Synthesis of Quaternary Carbon Centers via Hydroformylation

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Synthesis of Quaternary Carbon Centers via Hydroformylation

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SYNTHESIS OF QUATERNARY CARBON CENTERS VIA HYDROFORMYLATION

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Abstract. Utilization of directing groups in a general and efficient manner for highly regioselective hydroformylation of 1,1-disubstituted olefins.

Chapter One: Branched-selective hydroformylation of 1,1-disubstituted olefins for the formation of quaternary carbon centers.

Chapter Two: Enantioselective hydroformylation of 1,1-disubstituted olefins for the formation of all carbon quaternary stereogenic centers.

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I would like to thank Dr. Kian Tan for teaching and training me and for always being available to answer questions and to discuss chemistry. His approach to solving problems helped shape my way of thinking and allowed me to grow as a researcher. I would also like to thank Dr. James P. Morken and Dr. Jason S. Kingsbury for reading and critiquing this work. I thank Moriah Gagnon and Thomas Lightburn for training me, Xixi Sun for his collaboration, Matthew Hutchinson and Thomas Blaisdell for their help, Candice L. Joe and Omar DePaolis for their helpful discussions and Amanda D. Worthy for her helpful discussions and assistance in reviewing this work.

List of Abbreviations

CO	carbon monoxide
DIOP	(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4 bis(diphenylphosphino)butane
ppm	parts per million
dppb	diphenylphosphino butane
ee	enantiomeric excess
eq.	equation
equiv.	equivalent
EtOAc	ethyl acetate
H_2	hydrogen gas
i-PrOH	*iso*-propanol
MeOH	methanol
$NaBH_4$	sodium borohydride
NMR	nuclear magnetic resonance
p-TsOH	*para*-toluenesulfonic acid
PPh_3	triphenylphosphine
psi	pounds per square inch

pybox	2,6-Bis[(4R)-4-phenyl-2-oxazolinyl]pyridine
tdtbpp	tris(2,4-di-*tert*-butylphenyl)phosphite

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Synthesis of Quaternary Carbon Centers via Hydroformylation

Chapter Two

Asymmetric Synthesis of Quaternary Stereogenic Centers

Financial support was generously provided by Boston College. We are grateful to Dr. John Boylan for valuable assistance in the use and maintenance of the NMR facility; Mr. Marek Domin for his help in acquiring mass spectrometry; Dr. Bo Li for his expertise in acquiring and interpreting X-ray structures. The Boston College Mass Spectrometry Facility is supported by the NSF (grant DBI-0619576). The X-ray facility at Boston College is supported by Schering-Plough.

Chapter 1: Synthesis of Quaternary Carbon Centers via Hydroformylation

I. Use of Activated Substrates

In hydroformylation, alkene reactivity decreases with increasing substitution on the alkene. Thus, 1,2- and 1,1-disubstituted, and trisubstituted olefins are much less reactive than terminal alkenes. In general, 1,1-disubstituted and trisubstituted olefins provide only one regio-isomeric product, the linear aldehyde product.[1] Hence, formation of all carbon quaternary centers via hydroformylation is a significant challenge. The transformation is so unfavorable that in 1948 Keulemans stated "in hydroformylation, formyl groups are not produced at quaternary carbon centers" (Keulemans' rule).[2] Despite the definitive nature of Keulemans' statement, a limited number of examples have been reported that utilize both chelating and electronically activating groups, such as esters, to effect the formation of all carbon quaternary centers. For example, Alper and co-workers reported that hydroformylation of methyl methacrylate using zwitterionic rhodium compound [Rh(cod)(η^6-PhBPh$_3$)] and dppb as ligand gave a 54% isolated yield of the quaternary aldehyde **1.2** with a 9:1 regioselectivity (Figure 1.1).[3] Inspired by this result, Clarke and Roff sought a general procedure for branched-selective hydroformylation of unsaturated esters.[4] An earlier report by the Pittman group showed a pronounced temperature and pressure effect on the regioselectivity of **1.1**.[5] The group reported that at high pressure and lower temperatures (40 – 60 °C), high selectivity for the quaternary aldehyde **1.2**

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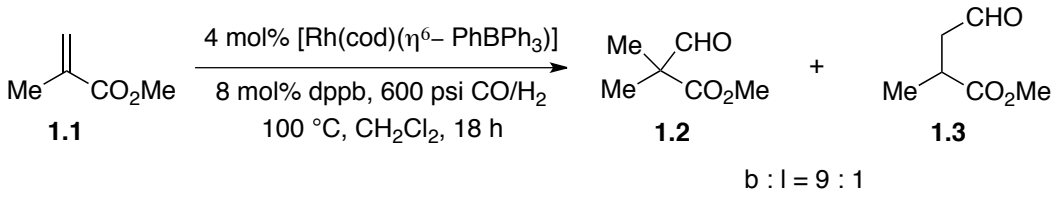
[1] Breit, B.; Seiche, W. *Synthesis* **2001**, *1*, 1.
[2] Keulemans, A. I. M.; Kwantes, A.; van Bavel, T. *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 298.
[3] Lee, C. W.; Alper, H. *J. Org. Chem.* **1995**, *60*, 499.
[4] Clarke, M. L.; Roff, G. J. *Chem. Eur. J.* **2006**, *12*, 7978.
[5] Pittman, C. U., Jr; Honnick, W. D.; Yang, J. J. *J. Org. Chem.* **1980**, *45*, 684.

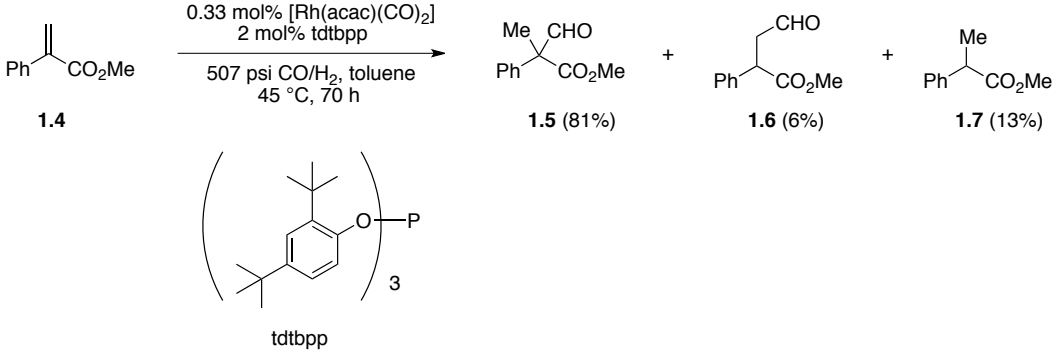
could be obtained using [$Rh(PPh_3)_3(CO)H$] as a catalyst. Unfortunately, at these lower temperatures catalytic activity was compromised.

Figure 1.1. Hydroformylation of methyl methacrylate using a zwitterionic rhodium compound



The Clarke group envisaged that highly reactive phosphite-based catalysts might help circumvent this problem and promote a high yielding regioselective hydroformylation. They reported that using a very reactive rhodium catalyst derived from the bulky phosphite ligand tdtbpp, hydroformylation of the atropate ester **1.4** resulted in the formation of the quaternary aldehyde **1.5** with a regioselectivity (b:l) of 13:1 as well as formation of 13% hydrogenated starting material (Figure 1.2).[6]

Figure 1.2. Hydroformylation of methyl atropate using bulky phosphite ligand



In collaboration with the Pringle group, the Clarke group had previously reported the remarkably high activity of phenylphosphatrioxaadamantane **1.8** (cage phosphane) in

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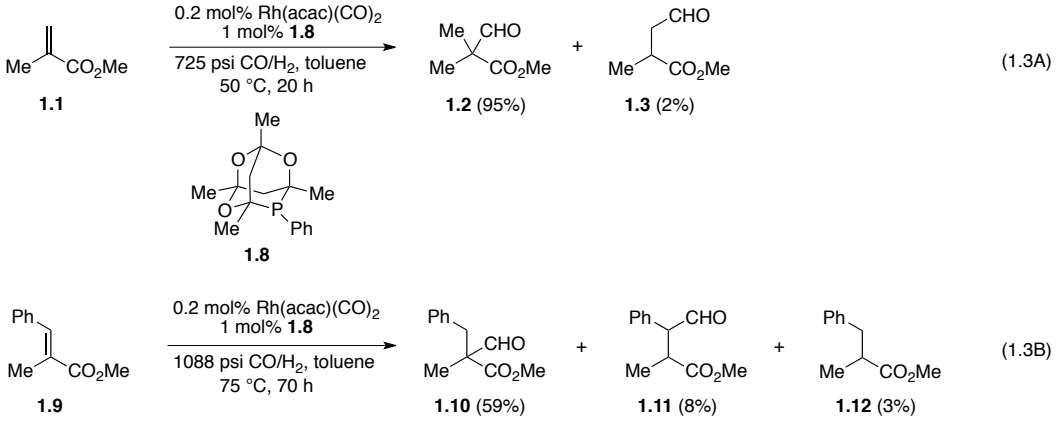
[6] Clarke, M. L. *Tet. Lett.* **2004**, *45*, 4043.

the rhodium-catalyzed hydroformylation of hex-1-ene.[7] In that paper the authors also disclosed that **1.8** seemed to hold some advantage in the hydroformylation of methyl atropate in two preliminary reactions under unoptimized conditions. This prompted them to investigate the hydroformylation of methyl methacrylate using **1.8** (Figure 1.3). At 50 °C under 725 psi of syngas (1:1 CO/H_2), hydroformylation of **1.1** gave a high quaternary/linear selectivity (Figure 1.3A).[4] The remarkable activity of **1.8** is also demonstrated in the hydroformylation of **1.9**, a trisubstituted alkene (Figure 1.3B).[4]

Figure 1.3. Hydroformylation of atropate esters using highly active cage phosphane



Trisubstituted alkenes are especially problematic substrates for hydroformylation. In addition to the quaternary aldehyde being disfavored by Keulemans' rule, it is well established that hydroformylation reactions are normally directed to benzylic positions.[8] However, as illustrated in Figure 1.3B, there is a clear preference for the quaternary aldehyde over the linear aldehyde. Clarke and Roff explained that this

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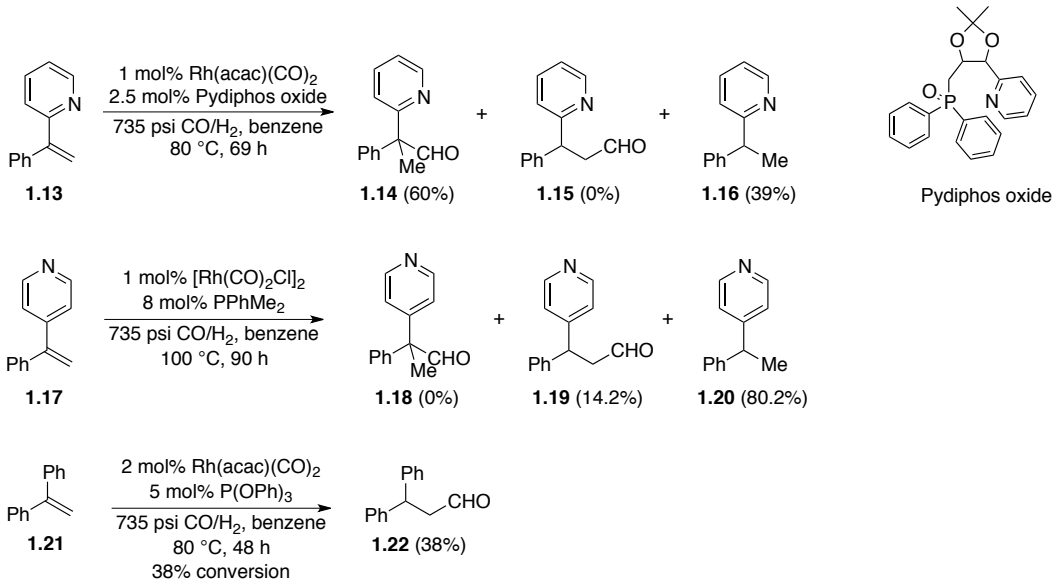
[7] Baber, R. A.; Clarke, M. L.; Heslop, K.; Marr, A.; Orpen, A. G.; Pringle, P. G.; Ward, A. M.; Zambrano-Williams, D. A. *Dalton Trans.* **2005**, 1079.

[8] Clarke, M. L. *Curr. Org. Chem.* **2005**, *9*, 701.

outcome is due to the ability of the ester group to chelate to the rhodium catalyst and, thus, direct the hydroformylation.

Another example of substrate-directed hydroformylation to form quaternary aldehyde was reported by the Botteghi group.[9] In this report the group showed that the formation of quaternary aldehydes from vinylpyridine derivatives is feasible depending on the position of the nitrogen atom of the pyridine moiety. Hydroformylation of **1.13** in which the nitrogen atom is in the 2-position of the pyridine moiety gave a 60% yield of the branched, quaternary aldehyde with no formation of the linear aldehyde (Figure 1.4).

Figure 1.4. Hydroformylation of vinylpyridine derivatives

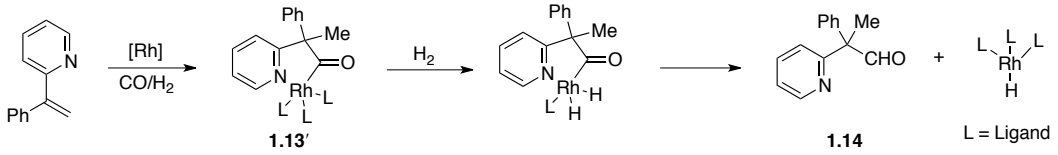


Conversely, hydroformylation of **1.17** in which the nitrogen atom is in the 4-position of the pyridine moiety did not yield any branched product, with hydrogenation of the substrate being the most predominant reaction. These results indicate that the position

[9] Botteghi, C.; Marchetti, M.; Paganelli, S.; Sechi, B. *J. Mol. Catal. A: Chemical* **1997**, *118*, 173.

of the pyridine nitrogen atom is crucial to the regioselectivity of the H insertion. In **1.13** the formation of a stabilized α-acyl complex **1.13′** due to the intramolecular coordination of the pyridine nitrogen atom to the metal through a five-membered ring favors the formation of the quaternary aldehyde. This stabilization may remarkably affect the energy of activation of the aldehyde formation process by hydrogenolysis of **1.13′** (Figure 1.5). The absence of such a stabilized α-acyl intermediate in the hydroformylation of **1.17** precludes the formation of the quaternary aldehyde. The fact that the pyridine nitrogen in **1.13** is strongly involved in the catalytic cycle of the reaction is further evidenced by results obtained in the hydroformylation of l,l-diphenylethene **1.21** and structurally related compounds, in which no heteroatoms are present. In these cases the more linear aldehyde, 3,3-diarylpropanal, was formed with a regioselectivity as high as 99% (Figure 1.4, see previous page).

Figure 1.5. Stabilized α-acyl complex

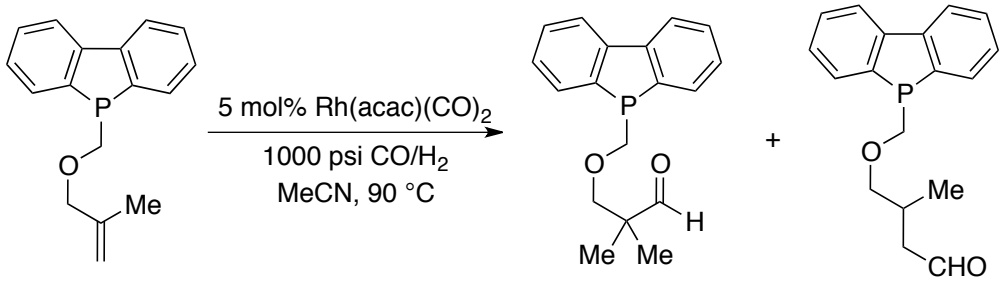


II. Use of Stoichiometric Cleavable Directing Groups

As discussed above, synthesis of quaternary carbon centers through hydroformylation can be achieved by using substrates that are both electronically activated toward forming the branched regioisomer and which contain an ester or a heteroatom such as nitrogen to serve as a chelating group. For unactivated substrates, Leighton and coworkers have shown that using a dibenzophospholyl directing group, formation of all carbon quaternary centers from 1,1-disubstituted allylic ethers is

achievable. [10] In this work, the group reported that **1.23** can undergo hydroformylation to form quaternary, protected β-hydroxyaldehyde in good yield (Figure 1.6).

Figure 1.6. Dibenzophospholyl-directed hydroformylation



1.23 **1.24** (81%) **1.25** (7%)

The obvious drawbacks of this strategy are the need for stoichiometric amounts of the phosphorus directing group, prior installation of the directing group onto the substrate and the need for its subsequent cleavage, which drastically diminishes the synthetic utility of this methodology. Furthermore, this methodology, in addition to the ones discussed above, all require either high pressures of syngas or long reaction times to effect good yield of the quaternary aldehyde. Hence, a new strategy that obviates these limitations would greatly enhance the practicality of branched-selective hydroformylation to form all carbon quaternary centers.

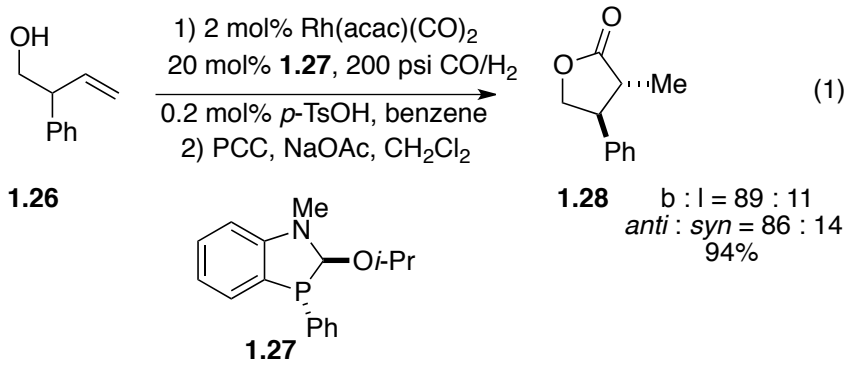
III. Use of Catalytic Directing Groups

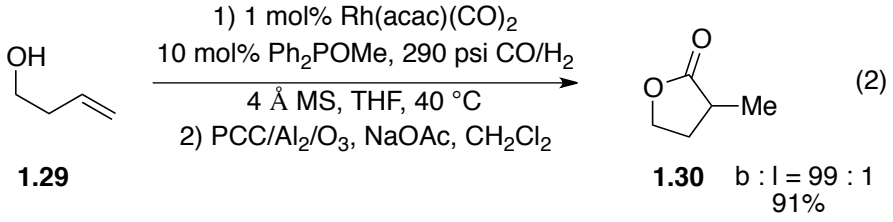
As illustrated in the example by the Leighton group, phosphorus-based directing groups can be used to reverse the inherent preference for linear aldehyde formation over the formation of the more hindered, branched aldehyde in the hydroformylation

[10] Krauss, I. J.; Wang, C. C.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 11514.

of 1,1-disubstituted olefins. In 2008, the Tan group (Figure 1.7, eq 1)[11] and the Breit group (Figure 1.7, eq 2)[12] reported that a catalytic amount of a directing group can be employed in the regioselective hydroformylation of homoallylic alcohols if the directing group reversibly and covalently links to the substrate.[13]

Figure 1.7. Regio- and diastereoselective hydroformylation





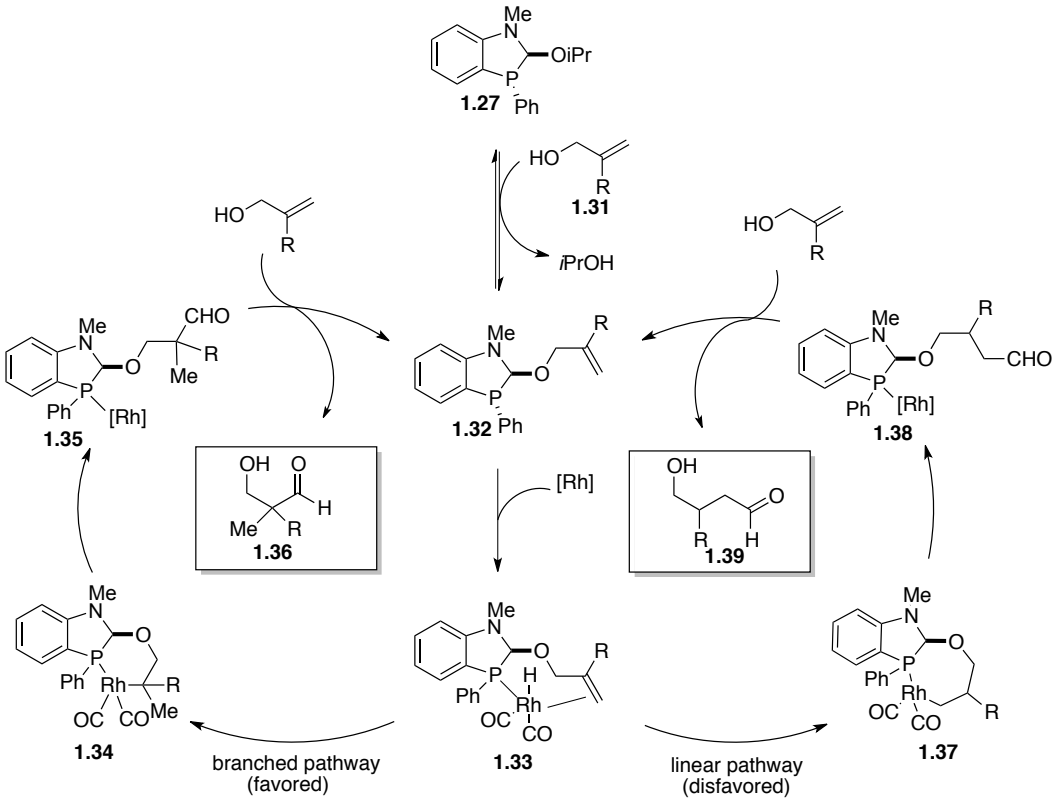
Ligand **1.27**, termed scaffolding ligand, simultaneously and reversibly binds a variety of organic functionalities as well as a metal-based catalyst. The unique ability of this ligand to achieve such scaffolding catalysis without both domains substantially interfering with each other allows for enhanced control of the selectivity of the transformation. Consequently, the directed reaction can be performed with a catalytic

[11] (a) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210. (b) Worthy, A. D.; Gagnon, M. M.; Dombrowski, M. T.; Tan, K. L. *Org. Lett.* **2009**, *11*, 2764. (c) Worthy, A. D.; Joe, L. C.; Lightburn, T.; Tan, K. L. *J. Am. Chem. Soc*. **2010**, *132*, 14757. (d) Lightburn, T. E.; De Paolis, O. A.; Cheng, K. A.; Tan, K. L. *Org. Lett.* **2011**, *13*, 2686.
[12] (a) Grunanger, C. U.; Breit, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 967. (b) Grunanger, C. U.; Breit, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 7346.
[13] Tan, K. L. *ACS Catal.* **2011**, *1*, 877.

amount of ligand and the ligand can be tuned for efficient catalysis without having to change the nature of the substrate.[11a]

We sought to investigate the application of scaffolding ligand **1.27** in the regioselective hydroformylation of 1,1-disubstituted olefins to form all carbon quaternary centers.[14] We envisioned a catalytic cycle as illustrated in Figure 1.8. Exchange of **1.27** onto substrate **1.31** is driven by release of *i*-PrOH.

Figure 1.8. Proposed catalytic cycle using scaffolding ligand 1.27



Association of the phosphorus atom in **1.27** to rhodium and subsequent coordination of the metal and alkene affords **1.33**, as the important regioselectivity determining intermediate. Formation of **1.34**, a six-membered rhodacycle, via the branched

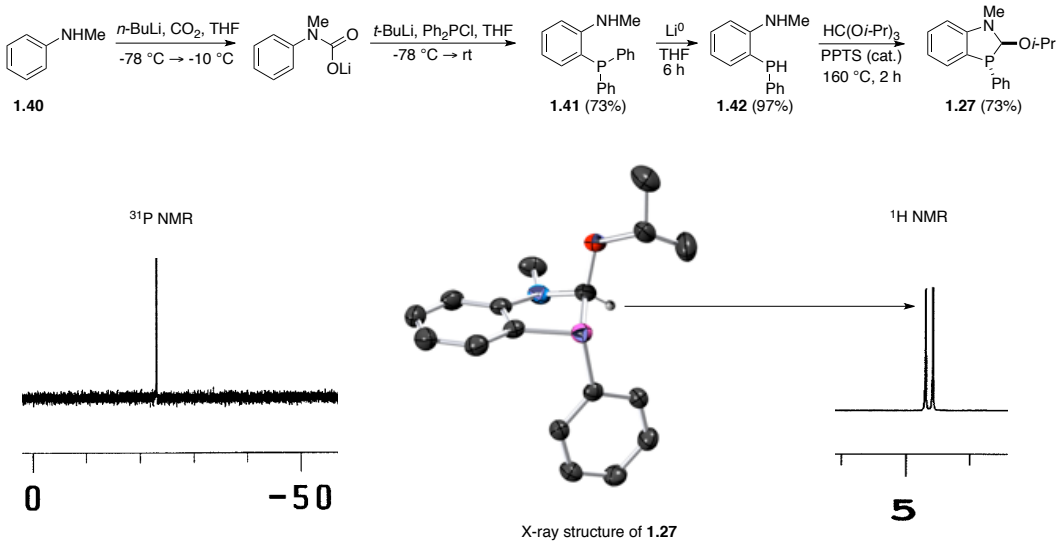
[14] Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841.

pathway was hypothesized to be more favored over formation of **1.37**, a seven-membered rhodacycle. Subsequent CO insertion yields **1.35**, followed by release of the branched aldehyde product **1.36** by exchange of **1.35** with an equivalent of substrate to achieve turnover.

IV. Synthesis of Scaffolding Ligand 1.27

The synthesis of **1.27** is shown in Figure 1.9. Starting from commercially available *N*-methylaniline, **1.27** is synthesized in a three-step sequence that requires no column chromatography, making it amenable to large-scale synthesis. Synthesis of **1.27** begins with deprotonation of *N*-methylaniline and trapping with CO_2, to yield a lithium carbamate. The lithium carbamate is then used to direct ortho lithiation, which is trapped with diphenylphosphine chloride. Acidic workup decomposes the lithium carbamate, releasing CO_2 to yield 2-(diphenylphosphino)-*N*-methylaniline **1.41**. The second step involves reduction of **1.41** with lithium wire selectively to remove a phenyl ring from phosphorus atom, affording the secondary phosphine **1.42** on workup. The secondary phosphine is then treated with triisopropyl orthoformate and catalytic acid to produce ligand **1.27** as a white solid after crystallization or distillation. The ligand is isolated as one major diastereomer, *anti*-diastereomer, as judged by ^{1}H and ^{31}P NMR. An X-ray crystal structure of **1.27** confirmed that the stereochemistry of the ligand was *anti*.[11a]

Figure 1.9. Synthesis of scaffolding ligand 1.27



V. Hydroformylation of 1,1-Disubstituted Olefins with Scaffolding Ligand 1.27

As a preliminary study, we investigated the hydroformylation of **1.43** (Figure 1.10). Though styrenyl olefins are known to have a preference for the branched regioisomer,[15] α-substituted styrenes have been shown to be highly linear-selective.[16] We hypothesized that use of scaffolding ligand **1.27** would lead to intermediates in the catalytic cycle that favor the branched pathway over the linear pathway (Figure 1.8). During the course of our studies we realized that the branched aldehyde product **1.44** is unstable to silica gel purification and also dimerizes to a small extent to the cyclic acetal **1.45**.[17] To circumvent these problems, Pinnick oxidation of the

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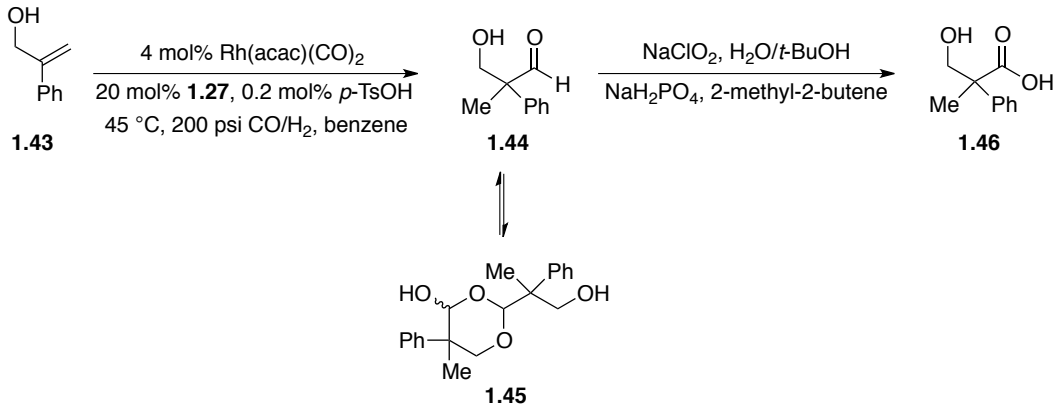
[15] (a) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251. (b) Dieguez, M.; Pamies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113. (c) Agbossou, F.; Carpentier, J. F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485.

[16] (a) Korneyeva, G. A.; Vladimirova, T. V.; Potarin, M. M.; Khromushina, E. I.; Slivinskii, Y. V.; Loktev, S. M. *Pet. Chem.* **1993**, *33*, 391. (b) Marchetti, M.; Mangano, G.; Paganelli, S.; Botteghi, C. *Tetrahedron Lett.* **2000**, *41*, 3717.

[17] Boeckman, R. K.; Miller, J. R. *Org. Lett.* **2009**, *11*, 4544.

unpurified reaction mixture was immediately performed to isolate the carboxylic acid product **1.46**.

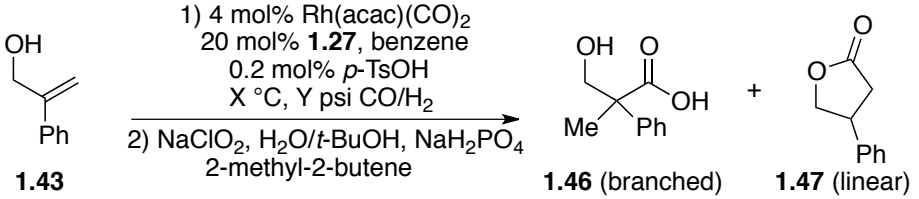
Figure 1.10. Initial Studies on the hydroformylation of 1.43



Hydroformylation of **1.43** with scaffolding ligand **1.27** afforded the branched product in 54% yield with a b: l regioselectivity of 96:4 (Table 1.1, entry 1). A temperature screen using **1.27** was performed to determine the temperature dependence of the reaction. At 45 °C the branched product is formed in 61% yield with excellent regioselectivity (b:l = 95:5, Table 1.1, entry 2). When the temperature is increased to 55 °C, there is a decreased yield of the branched product. This is attributed to slow product decomposition (Table 1.1, entry 3). Next, we optimized the pressure of the syngas and found that at 400 psi, the desired product could be isolated in 73% yield with b:l ratio of 97:3 (Table 1.1, entry 6). At pressures of 50 psi and 100 psi CO/H_2 the regioselectivity decreases to 89:11 and 94:6 respectively. These results suggest that the selectivity-determining step may be changing with pressure or higher pressure could be suppressing minor amounts of background reaction. The latter seems less likely based on the poor reactivity with PPh_3 at 45 °C (vide infra). There are two steps that could be rate limiting: hydride insertion or CO insertion. The

hydride insertion depends on the rhodium hydride species, and is not dependent on CO pressure. The rate of CO insertion depends on the CO pressure and, thus, as CO pressure increases the rate of CO insertion increases. As CO pressure is decreased, CO insertion may become rate limiting rather than the hydride insertion being rate limiting. Each step has a selectivity associated with it and if the CO pressure is altered, the selectivity-determining step may also change.[18]

Table 1.1. Optimization studies for hydroformylation of 1.43



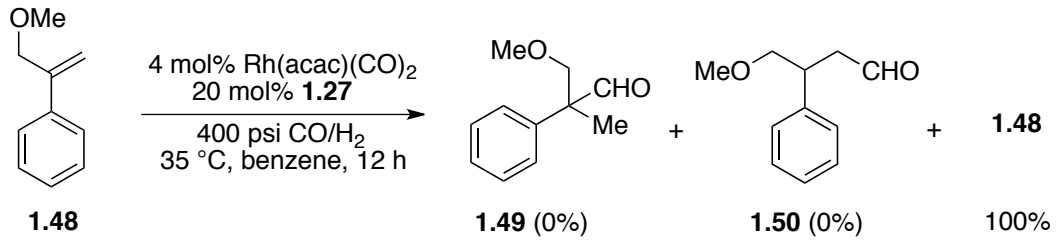
entry	ligand	pressure (psi)	temperature (°C)	b:l[a]	yield (%)[b]
1	**1.27**[c]	200	35	96:4	54
2	**1.27**[c]	200	45	95:5	61
3	**1.27**[c]	200	55	95:5	50
4	**1.27**[c]	50	45	89:11	38
5	**1.27**[c]	100	45	94:6	53
6	**1.27**[c]	400	45	97:3	70 (73)[e]
7	PPh_3[d]	400	45	-	0
8	PPh_3[d]	400	75	<2:98	66[f]

[a] Regioselectivities determined by ^1H NMR of crude reaction mixtures. [b] Yields of the branched product determined by ^1H NMR by comparison to internal standard. [c] 20 mol% **1.27**. [d] 8 mol% PPh_3. [e] Isolated yield of branched product. [f] Isolated yield of lactone.

[18] Landis, C. R.; Watkins, A. L. *J. Am. Chem. Soc.* **2010**, *132*, 10306.

Theoretical calculations performed by Alagona and coworkers on the branched pathway in the hydroformylation of 1,1-diphenylethene showed that all the transition states are close in energy with CO insertion, with H_2 addition or reductive elimination being the rate-limiting step.[19] As a control reaction, hydroformylation was carried out under the same reaction conditions as entry 6 in Table 1.1, except with PPh_3 as ligand (Table 1.1, entry 7). PPh_3 is known to be a good ligand for hydroformylation. However, under these conditions, no reaction was observed. The temperature had to be increased to 75 °C to observe any conversion. As anticipated, this reaction was linear selective. These results provide evidence that ligand **1.27** is a very active ligand for branched selective hydroformylation of **1.43**. A second control reaction was performed with the methyl ether of **1.43** and ligand **1.27**. The purpose of this control reaction was to determine if the alcohol functionality of **1.43** was essential for high selectivity. Substrate **1.48** provides no conversion to product under standard conditions, consistent with ligand **1.27** acting as directing group (Figure 1.11).

Figure 1.11. Control reaction of methyl ether

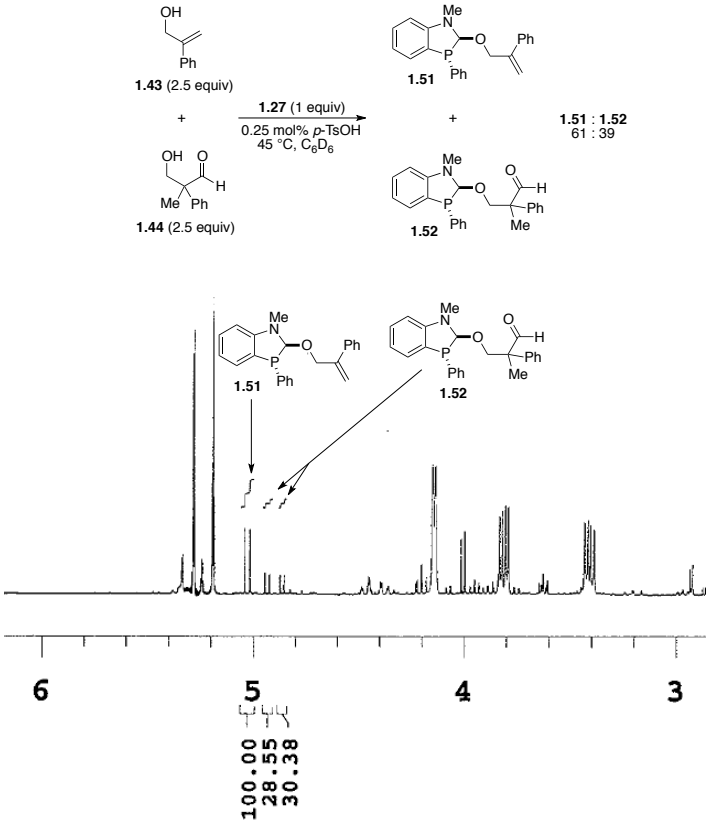


The uniqueness of ligand **1.27** is its ability to reversibly bind both substrate and catalyst. To achieve turnover in the hydroformylation reaction, it is beneficial, albeit not required, for the product to have a lower binding affinity to the ligand than the

[19] Ghio, C.; Lazzaroni, R.; Alagona, G. *Eur. J. Inorg. Chem.* **2009**, *1*, 98.

substrate to the ligand. To investigate the respective binding affinities of the substrate and product to the ligand, a binding study was performed by adding 2.5 equivalents of **1.43** and 2.5 equivalents of the aldehyde product **1.44** to ligand **1.27**. A 61:39 ratio of **1.43** bound to **1.27** over the product **1.44** bound to **1.27** was observed, indicating a slight preference for binding of **1.43** over the product (Figure 1.12). Under the exchange conditions the aldehyde product appears to dimerize to a small degree to the cyclic acetal **1.45**. This complicates trying to extract an equilibrium constant, but we feel this most accurately reflects the conditions in which hydroformylation is occurring. These results are consistent with ligand **1.27** serving as a catalytic directing group that controls the regioselectivity of the reaction and accelerates the overall process.

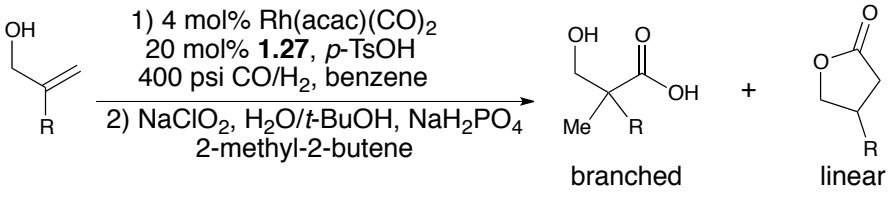
Figure 1.12. Equilibrium stabilities of substrates and products versus their scaffolded derivatives

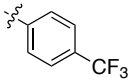
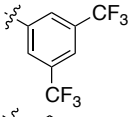
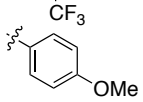
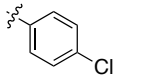
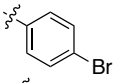
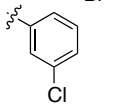
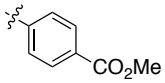
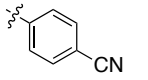
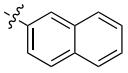


Once these initial promising results were obtained, the next step was to investigate the substrate scope of the reaction. We were particularly interested in electronic and steric effects on the reaction. As outlined in Table 1.2, the use of catalytic quantities of scaffolding ligand **1.27** can effect efficient formation of all carbon quaternary centers from 1,1-disubstituted styrenyl olefins under mild conditions for a wide range of electronically varied substrates with good yields and excellent regioselectivities. Substrates with electron withdrawing and electron donating substituents are all tolerated. For instance, the addition of electron-withdrawing groups to the aromatic ring leads to an increase in the yields of the branched product while maintaining high selectivity (Table 1.2, entries 1 and 2). This outcome is probably because the terminal carbon of the olefin becomes more electron deficient thus, favoring addition of the hydrogen to that carbon. An electron-rich aromatic ring is tolerated with a small decrease in the yield, while maintaining excellent regioselectivity (Table 1.2, entry 3). Halogens remain unperturbed during the reaction as shown in entries 4-6 (Table 1.2). Furthermore, π-electron-withdrawing groups such as nitriles and esters can be used in the reaction while maintaining an excellent regioselectivity of >98:2 (Table 1.2, entries 7 and 8). Heterocyclic aromatic rings and naphthalene-based substrates also yield the quaternary carbon products (Table 1.2, entries 9-12). The aldehyde products obtained for entries 11 and 12 were reduced to the respective diol with $NaBH_4$ because they decomposed under Pinnick oxidation conditions. To investigate the effect of sterics on the reaction, hydroformylation of an *o*-tolyl substrate was attempted with minimal conversion, suggesting that steric hindrance impedes the reaction. This methodology is also amenable to aliphatic substituted olefins. Hydroformylation of 2-methyl-propen-1-ol

results in the branched product being formed as the major product (b:l = 76:24; Table 1.2, entry 13).

Table 1.2. Substrate scope

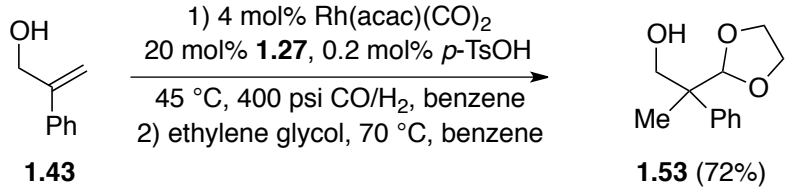


entry	R	temp (°C)	*p*-TsOH (mol%)	b:l[a]	yield (%)[b]
1		45	0.2	96:4	85
2		45	0.05	>98:2	80
3		35	0.2	>98:2	66
4		35	0.05	97:3	60
5		35	0.05	94:5	71
6		35	0.2	>98:2	77
7		45	0.05	>98:2	74
8		45	0.2	>98:2	67
9		35	0.05	95:5	85
10		45	0.2	95:5	70
11		45	0.2	98:2	68[c]
12		55	0.05	>98:2	64[c]
13		45	0.2	76:24	49

[a] Regioselectivities determined by ^{1}H NMR of crude reaction mixture. [b] Isolated yield of branched product. [c] Reduction to the diol with $NaBH_4$ was performed instead of oxidation.

To make this methodology more versatile, we investigated the possibility of isolating the product in the aldehyde oxidation state. This is achieved by treating the crude hydroformylation reaction mixture with ethylene glycol and catalytic *p*-TsOH to form the cyclic acetal **1.53** (Figure 1.13). Over the two steps the product was isolated in 72% yield, matching the results obtained from direct oxidation to the carboxylic acid.

