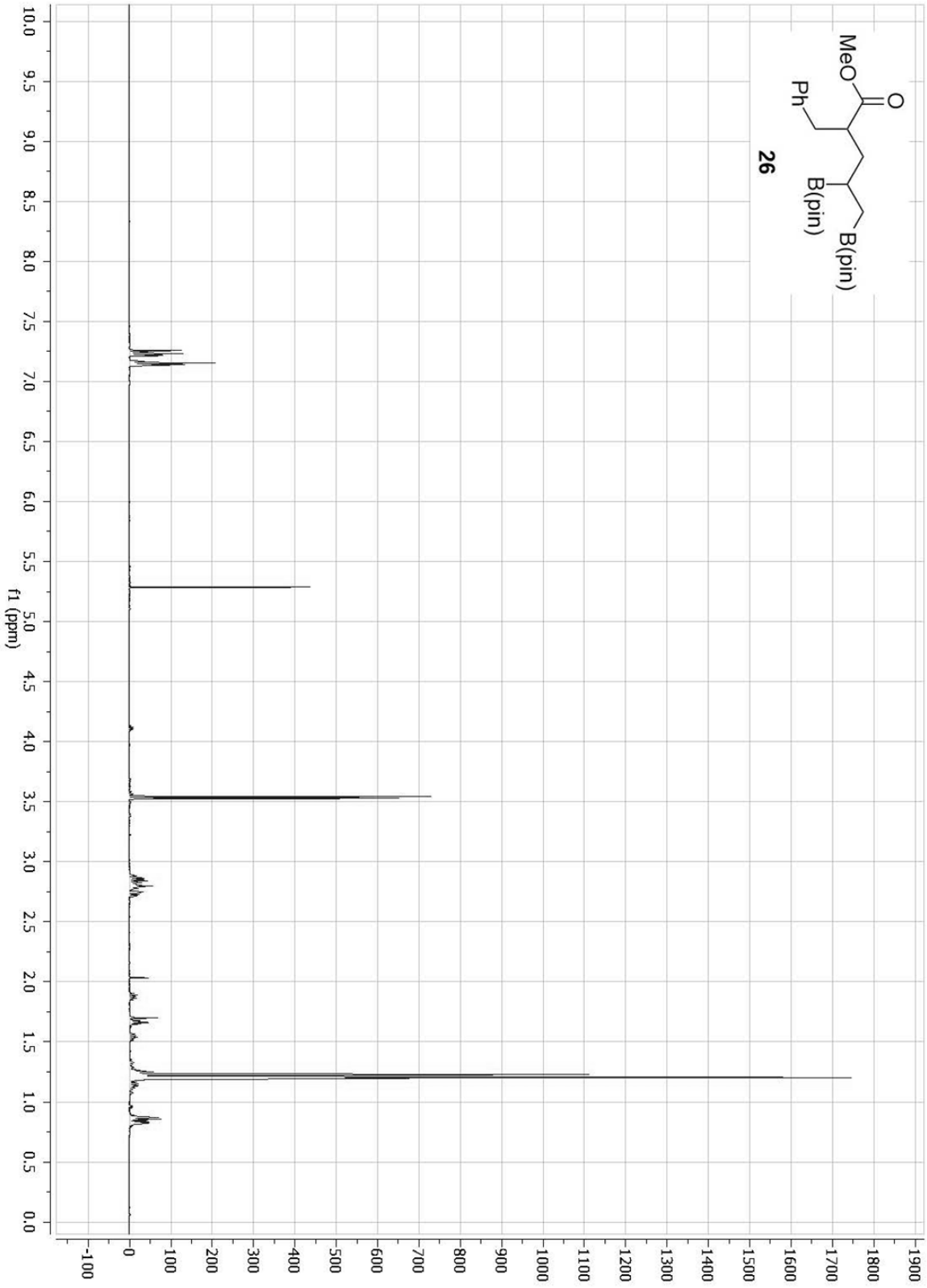
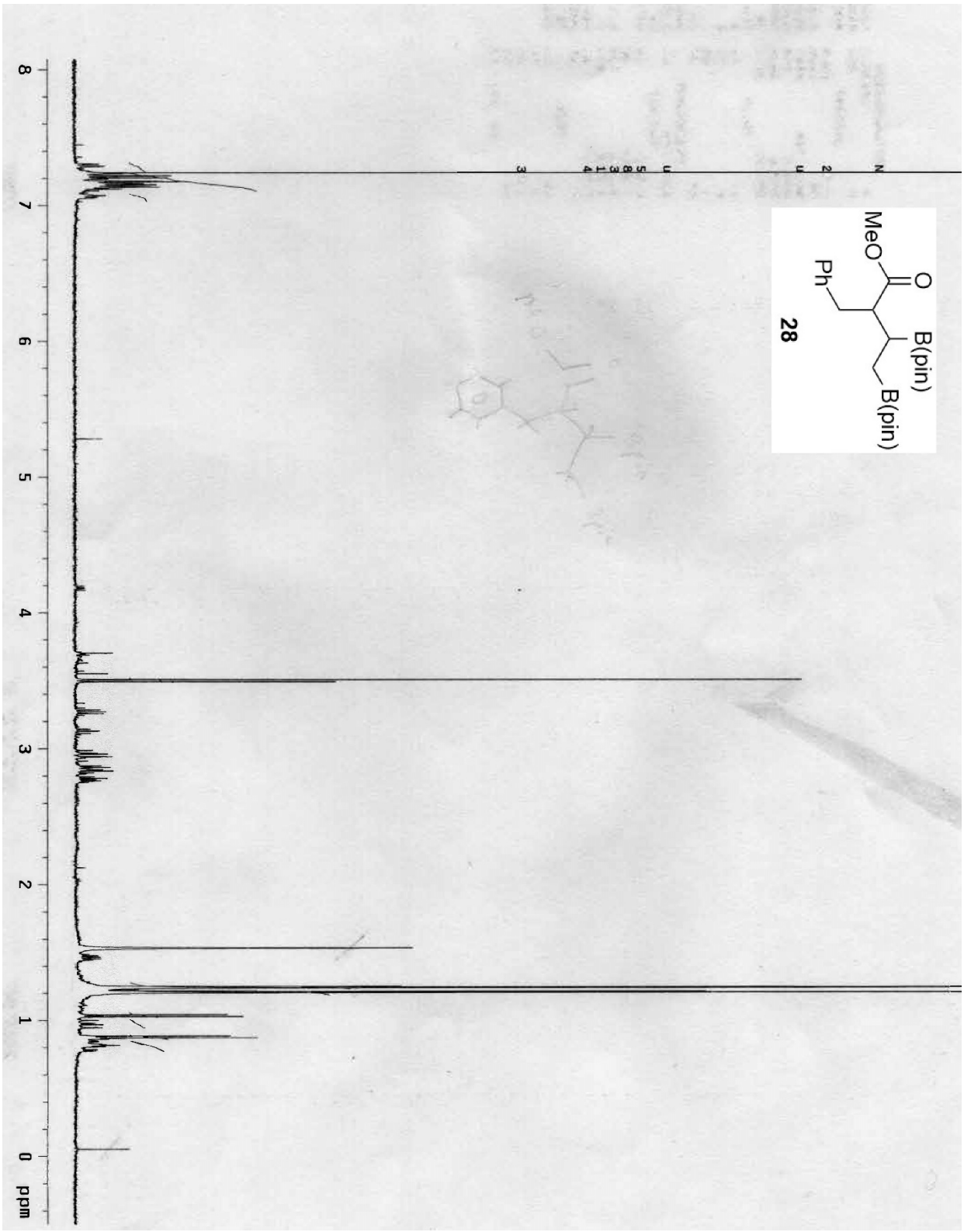
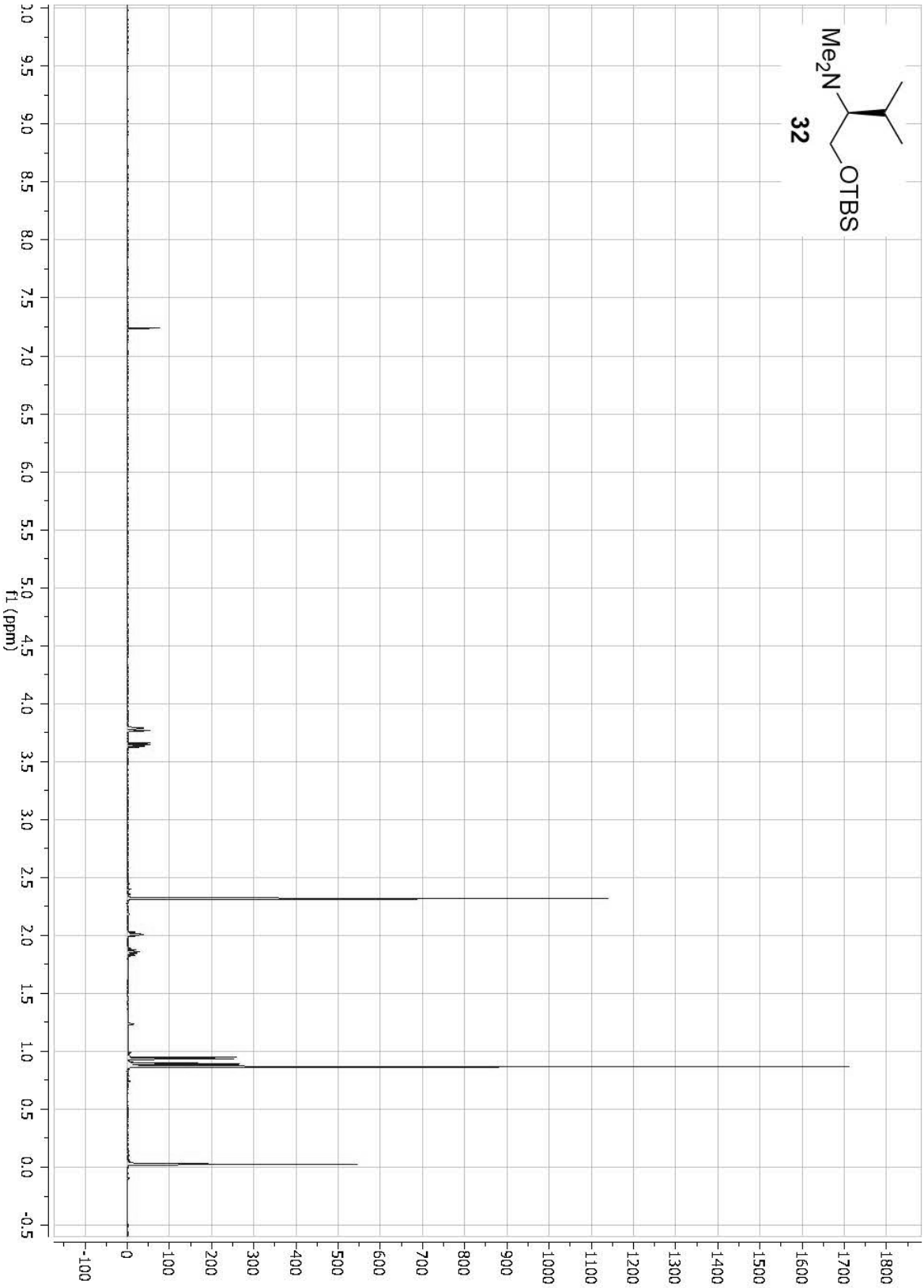