Figure 1.13. Acetal protection



1.43 **1.53** (72%)

VI. Conclusions

Formation of all carbon quaternary centers through hydroformylation can be achieved through the use of catalytic directing groups. Use of catalytic amounts of scaffolding ligand **1.27** promotes high regioselectivity for the more hindered, branched aldehyde in the hydroformylation of 1,1-disubstituted olefins – a contradiction to Keulemans' rule. The unique ability of this ligand to utilize reversible covalent bonds to transiently bind a variety of organic functionalities without substantially interfering with the metal-binding domain allows for enhanced control of the selectivity of the transformation. The advantages of this methodology are the use of catalytic amounts of the directing group, use of non-activated substrates and absence of prior installation of the directing group onto the substrate. Furthermore, low reaction temperatures and pressure make this methodology practical for the synthesis of all carbon quaternary centers. These results demonstrate

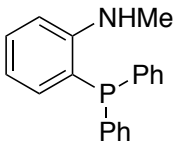
the power of directing groups to overturn inherent reaction selectivities even under mild reaction conditions.

VII. Experimental

General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringes, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). ^{1}H and ^{13}C were performed on either a Varian Unity INOVA 400 MHz or a Varian 500 MHz instrument. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C and external standard (neat H_3PO_4) for ^{31}P NMR. Coupling constants are reported in Hz. Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet), br s (broad singlet). All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm^{-1}. HRMS data were generated in Boston College facilities. Hydroformylation was performed in an Argonaut Technologies Endeavor Catalyst Screening System using 1:1 CO/H_2 supplied by Airgas, Inc.

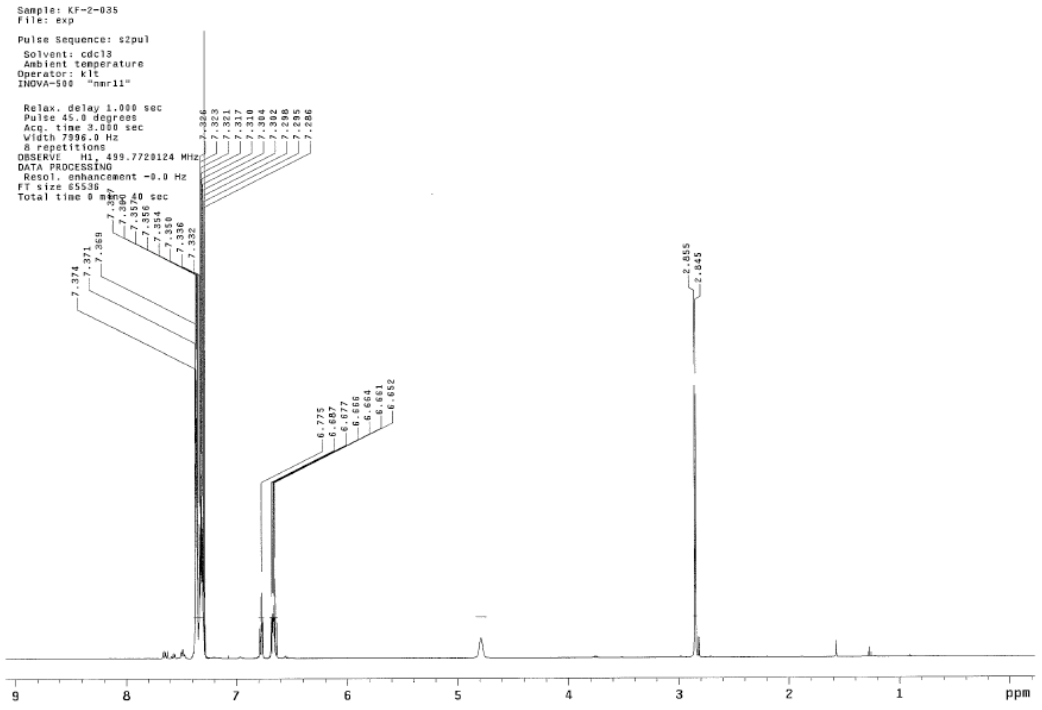
Scaffolding Ligand **1.27** Synthesis and Characterizations



1.41

2-(Diphenylphosphino)-*N*-methylaniline (1.41). To a flame dried 500 mL three-neck round bottom flask was added THF (100 mL) and *N*-methylaniline (5.3 g, 50.0 mmol, distilled from KOH). The solution was cooled to an internal temperature of -78 °C and *n*-BuLi (34 mL, 1.47 M, 50.0 mmol) was added dropwise at a rate that maintained a constant internal temperature of -70 °C. The resulting white suspension was allowed to warm to 0 °C and CO_2 was bubbled through the suspension, resulting in a clearing of the suspension and a rise in temperature to 10 °C. The solution was concentrated under high vacuum and the resulting foamy residue was dissolved in THF (100 mL) and cooled to -70 °C. To this, *t*-BuLi (32.5 mL, 1.54 M, 50.0 mmol) was added dropwise at a rate that maintained a constant internal temperature of -70 °C. The solution was allowed to warm to -20 °C by removing from cold bath for 30 minutes then re-cooled to -78 °C. Chlorodiphenylphosphine (10.2 mL, 55.0 mmol, distilled) was added as a solution in THF (30 mL). The resulting dark orange solution was allowed to warm slowly overnight to room temperature. The solution was added to 1 M HCl (120 mL) and stirred for 45 minutes. The solution was adjusted to pH 14 with 6 M NaOH, the organic layer was collected, and the aqueous layer was extracted with ethyl acetate (4 x 100 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to a yellow solid that was recrystallized from absolute ethanol (75 mL) containing THF (5 mL). The resulting off white

crystals that formed were washed with cold ethanol and collected via vacuum filtration (9.9 g, 73%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.38-7.24 (m, 11H), 6.73-6.79 (m, 1H), 6.58-6.69 (m, 2H), 4.76 (br s, 1H), 2.82 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 152.3 (J_{P-C} = 19.0), 135.8 (J_{P-C} = 7.0), 134.5, 133.8 (J_{P-C} = 19.0), 130.9, 128.9, 128.7 (J_{P-C} = 7.0), 118.8 (J_{P-C} = 7.1), 117.2, 109.8, 31.1; **^{31}P NMR** ($CDCl_3$, 121 MHz) δ -22.2; **IR**: 3383, 3069, 3053, 2931, 2859, 1587, 1504, 1434, 1310, 1168, 744, 696, 479 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{19}H_{19}NP^{+}[M+H]^{+}$: 292.1258, found: 292.1267.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Solvent: cdcl3
Ambient temperature
Operator: klt
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Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 7896.0 Hz
8 repetitions
OBSERVE H1, 499.7729124 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 40 sec
7.326
7.323
7.321
7.317
7.310
7.304
7.302
7.298
7.295
7.286
7.387
7.384
7.359
7.356
7.354
7.350
7.336
7.332
7.374
7.371
7.369
6.775
6.687
6.677
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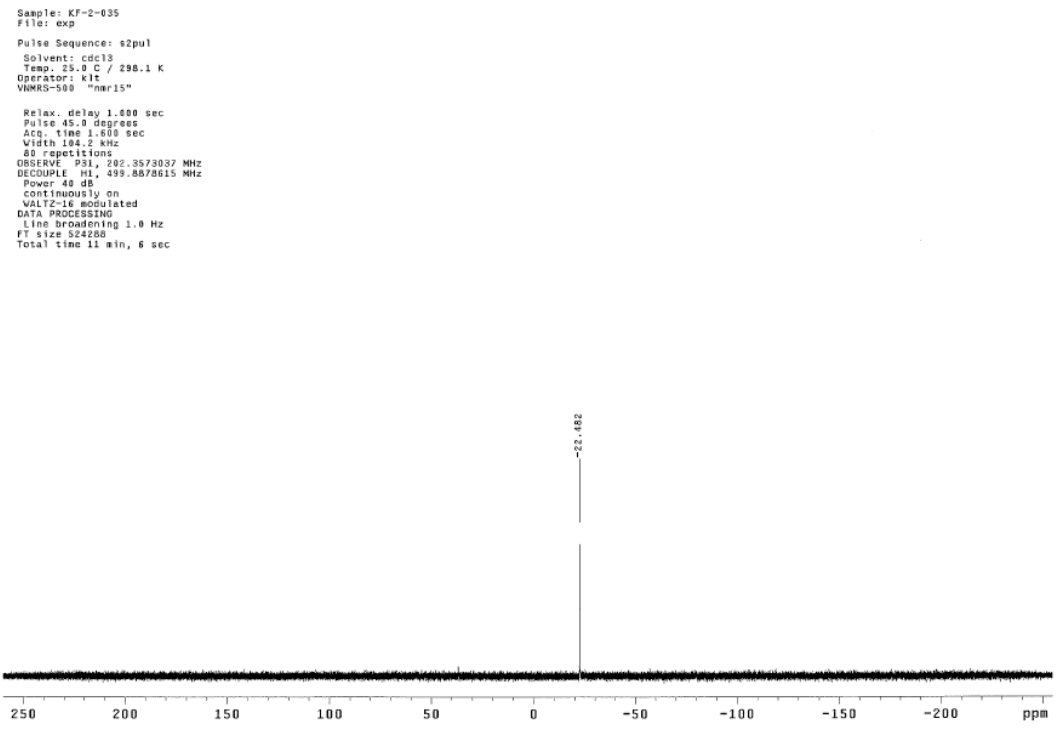
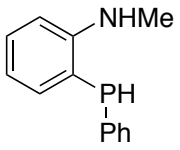
9
8
7
6
5
4
3
2
1
ppm


Sample: KF-2-035
File: exp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"
Relax. delay 1.800 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 104.2 kHz
80 repetitions
OBSERVE P31, 202.3573037 MHz
DECOUPLE H1, 499.8878615 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 524288
Total time 11 min, 6 sec
22.482
250
200
150
100
50
0
-50
-100
-150
-200
ppm



1.42

***N*-Methyl-2-(phenylphosphino)aniline (1.42)**. To a flame dried 100 mL round bottom flask was added THF (60 mL) and 2 (diphenylphosphino)-*N*-methylaniline (9.9 g, 33.9 mmol). The solution was sparged with argon for 15 minutes. Lithium wire (706 mg, 101.2 mmol) was washed with THF to remove mineral oil and added as small pieces. The reaction was stirred at room temperature for 4 hours after sparging with argon for an additional 15 minutes. Degassed, deionized water (7.4 mL) was added via syringe to the deep orange solution. The solution cleared and a white ppt. formed. The reaction was stirred for five minutes and the solvent removed under high vacuum. The residue was quickly extracted with dry, degassed CH_2Cl_2, dried over anhydrous magnesium sulfate, filtered, and concentrated under high vacuum. The crude residue was distilled (120 °C @ 0.3 mmHg) resulting in the title compound as a pale yellow oil (7.0 g, 96%). [Note: Stench! All steps were performed in a fume hood, including solvent removal which was performed using high vacuum and trapping in a cold finger.] **^{1}H NMR** (C_6D_6, 400 MHz) δ 7.46-7.26 (m, 7H), 6.71 (dd, 1H, J = 8.3, 7.4), 6.63 (d, 1H, J = 7.9), 5.46 (d, 1H, $J_{P\text{-}H}$ = 222.3), 4.31 (br s, 1H), 2.80 (d, 3H, J = 5.1); **^{13}C NMR** (C_6D_6, 100 MHz) δ 151.8, 138.1 ($J_{P\text{-}C}$ = 21.9), 134.3, 132.4 ($J_{P\text{-}C}$ = 15.7), 131.7, 129.54 ($J_{P\text{-}C}$ = 4.7), 127.9, 117.1 ($J_{P\text{-}C}$ =8.6), 115.6, 109.8, 30.1; **^{31}P NMR** (C_6D_6, 121 MHz) δ -61.3; **IR**: 3470 (br), 3052, 3000, 2908, 2812, 1588, 1570, 1502, 1452, 1434, 1422, 1310, 1286, 1168, 743, 718, 692, 495 cm^{-1}; **HRMS** (DART TOF) calcd. for $C_{13}H_{15}NP^+$ $[M+H]^+$: 216.0942, found: 216.0954.

distilled

Sample Name:
KF-2-041
Archive directory:

Sample directory:

FidFile: KF-2-041-distilled-H

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Feb 28 2010

Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

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Pulse 45.0 degrees
Acq. time 2.049 sec
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8 repetitions
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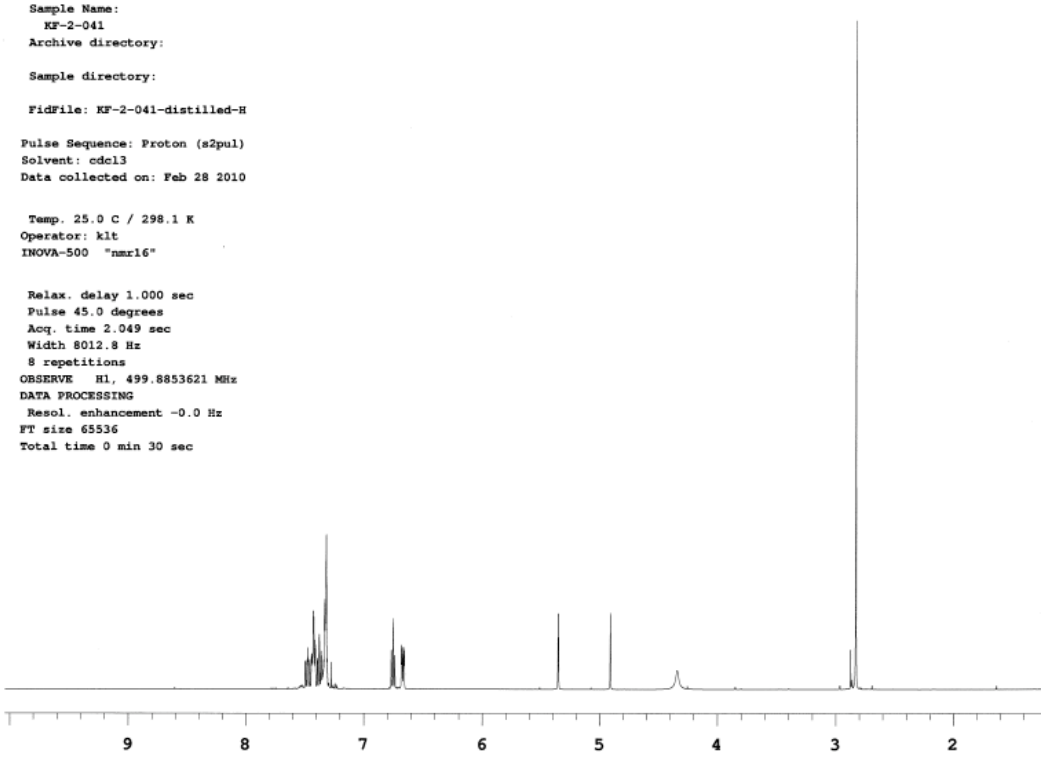
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec



2

Sample: KF-1-266
File: exp

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Solvent: cdcl3
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Pulse 45.0 degrees
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Width 83333.3 Hz
32 repetitions
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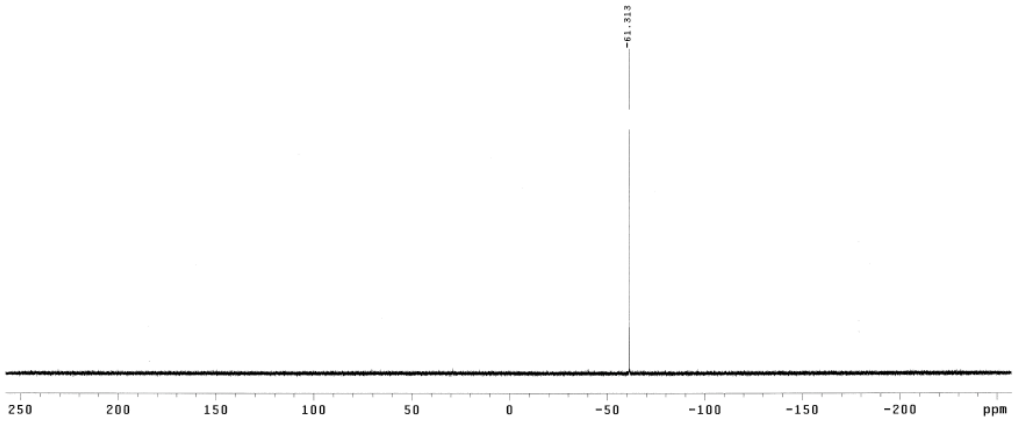
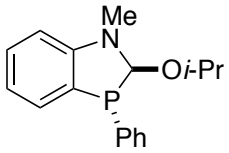
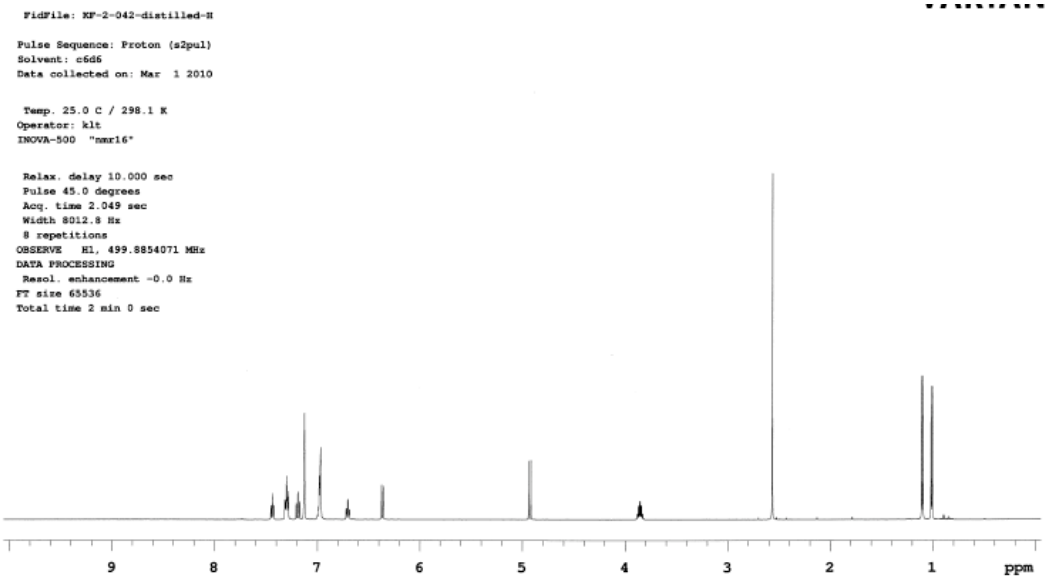
Total time 2 min, 46 sec





1.27

2-Isopropoxy-2,3-dihydro-1*H*-benzo[*d*][1,3]azaphosphole (**1.27**). To a flame dried two-neck 500 mL round bottom flask with reflux condenser was added triisopropyl orthoformate (150 mL) and the solution was sparged with argon for 20 minutes. *N*-methyl-2-(phenylphosphino)aniline (7.0 g, 32.6 mmol) was added and the solution was sparged with argon for an additional 15 minutes. Pyridinium *p*-toluene sulfonate (409 mg, 1.6 mmol) was added to the solution and the flask was immersed in a preheated oil bath (108 °C) and stirred for 1 hour at 160 ˚C. The solvent was distilled off under high vacuum, the flask brought into a dry box under a nitrogen atmosphere and extracted with degassed pentanes (3 x 50 mL). The combined organics were concentrated and Kugelrohr distilled (150 °C @ 0.05 mmHg) affording a clear oil that crystallizes from pentanes to give a white solid (6.8 g, 73%). **^{1}H NMR** (C_6D_6, 300 MHz) δ 7.39 (dd, 1H, J = 7.1, 6.8), 7.26-7.15 (m, 3H), 6.95- 6.92 (m, 3H), 6.68 (dd, 1H, J = 10.0, 6.4), 6.32 (d, 1H, J = 8.0), 4.88 (d, 1H, $J_{P\text{-}H}$ = 8.4), 3.08 (s, 3H), 2.53 (s, 3H); **^{13}C NMR** (C_6D_6, 100 MHz) δ 155.0, 137.4 ($J_{P\text{-}C}$ = 19.5), 133.0 ($J_{P\text{-}C}$ = 23.6), 132.8 ($J_{P\text{-}C}$ = 18.7), 131.7, 129.5, 129.2 ($J_{P\text{-}C}$ = 6.2), 121.6, 118.6 ($J_{P\text{-}C}$ = 7.8), 107.7, 103.9 ($J_{P\text{-}C}$ = 4.7), 52.9 ($J_{P\text{-}C}$ = 13.2), 33.1; **^{31}P NMR** (C_6D_6, 121 MHz) δ -26.5; **IR**: 3053, 2984, 2928, 2882, 2816, 1586, 1472, 1297, 1052, 914, 737, 694, 491 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{15}H_{17}NOP^{+}$ $[M+H]^{+}$: 258.1048, found: 258.1056.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Operator: klt
INOVA-500 "nmr16"
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Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8854071 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 2 min 0 sec
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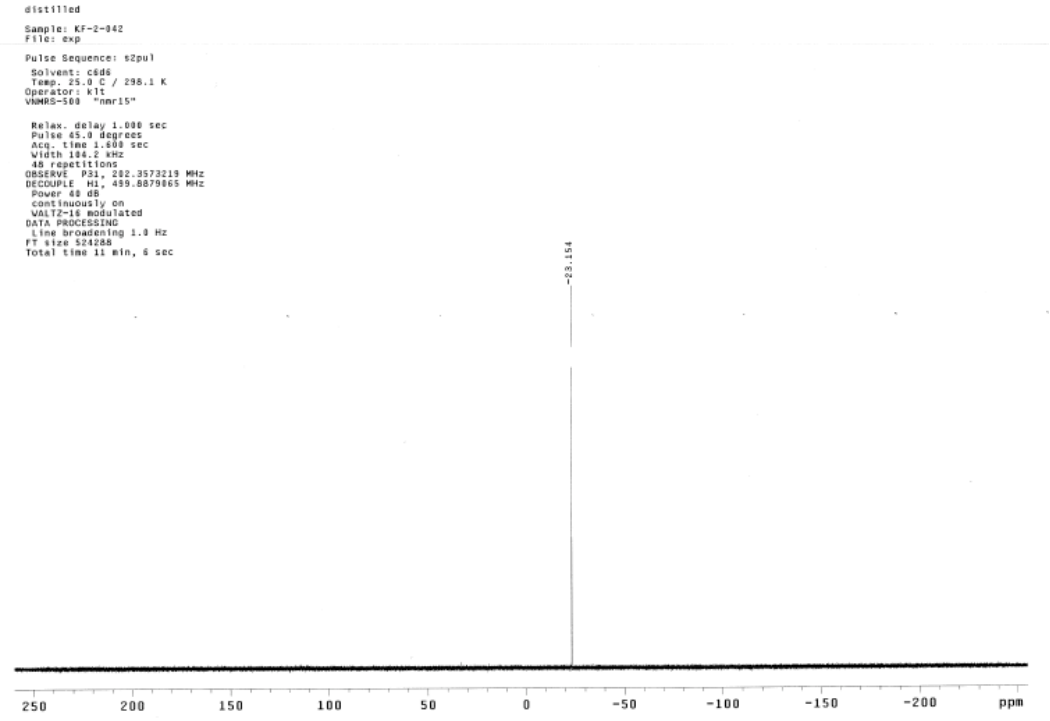
4
3
2
1
ppm


distilled
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Operator: klt
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Pulse 45.0 degrees
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DECOUPLE H1, 499.8879865 MHz
Power 48 dB
continuously on
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FT size 524288
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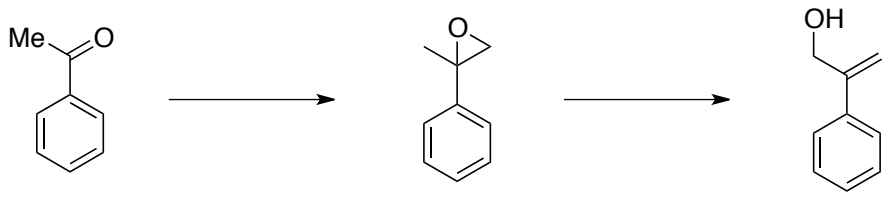
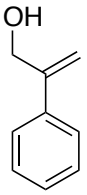
ppm

Substrate Syntheses and Characterizations

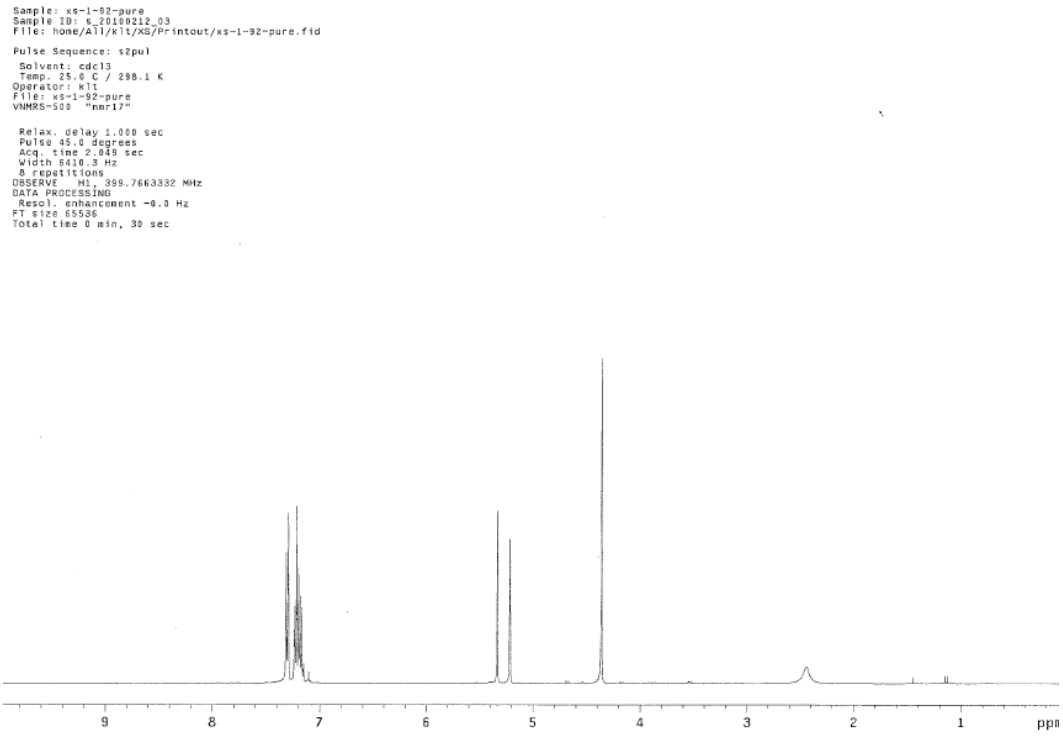


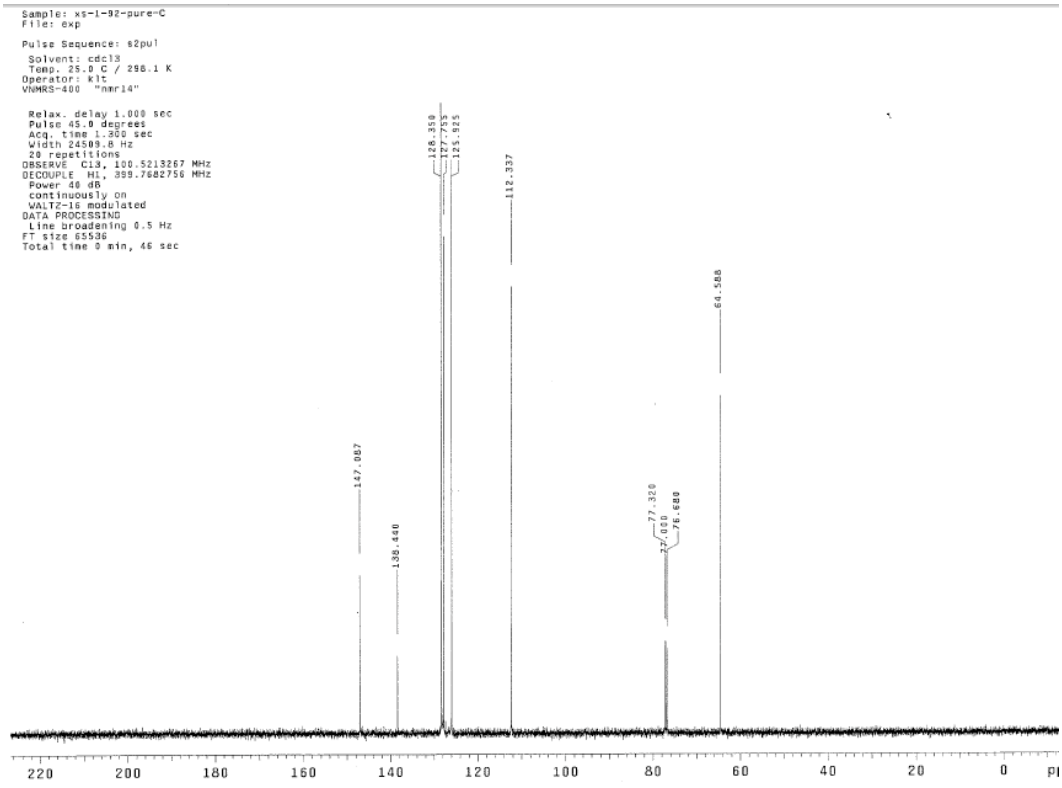
General Procedure A. The substrates were synthesized from the corresponding ketone precursors according to modified literature procedure[1, 2]: To a stirring solution of corresponding ketone substrate (40 mmol) in anhydrous THF (100 mL) was added diiodomethane (4.8 mL, 60 mmol) under nitrogen. Methyllithium (27 mL of 3.0 M in diethoxymethane, 80 mmol) was added dropwise at 0 °C. After stirring at 0 °C for 30 min, the mixture was stirred for one additional hour at room temperature. The resulting mixture was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed to afford crude epoxide, which was used without further purification. To a stirring solution of dry diisopropylamine (8.5 mL, 60 mmol) in anhydrous Et_2O (60 mL), *n*-butyllithium (38 mL of 1.6 M in hexanes, 60 mmol) was added at room temperature under nitrogen. The solution was stirred for 45 min, and then a solution of the crude epoxide in anhydrous Et_2O (80 mL) was added dropwise via syringe pump over a period of 1 h. The solution was stirred at room temperature overnight, followed by refluxing for 4 h. The reaction was quenched with aqueous ammonium chloride and extracted with Et_2O (3 × 50 mL), the combined organic layers were washed with 1.0 N HCl (30 mL), aqueous sodium carbonate (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated. Flash column chromatography

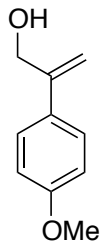
(Hex/EtOAc = 8:1) followed by vacuum distillation (bulb-to-bulb) afforded pure alcohol product.



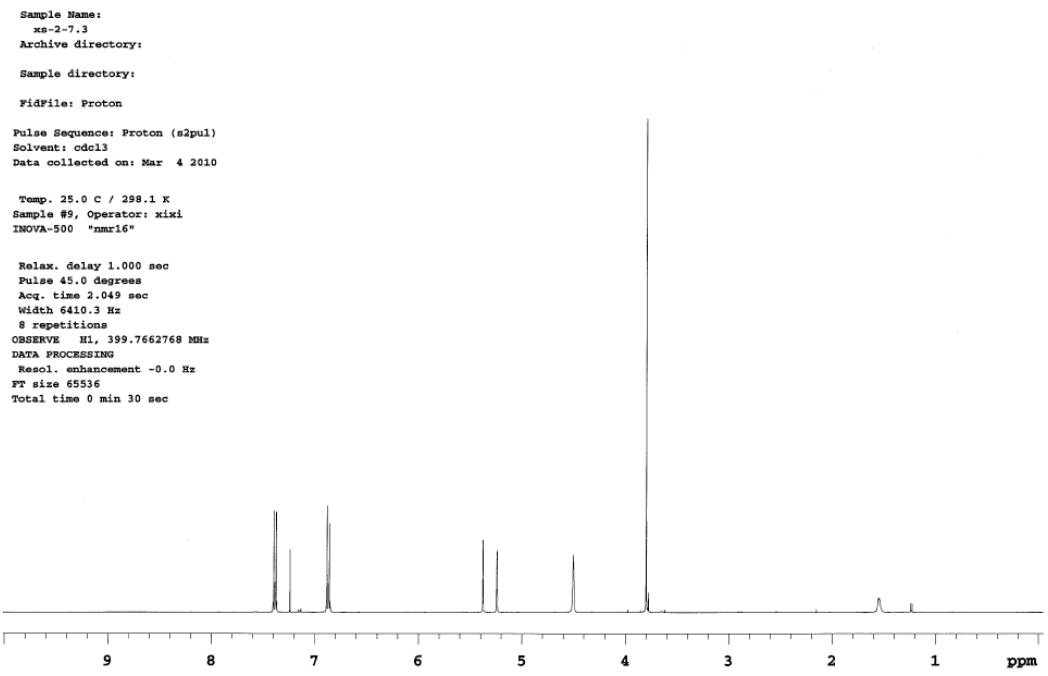
2-Phenylprop-2-en-1-ol (2.28). Using General Procedure A, the alcohol was synthesized from acetophenone and was obtained as a colorless liquid (1.3 g, 24%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.46-7.43 (m, 2H), 7.38-7.29 (m, 3H), 5.48 (s, 1H), 5.36 (d, 1H, J = 0.8), 4.51 (s, 2H), 2.58 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 147.1, 138.4, 128.4, 127.8, 125.9, 112.3, 64.6; **IR**: 3332, 1495, 1444, 1024, 902, 778, 705 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_9H_{11}O$ $[M+H]^+$: 135.08099, found: 135.08081.

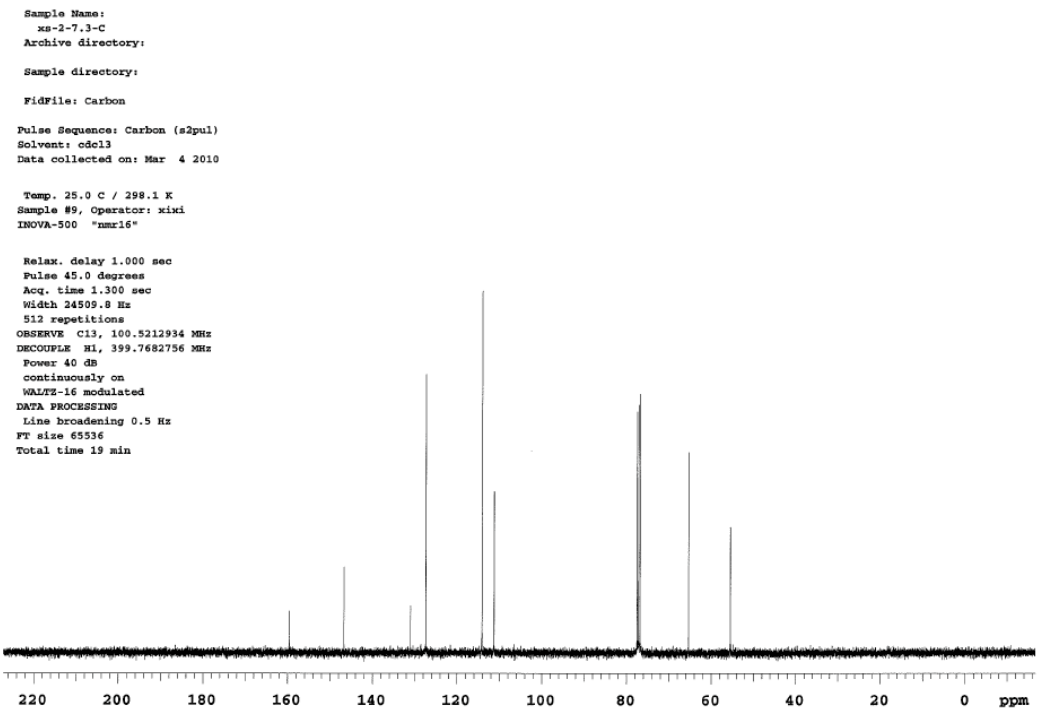


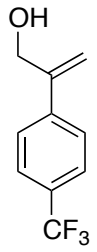




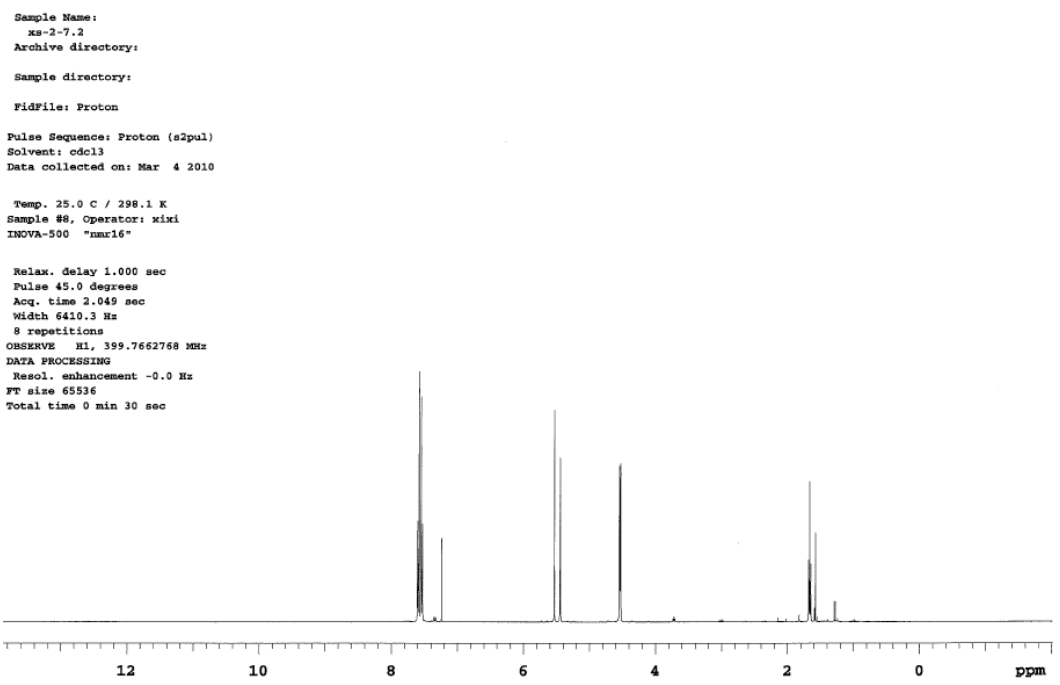
2-(4-Methoxyphenyl)prop-2-en-1-ol. Using General Procedure A, the alcohol was synthesized from 4'-methoxyacetophenone and was obtained as a white solid (2.0 g, 31%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39 (d, 2H, J = 9.2), 6.87 (d, 2H, J = 9.2), 5.38 (d, 1H, J = 0.6), 5.24 (d, 1H, J = 0.9), 4.50 (s, 2H), 3.80 (s, 3H), 1.54 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 159.4, 146.6, 130.8, 127.2, 113.9, 111.1, 65.2, 55.3; **IR**: 3240, 1515, 1253, 1186, 1110, 1029, 897, 838 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{13}O_2$ $[M+H]^+$: 165.09155, found: 165.09171.

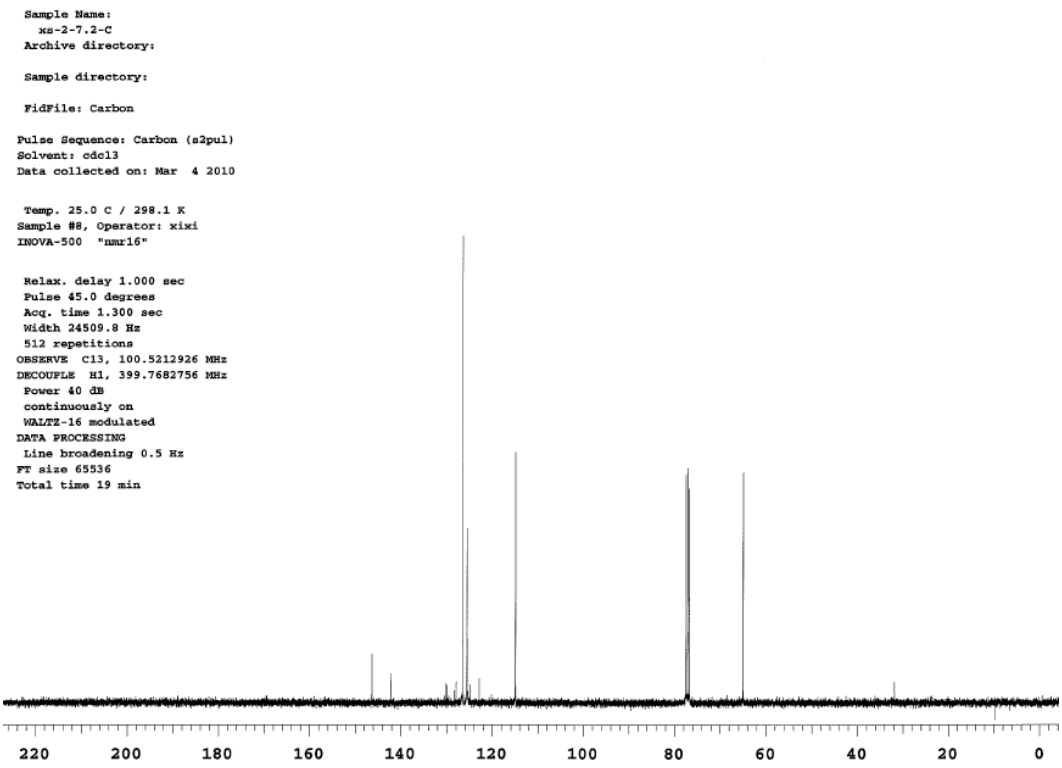

Sample Name:
xs-2-7.3
Archive directory:
Sample directory:
FidFile: Proton
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 4 2010
Temp. 25.0 C / 298.1 K
Sample #9, Operator: xixi
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7662768 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec
9
8
7
6
5
4
3
2
1
ppm

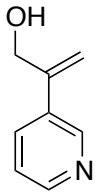

Sample Name:
xs-2-7.3-C
Archive directory:
Sample directory:
FidFile: Carbon
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Mar 4 2010
Temp. 25.0 C / 298.1 K
Sample #9, Operator: xixi
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
512 repetitions
OBSERVE C13, 100.5212934 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min
220
200
180
160
140
120
100
80
60
40
20
0
ppm



2-(4-(Trifluoromethyl)phenyl)prop-2-en-1-ol. Using General Procedure A, the alcohol was synthesized from 4'-(trifluoromethyl)acetophenone and was obtained as a white solid (2.3 g, 28%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.59 (d, 2H, *J* = 8.4), 7.54 (d, 2H, *J* = 8.4), 5.53 (d, 1H, *J* = 0.8), 5.44 (d, 1H, *J* = 1.0), 4.54 (d, 2H, *J* = 5.6), 1.66 (t, 1H, *J* = 2.0); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 146.1,142.1, 129.9 (q, *J* =32.0), 126.4, 125.4, 123.8 (q, *J* = 205.4), 114.8, 64.8 ; **IR**: 3320, 1326, 1166, 1117, 1068, 845 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{10}F_3O$ $[M+H]^+$: 203.06837, found: 203.06881.







2-(pyridin-3-yl)prop-2-en-1-ol. Using General Procedure A, the alcohol was synthesized from 3-acetylpyridine and was obtained as a colorless liquid (0.63 g, 12%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.66 (d, 1H, J = 2.0), 8.49-8.48 (m, 1H), 7.79-7.77 (m, 1H), 7.29-7.26 (m, 1H), 5.51 (d, 1H, J = 0.7), 5.48 (d, 1H, J = 1.2), 4.54 (s, 2H), 3.57 (br s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 148.6, 147.3, 144.7, 134.6, 133.8, 123.4, 114.4, 64.4; **IR**: 3212, 1414, 1024, 908, 815, 700, 632 cm^{-1}; **HRMS** (DART-TOF) calcd. for C_8H_9NO $[M+H]^+$: 136.07624, found: 136.07601.

Sample Name:
xs-1-224-pure
Archive directory:

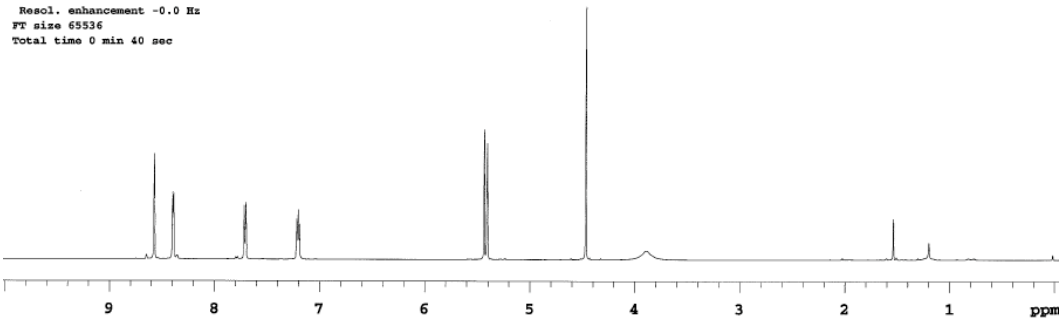
Sample directory:

FidFile: Proton

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jul 17 2010

Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 7996.0 Hz
8 repetitions
OBSERVE H1, 499.7720124 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 40 sec



Sample Name:
xs-1-224-pure-C
Archive directory:

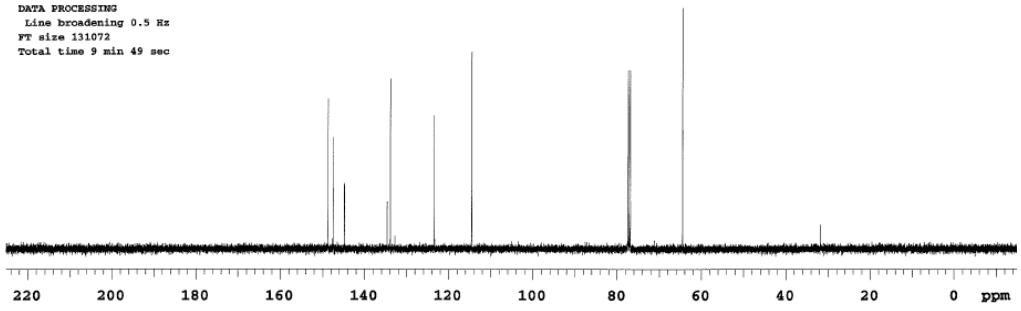
Sample directory:

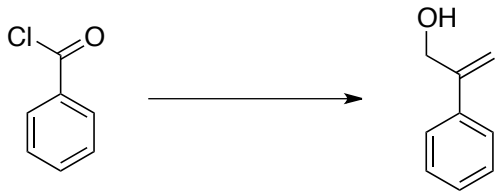
FidFile: Carbon

Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Jul 16 2010

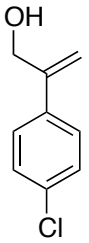
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
40 repetitions
OBSERVE C13, 125.6677582 MHz
DECOUPLE H1, 499.7745112 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 9 min 49 sec

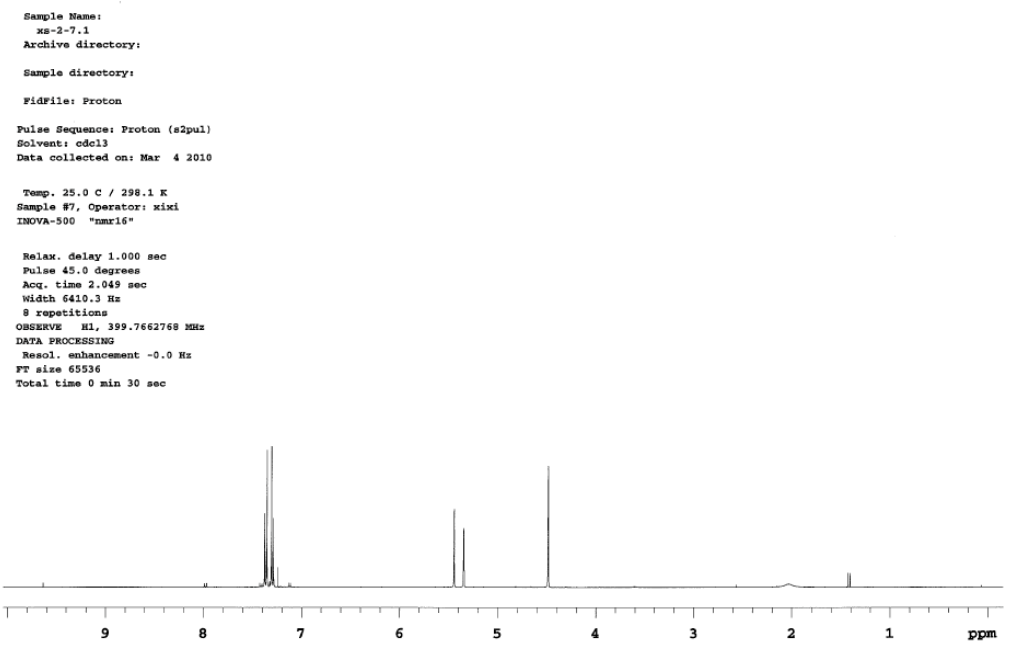


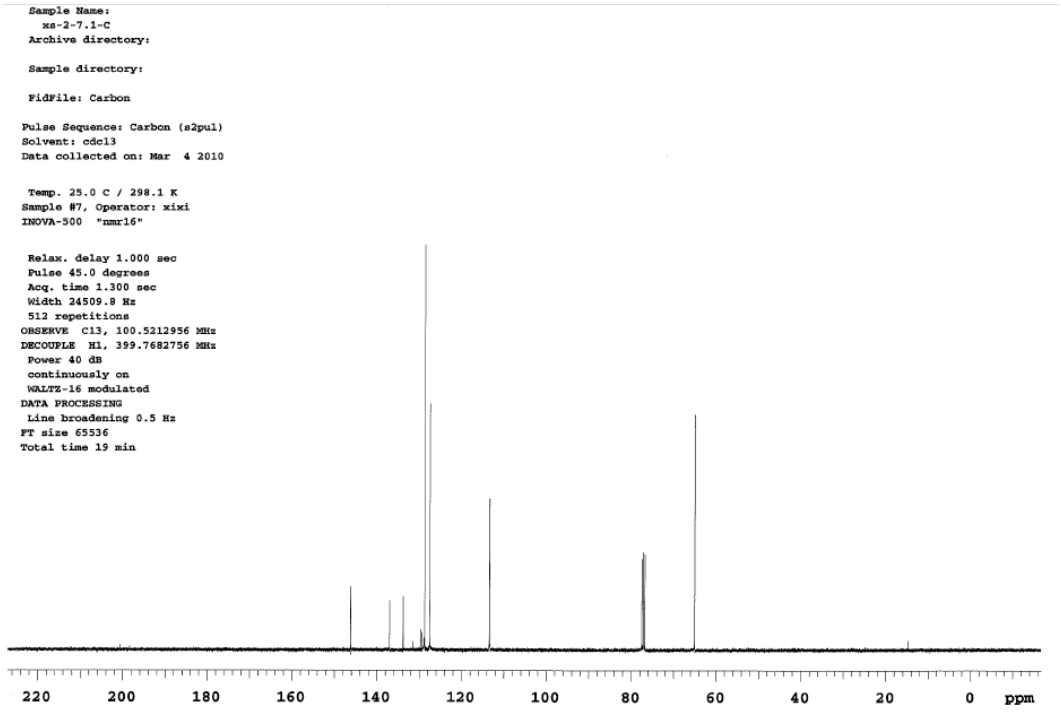


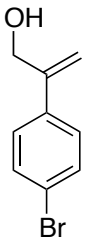
General Procedure B. Substrates were synthesized from the corresponding benzoyl chloride precursors according to literature procedure[3]: To a stirring solution of lithium bromide (3.8 g, 44 mmol), corresponding benzoyl chloride (20 mmol) and chloroiodomethane (3.2 mL, 44 mmol) in anhydrous THF (60 mL) under nitrogen, methyllithium (15 mL of 3.0 M in diethoxymethane, 46 mmol) was added dropwise over 30 min at -78 °C. After stirring at -78 °C for 1 h, the mixture was warmed to room temperature and stirred overnight. Lithium iodide (2.7 g, 20 mmol) was added and solution was stirred for additional 40 h. The reaction was quenched with aqueous ammonium chloride and the solvent was removed. The residue was extracted with Et_2O (3 × 50 mL). Combined organic layers were washed with 0.5 M aqueous sodium thiosulfate (30 mL) and aqueous sodium bicarbonate (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography (Hex/EtOAc = 8:1), followed by vacuum distillation (bulb-to-bulb), afforded pure alcohol product.



2-(4-Chlorophenyl)prop-2-en-1-ol. Using General Procedure B, the alcohol was synthesized from 4-chlorobenzoyl chloride and was obtained as a colorless liquid (0.91 g, 27%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36 (d, 2H, *J* = 8.8), 7.30 (d, 2H, *J* = 8.8), 5.44 (d, 1H, *J* = 0.8), 5.34 (d, 1H, *J* = 1.2), 4.48 (dd, 2H, *J* = 0.8, 1.2), 2.03 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 146.1, 136.9, 133.7, 128.6, 127.4, 113.3, 64.9; **IR**: 3338, 1493, 1091, 1012, 909, 832 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_9H_{10}Cl_1O$ $[M+H]^+$: 169.04202, found: 169.04258.







2-(4-Bromophenyl)prop-2-en-1-ol. Using General Procedure B, the alcohol was synthesized from 4-bromobenzoyl chloride and was obtained as a slightly yellow solid (1.3 g, 30%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45 (d, 2H, *J* = 8.4), 7.30 (d, 2H, *J* = 8.4), 5.45 (d, 1H, *J* = 0.8), 5.34 (d, 1H, *J* = 1.2), 4.48 (s, 2H), 1.77 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 146.1, 137.4, 131.6, 127.7, 121.9, 113.3, 64.8; **IR**: 3326, 1488, 1072, 1007, 907, 828 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_9H_{10}Br_1O$ $[M+H]^+$: 212.99150, found: 212.99138.

Sample Name:
xs-2-7.5
Archive directory:

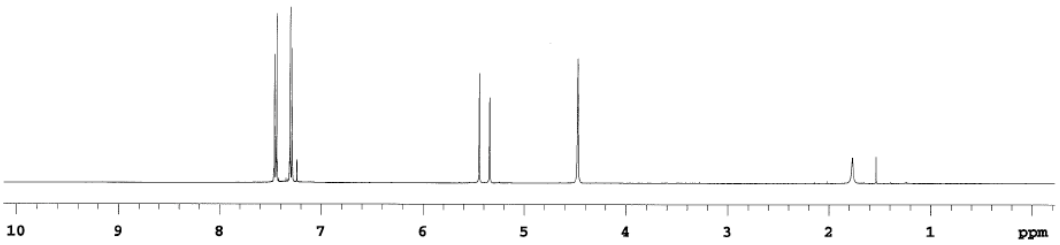
Sample directory:

FidFile: Proton

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 4 2010

Temp. 25.0 C / 298.1 K
Sample #11, Operator: xixi
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7662768 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec



Sample Name:
xs-2-7.5-C
Archive directory:

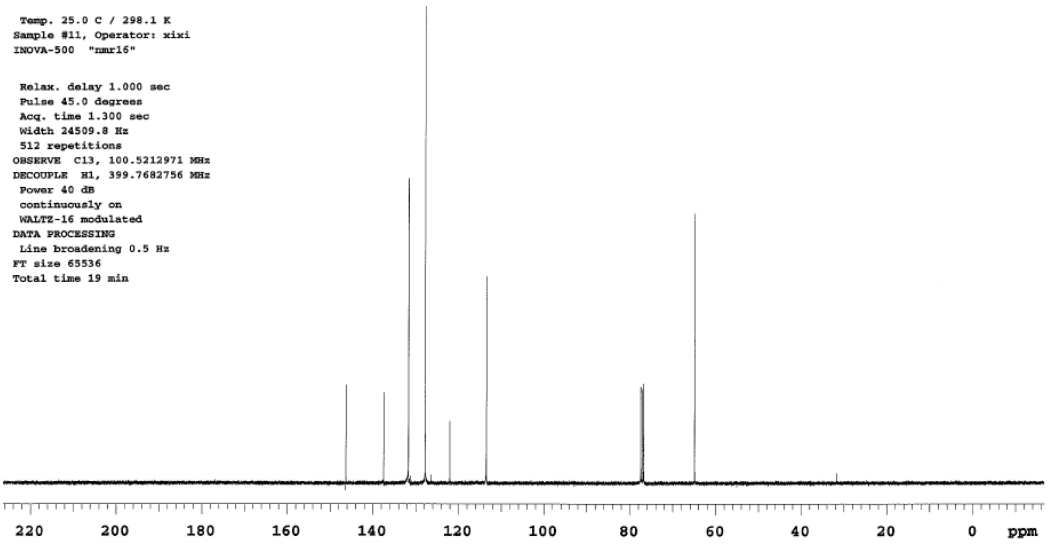
Sample directory:

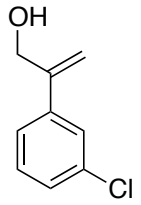
FidFile: Carbon

Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Mar 4 2010

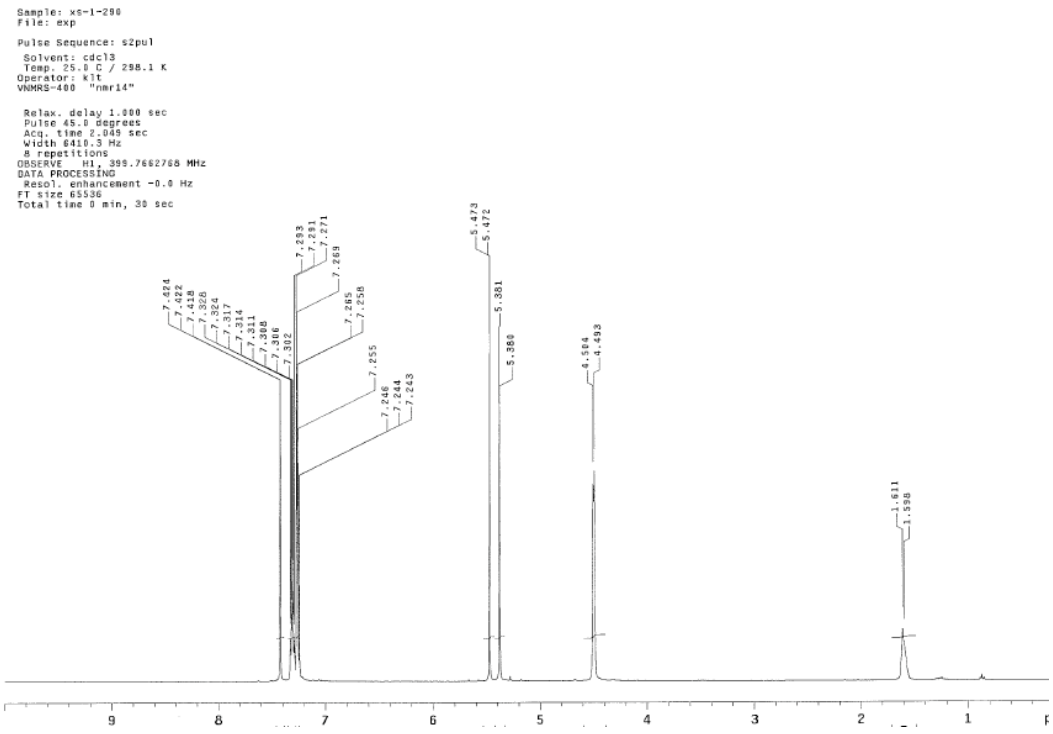
Temp. 25.0 C / 298.1 K
Sample #11, Operator: xixi
INOVA-500 "nmr16"

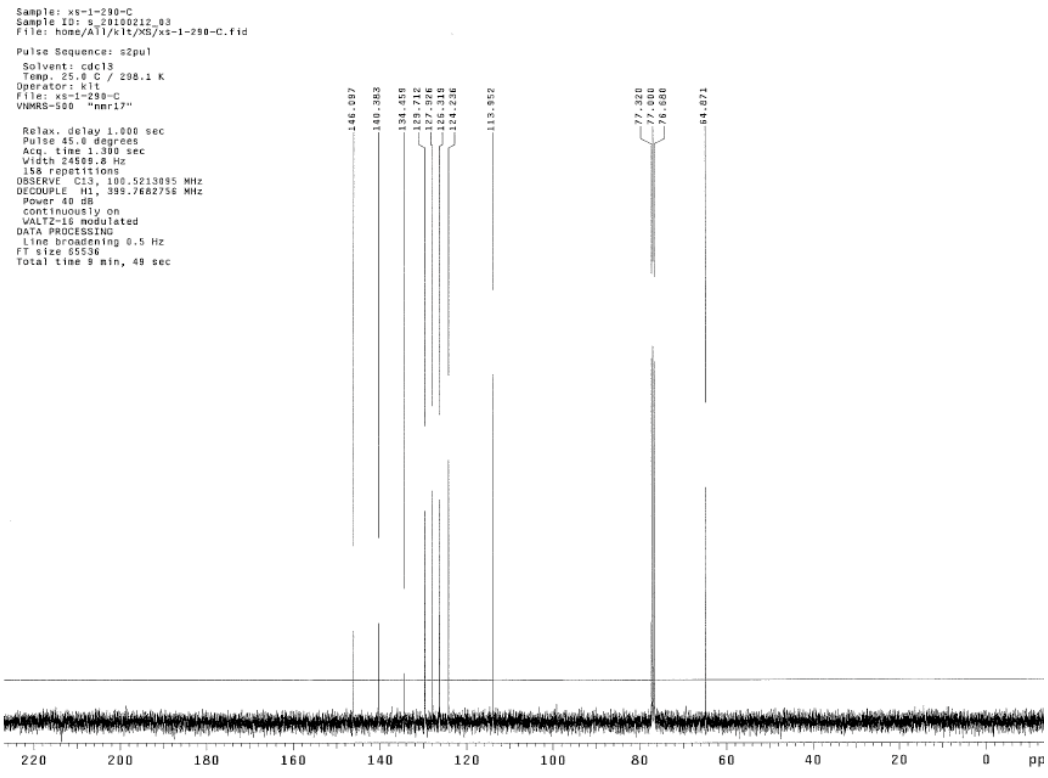
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
512 repetitions
OBSERVE C13, 100.5212971 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min

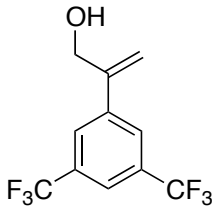




2-(3-Chlorophenyl)prop-2-en-1-ol. Using General Procedure B, the alcohol was synthesized from 3-chlorobenzoyl chloride and was obtained as a colorless liquid (0.78 g, 23%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.42 (s, 1H), 7.33-7.24 (m, 3H), 5.47 (d, 1H, J = 0.4), 5.38 (d, 1H, J = 0.4), 4.50 (s, 2H), 1.61 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 146.1, 140.4, 134.4, 129.7, 127.9, 126.3, 124.2, 114.0, 64.9; **IR**: 3318, 2924, 1593, 1562, 1478, 1044, 911, 789, 690 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_9H_{10}Cl_1O$ $[M+H]^+$: 169.04202, found: 169.04174.

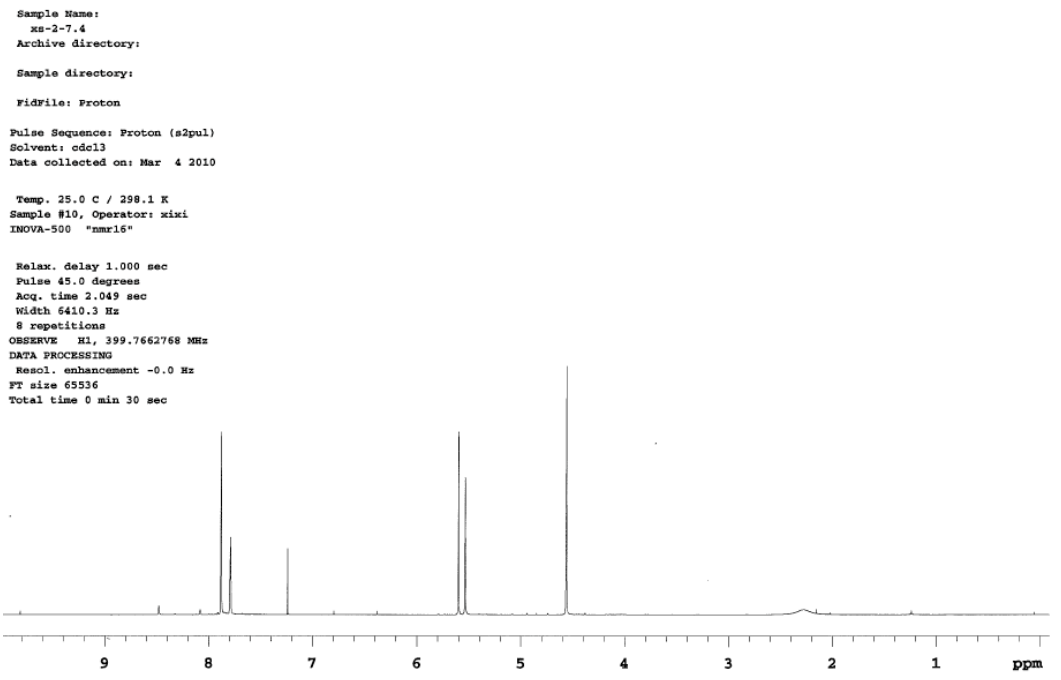


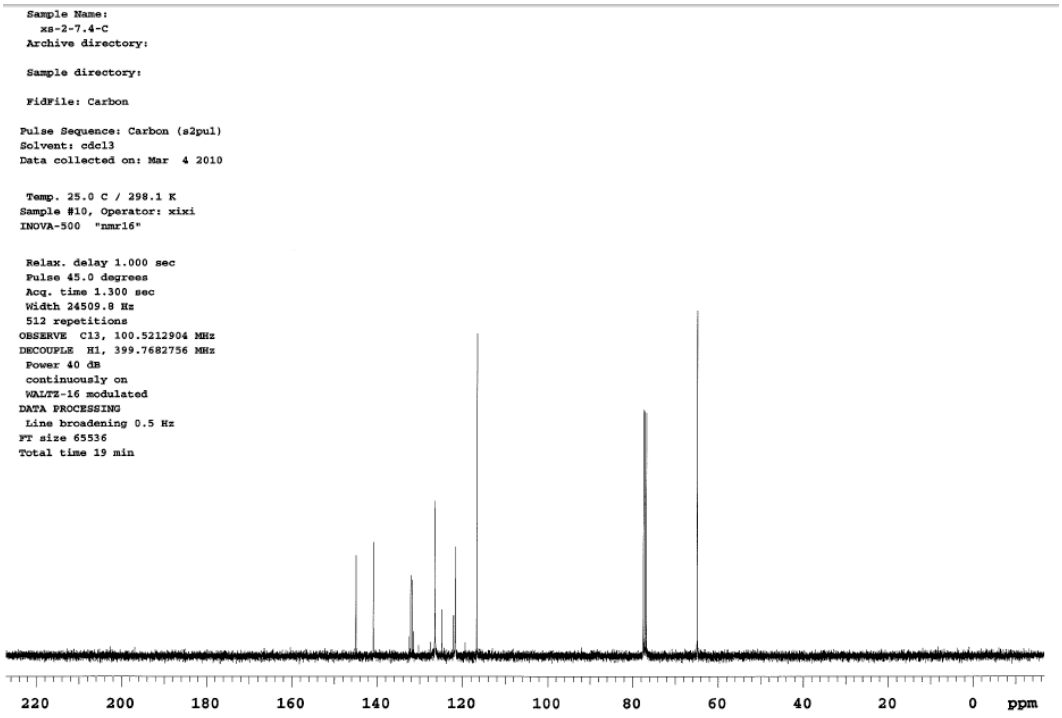


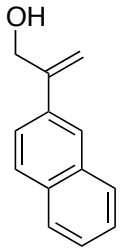


2-(3,5-Bis(trifluoromethyl)phenyl)prop-2-en-1-ol. Using General Procedure B, the alcohol was synthesized from 3,5-bis(trifluoromethyl)benzoyl chloride and was obtained as a colorless liquid (1.3 g, 24%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.88 (s, 2H), 7.79 (s, 1H,), 5.60 (s, 1H), 5.54 (t, 1H, *J* = 1.2), 4.56 (s, 2H), 2.28 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 144.8, 140.7, 131.8 (q, *J* = 33.5), 126.3, 123.2 (q, *J* = 271.6), 121.5, 116.4, 64.7 ; **IR**: 3328, 1375, 1274, 1171, 1120, 897, 846,

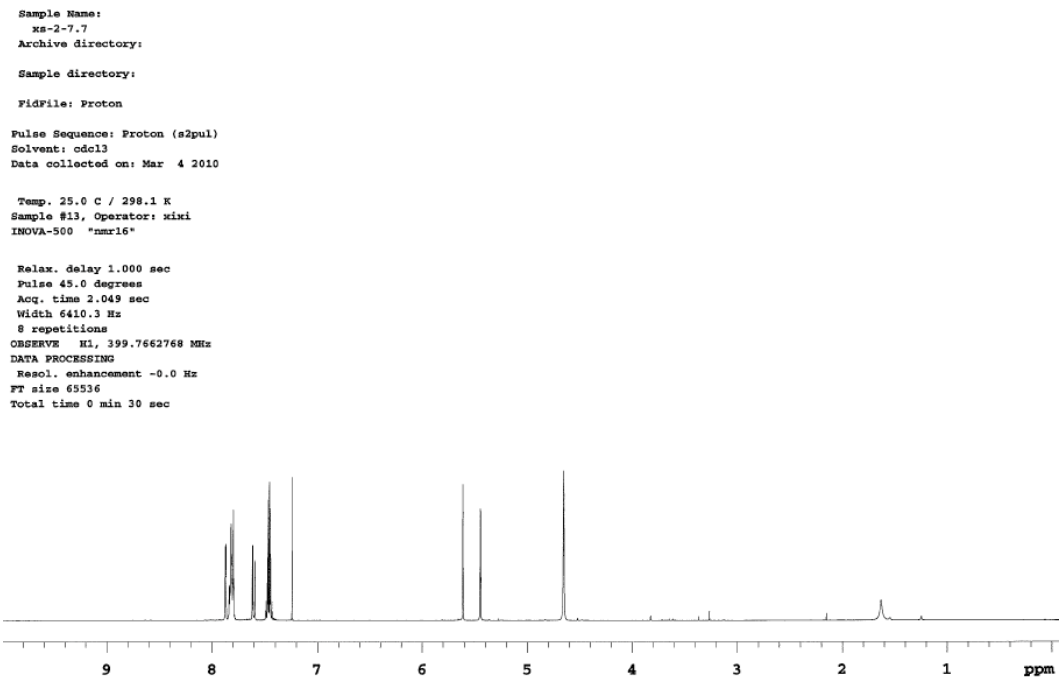
700, 682 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_9F_6O$ $[M+H]^+$: 271.05576, found: 271.05627.

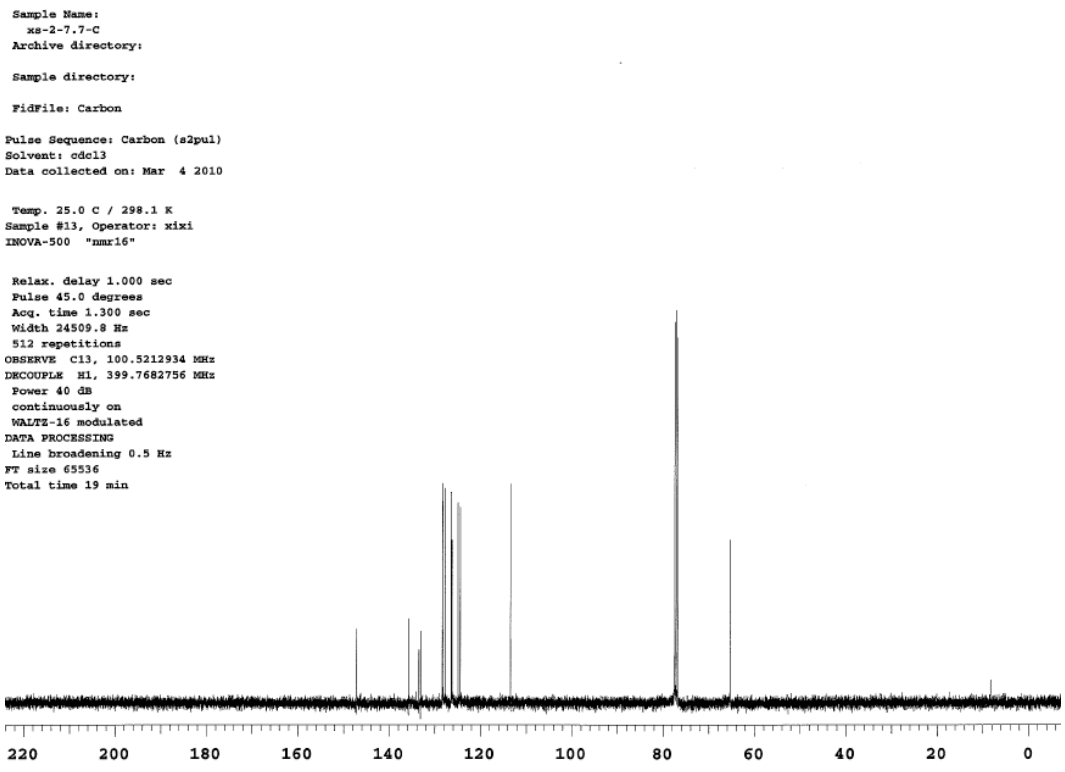


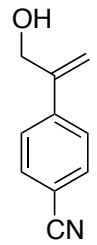




2-(Naphthalen-2-yl)prop-2-en-1-ol. Using General Procedure B, the alcohol was synthesized from 2-naphthoyl chloride and was obtained as a white solid (0.68 mg, 19%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.87 (s, 1H), 7.84-7.79 (m, 3H), 7.60 (dd, 1H, J = 2.0, 8.4), 7.47-7.44 (m, 2H), 5.61 (d, 1H, J = 0.8), 5.45 (d, 1H, J = 1.2), 4.66 (s, 2H), 1.63 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 147.0, 135.6, 133.3, 133.0, 128.2, 128.1, 127.5, 126.2, 126.1, 124.8, 124.3, 113.2, 65.2; **IR**: 3302, 1091, 1044, 901, 860, 824, 746, 480 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{13}H_{13}O$ $[M]^+$: 184.08881, found: 184.08846.