Ph
OH
OH
OH
20
f1 (ppm)

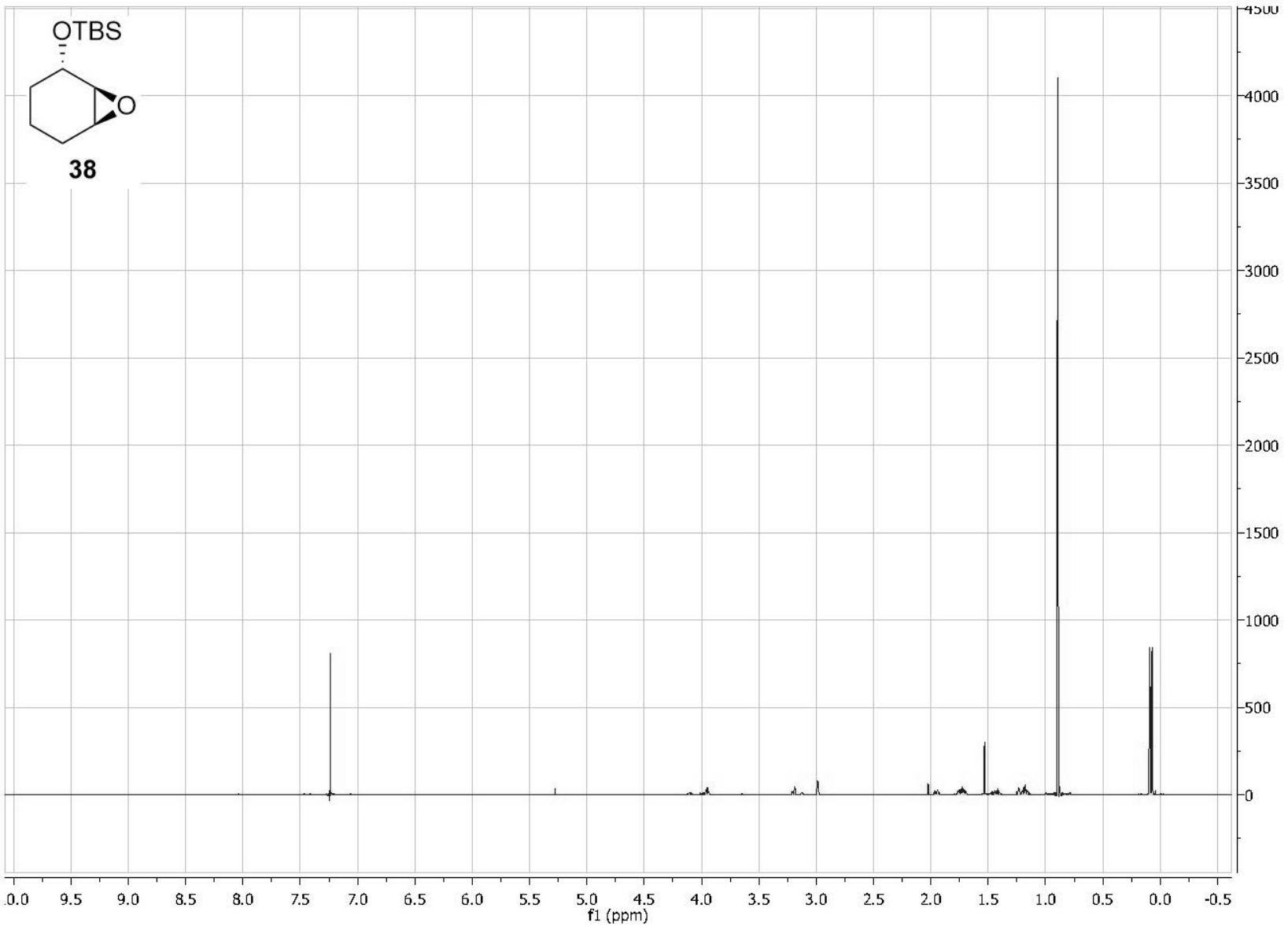

Me
OH
OH
OH
22
H2O
f1 (ppm)