4-(3-Hydroxyprop-1-en-2-yl)benzonitrile. Using General Procedure B, the alcohol was synthesized from 4-cyanobenzoyl chloride and was obtained as a colorless liquid (760 mg, 24%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.67-7.65 (m, 2H), 7.60-7.57 (m, 2H), 5.61 (d, 1H, J = 0.6), 5.53 (d, 1H, J = 0.6), 4.57 (s, 2H), 1.81 (br s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 145.7, 143.1, 132.3, 126.8, 118.8, 115.9, 111.3, 64.6; **IR**: 3414, 2227, 1605, 1504, 1403, 1105, 1016, 914, 842, 542 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{10}NO$ $[M+H]^+$: 160.07624, found: 160.07571.

```
 Sample Name:
   KF-2-053
 Archive directory:

 Sample directory:

 FidFile: KF-2-053

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 18 2010

Operator: klt
INOVA-500  "nmr16"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 3.000 sec
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 8 repetitions
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DATA PROCESSING
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FT size 65536
Total time 0 min 40 sec
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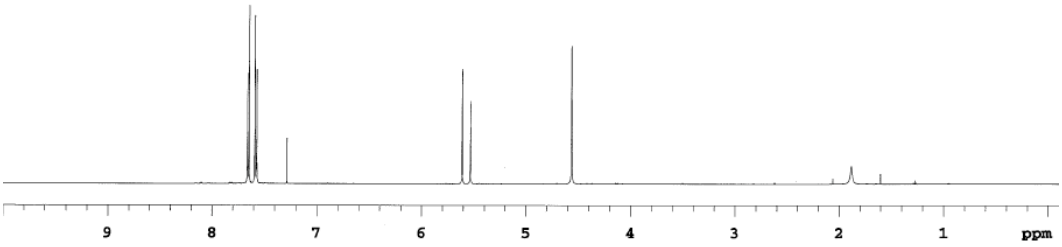


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  Archive directory:

  Sample directory:

  FidFile: KF-2-053-C_2_053_01

 Pulse Sequence: Carbon (s2pul)
 Solvent: cdcl3
 Data collected on: Mar 17 2010

  Temp. 25.0 C / 298.1 K
 Sample #40, Operator: kwame
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  Width 26595.7 Hz
  512 repetitions
 OBSERVE  C13, 100.5212962 MHz
 DECOUPLE  H1, 399.7682756 MHz
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 DATA PROCESSING
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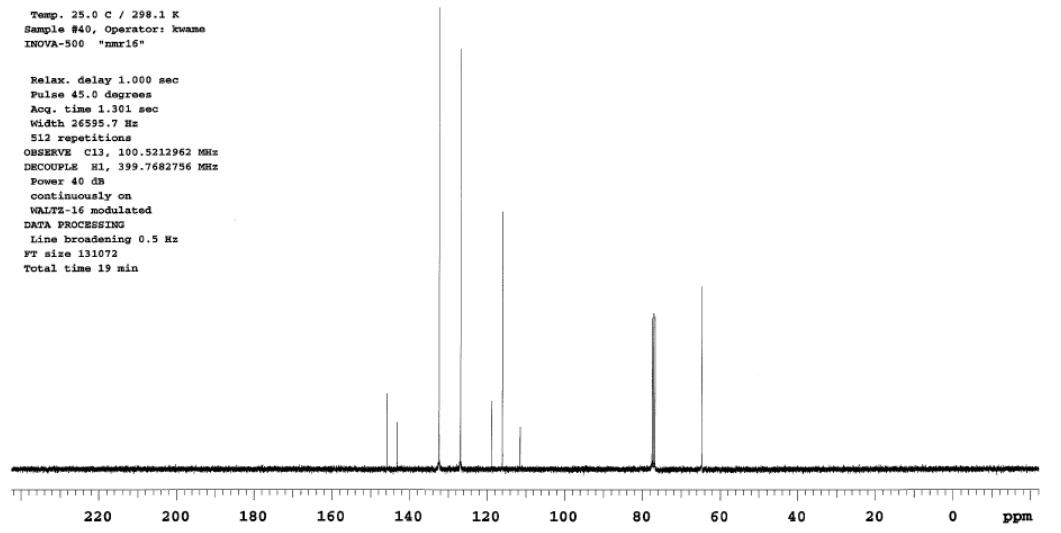
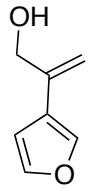
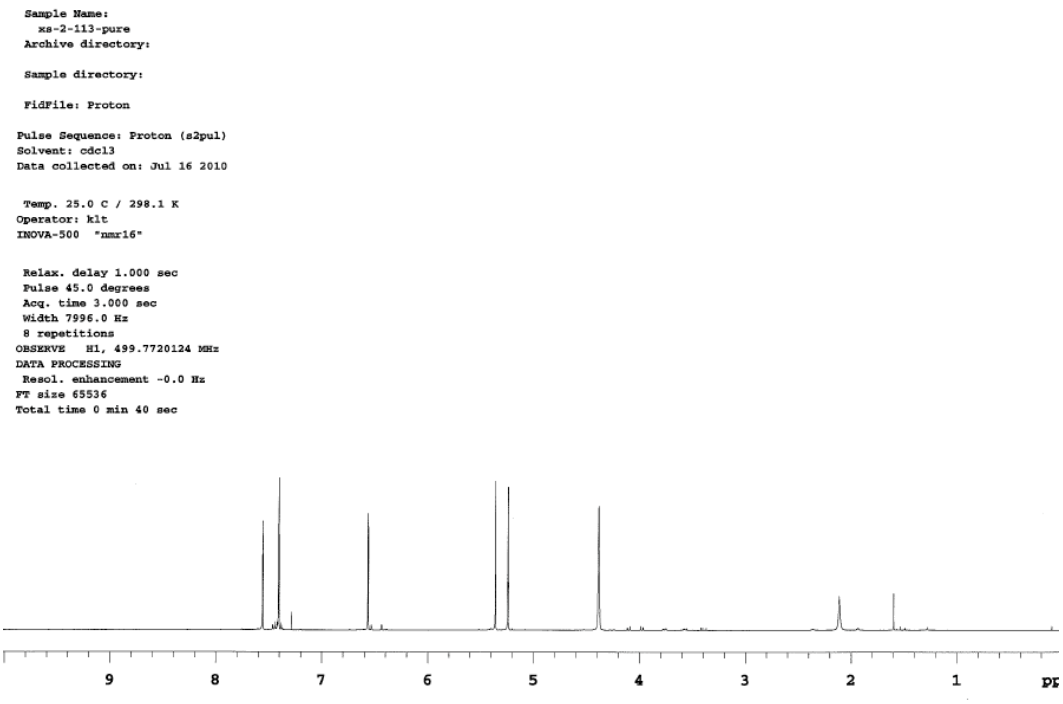
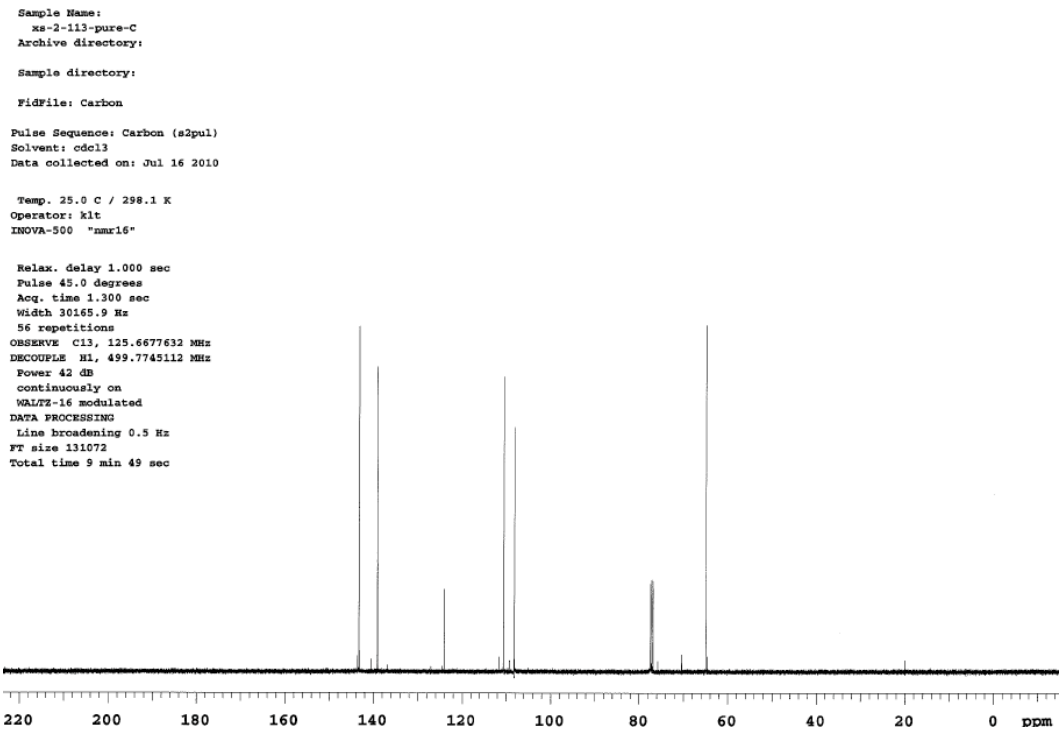
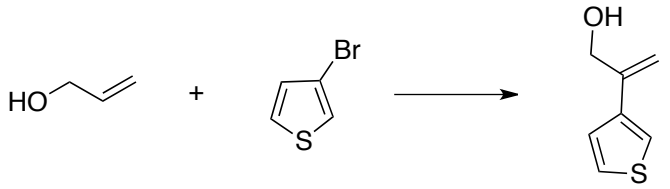




2-(furan-3-yl)prop-2-en-1-ol. The alcohol was synthesized from 3-furoyl chloride and was obtained as a light yellow liquid (0.96 g, 39%). Characterization data of this compound was previously reported.[4]

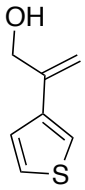






General Procedure C. Substrates were synthesized from allyl alcohol and the corresponding aryl bromide precursors according to literature procedure[5]. To the oven dried 25 mL round bottomed flask charged with palladium(II) acetate (90 mg, 0.40 mmol) and 1,3-bis(diphenylphosphino)propane (330 mg, 0.80 mmol), corresponding aryl bromide (10 mmol, see below), solvent (20 mL, see below), 2-propen-1-ol (3.4 mL, 50 mmol) and triethylamine (2.2 mL, 16 mmol) were added under nitrogen. After stirring at 125 °C for 30 h, the reaction was cooled to room temperature and 1.0 N HCl (100 mL) was added, followed by stirring at rt for 1 h. Aqueous sodium carbonate (100 mL) was added and reaction was stirred for additional 10 min. The resulting mixture was extracted with CH_2Cl_2 (3 × 80 mL). Combined organic layers

were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, and solvent was removed. Flash column chromatography (Hex/EtOAc = 8:1) afforded pure alcohol product.



2-(Thiophen-3-yl)prop-2-en-1-ol. Using General Procedure C, the alcohol was synthesized from 3-bromothiophene with anhydrous [bmim][BF_4] as solvent and was obtained as a white solid (210 mg, 15%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31-7.24 (m, 3H), 5.48 (s, 1H), 5.30 (s, 1H), 4.49 (s, 2H), 1.57 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 142.0, 139.7, 125.6, 120.8, 111.4, 79.2, 65.2; **IR**: 3333, 3104, 2923, 1461, 1106, 1038, 901, 872, 790, 730, 602 cm^{-1}; **HRMS** (DART-TOF) calcd. for C_7H_9OS $[M+H]^+$: 141.03741, found: 141.03739.

Sample Name:
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Archive directory:

Sample directory:

FidFile: Proton

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Apr 14 2010

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INOVA-500 "nmr16"

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Pulse 45.0 degrees
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DATA PROCESSING
Resol. enhancement -0.0 Hz
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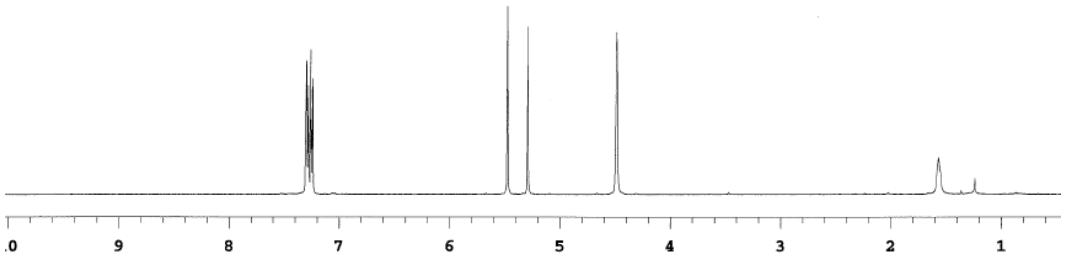
Total time 0 min 30 sec



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Archive directory:

Sample directory:

FidFile: Carbon

Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Apr 14 2010

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Sample #6, Operator: xixi
INOVA-500 "nmr16"

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Pulse 45.0 degrees
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DATA PROCESSING
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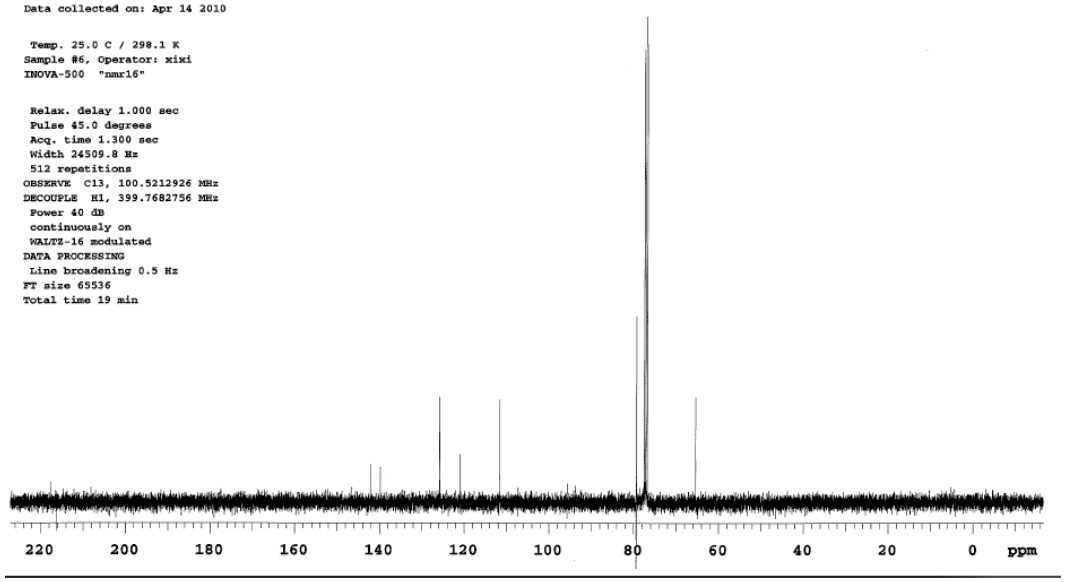
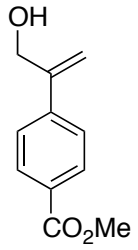
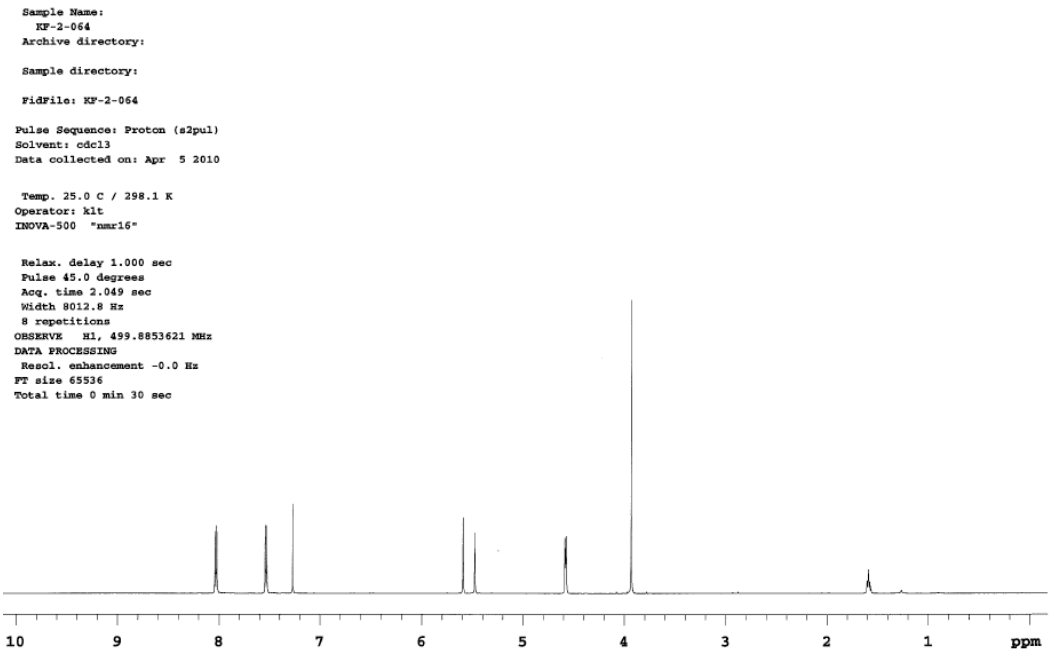
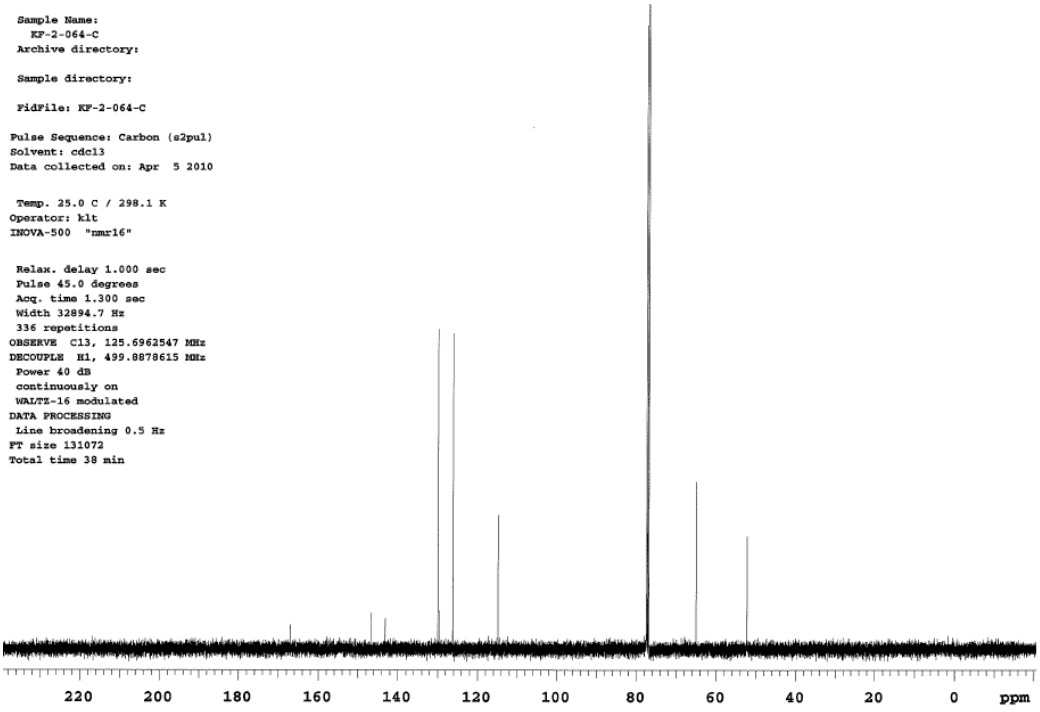
Total time 19 min





Methyl 4-(3-hydroxyprop-1-en-2-yl)benzoate. Using General Procedure C, the alcohol was synthesized from methyl 4-bromobenzoate with anhydrous [bmim][BF_4] and anhydrous DMSO (1:1) as solvent and was obtained as a slightly yellow solid (810 mg, 42%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.03 (d, 2H, *J* = 7.0), 7.41 (d, 2H, *J* = 7.0), 5.59 (s, 1H), 5.48 (s, 1H), 4.58 (d, 2H, *J* = 5.5), 3.93 (s, 3H), 1.59 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 166.8, 146.5, 143.0, 129.8, 129.5, 126.0, 114.7, 64.8, 52.1; **IR**: 3315, 1718, 1432, 1284, 1193, 1099, 905, 722 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{13}O_3$ $[M+H]^+$: 193.08647, found: 193.08643.





Optimization of Branch Selective Hydroformylation

General Hydroformylation Procedure A. The oven dried glass reaction vial was placed in the Endeavor, and 2-phenylprop-2-en-1-ol, **1.43** (20 mg, 0.15 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium(I) (1.6 mg, 6.0×10^{-3} mmol, 4.0 mol%), ligand **1.27** (8.6 mg, 3.0×10^{-2} mmol, 20 mol%), *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol, 0.20 mol%) and benzene (to total volume of 1 mL) was injected, followed by injection of additional benzene (0.5 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at corresponding temperature (see below) for 10 minutes. Stirring was stopped, the Endeavor was charged with corresponding pressure (see below) of CO/H_2, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant

temperature (see below) and pressure (see below) of CO/H_2 for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction mixture was removed from the Endeavor and concentrated. The residue was redissolved in *t*-butanol (0.75 mL) and 2-methyl-2-butene (0.16 mL, 1.5 mmol, 10.0 eq.) followed by addition of a solution of $NaClO_2$ (80%, 68 mg, 0.60 mmol, 4.0 eq.) and NaH_2PO_4 (72 mg, 0.60 mmol, 4.0 eq.) in H_2O (0.4 mL). The solution was stirred at room temperature overnight. The resulting mixture was concentrated and redissolved in EtOAc (0.75 mL), followed by addition of 10% HCl (0.18 ml) and brine (0.18 mL). The solution was extracted with EtOAc (3 × 5 mL). Combined organic layers were dried over $MgSO_4$, filtered and solvent was removed. 1,3,5-Trimethoxybenzene (100 mL of 0.15 M in $CDCl_3$, 0.015 mmol) was added as standard and ^1H NMR was taken to analyze yields and selectivities.

General Hydroformylation Procedure B. The oven dried glass reaction vial was placed in the Endeavor, and 2-phenylprop-2-en-1-ol, **1.43** (80 mg, 0.60 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium(I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol%), triphenylphosphine (13 mg, 4.8×10^{-2} mmol, 8.0 mol%) and benzene (to total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 45 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi CO/H_2, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature and pressure of 45 °C and 400 psi CO/H_2 for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction was

removed from the Endeavor and concentrated. 1,3,5-Trimethoxybenzene (400 mL of 0.15 M in $CDCl_3$, 0.060 mmol) was added as standard and ^1H NMR was taken to analyze conversion.

General Hydroformylation Procedure C. The oven dried glass reaction vial was placed in the Endeavor, and 2-phenylprop-2-en-1-ol, **1.43** (80 mg, 0.60 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium(I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol%), triphenylphosphine (13 mg, 4.8×10^{-2} mmol, 8.0 mol%) and benzene (to total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 75 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi CO/H_2, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature and pressure of 75 °C and 400 psi CO/H_2 for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction was removed from the Endeavor and concentrated. The residue was redissolved in t-butanol (3 mL) and 2-methyl-2-butene (0.64 mL, 6.0 mmol, 10.0 eq.) followed by addition of a solution of $NaClO_2$ (80%, 270 mg, 2.4 mmol, 4.0 eq.) and NaH_2PO_4 (290 mg, 2.4 mmol, 4.0 eq.) in H_2O. The solution was stirred at room temperature overnight. The resulting mixture was concentrated and redissolved in EtOAc (3 mL), followed by addition of 10% HCl (0.75 ml) and brine (0.75 mL). The solution was extracted with EtOAc (3 × 20 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. ^1H NMR was taken to analyze selectivity. Flash

column chromatography (Hex/EtOAc = 8/1) was performed to determine isolated yields.

Table 1.1, Entry 1: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using General Procedure A with 200 psi CO/H_2 at 35 °C. Analysis of crude mixture after oxidation by ^1H NMR showed a b:l selectivity of 96:4 and yield of 54%.

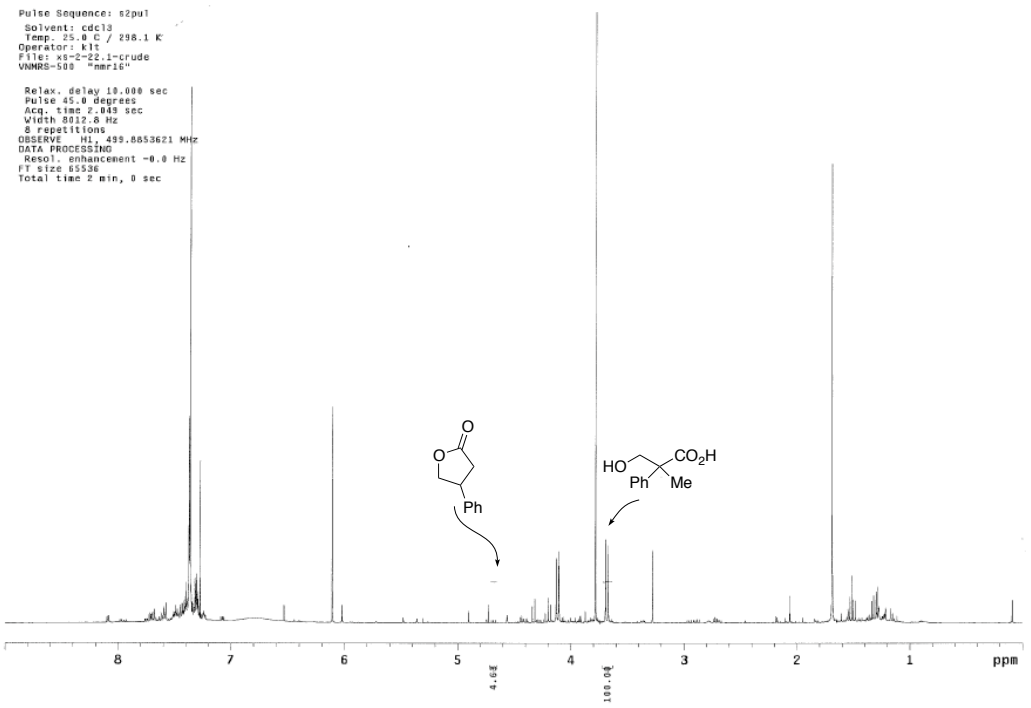


Table 1.1, Entry 2: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using General Procedure A with 200 psi CO/H_2 at 45 °C. Analysis of crude mixture after oxidation by ^1H NMR showed a b:l selectivity of 95:5 and yield of 61%.

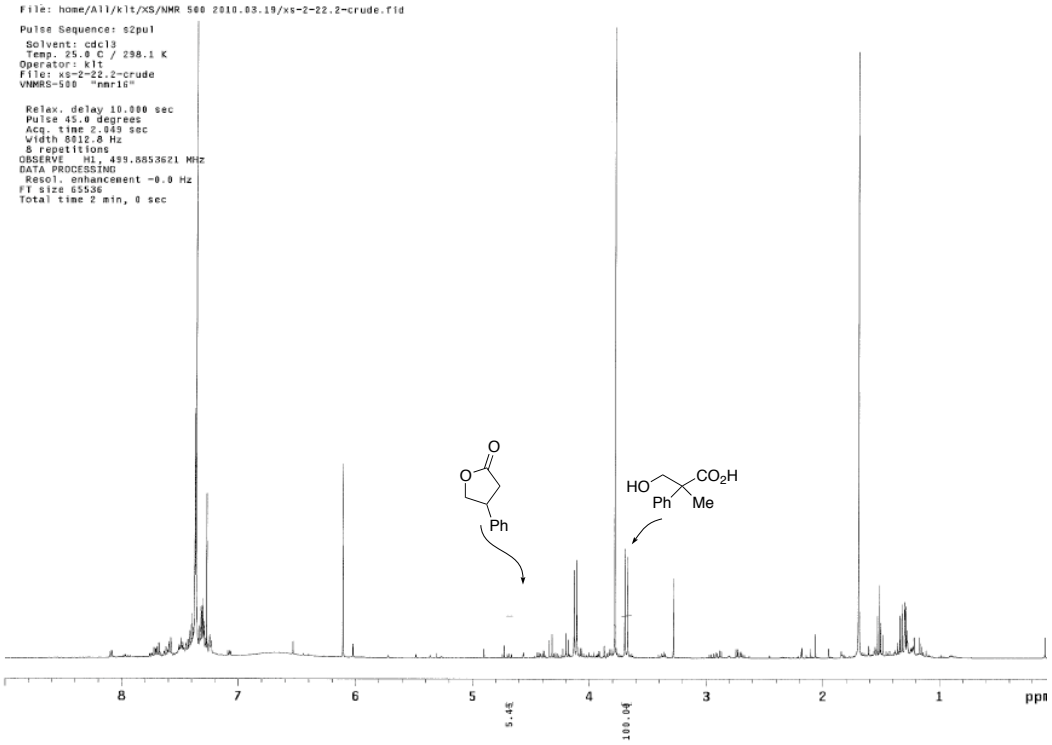


Table 1.1, Entry 3: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using General Procedure A with 200 psi CO/H_2 at 55 °C. Analysis of crude mixture after oxidation by ^1H NMR showed a b:l selectivity of 95:5 and yield of 50%.

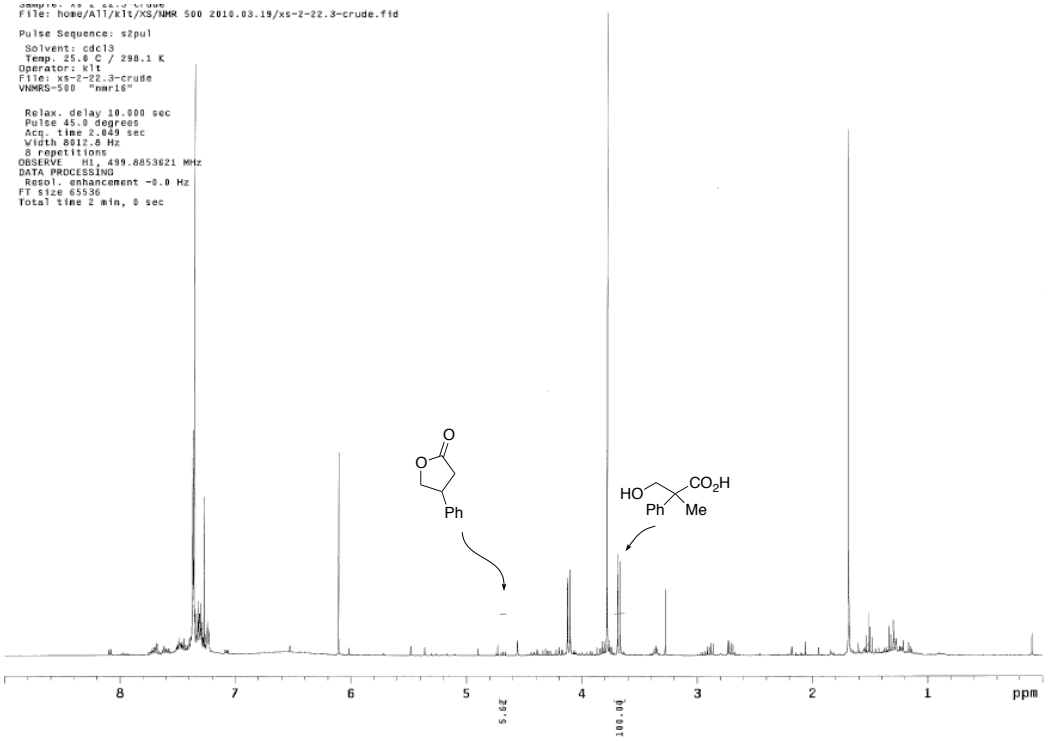


Table 1.1, Entry 4: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using General Procedure A with 50 psi CO/H_2 at 45 °C. Analysis of crude mixture after oxidation by ^1H NMR showed a b:l selectivity of 89:11 and yield of 38%.

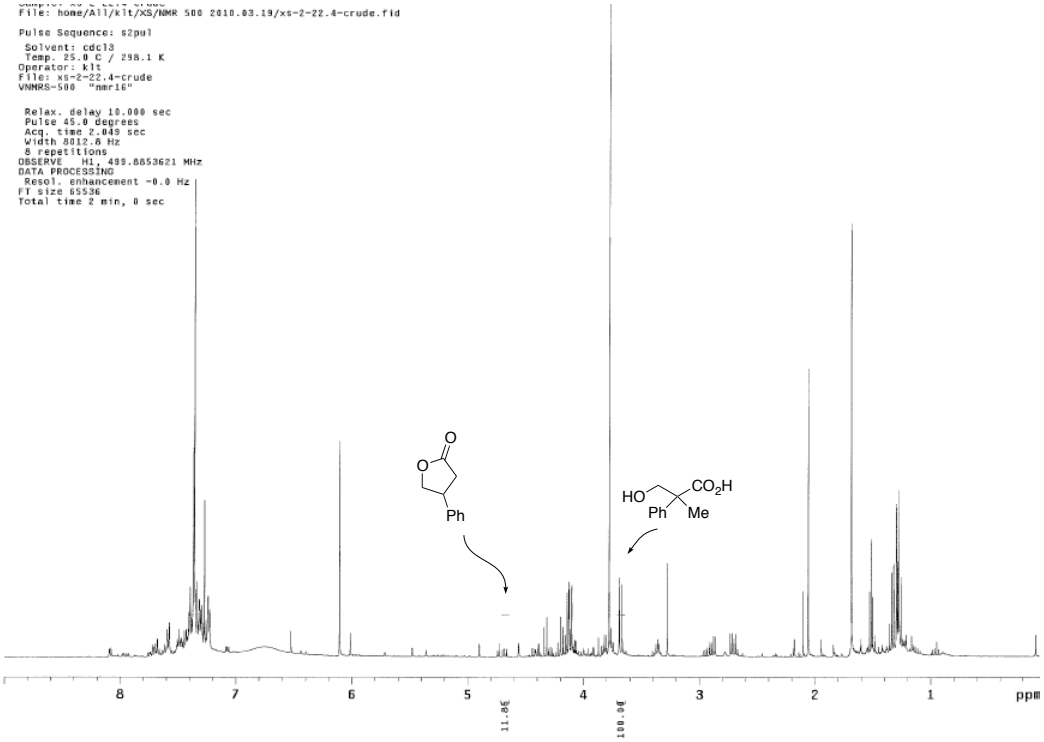


Table 1.1, Entry 5: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using General Procedure A with 100 psi CO/H_2 at 45 °C. Analysis of crude mixture after oxidation by ^1H NMR showed a b:l selectivity of 94:6 and yield (53%).

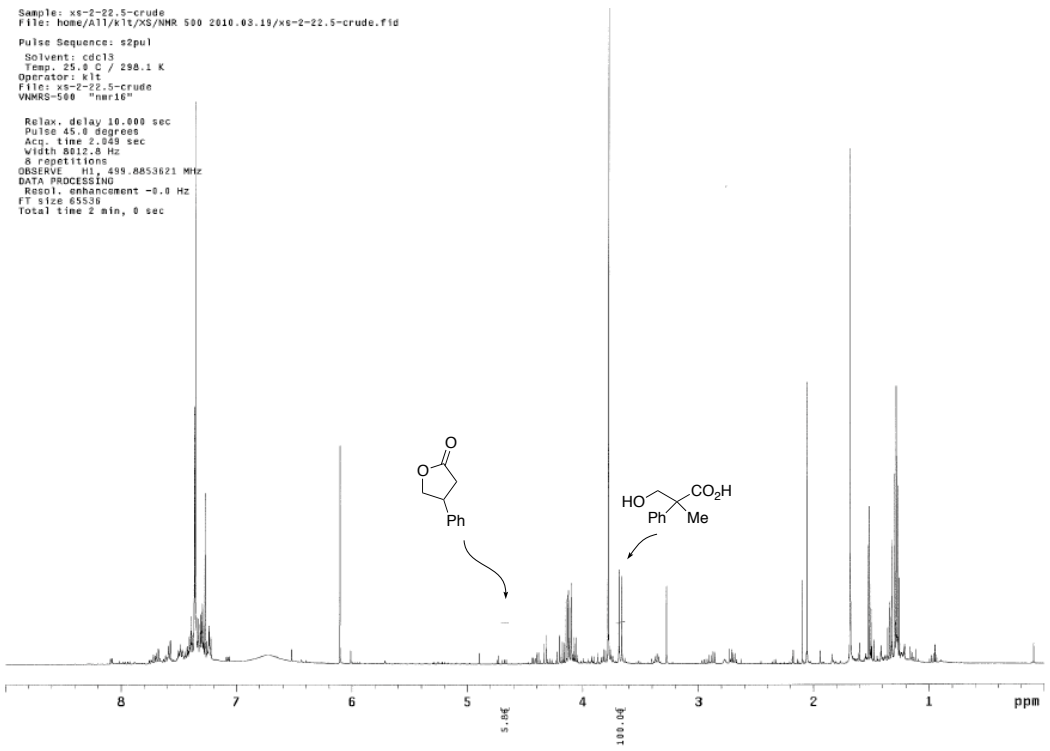
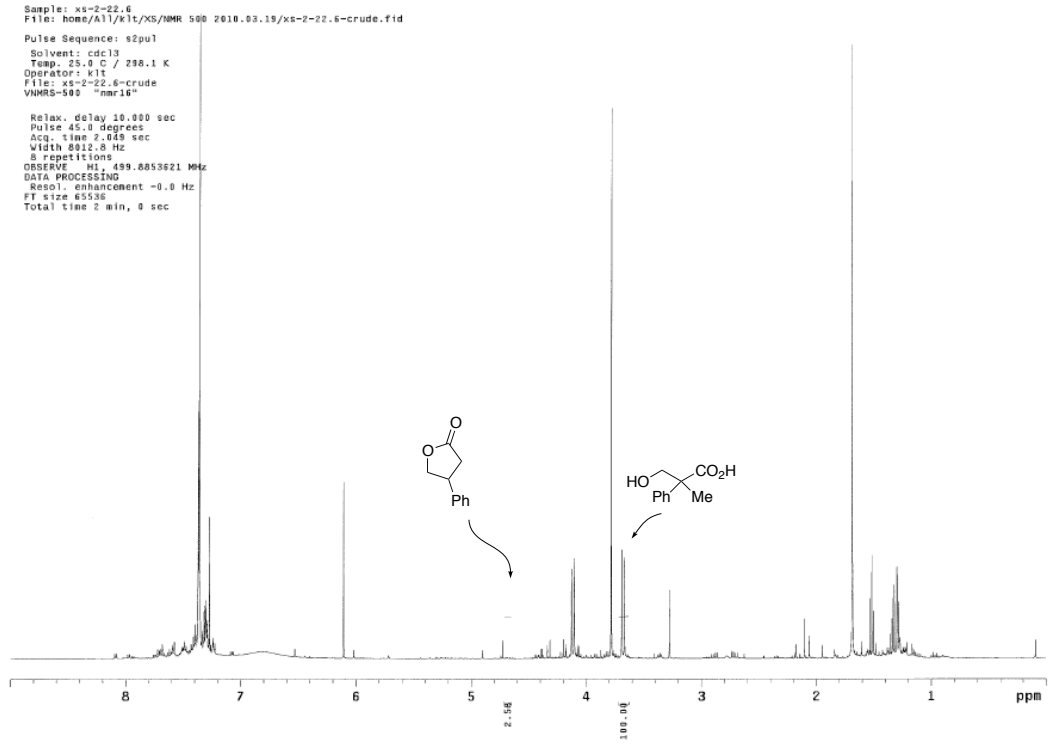


Table 1.1, Entry 6: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using General Procedure A with 400 psi CO/H_2 at 45 °C. Analysis of crude mixture after oxidation by ^1H NMR showed a b:l selectivity of 97:3 and yield of 70%.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Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
File: xs-2-22.6-crude
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Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 2.849 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8853621 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 2 min, 0 sec
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CO2H
Ph
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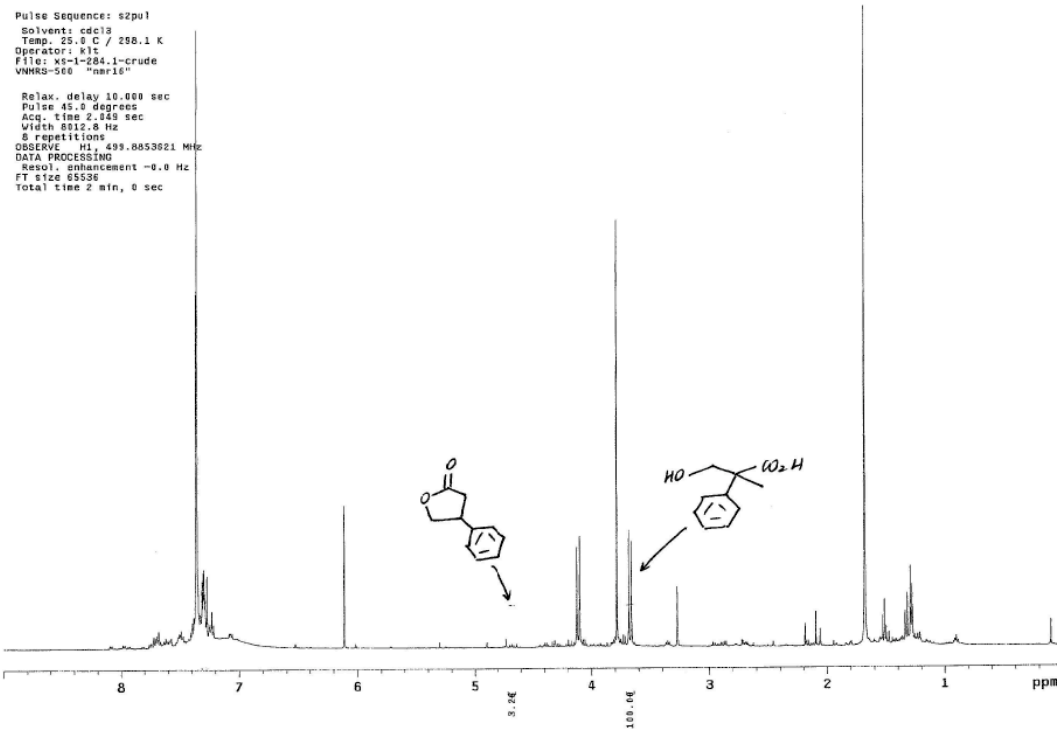
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
File: xs-1-284.1-crude
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Pulse 45.0 degrees
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8 repetitions
OBSERVE H1, 499.8853621 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
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Total time 2 min, 0 sec
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HO
CO2H
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7
6
5
4
3
2
1
ppm
3.24
100.00

Table 1.1, Entry 7: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using General Procedure B. Analysis of crude mixture after hydroformylation by ^{1}H NMR showed 0% conversion.

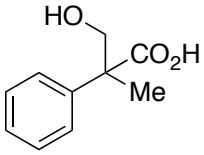
Table 1.1, Entry 8: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using General Procedure C. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of <2:98. Linear product was isolated as a white solid (64.0 mg, 66%).

Hydroformylation Using Ligand **1.27** and Product Characterizations

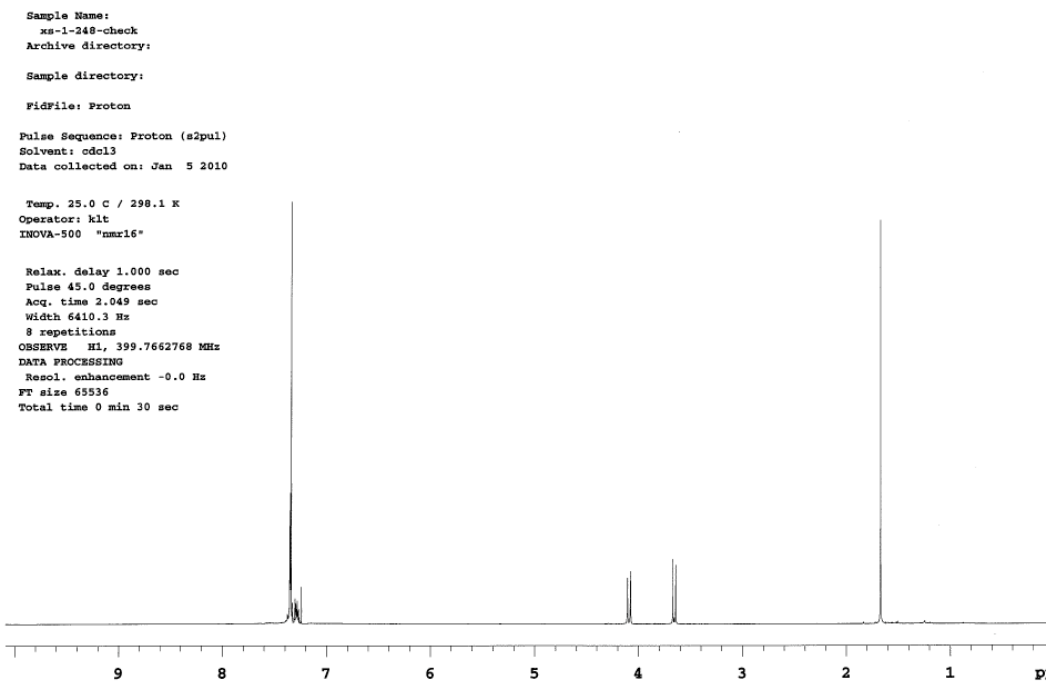
General Hydroformylation Procedure. The oven dried glass reaction vial was placed in the Endeavor, and corresponding alcohol substrate (0.60 mmol, see below) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium(I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol%), ligand **1.27** (34 mg, 0.12 mmol, 20 mol%), *p*-toluenesulfonic acid (see below) and benzene (to total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 35 °C (or 45 °C, see below) for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi CO/H_2, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature (see below) and pressure (see below) of CO/H_2 for 12 h (or 16 h, see below). The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction was removed from the Endeavor and concentrated. The residue was redissolved in *t*-butanol (3 mL) and 2-methyl-2-butene (0.64 mL, 6.0 mmol, 10.0 eq.) followed by addition of a solution of $NaClO_2$ (80%, 270 mg, 2.4 mmol, 4.0 eq.) and NaH_2PO_4 (290 mg, 2.4 mmol, 4.0 eq.)

in H_2O. The solution was stirred at room temperature overnight. The resulting mixture was concentrated and redissolved in EtOAc (3 mL), followed by addition of 10% HCl (0.75 ml) and brine (0.75 mL). The solution was extracted with EtOAc (3 × 20 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated. ^{1}H NMR was taken to analyze selectivities. Flash column chromatography (Hex/EtOAc = 4/1) afforded pure branched products.

Table 1.1, Entry 6:



3-Hydroxy-2-methyl-2-phenylpropanoic acid (1.46). 2-Phenylprop-2-en-1-ol (80 mg, 0.60 mmol) was hydroformylated with 0.20 mol% *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 45 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed selectivity (b:l = 97:3). Branched product was isolated as a white solid (79 mg, 73%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36-7.24 (m, 5H), 6.98 (br s, 1H), 4.09 (d, 1H, J = 11.6), 3.66 (d, 1H, J = 11.2), 1.67 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 181.2, 139.5, 128.7, 127.6, 126.3, 69.1, 52.4, 20.0; **IR**: 2982, 1701, 1239, 1026, 698 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{16}NO_3$ $[M+NH_4]^+$: 198.11302, found: 198.11247.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xs-1-248-check
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Sample directory:
FidFile: Proton
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jan 5 2010
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7662768 MHz
DATA PROCESSING
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FT size 65536
Total time 0 min 30 sec
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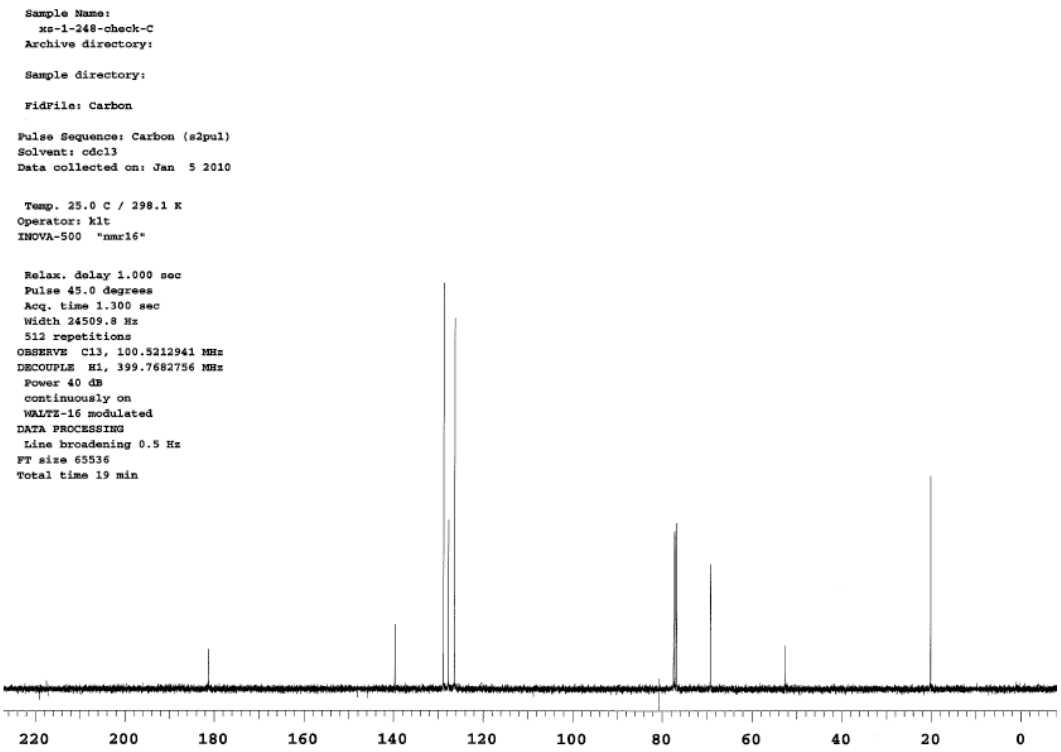
8
7
6
5
4
3
2
1
p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Archive directory:
Sample directory:
FidFile: Carbon
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Jan 5 2010
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
512 repetitions
OBSERVE C13, 100.5212941 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min
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200
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160
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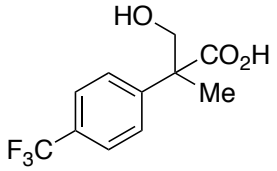
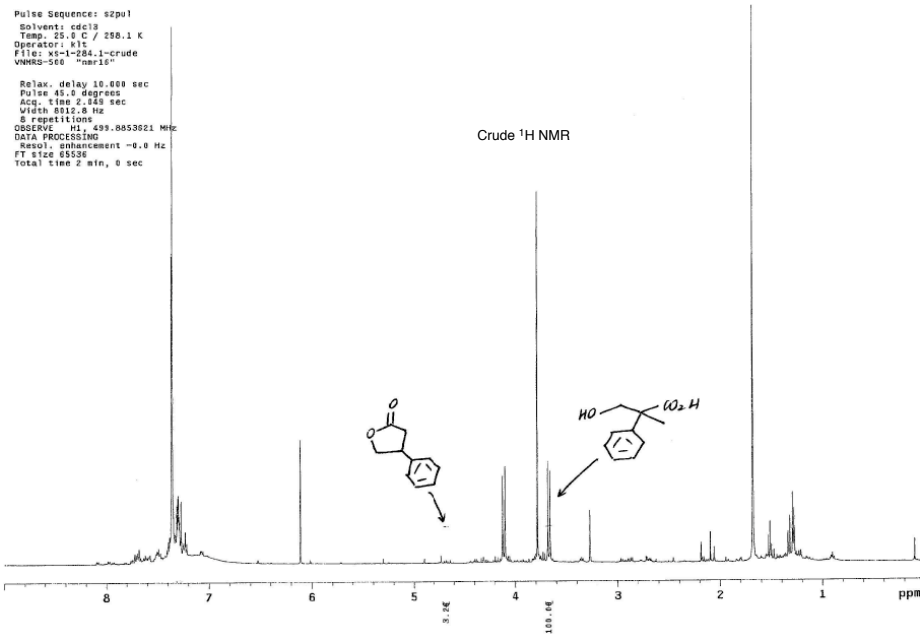
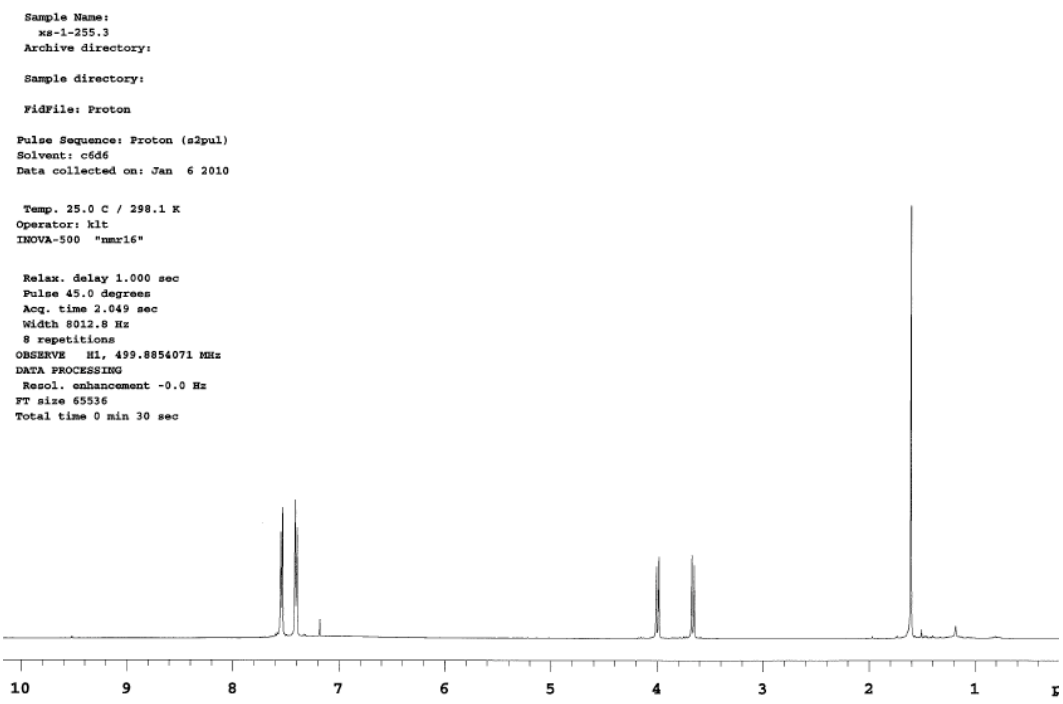
120
100
80
60
40
20
0

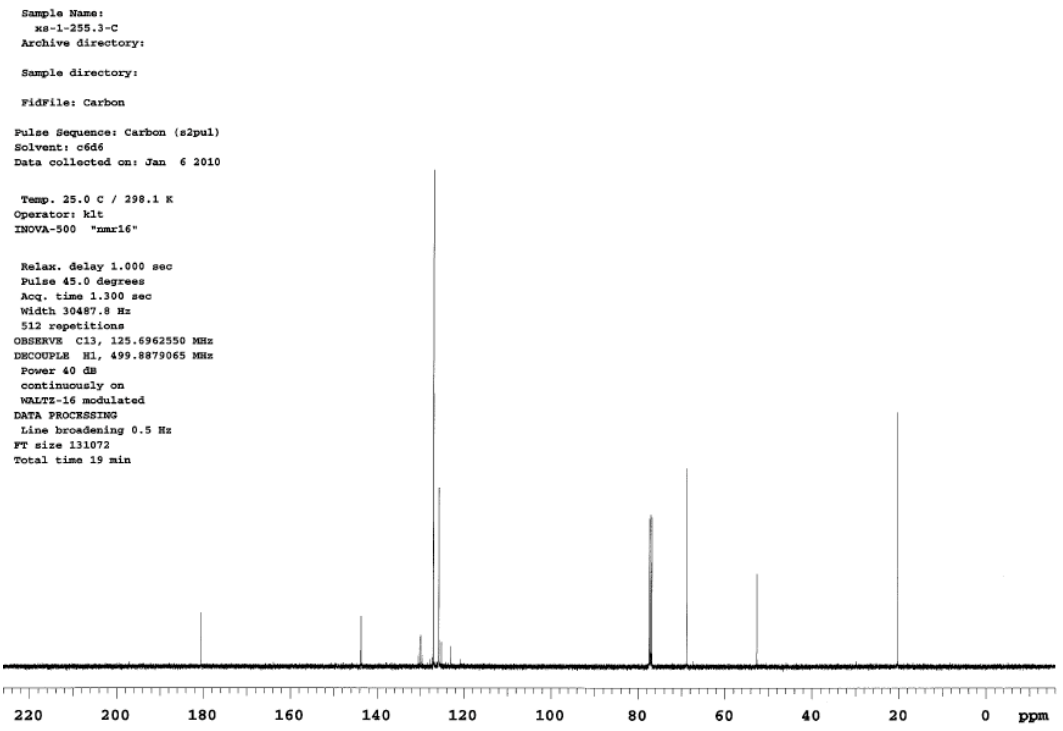
Table 1.2, Entry 1:



3-Hydroxy-2-methyl-2-(4-(trifluoromethyl)phenyl)propanoic acid. 2-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (120 mg, 0.60 mmol) was hydroformylated with 0.20 mol% *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 45 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 96:4. Branched product was isolated as a white solid (126 mg, 85%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.54 (d, 2H, J = 8.5), 7.41 (d, 2H, J = 8.5), 7.12 (br s, 1H), 4.00 (d, 1H, J = 11.5), 3.66 (d, 1H, J = 11.5), 1.61 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 180.4, 143.6, 129.9 (q, J = 32.5), 126.9, 125.6, 123.9 (q, J = 270.1), 68.7, 52.5, 20.2; **IR**: 2946, 1708, 1328, 1167, 1124, 1066, 1016, 837 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{12}F_3O_3$ $[M+H]^+$: 249.07385, found: 249.07392.




Sample Name:
xs-1-255.3
Archive directory:
Sample directory:
FidFile: Proton
Pulse Sequence: Proton (s2pul)
Solvent: c6d6
Data collected on: Jan 6 2010
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8854071 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec
10
9
8
7
6
5
4
3
2
1


Sample Name:
xs-1-255.3-C
Archive directory:
Sample directory:
FidFile: Carbon
Pulse Sequence: Carbon (s2pul)
Solvent: c6d6
Data collected on: Jan 6 2010
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
512 repetitions
OBSERVE C13, 125.6962550 MHz
DECOUPLE H1, 499.8879065 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
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160
140
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100