F3C
Ph
OH
23
f1 (ppm)


MeO
O
Ph
B(pin)
B(pin)
26
f1 (ppm)


B(pin)
MeO
O
Ph
B(pin)
28
8
7
6
5
4
3
2
1
0
ppm


Me2N
OTBS
32
f1 (ppm)


OTBS
O
38
4500
4000
3500
3000
2500
2000
1500
1000
500
0
.0.0
9.5
9.0
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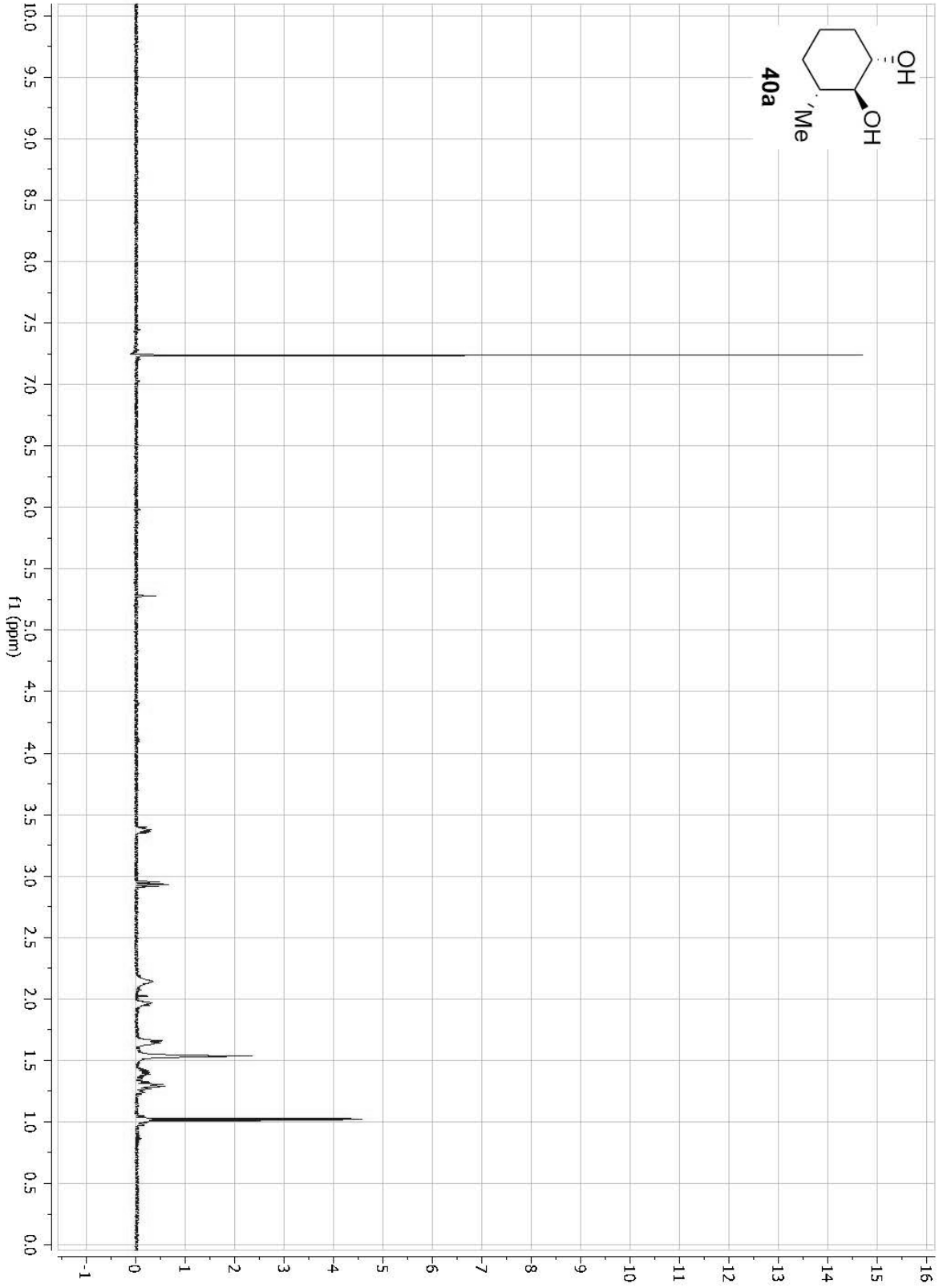
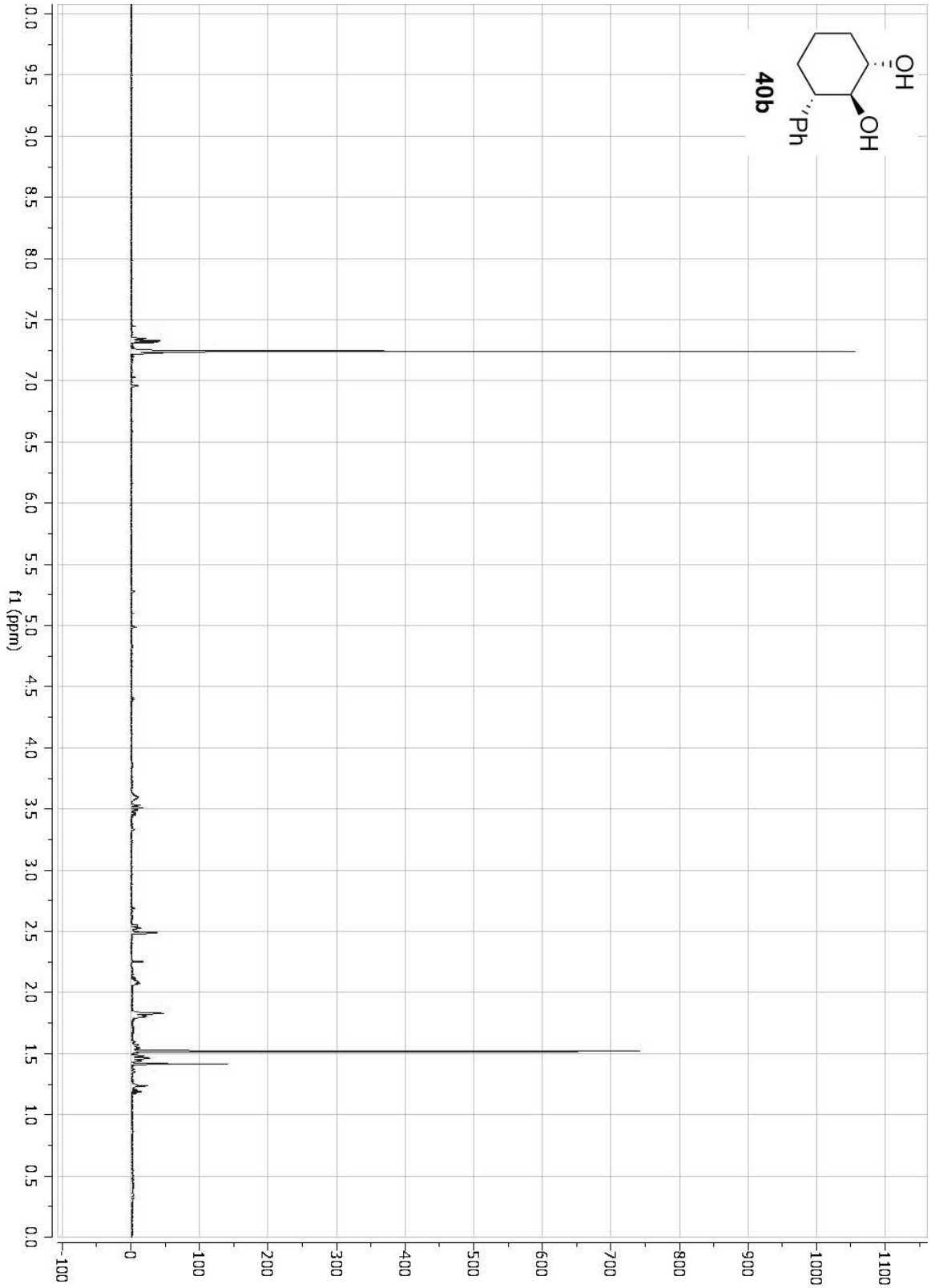
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


OH
OH
Me
40a
f1 (ppm)


OH
OH
Ph
40b
f1 (ppm)