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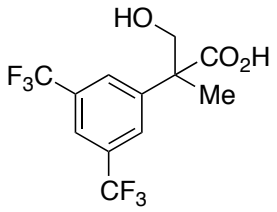
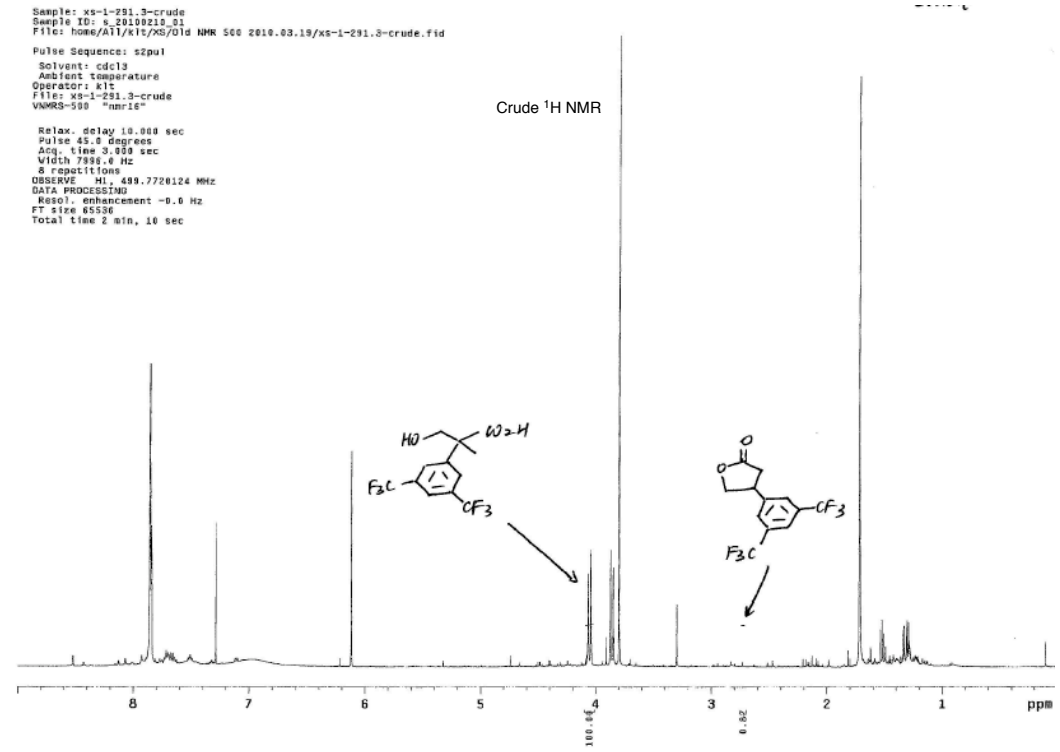
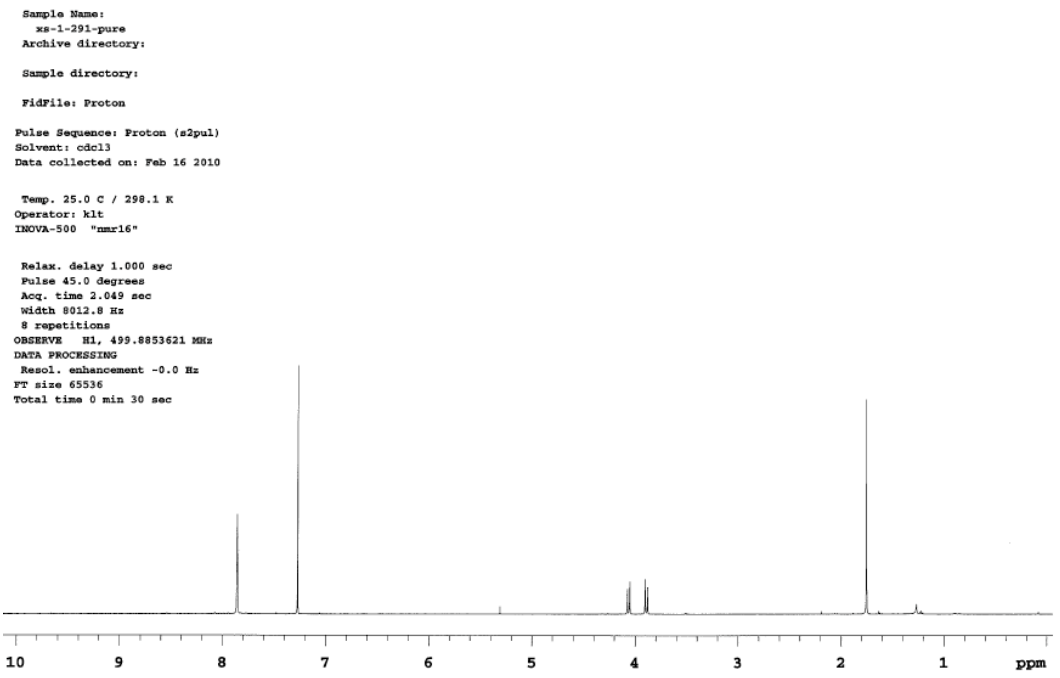
60
40
20
0
ppm

Table 1.2, Entry 2:



2-(3,5-Bis(trifluoromethyl)phenyl)-3-hydroxy-2-methylpropanoic acid. 2-(3,5-Bis(trifluoromethyl)phenyl)prop-2-en-1-ol (160 mg, 0.60 mmol) was hydroformylated with 0.05 mol% *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 45 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of >98:2. Branched product was isolated as a white solid (152 mg, 80%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.86 (s, 3H), 4.06 (d, 1H, J = 11.5), 3.89 (d, 1H, J = 11.5), 1.75 (s, 3H); **^{13}C NMR** (Acetone d-6, 125 MHz) δ 174.6, 145.3, 130.9 (q, J = 32.9), 127.9, 123.7 (q, J = 270.1), 120.6, 67.6, 52.5, 20.1; **IR**: 2924, 1711, 1373, 1287, 1187, 1132 cm^{-1}; **HRMS** (DART-TOF) calcd. For $C_{12}H_{14}F_6NO_3$ $[M+NH_4]^+$: 334.08779, found: 334.08865.


Sample: xs-1-291.3-crude
Sample ID: s_20100210_01
File: home/All/klt/XS/Old NMR 500 2010.03.19/xs-1-291.3-crude.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: klt
File: xs-1-291.3-crude
VNMRS-500 "nmr16"
Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 7986.0 Hz
8 repetitions
OBSERVE H1, 499.7728124 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 2 min, 10 sec
Crude 1H NMR
HO
CO2H
F3C
CF3
O
O
CF3
F3C
8
7
6
5
4
3
2
1
ppm
100.00
0.82


Sample Name:
xs-1-291-pure
Archive directory:
Sample directory:
FidFile: Proton
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Feb 16 2010
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8853621 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec
10
9
8
7
6
5
4
3
2
1
ppm

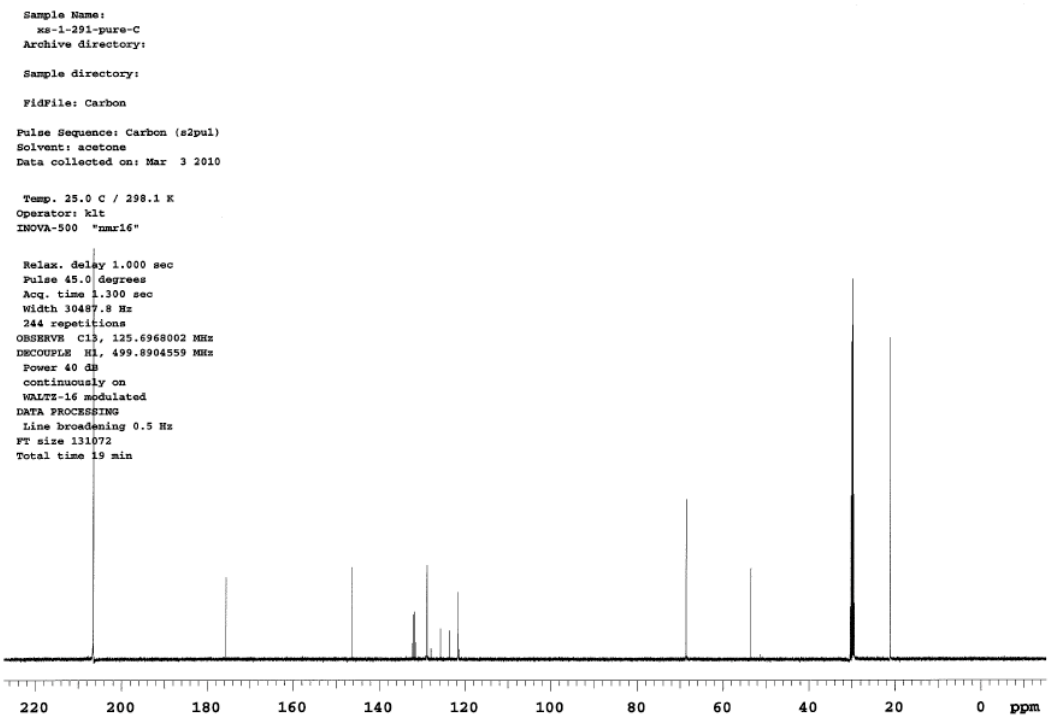
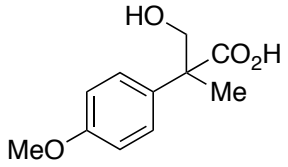
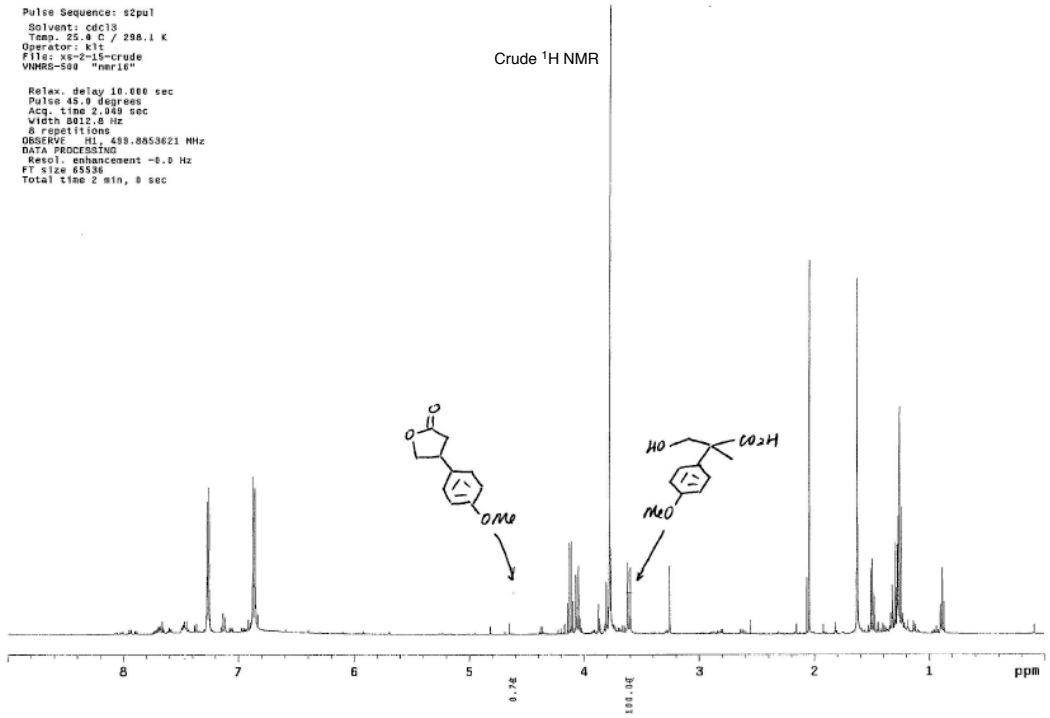


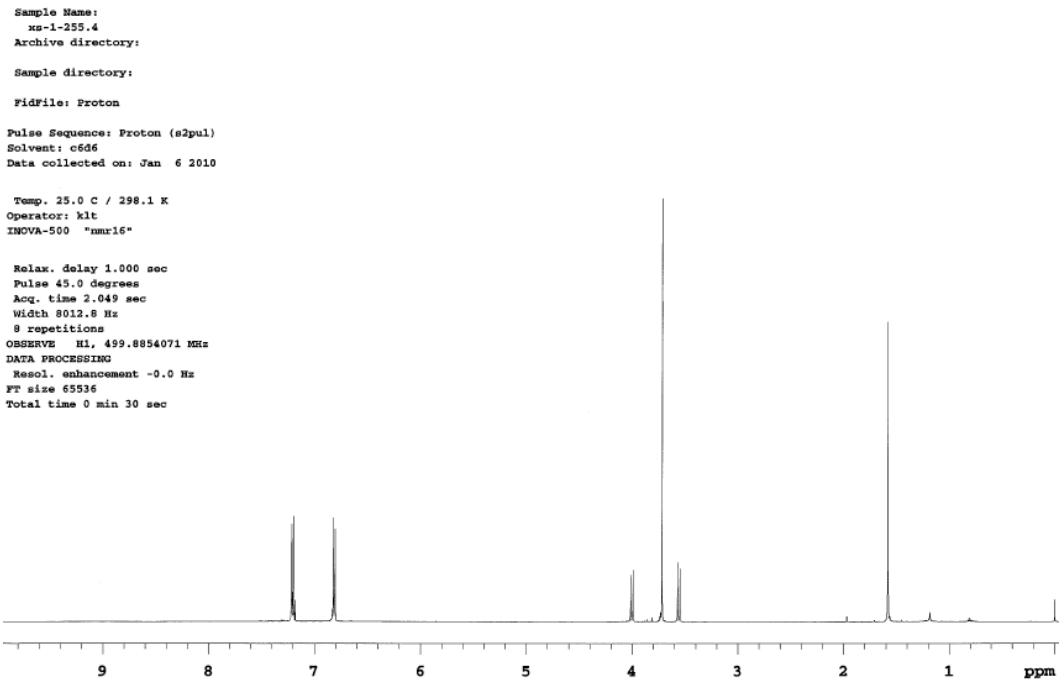
Table 1.2, Entry 3:



3-Hydroxy-2-(4-methoxyphenyl)-2-methylpropanoic acid. 2-(4-Methoxyphenyl)prop-2-en-1-ol (98 mg, 0.60 mmol) was hydroformylated with 0.20 mol% *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 35 °C for 16 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of >98:2. Branched product was isolated as a white solid (83 mg, 66%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.21 (d, 2H, J = 8.5), 6.99 (br s, 1H), 6.81 (d, 2H, J = 8.5), 4.00 (d, 1H, J = 11.5), 3.72 (s, 3H), 3.56 (d, 1H, J = 11.5), 1.58 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 181.3, 158.9, 131.5, 127.4, 114.1, 69.1, 55.2, 51.6, 20.1;

IR: 2937, 1703, 1514, 1253, 1187, 1029, 829 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{18}NO_4$ $[M+NH_4]^+$: 228.12358, found: 228.12384.





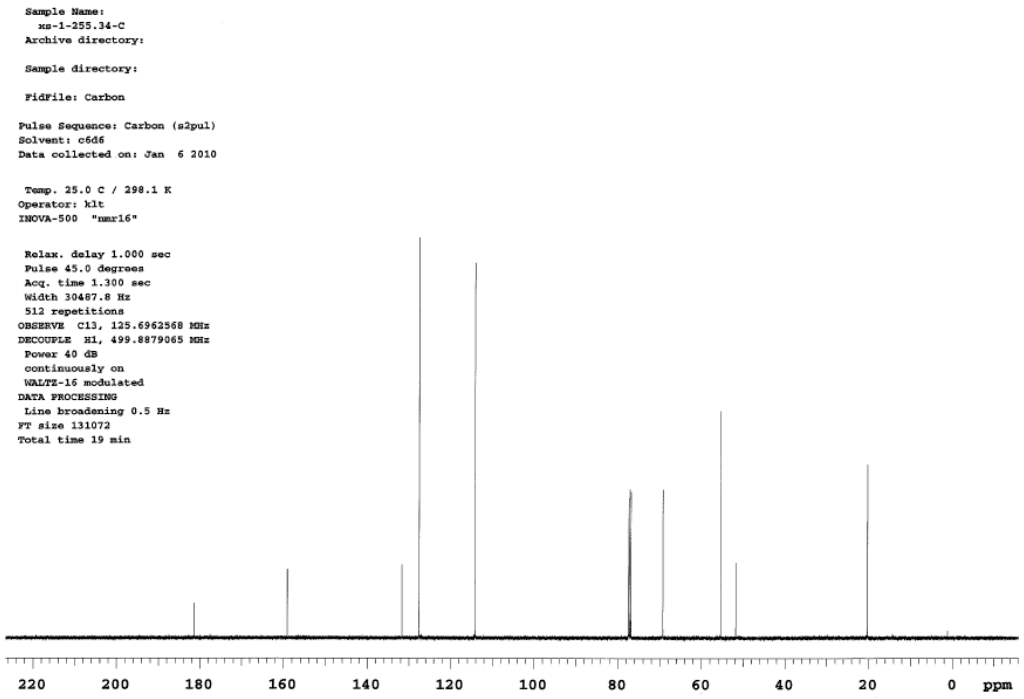
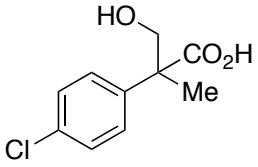
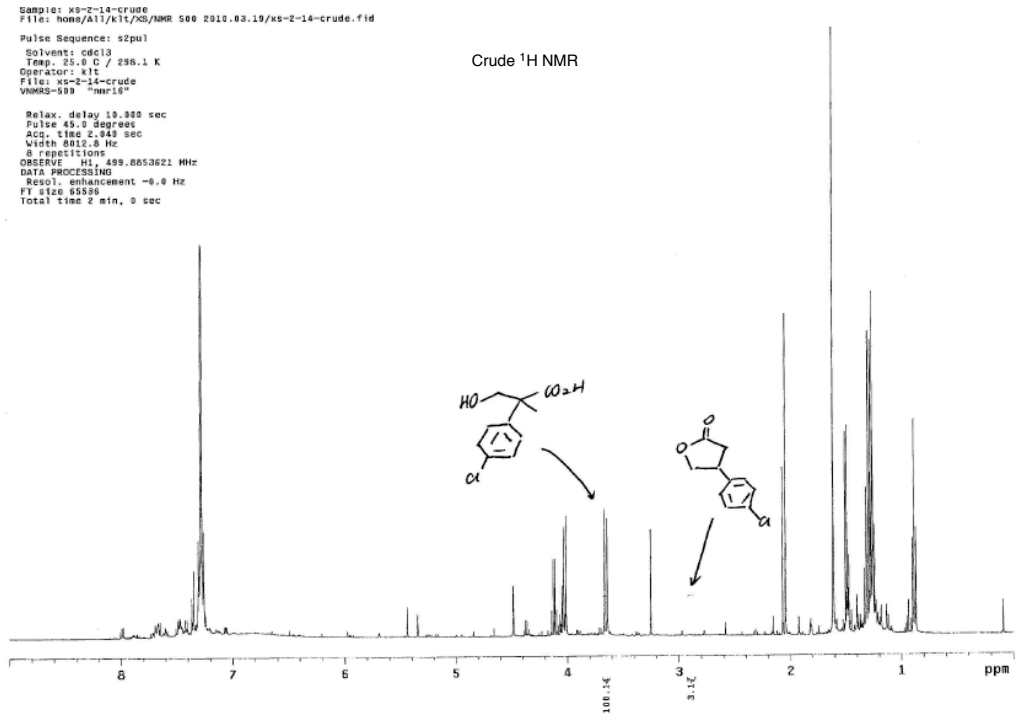


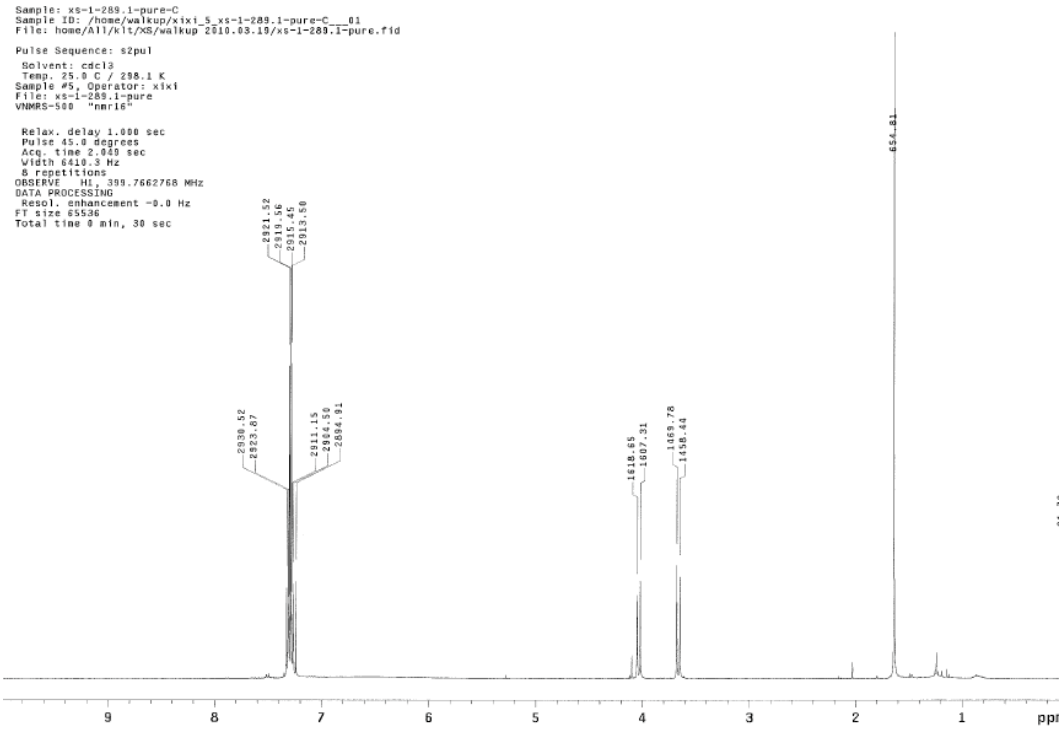
Table 1.2, Entry 4:



2-(4-Chlorophenyl)-3-hydroxy-2-methylpropanoic acid. 2-(4-Chlorophenyl)prop-2-en-1-ol (100 mg, 0.60 mmol) was hydroformylated with 0.05 mol% *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 35 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 97:3. Branched product was isolated as a white solid (78 mg, 60%)**.** **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33-7.24 (m, 4H), 6.54 (br s, 1H), 4.04 (d, 1H, J = 11.2), 3.66 (d, 1H, J = 11.6), 1.64 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 180.6, 138.1, 133.6, 128.8, 127.8, 68.9, 52.0, 20.1; **IR**: 2941, 1702, 1494, 1260, 1098, 1034, 1013,

824 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{15}Cl_1NO_3$ $[M+NH_4]^+$: 232.07405, found: 232.07432.





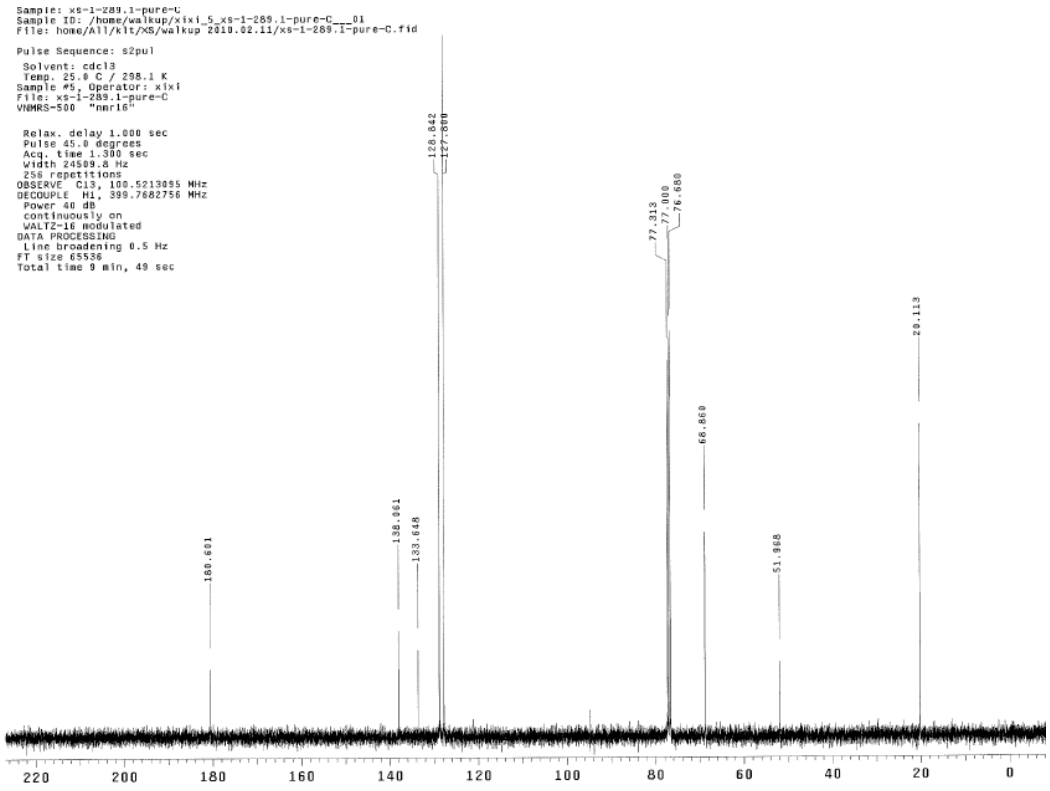
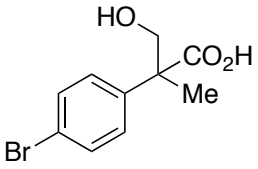
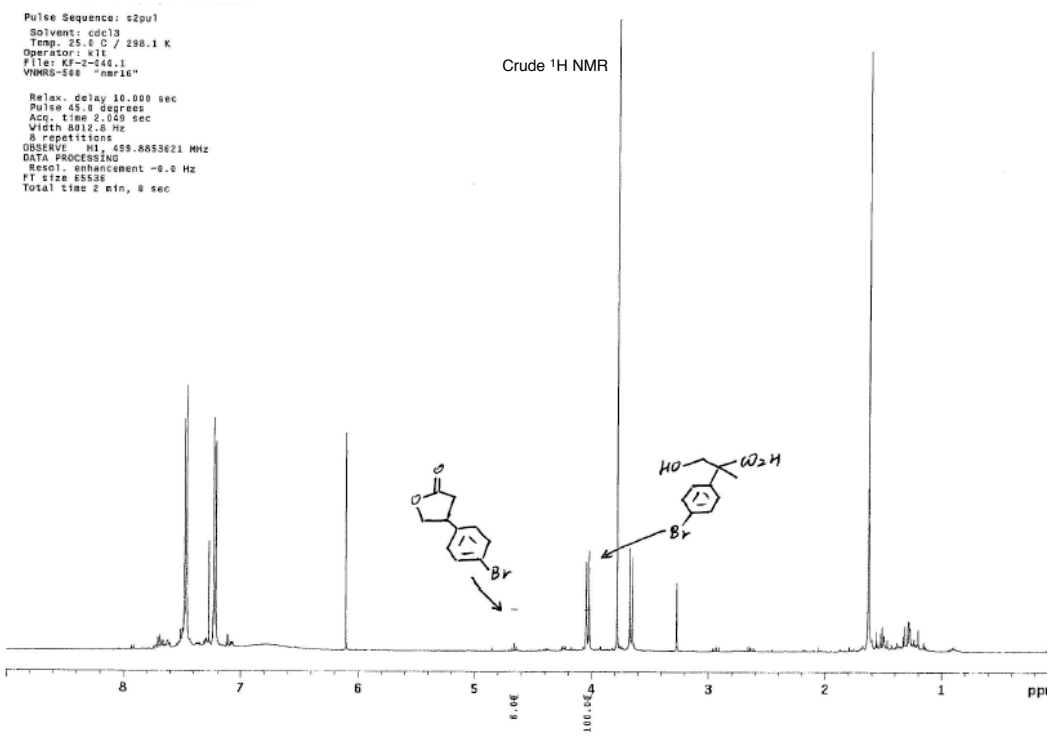


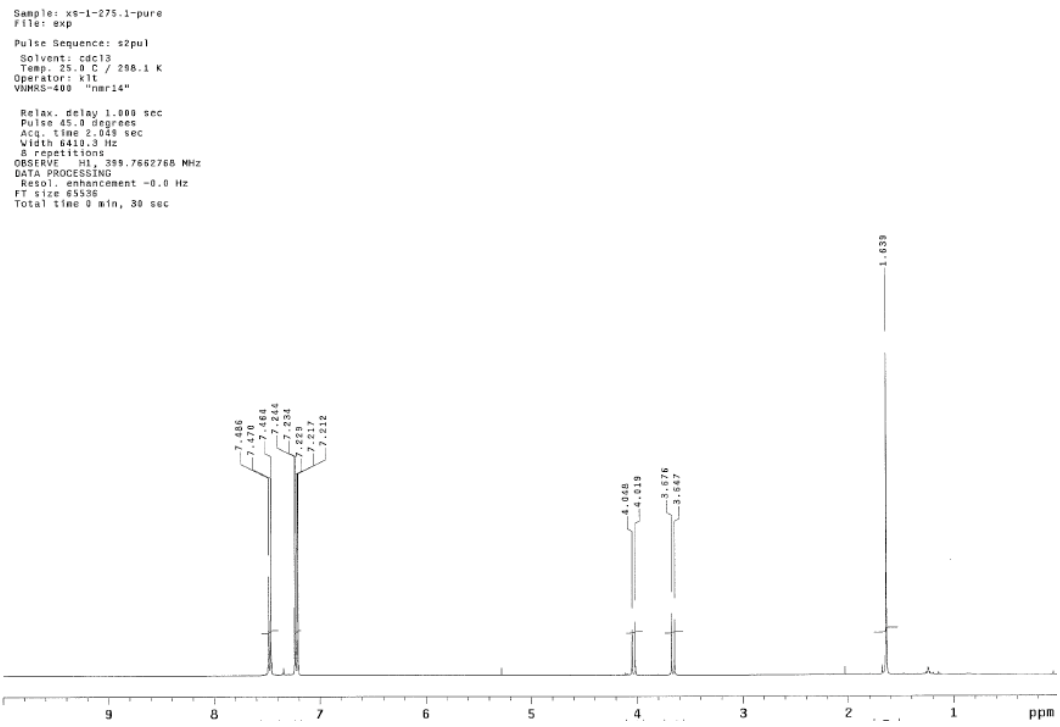
Table 1.2, Entry 5:



2-(4-Bromophenyl)-3-hydroxy-2-methylpropanoic acid. 2-(4-Bromophenyl)prop-2-en-1-ol (130 mg, 0.60 mmol) was hydroformylated with 0.05 mol% *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 35 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 94:6. Branched product was isolated as a white solid (110 mg, 71%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48 (d, 1H, *J* = 8.8), 7.22 (d, 1H, *J* = 8.8), 7.05 (br s, 1H), 4.03 (d, 1H, *J* = 11.6), 3.66 (d, 1H, *J* = 11.6), 1.64 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 180.7, 138.5, 131.8, 128.1, 121.8, 68.8, 52.0, 20.0; **IR**: 2938, 1703, 1491,

1398, 1241, 1034, 1009, 820 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{15}Br_1NO_3$ $[M+NH_4]^+$: 276.02353, found: 276.02357.





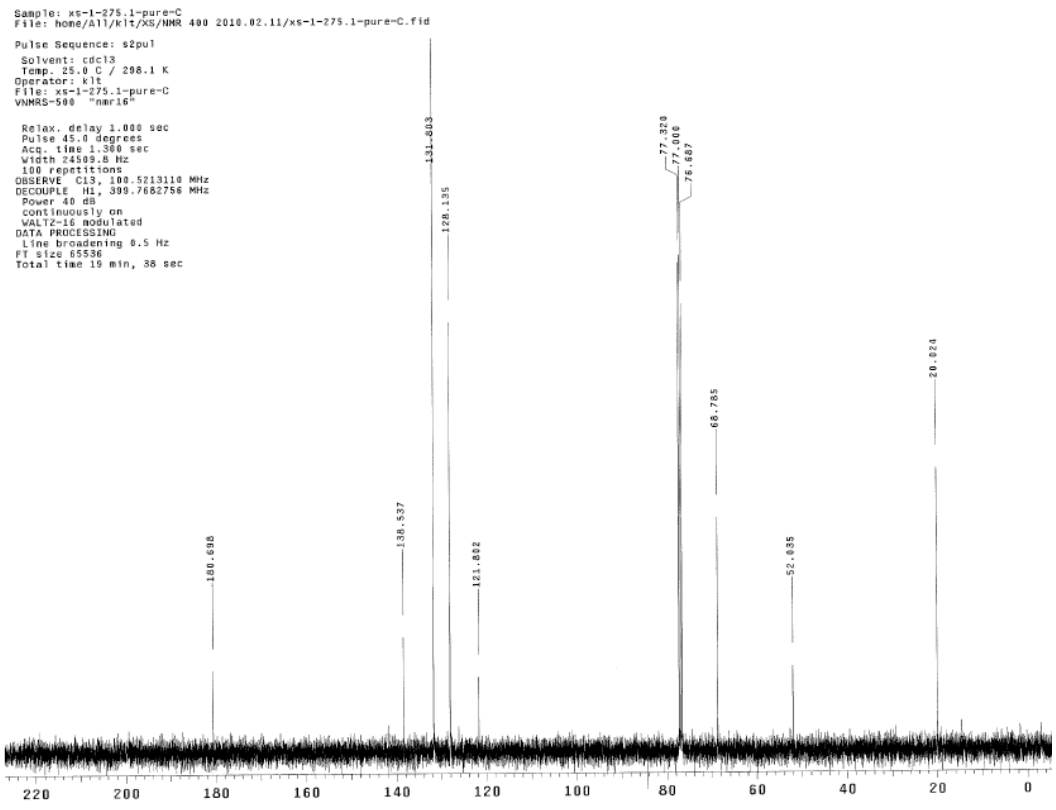
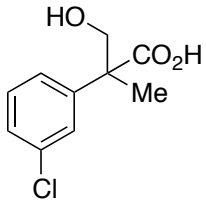
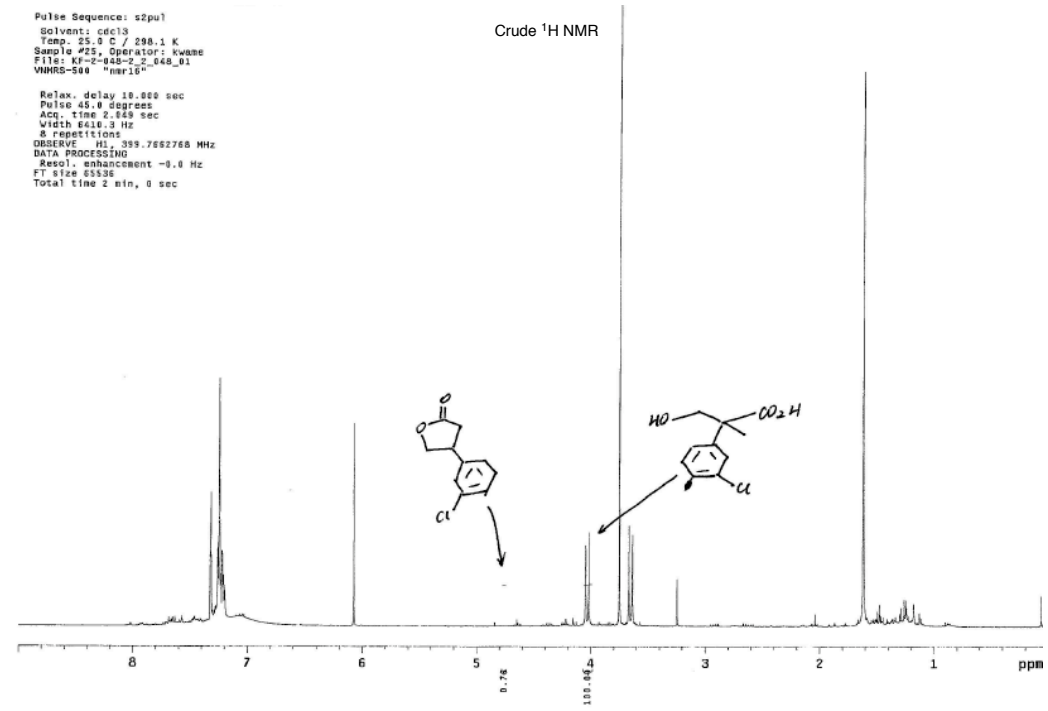


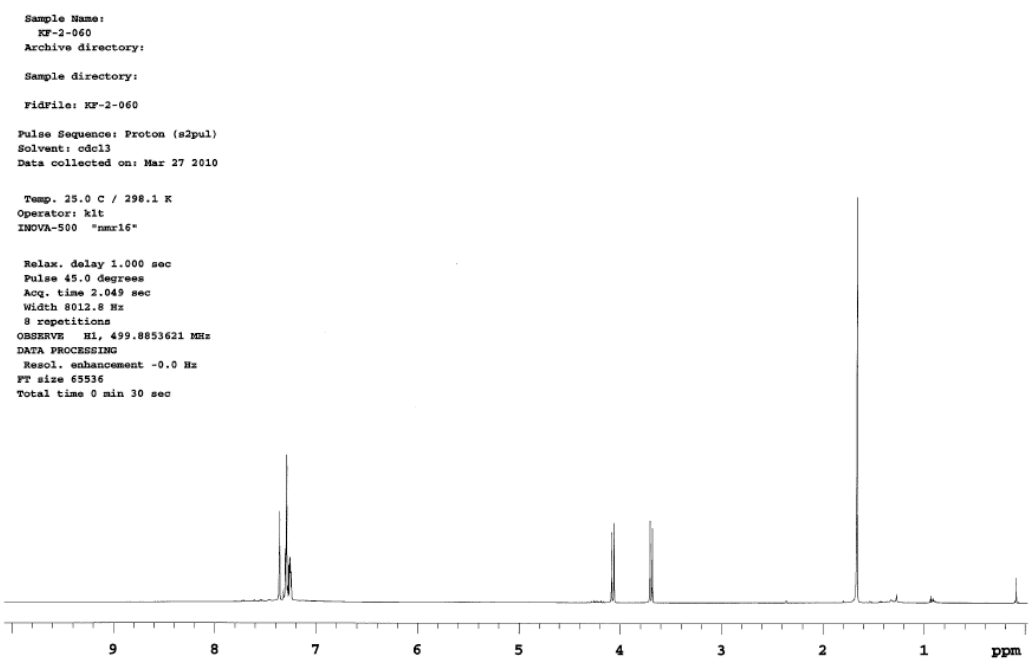
Table 1.2, Entry 6:



2-(3-Chlorophenyl)-3-hydroxy-2-methylpropanoic acid. 2-(3-Chlorophenyl)prop-2-en-1-ol (100 mg, 0.60 mmol) was hydroformylated with 0.20 mol% *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 35 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of >98:2. Branched product was isolated as a white solid (99 mg, 77%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33 (s, 1H), 7.27-7.20 (m, 3H), 7.25 (br s, 1H), 4.04 (d, 1H, J = 11.2), 3.66 (d, 1H, J = 11.6), 1.63 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ

180.3, 141.6, 134.6, 129.9, 127.8, 126.7, 124.6, 68.7, 52.2, 20.0; **IR**: 2982, 1703, 1244, 1035, 698 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{12}Cl_1O_3$ $[M+H]^+$: 215.04750, found: 215.04853.





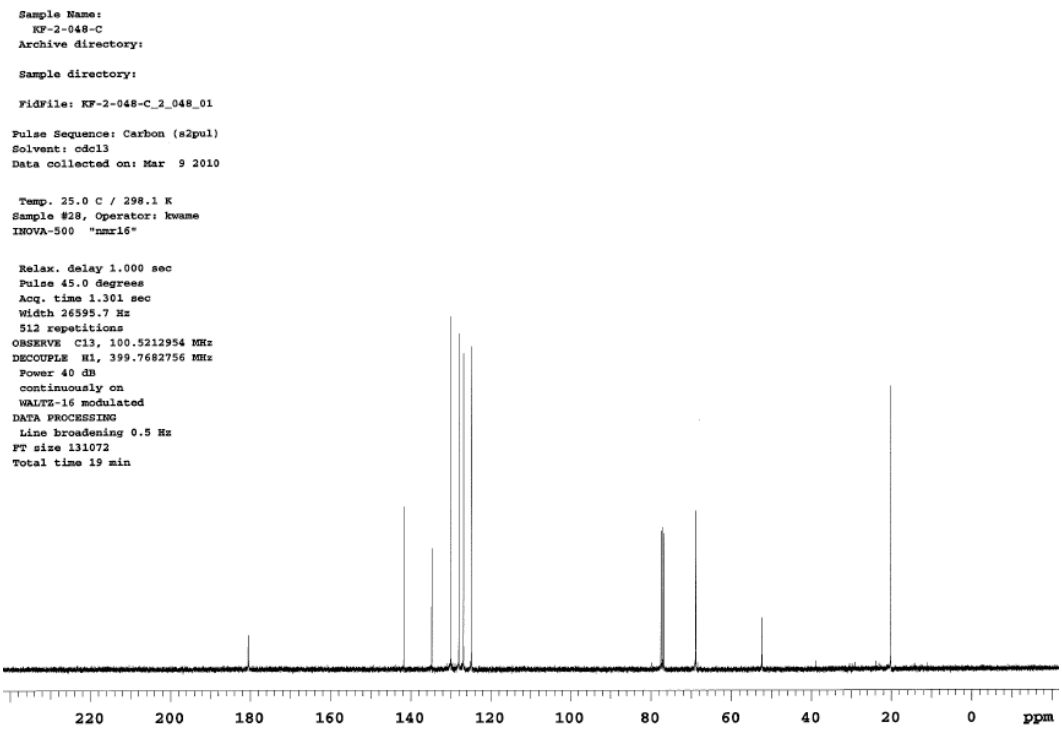
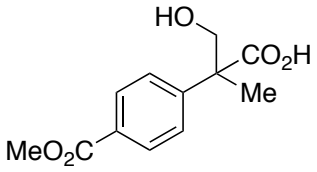
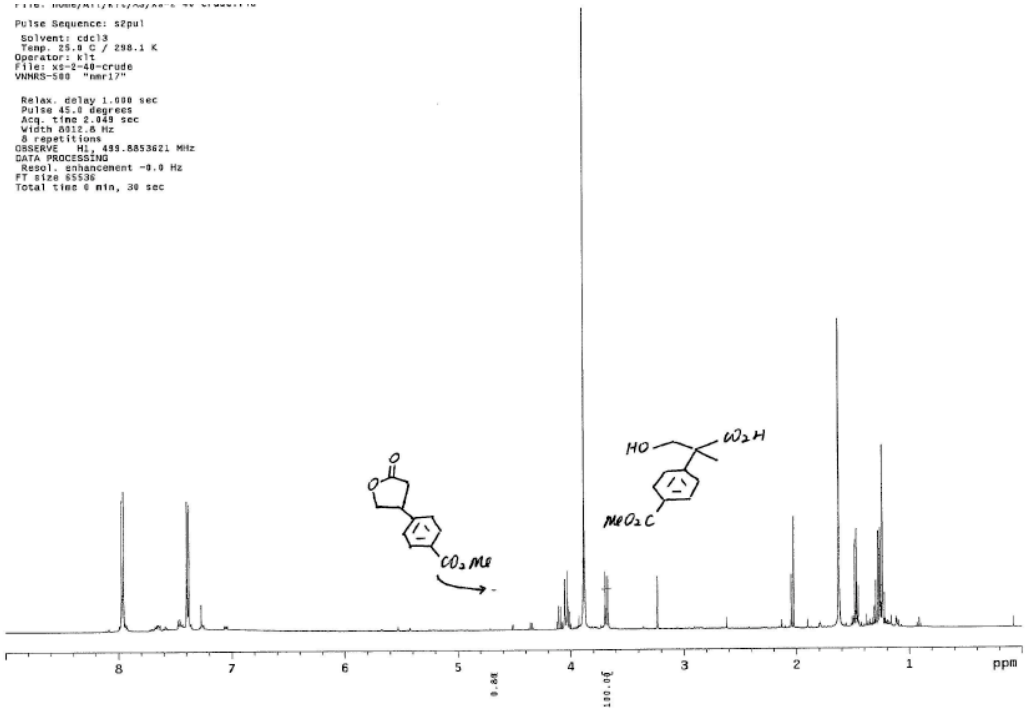


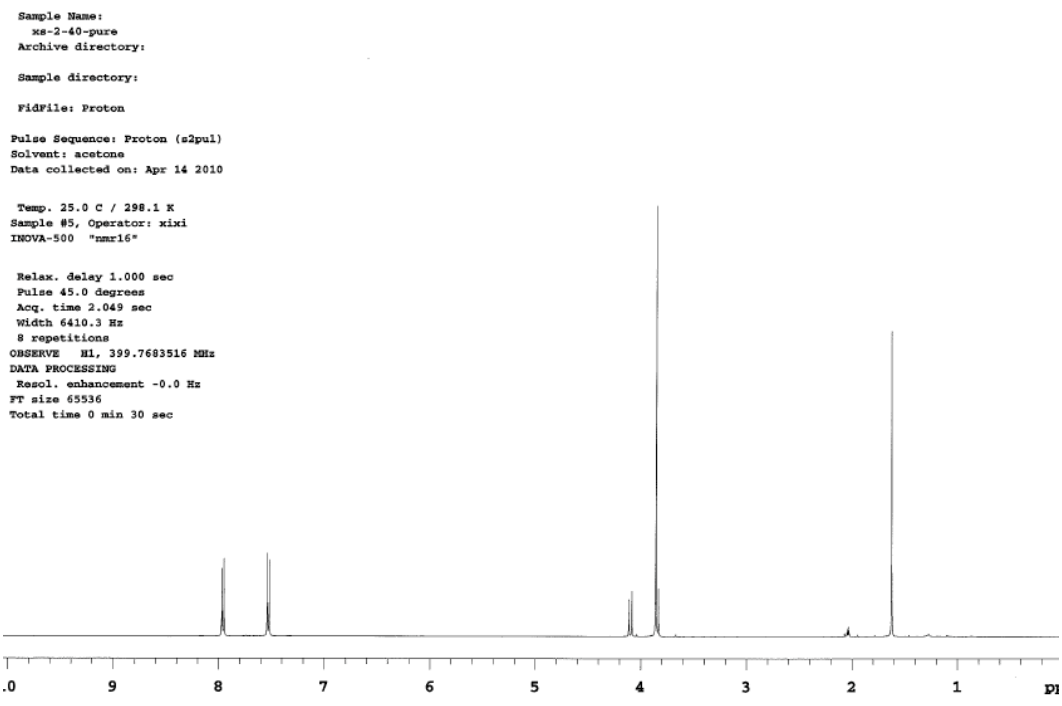
Table 1.2, Entry 7:



3-Hydroxy-2-(4-(methoxycarbonyl)phenyl)-2-methylpropanoic acid. Methyl 4-(3-hydroxyprop-1-en-2-yl)benzoate (120 mg, 0.60 mmol) was hydroformylated with 0.05 mol% *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 45 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of >98:2. Branched product was isolated as a white solid (106 mg, 74%). **^{1}H NMR** (Acetone d-6, 400 MHz) δ 7.96 (d, 2H, *J* = 8.6), 7.53 (d, 2H, *J* = 8.6), 4.10 (d, 1H, *J* = 10.8), 3.86 (s, 3H), 3.84 (d, 1H, *J* = 10.8), 1.62 (s, 3H); **^{13}C NMR** (Acetone d-6, 100 MHz) δ 175.2, 166.1, 147.3,

129.2, 128.7, 126.7, 67.9, 52.5, 51.4, 20.2; **IR**: 2952, 1719, 1437, 1282, 1194, 1115, 1018, 707 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{15}O_5$ $[M+H]^+$: 239.09195, found: 239.09209.





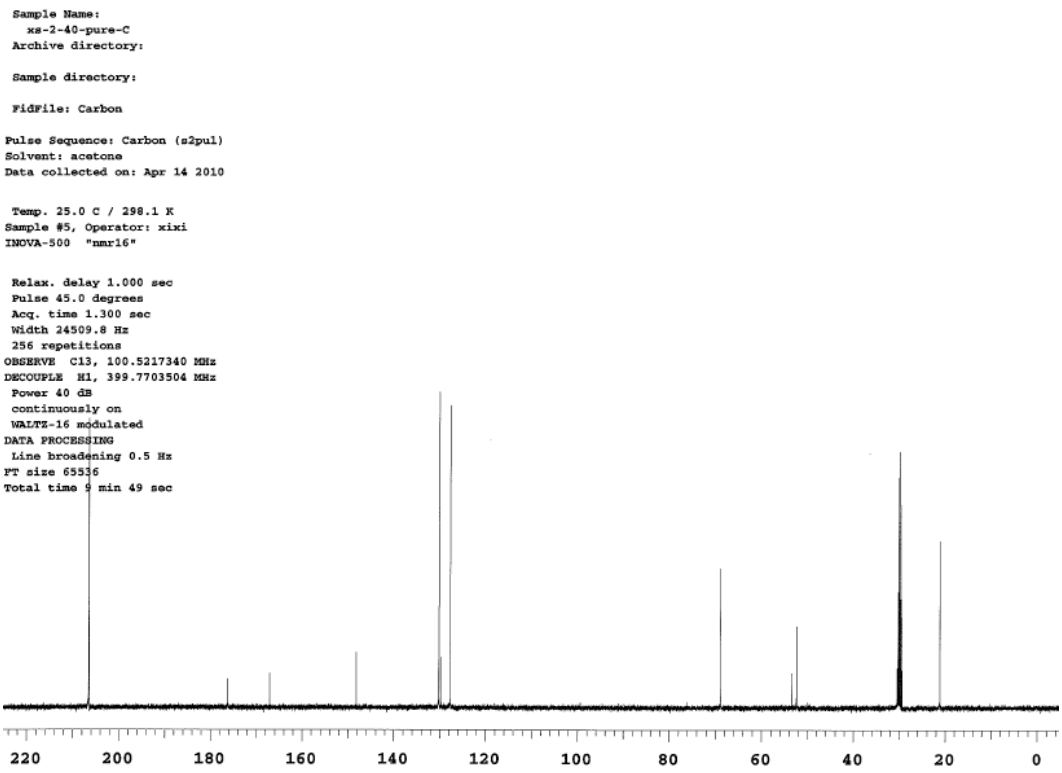
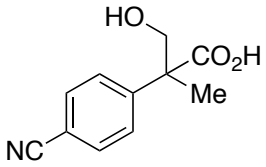
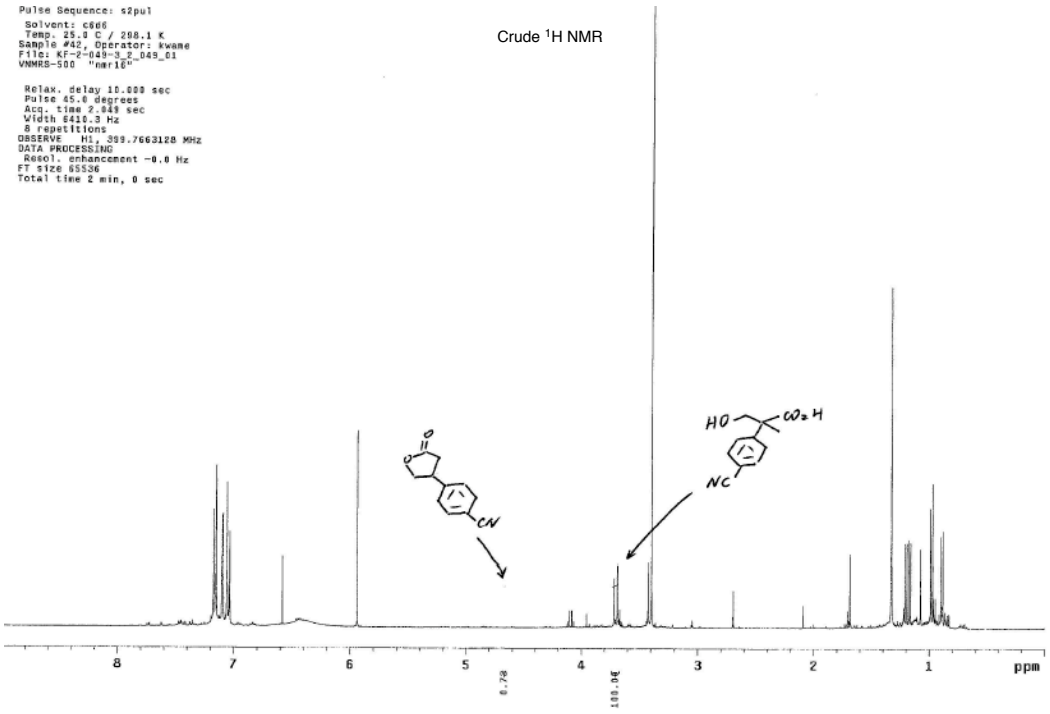


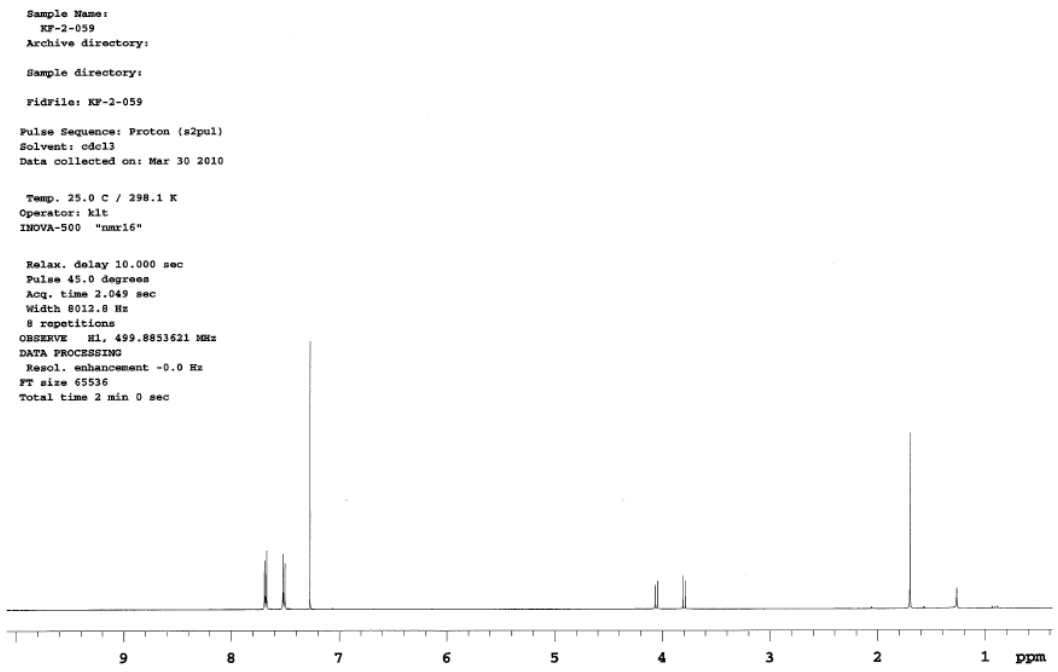
Table 1.2, Entry 8:



2-(4-Cyanophenyl)-3-hydroxy-2-methylpropanoic acid. 4-(3-Hydroxyprop-1-en-2-yl)benzonitrile (96 mg, 0.60 mmol) was hydroformylated with 0.20 mol% *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 45 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of >98:2. Branched product was isolated as a white solid (82 mg, 67%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40 (br s, 1H), 7.64 (d, 2H, J = 8.4), 7.48 (d, 2H, J = 8.4), 4.02 (d, 1H, J = 11.2), 3.76 (d, 1H, J = 11.2), 1.66 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 179.5, 145.0, 132.4, 127.4, 118.3, 111.6, 68.5, 52.6, 20.2; **IR**:

3362, 2240, 1721, 1220, 1034, 836, 677, 558 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{12}NO_3$ $[M+H]^+$: 206.08172, found: 206.08261.





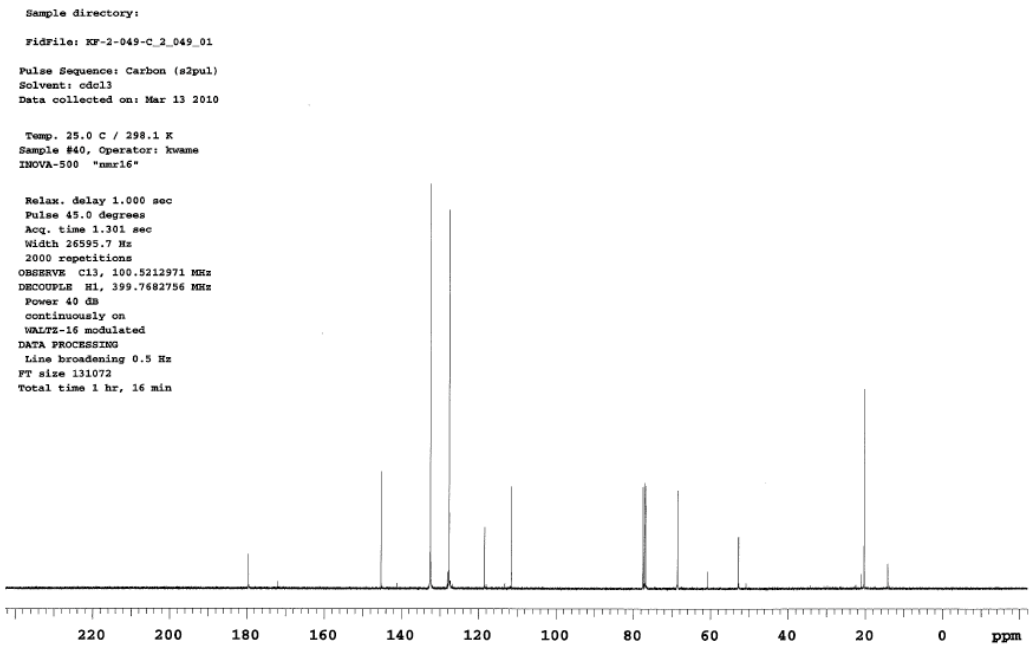
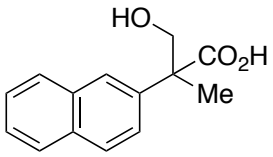
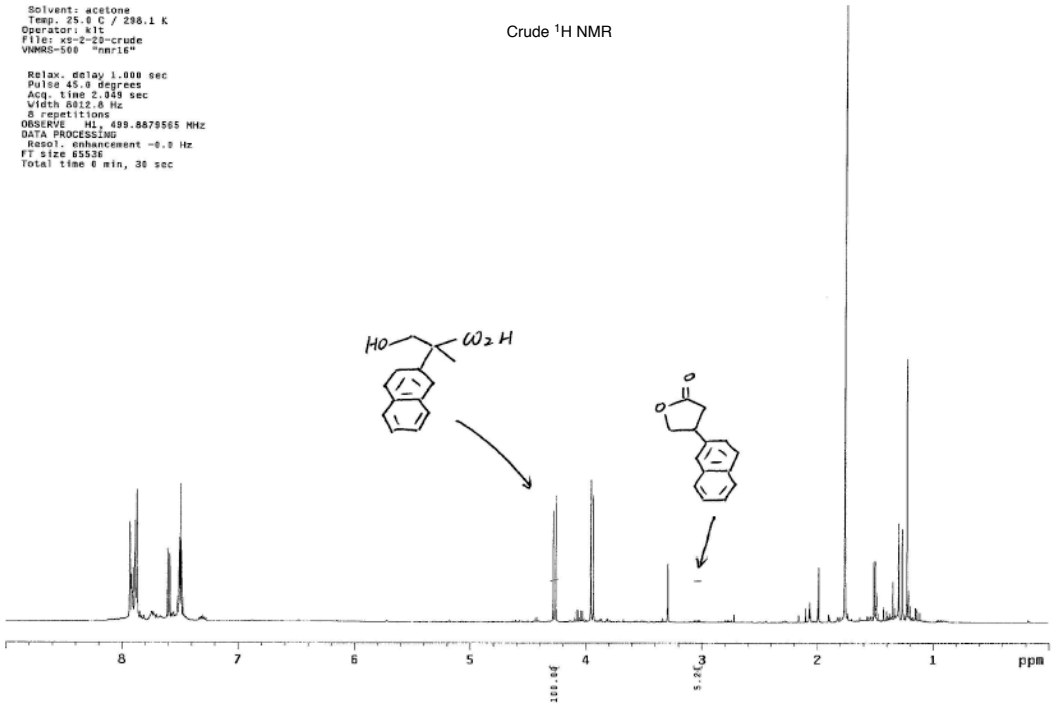


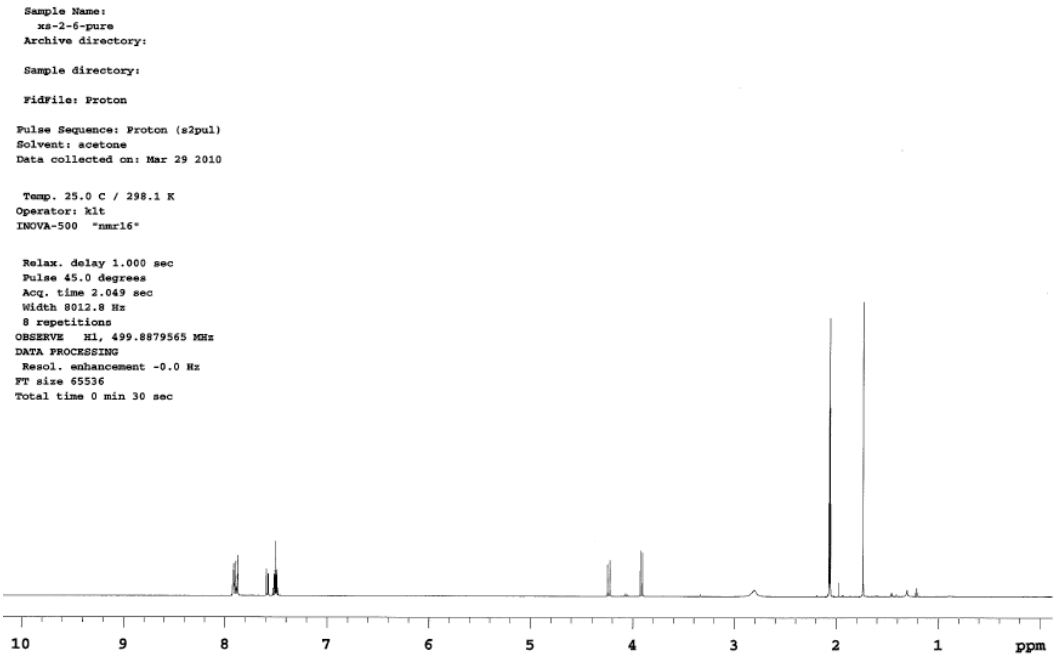
Table 1.2, Entry 9:



3-Hydroxy-2-methyl-2-(naphthalen-2-yl)propanoic acid. 2-(Naphthalen-2-yl)prop-2-en-1-ol (110 mg, 0.60 mmol) was hydroformylated with 0.05 mol% *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 35 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 95:5. Branched product was isolated as a white solid (117 mg, 85%). **^{1}H NMR** (Acetone d-6, 500 MHz) δ 7.94-7.87 (m, 4H), 7.61-7.59 (m, 1H), 7.51-7.49 (m, 2H), 5.15-3.23 (br s, 1H), 4.28 (d, 1H, J = 10.5), 4.19 (br s, 1H), 3.95 (d, 1H, J = 11.0), 2.81 (s, 1H), 1.77 (s, 3H); **^{13}C NMR** (Acetone d-6, 125 MHz) δ 175.9, 139.4, 133.5, 132.5, 128.0, 127.8, 127.4, 126.0, 125.9, 125.0, 125.0, 68.2, 52.4, 20.4; **IR**:

2921, 1697, 1027, 816, 751, 477 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{14}H_{18}NO_3$ $[M+NH_4]^+$: 248.12867, found: 248.12972.





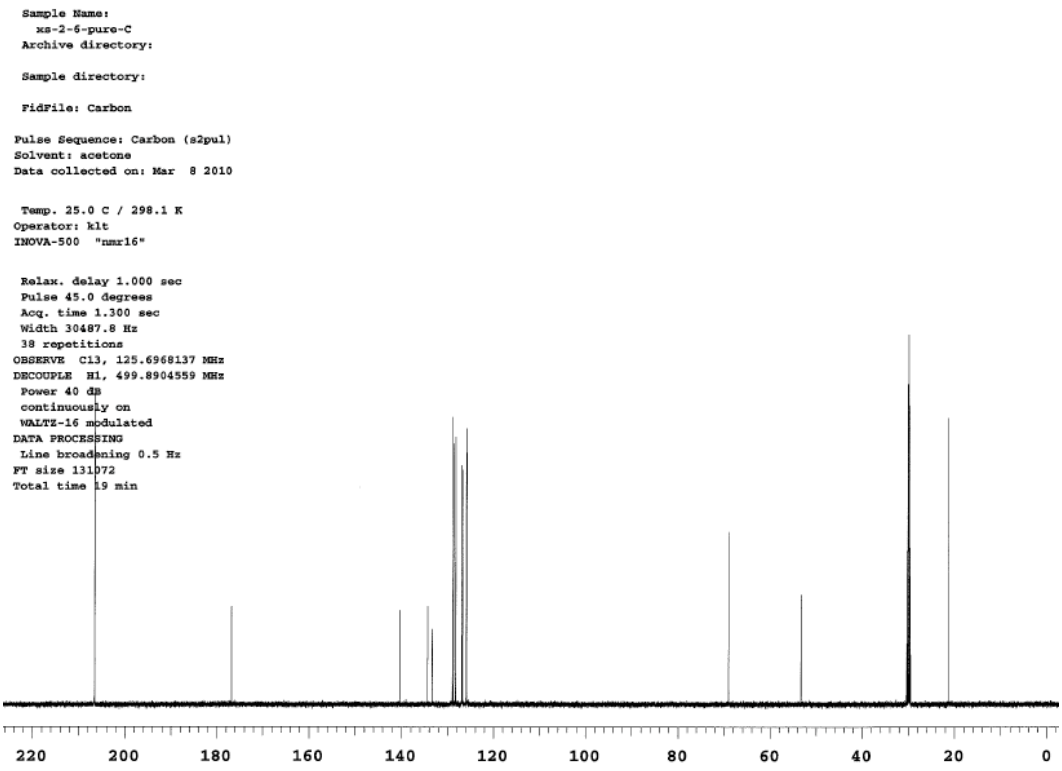
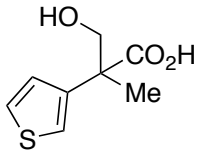
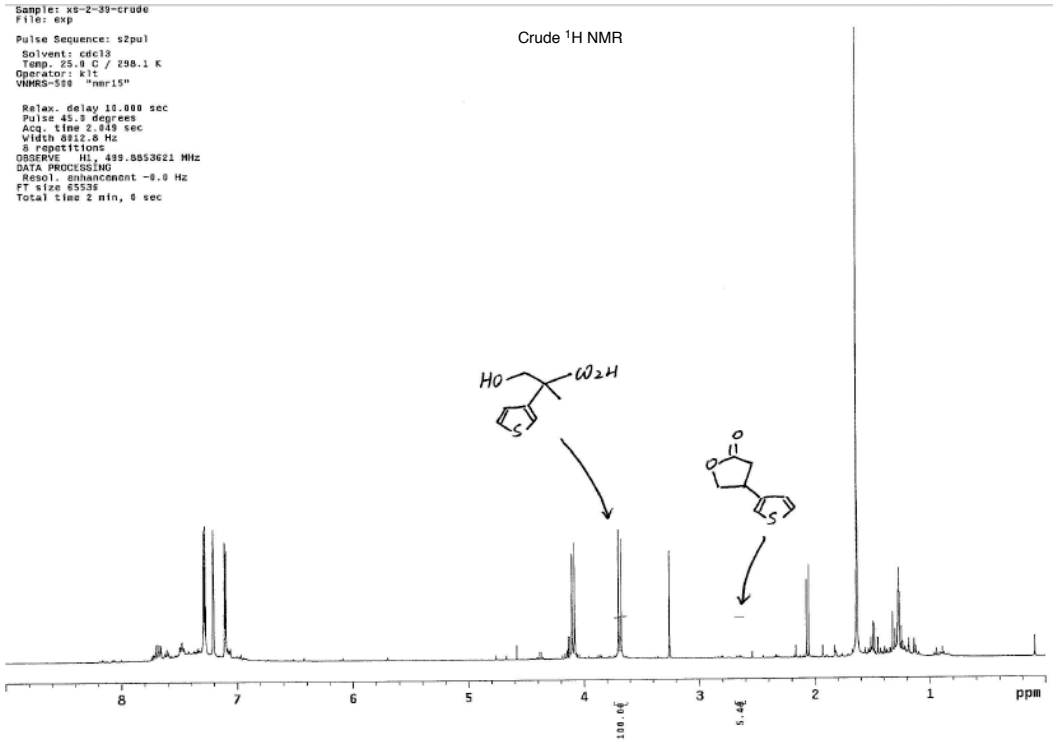


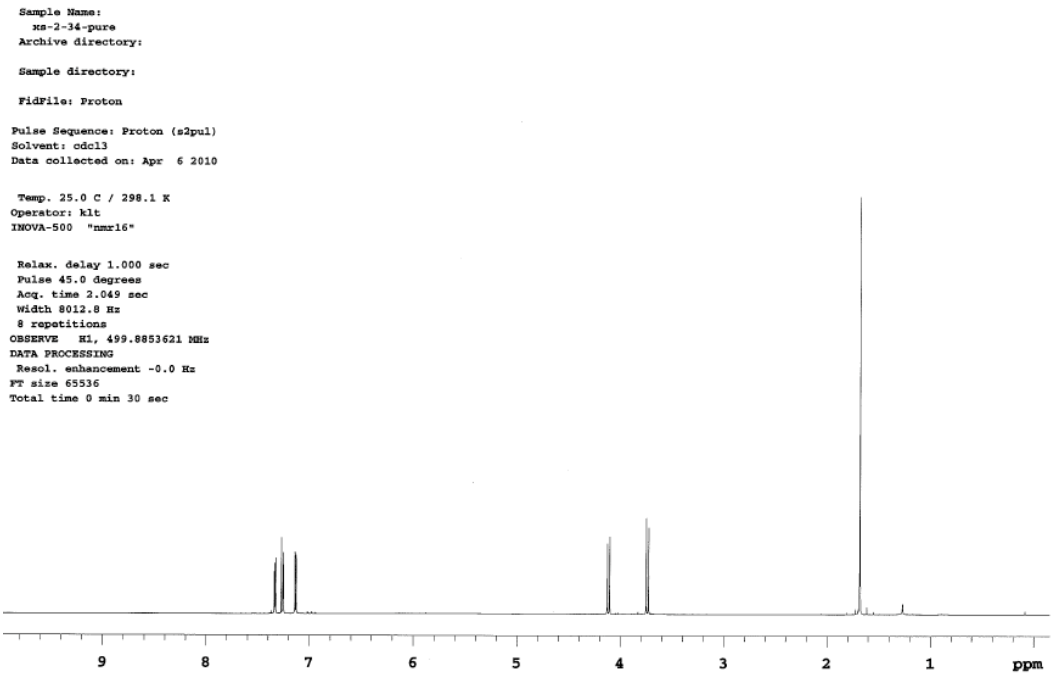
Table 1.2, Entry 10:



3-Hydroxy-2-methyl-2-(thiophen-3-yl)propanoic acid. 2-(Thiophen-3-yl)prop-2-en-1-ol (84 mg, 0.60 mmol) was hydroformylated with 0.20 mol% *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 45 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 95:5. Branched product was isolated as a white solid (78 mg, 70%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.32-7.31 (m, 1H), 7.24 (d, 1H, J = 1.5), 7.13-7.12 (m, 1H), 6.87 (br s, 1H), 4.11 (d, 1H, J = 11.2), 3.72 (d, 1H, J = 11.2), 1.67 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 180.3, 140.5, 126.3, 125.9, 121.7, 68.7, 50.1, 20.6; **IR**:

2925, 1698, 1222, 1029, 871, 782, 684 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_8H_{10}O_3S$ $[M+NH_4]^+$: 204.06944, found: 204.07035.





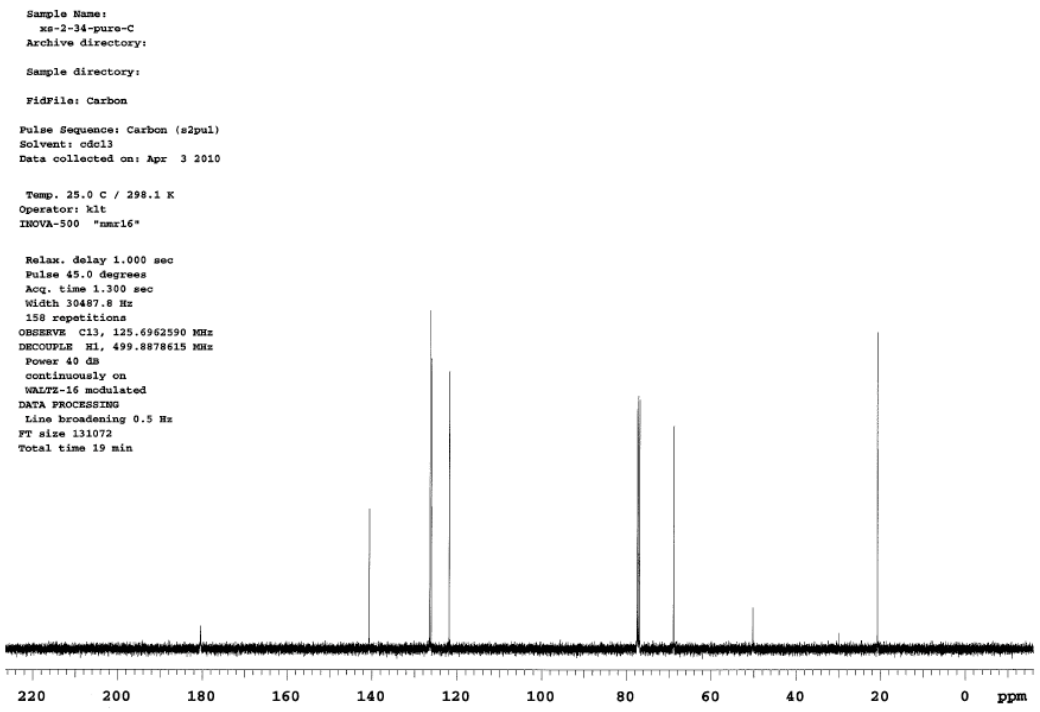
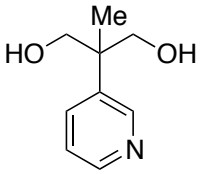


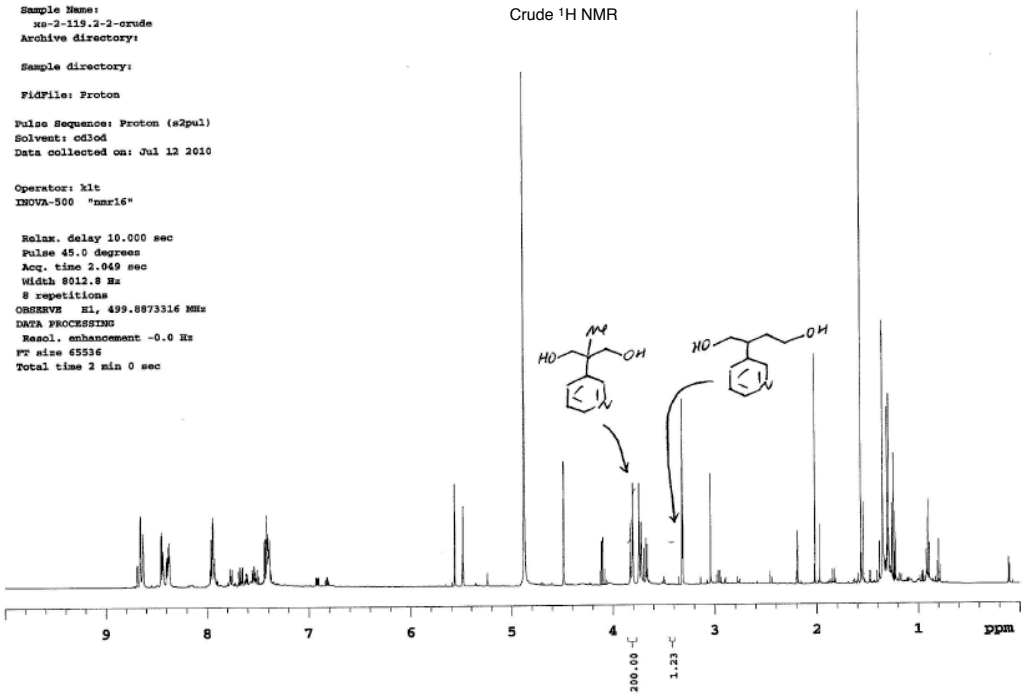
Table 1.2, Entry 11:

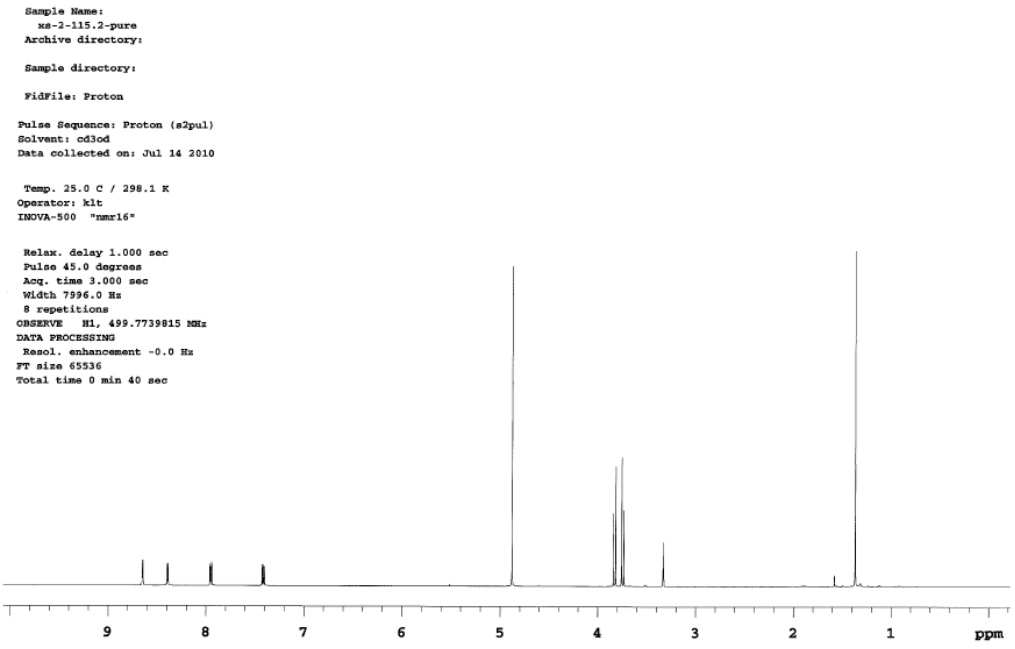


2-methyl-2-(pyridin-3-yl)propane-1,3-diol. 2-(pyridin-3-yl)prop-2-en-1-ol (20 mg, 0.15 mmol) was hydroformylated with 0.20 mol% *p*-toluenesulfonic acid (0.50 mL of 6.0×10^{-4} M in benzene, 0.30×10^{-3} mmol) at 45 °C for 12 h. Reduction with $NaBH_4$ (17 mg, 0.45 mmol) and MeOH (3.0 mL) at r.t. for 2 h was performed instead of oxidation. Analysis of crude mixture after reduction by ^{1}H NMR showed a b:l selectivity of 98:2. Branched product was isolated as a white solid (17 mg, 68%). **^{1}H NMR** (Methanol d-4, 500 MHz) δ 8.65 (d, 1H, *J* = 1.7), 8.39 (dd, 1H, *J* = 1.5, 4.9), 7.96-7.94 (m, 1H), 7.43-7.40 (m, 1H), 3.84 (d, 2H, *J* = 11.0), 3.75 (d, 2H, *J* =

11.0), 1.37 (s, 3H); **^{13}C NMR** (Methanol d-4, 125 MHz) δ 147.7, 146.0, 140.7, 135.9, 123.4, 77.0, 43.8, 18.8; **IR**: 3346, 2812, 1416, 1020, 820, 713, 632 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_9H_{14}NO_2$ $[M+H]^+$: 168.10245, found: 168.10277.

Crude ^{1}H NMR





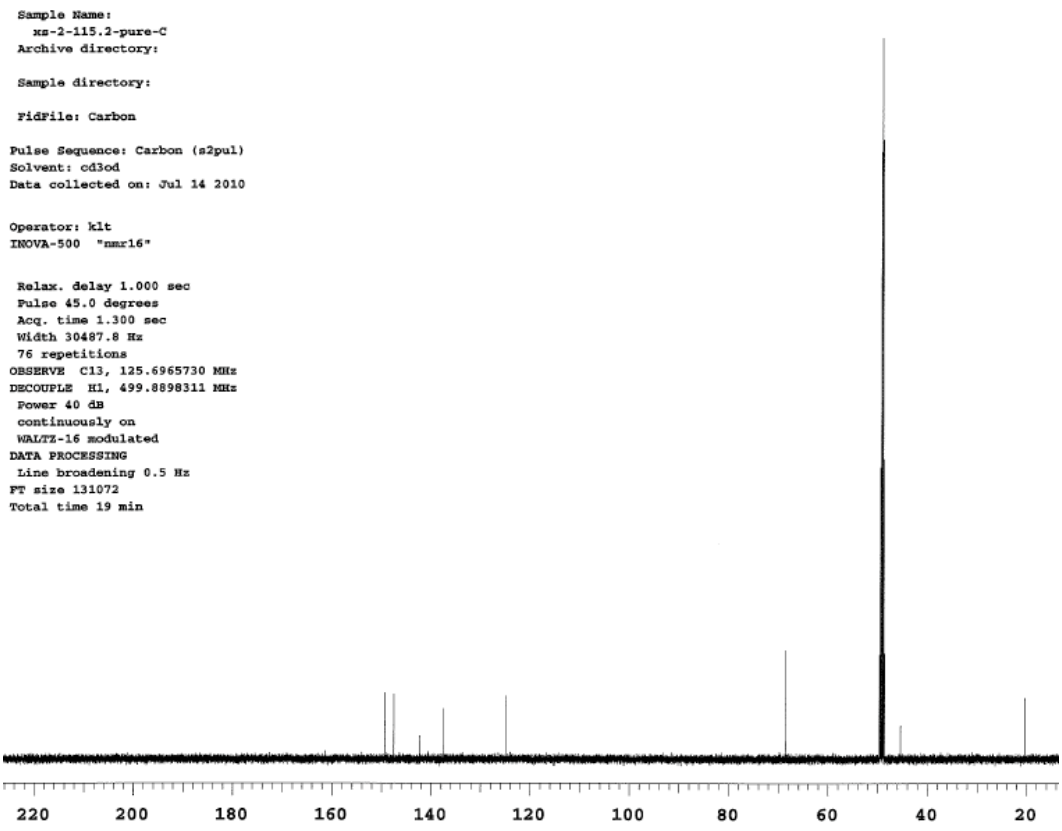
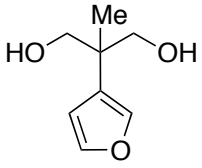
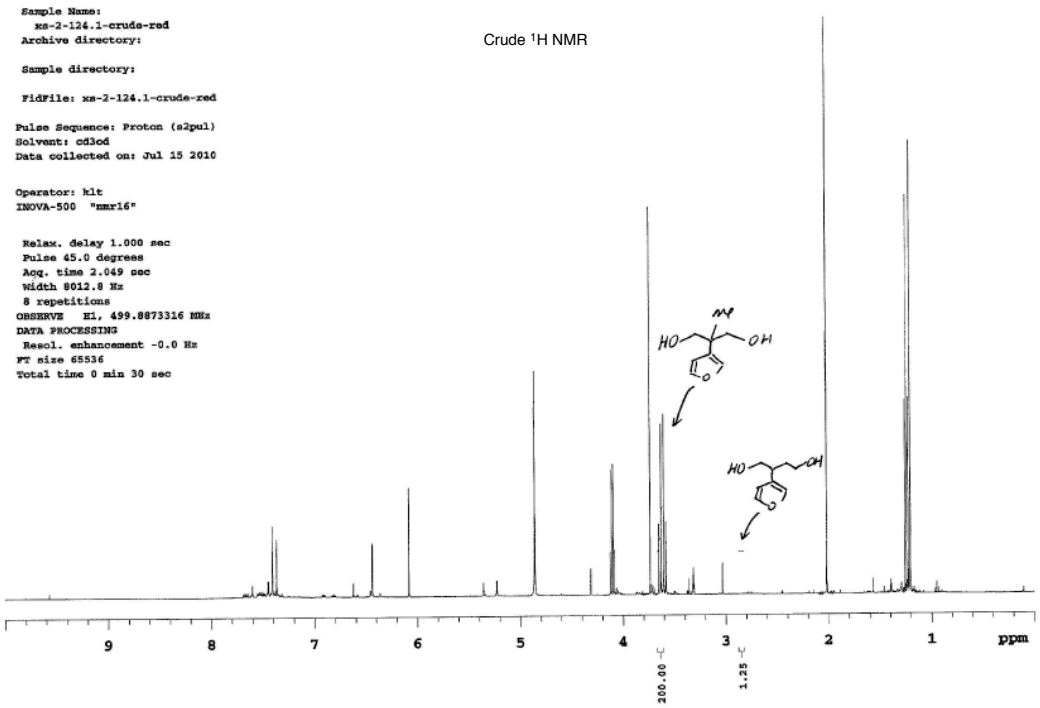


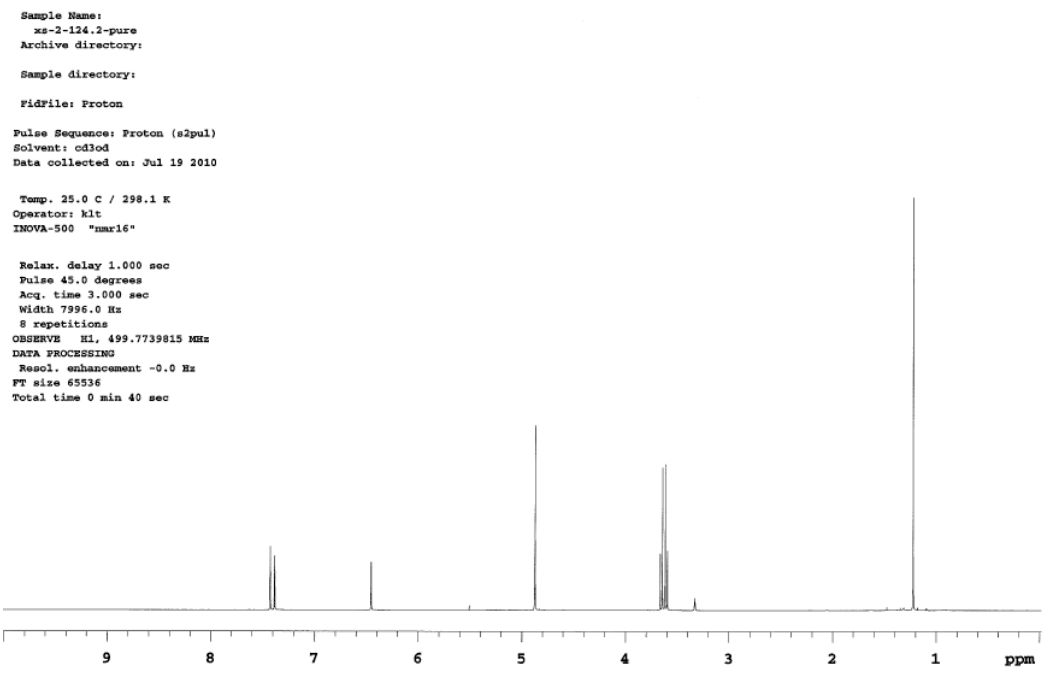
Table 1.2, Entry 12:

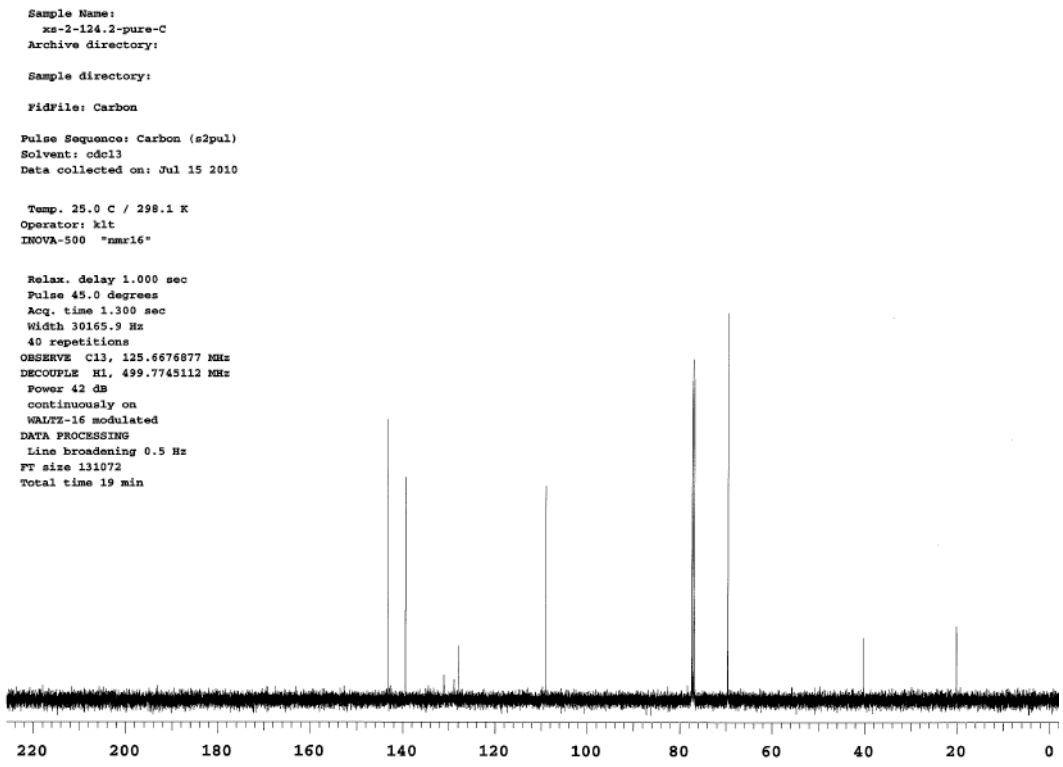


2-(furan-3-yl)-2-methylpropane-1,3-diol. 2-(furan-3-yl)prop-2-en-1-ol (37 mg, 0.30 mmol) was hydroformylated with 0.05 mol% *p*-toluenesulfonic acid (0.25 mL of 6.0×10^{-4} M in benzene, 0.15×10^{-3} mmol) at 55 °C for 16 h. Reduction with $NaBH_4$ (34 mg, 0.90 mmol) and MeOH (6.0 mL) at rt for 2h was performed instead of oxidation. Analysis of crude mixture after reduction by ^{1}H NMR showed a b:l selectivity of >98:2. Branched product was isolated as a white solid (30 mg, 64%). **^{1}H NMR** (Methanol d-4, 500 MHz) δ 7.42 (t, 1H, J = 1.8), 7.38 (dd, 1H, J = 1.0, 1.5),

6.46 (dd, 1H, *J* = 1.0, 2.0), 3.65 (d, 2H, *J* = 10.8), 3.61 (d, 2H, *J* = 10.8), 1.22 (s, 3H); **^{13}C NMR** (Methanol d-4, 125 MHz) δ 142.2, 139.0, 128.8, 109.0, 67.1, 40.0, 18.8; **IR**: 3363, 2934, 2879, 1027, 875, 789, 601 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_8H_{13}O_3$ $[M+H]^+$: 157.08647, found: 157.08589.




Sample Name:
xs-2-124.2-pure
Archive directory:
Sample directory:
FidFile: Proton
Pulse Sequence: Proton (s2pul)
Solvent: cd3od
Data collected on: Jul 19 2010
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 7996.0 Hz
8 repetitions
OBSERVE H1, 499.7739815 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 40 sec
9
8
7
6
5
4
3
2
1
ppm


Sample Name:
xs-2-124.2-pure-C
Archive directory:
Sample directory:
FidFile: Carbon
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Jul 15 2010
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
40 repetitions
OBSERVE C13, 125.6676877 MHz
DECOUPLE H1, 499.7745112 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
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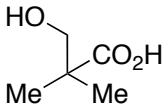
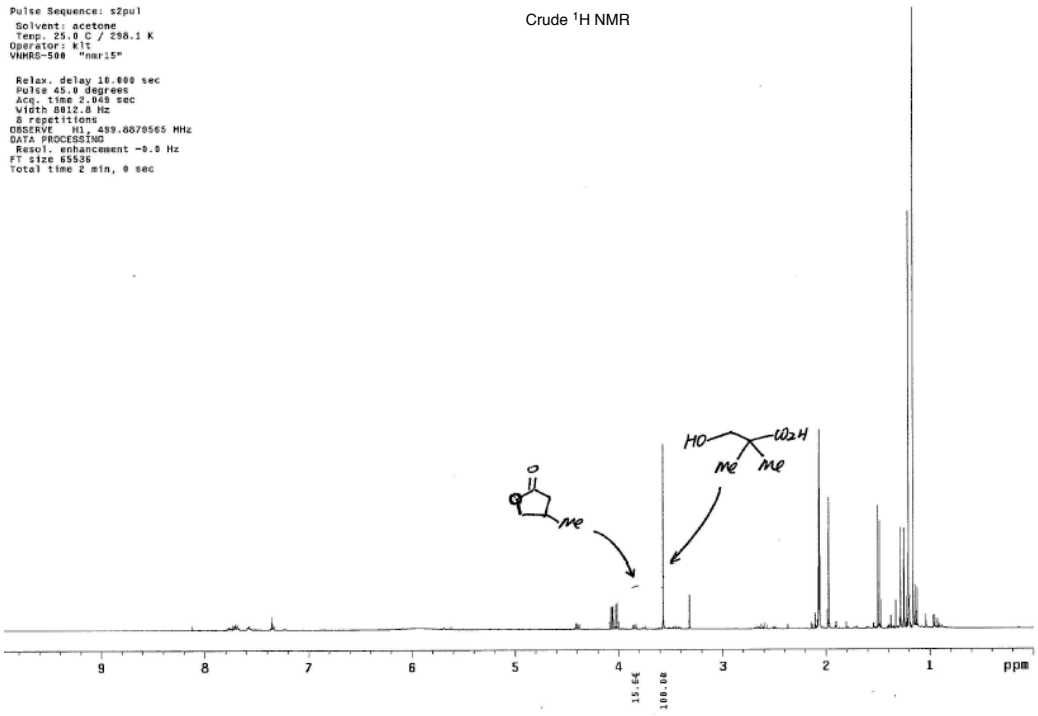
Total time 19 min
220
200
180
160
140
120
100
80
60
40
20
0

Table 1.2, Entry 13:



3-hydroxy-2,2-dimethylpropanoic acid. 2-methylprop-2-en-1-ol (43 mg, 0.60 mmol) was hydroformylated with 0.20 mol% *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 45 °C for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 76:24. Branched product was isolated as a white solid (35 mg, 49%). **^{1}H NMR** (Acetone d-6, 500 MHz) δ 3.57 (s, 2H), 1.16 (s, 6H); **^{13}C NMR** (Acetone d-6, 125 MHz) δ 117.8, 68.8, 43.8, 21.4; **IR**: 2933, 1692, 1236, 1044 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_5H_{14}NO_3$ $[M+NH_4]^+$: 136.09737, found: 136.09743.



Sample Name:
xs-2-45.3-f6-15-pure
Archive directory:

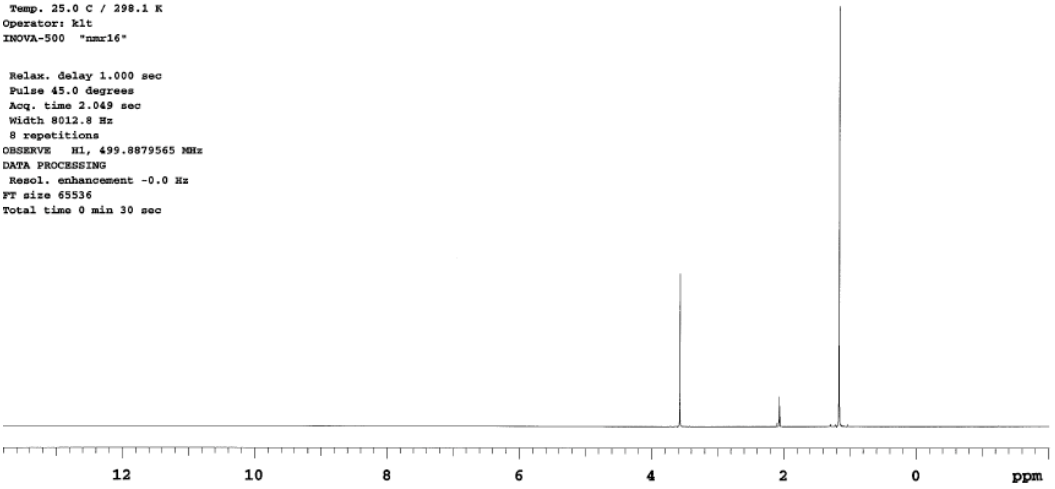
Sample directory:

FidFile: Proton

Pulse Sequence: Proton (s2pul)
Solvent: acetone
Data collected on: Apr 23 2010

Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8879565 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec



Sample Name:
xs-2-45.3-f6-15-C
Archive directory:

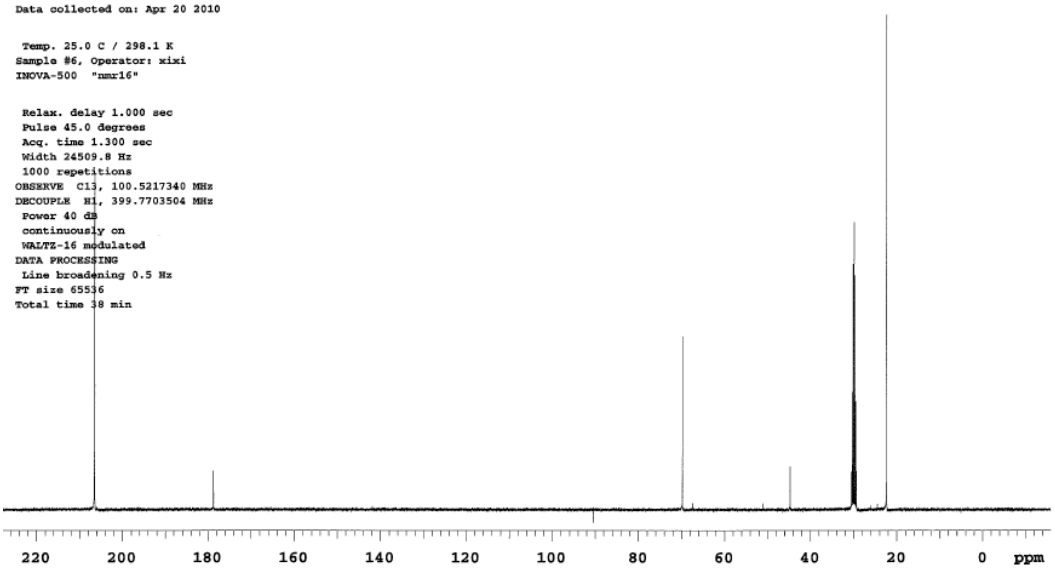
Sample directory:

FidFile: Carbon

Pulse Sequence: Carbon (s2pul)
Solvent: acetone
Data collected on: Apr 20 2010

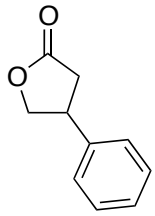
Temp. 25.0 C / 298.1 K
Sample #6, Operator: xixi
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
1000 repetitions
OBSERVE C13, 100.5217340 MHz
DECOUPLE H1, 399.7703504 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 38 min

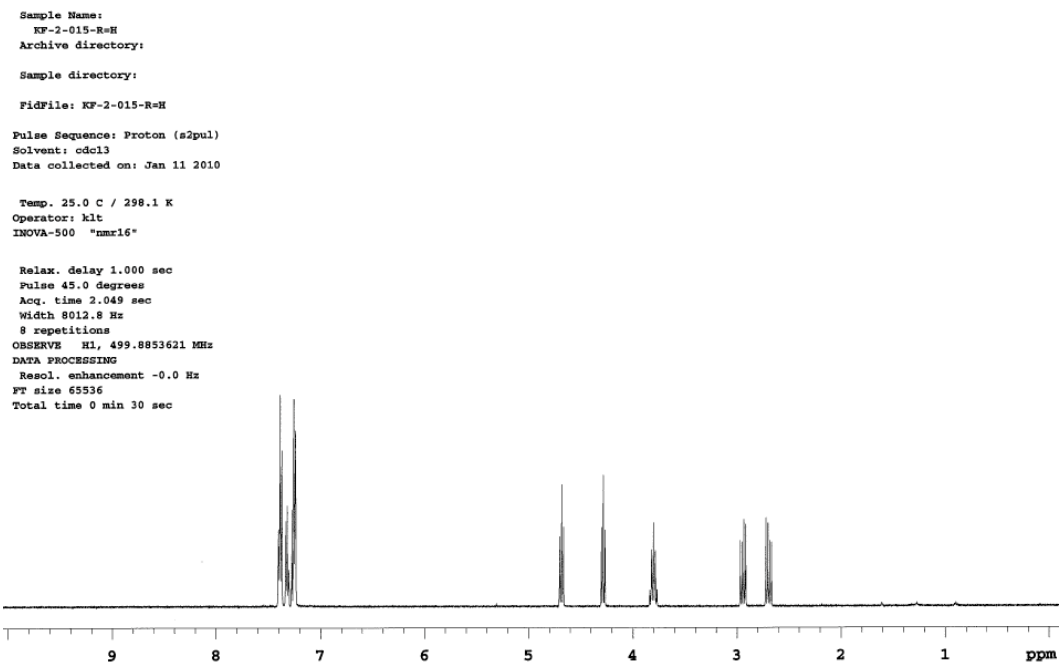


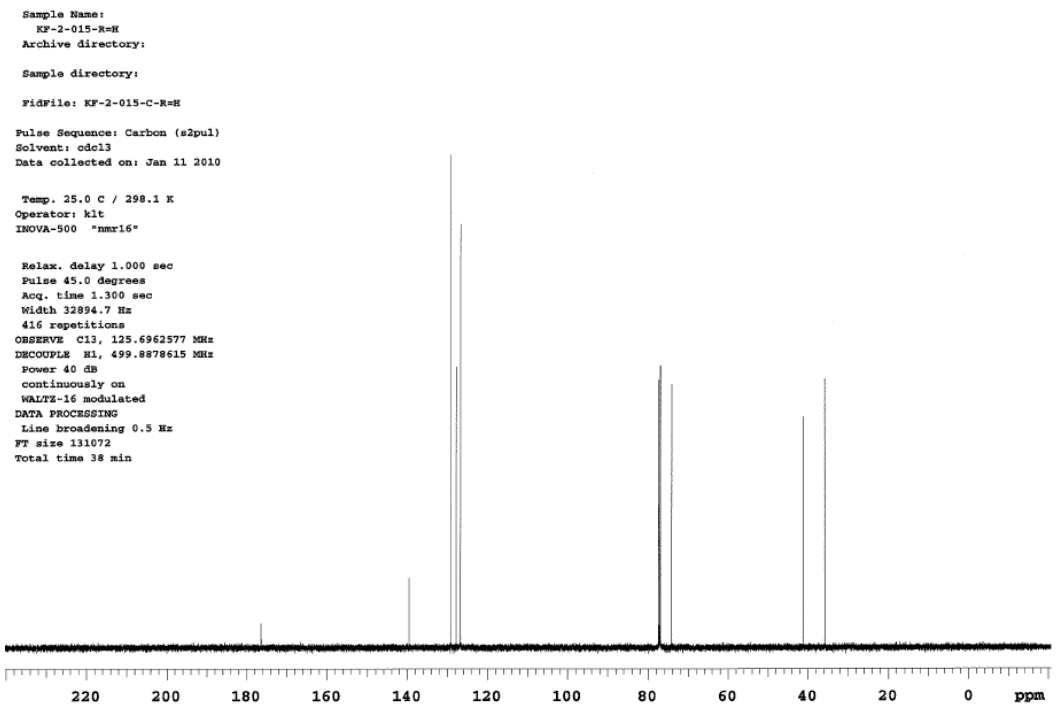
Linear Product Syntheses and Characterizations

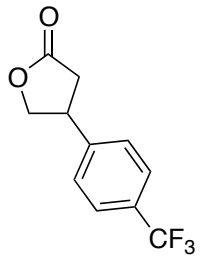
General Procedure. The oven dried glass reaction vial was placed in the Endeavor, and corresponding alcohol substrates (0.60 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium(I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol%), triphenylphosphine (13 mg, 4.8×10^{-2} mmol, 8.0 mol%) and benzene (to total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 75 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi CO/H_2, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature and pressure of 75 °C and 400 psi CO/H_2 for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The sample was removed and concentrated. The crude residue was dissolved in CH_2Cl_2 (9 mL) and pyridinium chlorochromate (390 mg, 1.8 mmol, 3.0 eq.), sodium acetate (25 mg, 0.30 mmol, 0.50 eq.), and 3Å molecular sieves (1.2 g, 4-8 mesh) were added and the solution was agitated on an orbital shaker for 12 hours. Flash column chromatography (Hex/EtOAc = 8/1) afforded pure products.



4-Phenyldihydrofuran-2(3*H*)-one, (1.47) (83 mg, 85%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.39 (t, 2H, *J* = 7.6), 7.31 (t, 1H, *J* = 7.3), 7.25 (d, 2H, *J* = 7.6), 4.69 (dd, 1H, *J* = 7.8, 9.1), 4.28 (dd, 1H, *J* = 8.1, 9.1), 3.80 (m, 1H), 2.94 (dd, 1H, *J* = 8.8, 17.6), 2.69 (dd, 1H, *J* = 9.0, 17.4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 176.3, 139.4, 129.2, 127.7, 126.7, 74.0, 41.1, 35.7; **IR** 1759, 1156, 1007, 760, 702 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{11}O_2$ $[M+H]^+$: 163.07590, found 163.07652.







4-(4-(Trifluoromethyl)phenyl)dihydrofuran-2(3H)-one (118 mg, 85%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.61 (d, 2H, *J* = 8.4), 7.35 (d, 2H, *J* = 8.2), 4.70-4.65 (dd, 1H, *J* = 7.8, 9.2), 4.29-4.24 (dd, 1H, *J* = 7.6, 9.2), 3.88-3.80 (m, 1H), 2.95 (dd, 1H, *J* = 8.8, 17.4), 2.65 (dd, 1H, *J* = 8.4, 17.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 175.7, 143.7, 130.1 (q, *J* = 32.5), 127.2, 126.1, 123.9 (q, *J* = 270.5), 73.4, 40.8, 35.5; **IR** 1771, 1324, 1164, 1117, 1066, 1018, 833 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{10}F_3O_2$ $[M+H]^+$: 231.06329, found 231.06376.

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   KF-2-015-R=CF3_H
 Archive directory:

 Sample directory:

 FidFile: KF-2-015-R=CF3_H_2_015_01

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar  9 2010

 Temp. 25.0 C / 298.1 K
Sample #23, Operator: kwame
INOVA-500  "nmr16"

 Relax. delay 10.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
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 8 repetitions
OBSERVE   H1, 399.7662768 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 2 min 0 sec
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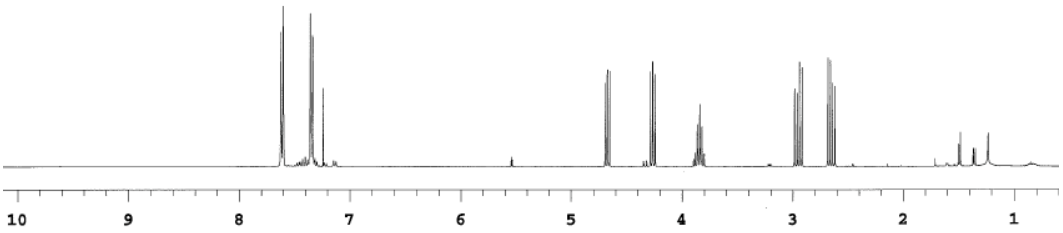


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  Sample Name:
    KF-2-015-R=CF3
  Archive directory:

  Sample directory:

  FidFile: KF-2-015-C-R=CF3

 Pulse Sequence: Carbon (s2pul)
 Solvent: cdcl3
 Data collected on: Jan 14 2010

  Temp. 25.0 C / 298.1 K
 Operator: klt
 INOVA-500  "nmr16"

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 1.300 sec
  Width 32894.7 Hz
  15360 repetitions
 OBSERVE  C13, 125.6962597 MHz
 DECOUPLE  H1, 499.8878615 MHz
  Power 40 dB
  continuously on
  WALTZ-16 modulated
 DATA PROCESSING
  Line broadening 0.5 Hz
 FT size 131072
 Total time 11 hr, 30 min
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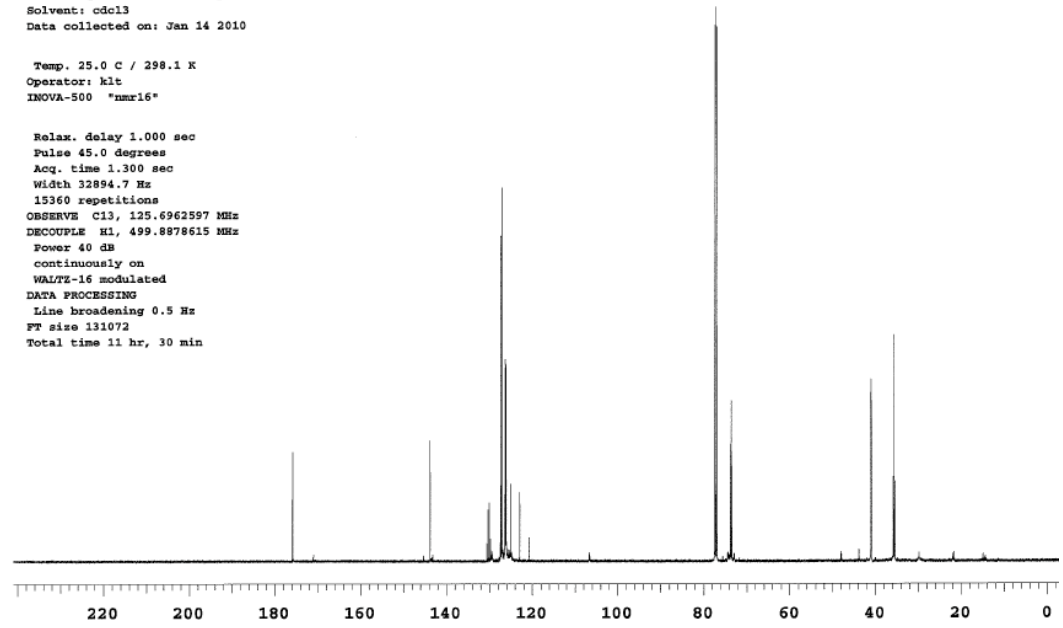
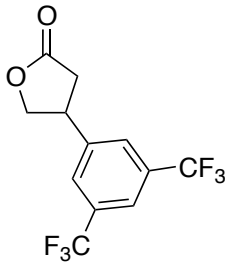
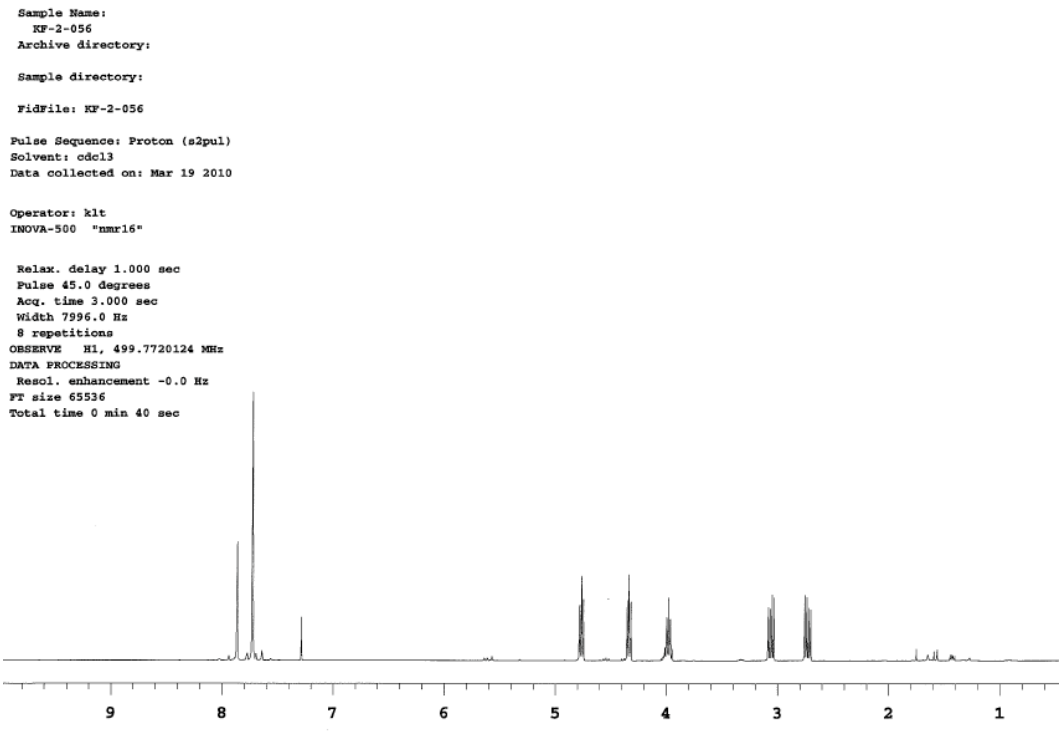
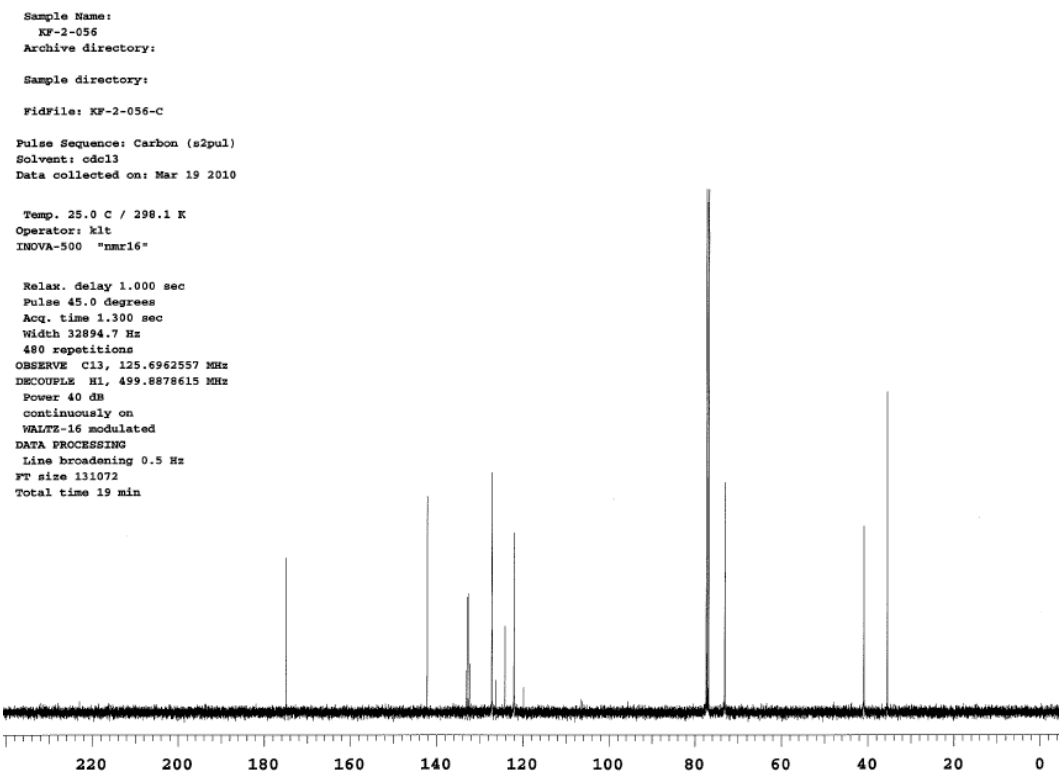
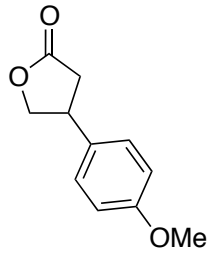




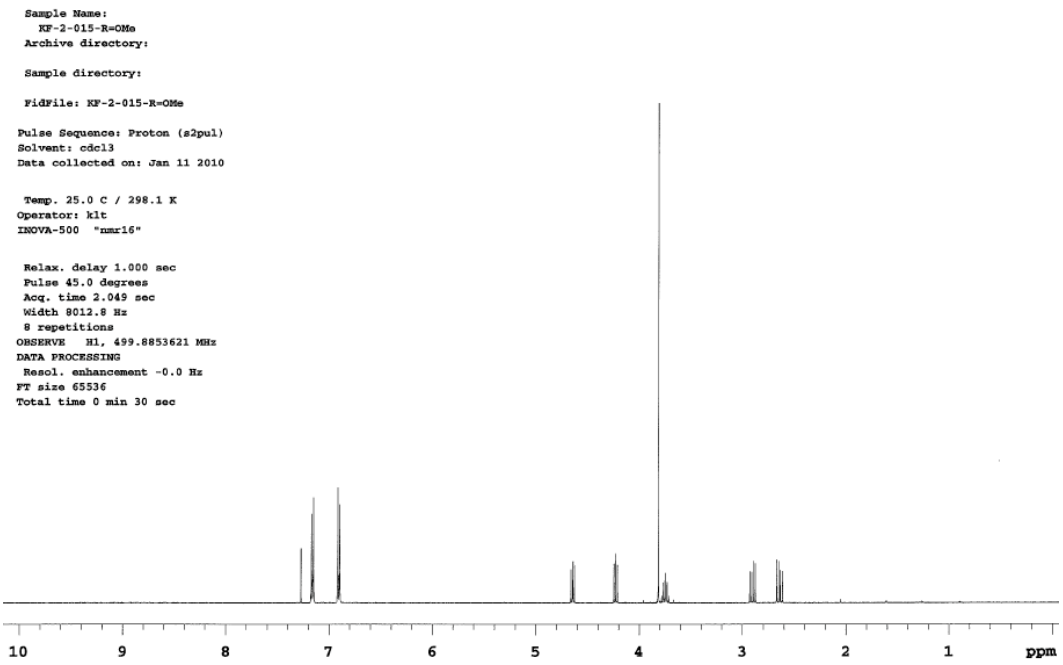
4-(3,5-Bis(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one (130 mg, 72%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.86 (s, 1H), 7.28 (s, 2H), 4.77 (dd, 1H, *J* = 8.1, 9.0), 4.34 (dd, 1H, *J* = 8.1, 9.3), 3.98 (m, 1H), 3.06 (dd, 1H, *J* = 8.8, 17.6), 2.73 (dd, 1H, *J* = 8.8, 17.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 174.9, 142.1, 132.7 (q, *J* = 34.4), 127.1, 123.0 (q, *J* = 271.1), 121.9, 72.9, 40.8, 35.3; **IR** 1786, 1374, 1276, 1170, 1110, 1030, 899, 842, 707, 682 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_9F_6O_2$ $[M+H]^+$: 299.05067, found 299.05024.

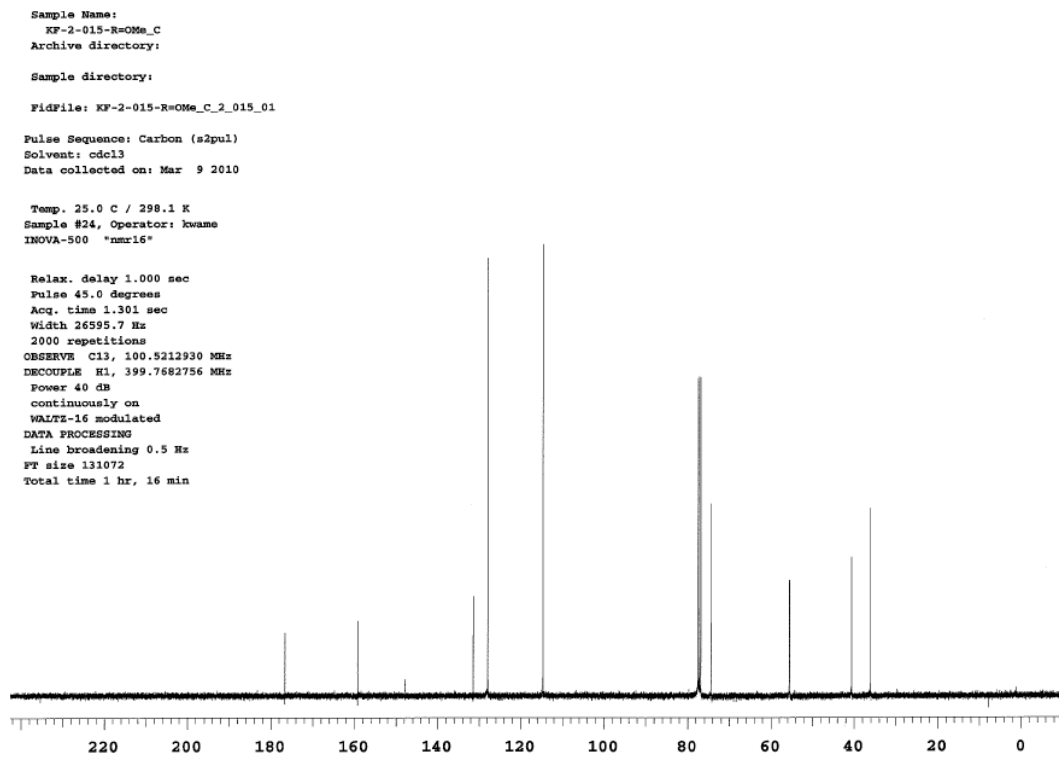


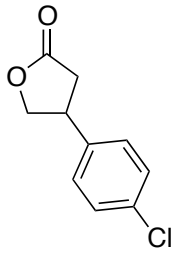




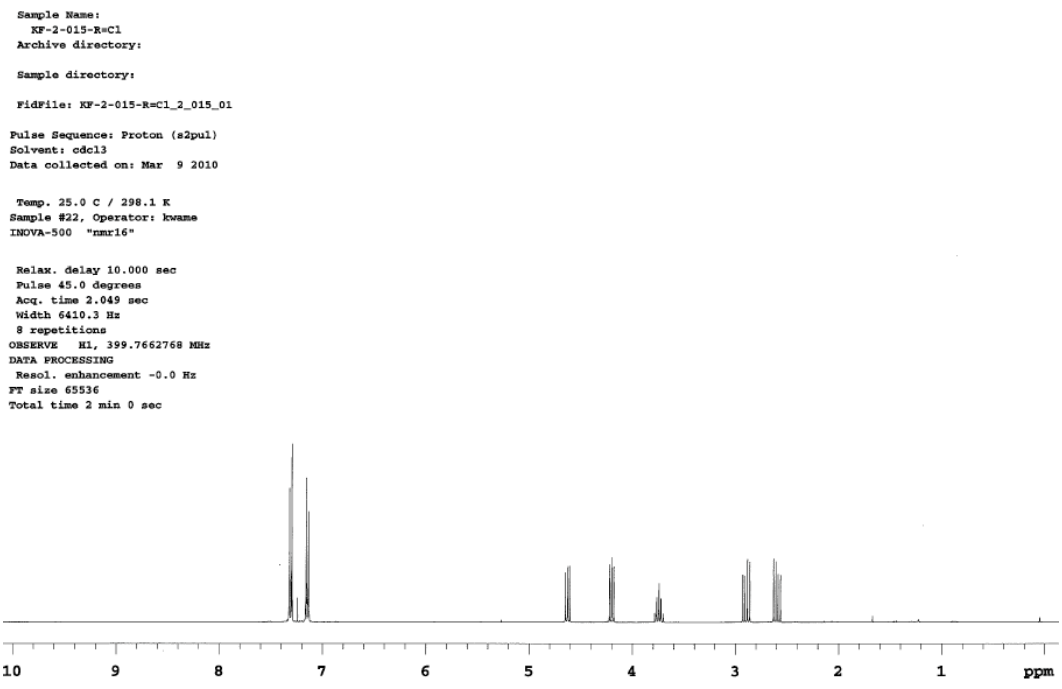
4-(4-Methoxyphenyl)dihydrofuran-2(3H)-one (74 mg, 64%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.13 (d, 2H, *J* = 8.8), 6.90 (d, 2H, *J* = 8.8), 4.62 (dd, 1H, *J* = 8.1, 9.1), 4.20 (dd, 1H, *J* = 8.1, 9.1), 3.79 (s, 3H), 3.72 (m, 1H), 2.88 (dd, 1H, *J* = 8.6, 17.4), 2.61 (dd, 1H, *J* = 9.3, 17.4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 176.4, 159.0, 131.3, 127.7, 114.5, 74.2, 55.3, 40.4, 35.9; **IR** 1765, 1511, 1454, 1254, 1164, 1014, 838, 602, 554 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{13}O_3$ $[M+H]^+$: 193.08647, found 193.08682.

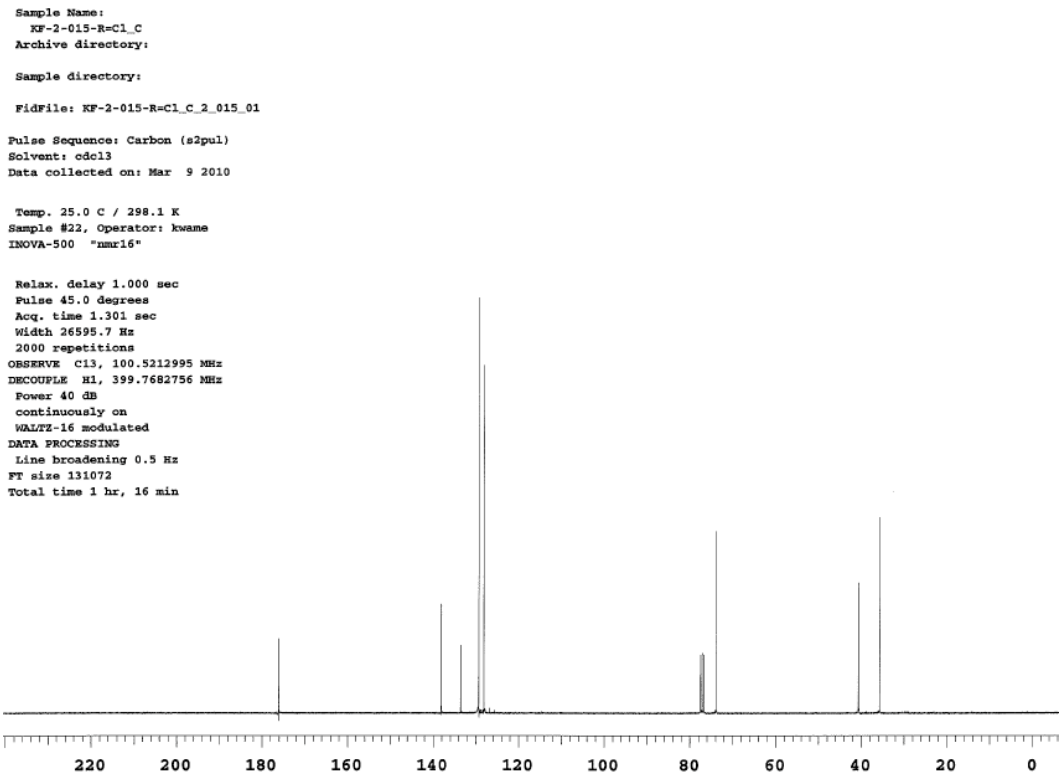

Sample Name:
KF-2-015-R=OMe
Archive directory:
Sample directory:
FidFile: KF-2-015-R=OMe
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jan 11 2010
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8853621 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec
10
9
8
7
6
5
4
3
2
1
ppm

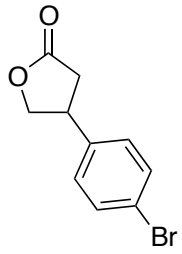

Sample Name:
KF-2-015-R=OMe_C
Archive directory:
Sample directory:
FidFile: KF-2-015-R=OMe_C_2_015_01
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Mar 9 2010
Temp. 25.0 C / 298.1 K
Sample #24, Operator: kwame
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.301 sec
Width 26595.7 Hz
2000 repetitions
OBSERVE C13, 100.5212930 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 1 hr, 16 min
220
200
180
160
140
120
100
80
60
40
20
0



4-(4-Chlorophenyl)dihydrofuran-2(3H)-one (73 mg, 62%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31 (d, 2H, *J* = 8.6), 7.29 (d, 2H, *J* = 8.4), 4.63 (dd, 1H, *J* = 7.8, 9.2), 4.20 (dd, 1H, *J* = 7.6, 9.0), 3.79-3.70 (m, 1H), 2.90 (dd, 1H, *J* = 8.8, 17.6), 2.60 (dd, 1H, *J* = 8.8, 17.4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 176.0, 138.0, 133.5, 129.3, 128.1, 73.7, 40.5, 35.6; **IR** 1774, 1485, 1425, 1161, 1093, 1011, 832, 680, 511, 496 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{10}ClO_2$ $[M+H]^+$: 197.03693, found 197.03745.







4-(4-Bromophenyl)dihydrofuran-2(3H)-one (110 mg, 76%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.49 (d, 2H, *J* = 8.6), 7.12 (d, 2H, *J* = 8.3), 4.66 (dd, 1H, *J* = 7.8, 9.0), 4.23 (dd, 1H, *J* = 7.6, 9.1), 3.76 (m, 1H), 2.92 (dd, 1H, *J* = 8.6, 17.4), 2.62 (dd, 1H, *J* = 8.8, 17.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 175.9, 138.6, 132.3, 128.4, 121.6, 73.7, 40.6, 35.6; **IR** 1764, 1486, 1422, 1154, 1010, 825, 539, 491 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{10}BrO_2$ $[M+H]^+$: 240.98642, found 240.98681.

Sample Name:
xs-1-276
Archive directory:

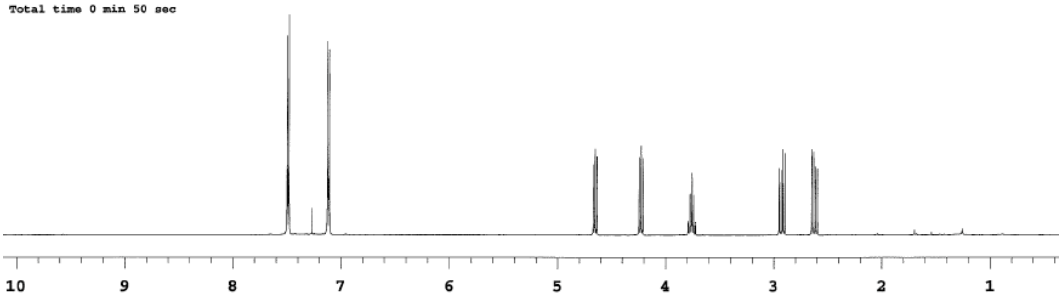
Sample directory:

FidFile: Proton

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jan 30 2010

Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8853621 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 50 sec



Sample Name:
xs-1-276
Archive directory:

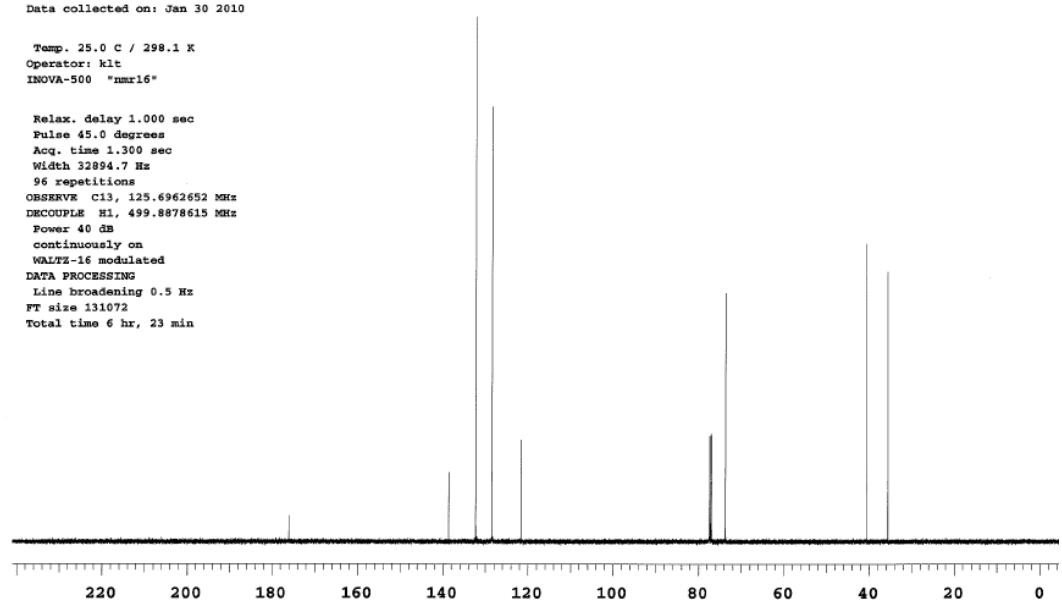
Sample directory:

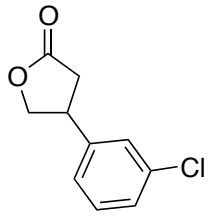
FidFile: Carbon

Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Jan 30 2010

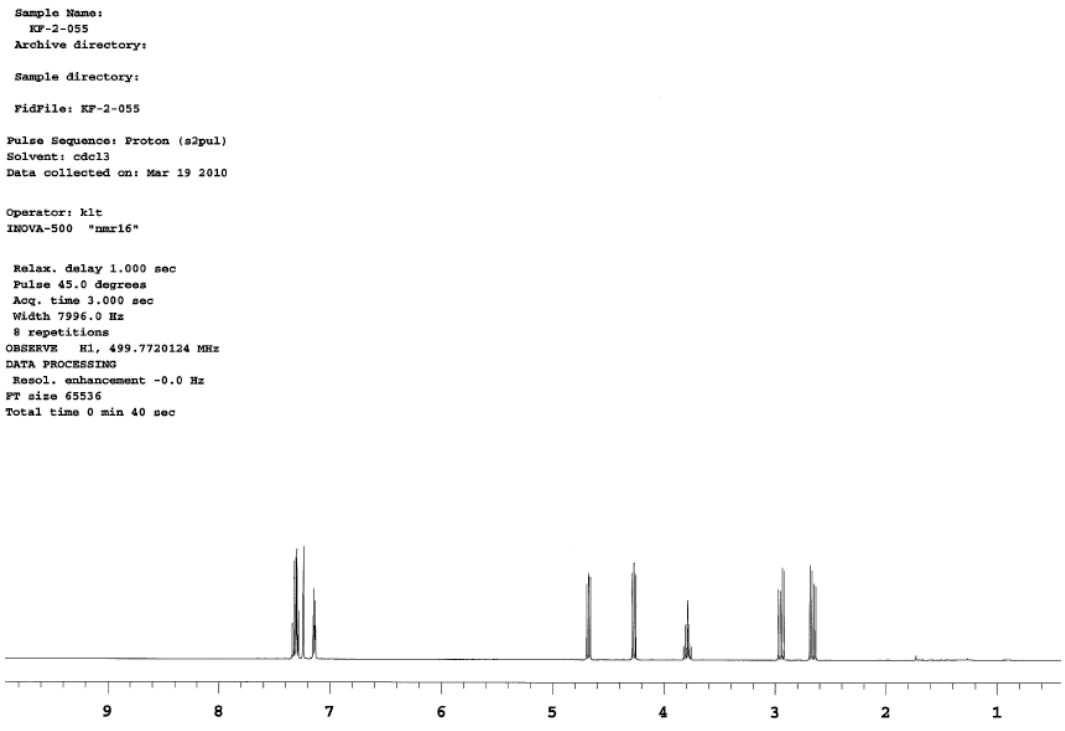
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

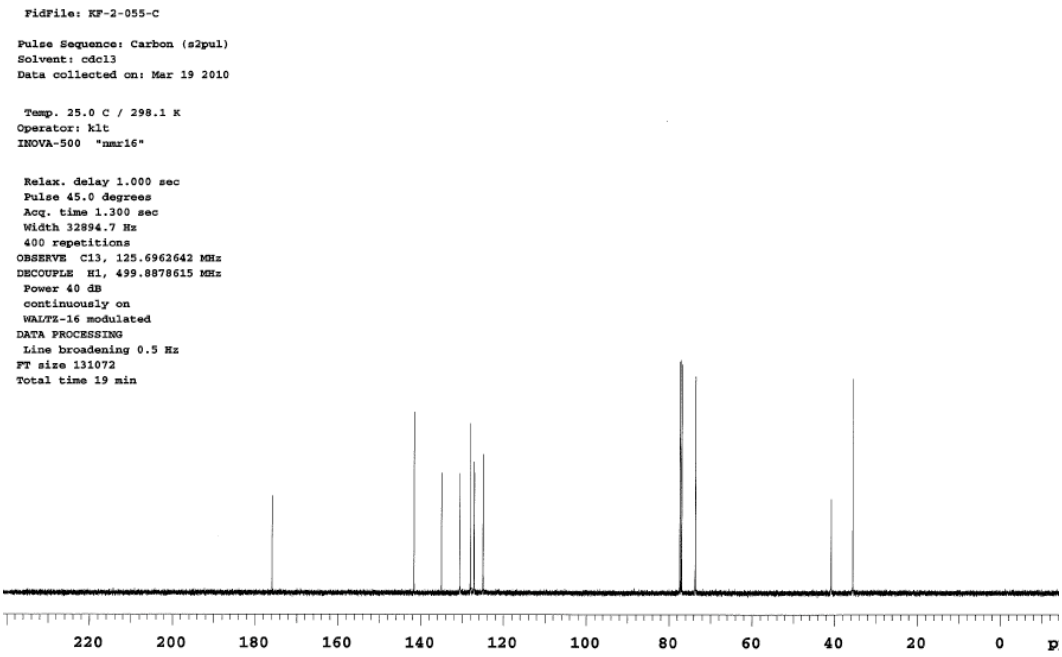
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 32894.7 Hz
96 repetitions
OBSERVE C13, 125.6962652 MHz
DECOUPLE H1, 499.8878615 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 23 min

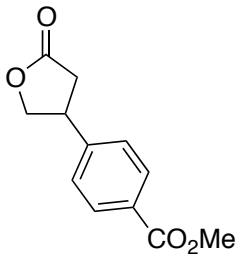




4-(3-Chlorophenyl)dihydrofuran-2(3H)-one (95 mg, 81%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.31 (m, 1H), 7.24 (s, 1H), 7.14 (d, 2H, *J* = 8.3), 4.68 (dd, 1H, *J* = 7.8, 9.0), 4.27 (dd, 1H, *J* = 7.6, 9.0), 3.79 (m, 1H), 2.95 (dd, 1H, *J* = 8.5, 17.3), 2.66 (dd, 1H, *J* = 8.8, 17.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 175.9, 141.6, 135.0, 127.9, 127.1, 124.9, 73.6, 40.7, 35.5; **IR** 1773, 1598, 1480, 1164, 1083, 1019, 907, 785, 729, 693, 441 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{10}ClO_2$ $[M+H]^+$: 197.03693, found 197.03729.







Methyl 4-(5-oxotetrahydrofuran-3-yl)benzoate (63 mg, 48%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.01 (d, 2H, *J* = 8.5),7.30 (d, 2H, *J* = 8.5), 4.67 (dd, 1H, *J* = 7.8, 9.0), 4.26 (dd, 1H, *J* = 7.8, 9.3), 3.89 (s, 3H), 3.86-3.83 (m, 1H), 2.94 (dd, 1H, *J* = 8.8, 17.6), 2.66 (dd, 1H, *J* = 8.8, 17.4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 175.9, 166.5, 144.7, 130.4, 129.6, 126.8, 73.5, 52.2, 41.0, 35.4; **IR** 1778, 1717, 1280, 1168, 1109, 1019 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{13}O_4$ $[M+H]^+$: 221.08138, found 221.08169.

Sample Name:
xs-2-36-f58-75
Archive directory:

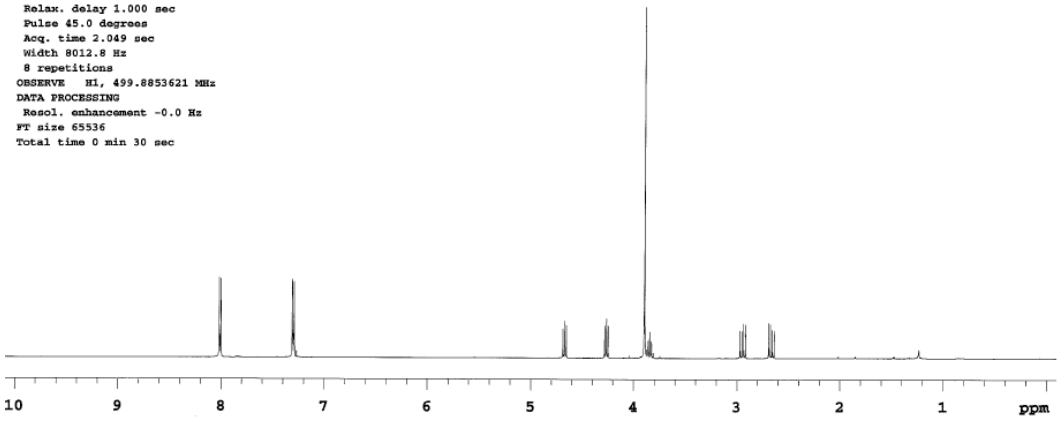
Sample directory:

FidFile: Proton

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Apr 10 2010

Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8853621 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec



Sample Name:
xs-2-36-f58-75-C
Archive directory:

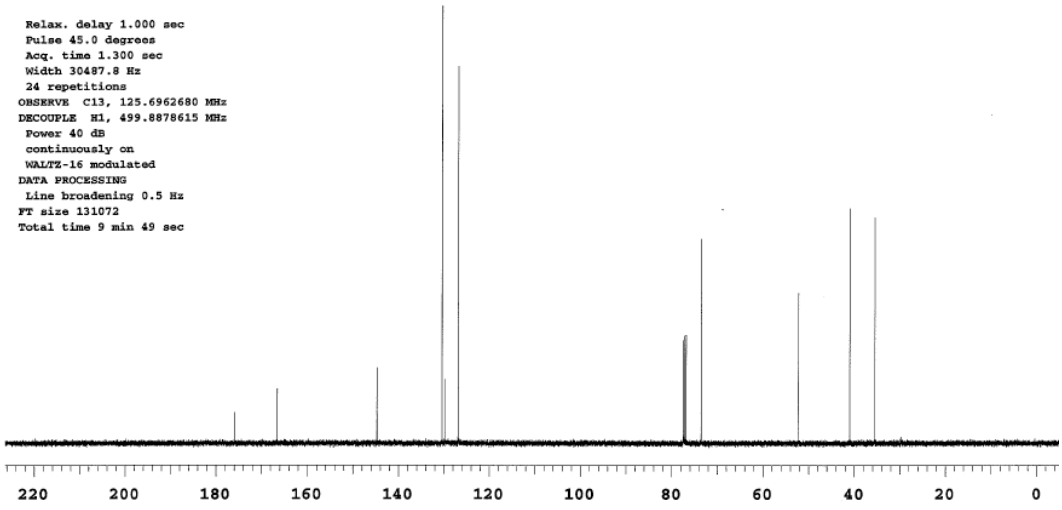
Sample directory:

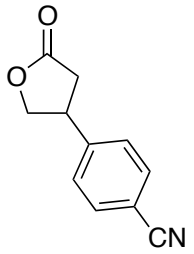
FidFile: Carbon

Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Apr 10 2010

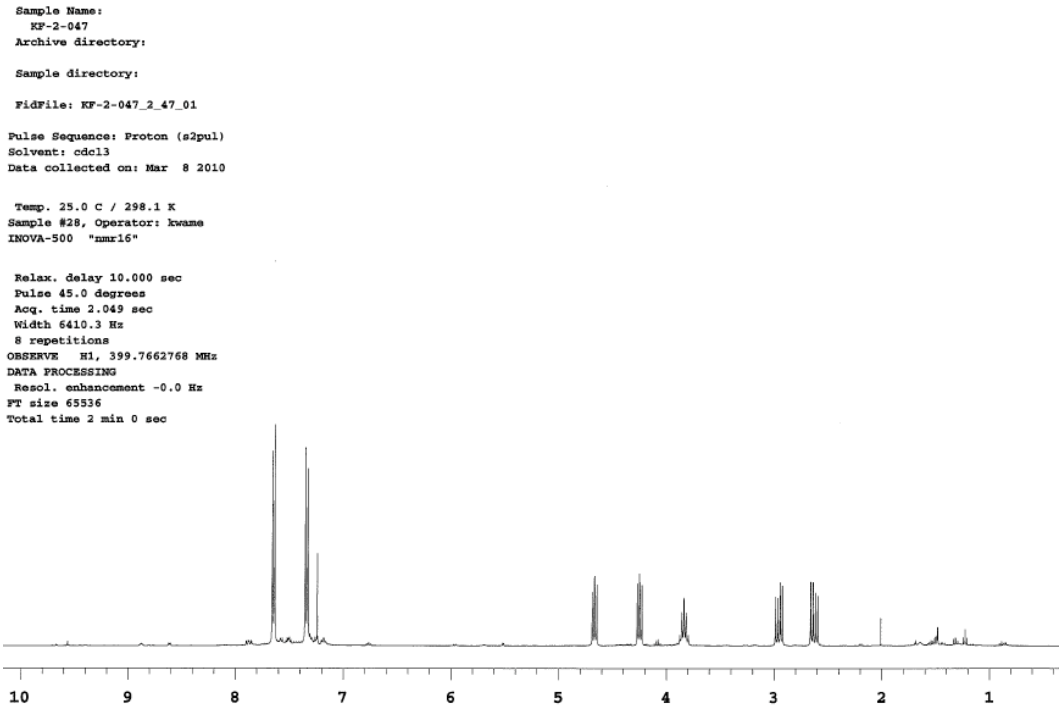
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

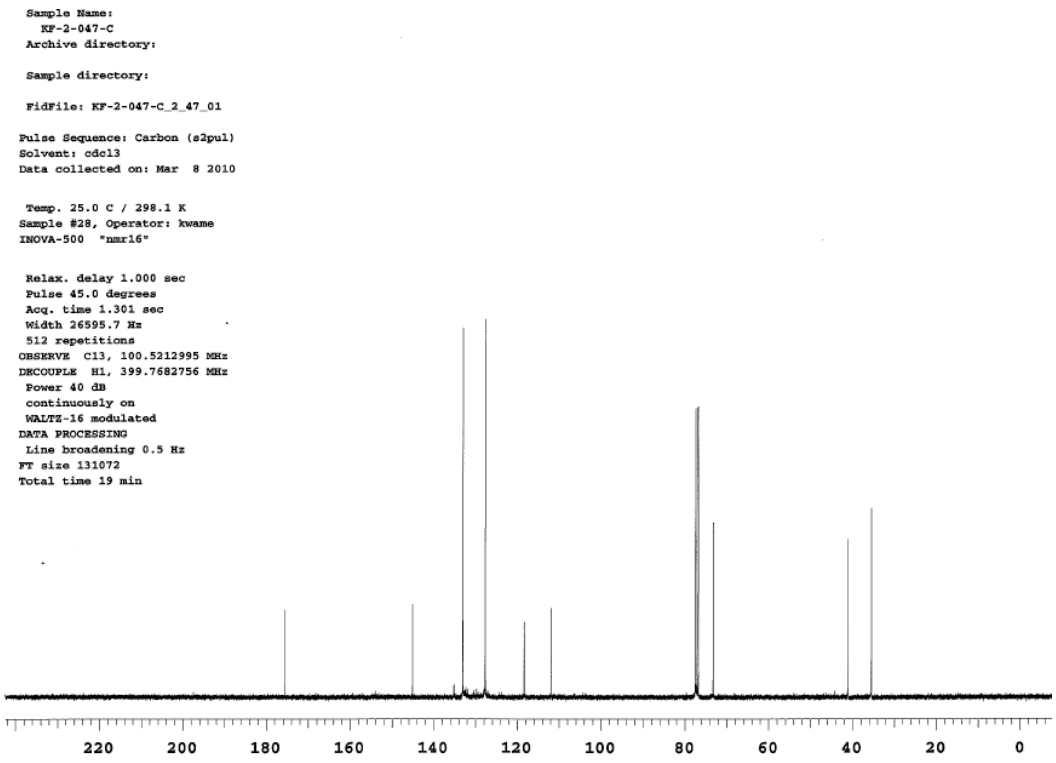
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
24 repetitions
OBSERVE C13, 125.6962680 MHz
DECOUPLE H1, 499.8878615 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 9 min 49 sec

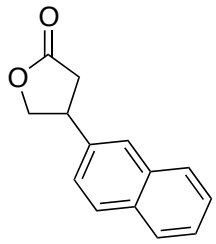




4-(5-Oxotetrahydrofuran-3-yl)-benzonitrile (82 mg, 72%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.65 (d, 2H, *J* = 8.2), 7.34 (d, 2H, *J* = 8.4), 4.67 (dd, 1H, *J* = 7.8, 9.2), 4.25 (dd, 1H, *J* = 7.4, 9.2), 3.84 (m 1H), 2.96 (dd, 1H, *J* = 8.8, 17.4), 2.63 (dd, 1H, *J* = 8.4, 17.6); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 175.4, 145.0, 133.0, 127.6, 118.3, 111.8, 73.2, 41.0, 35.4; **IR** 2225, 1763, 1609, 1507, 1166, 1013, 832, 729, 561 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{10}NO_2$ $[M+H]^+$: 188.07115, found 188.07101.







4-(Naphthalen-2-yl)dihydrofuran-2(3H)-one (97 mg, 76%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.87 (m, 3H), 7.69 (s, 1H), 7.54 (m, 2H), 7.35 (d, 1H, J = 8.3), 4.74 (dd, 1H, J = 7.8, 9.0), 4.38 (dd, 1H, J = 7.8, 9.0), 3.95 (m, 1H), 3.01 (dd, 1H, J = 8.8, 17.6), 2.80 (dd, 1H, J = 9.0, 17.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 176.4, 136.8, 133.4, 132.7, 129.1, 127.7, 126.7, 126.3, 125.5, 124.5, 73.9, 41.2, 35.7; **IR** 1759, 1158, 1006, 831, 749, 477 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{14}H_{13}O_2$ $[M+H]^+$: 213.09155, found 213.09151.

Sample Name:
KF-2-057
Archive directory:

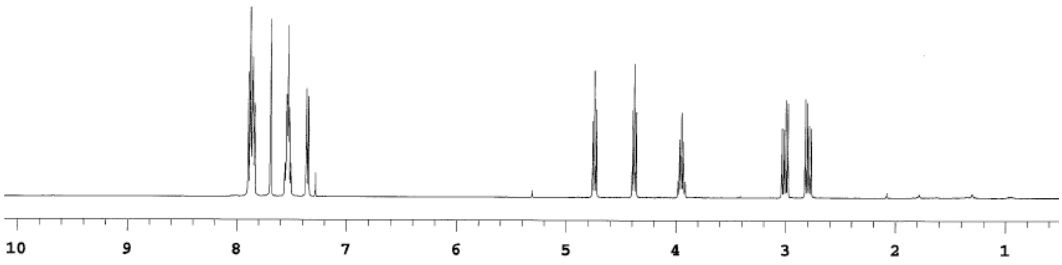
Sample directory:

FidFile: KF-2-057

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 19 2010

Operator: klt
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 7996.0 Hz
8 repetitions
OBSERVE H1, 499.7720124 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 40 sec

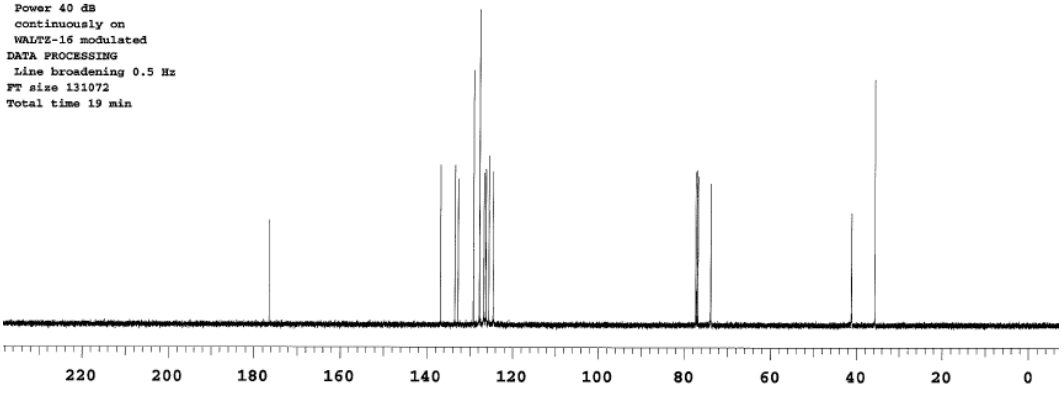


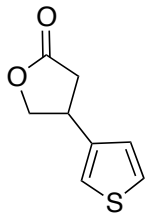
FidFile: KF-2-057-C

Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Mar 19 2010

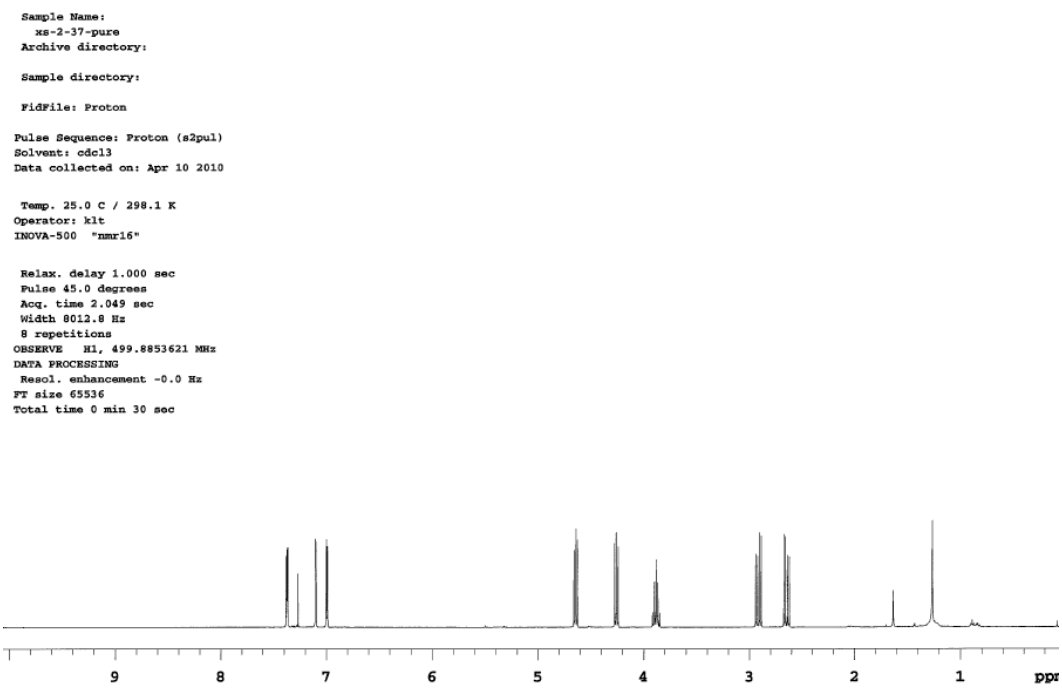
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

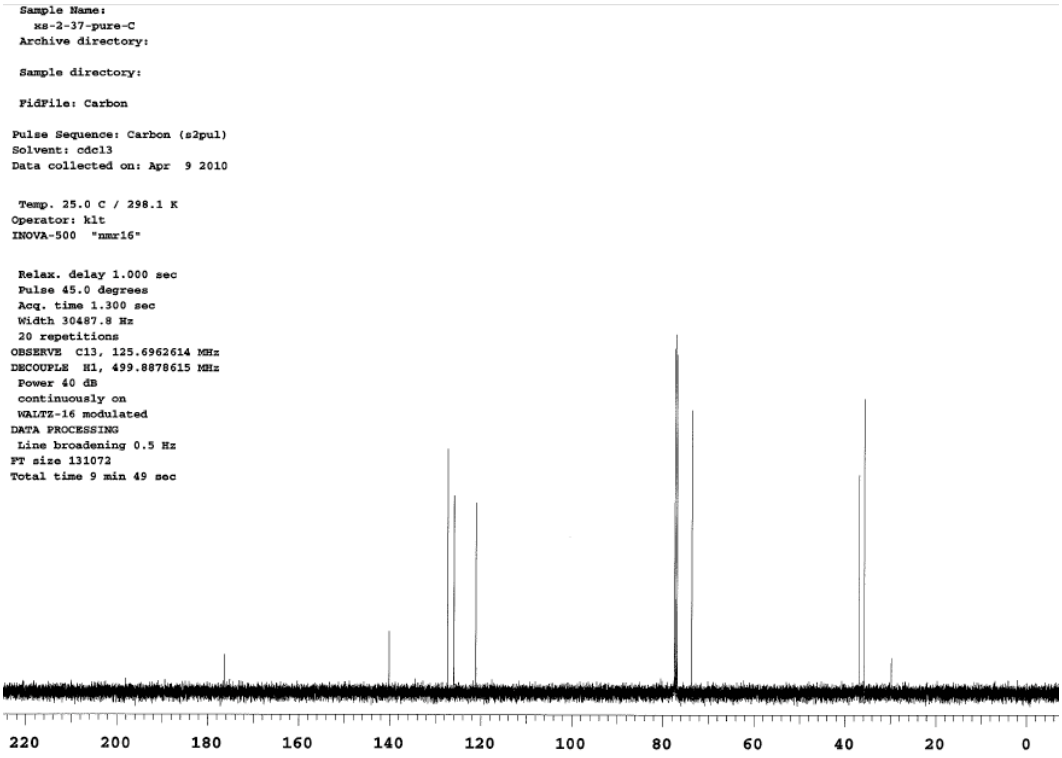
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 32894.7 Hz
192 repetitions
OBSERVE C13, 125.6962718 MHz
DECOUPLE H1, 499.8878615 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min

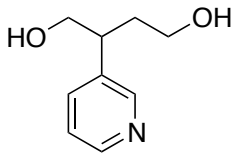




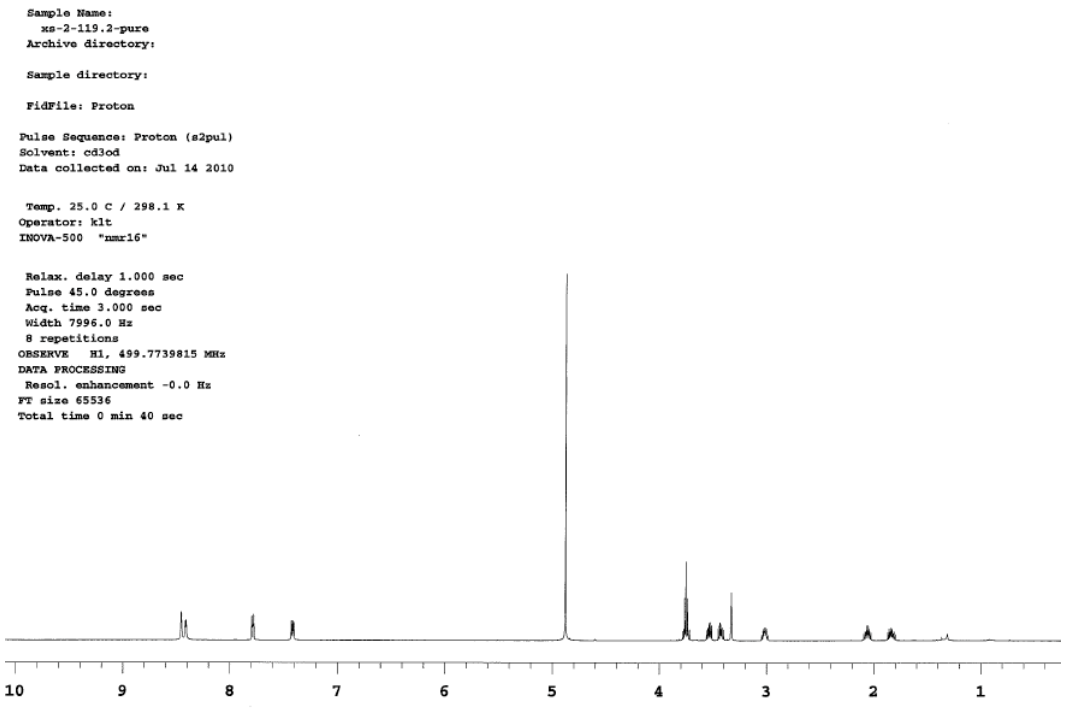
4-(Thiophen-3-yl)dihydrofuran-2(3H)-one (50 mg, 50%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.38-7.36 (m, 1H), 7.11-7.10 (m, 1H), 7.00-6.99 (m, 1H), 4.64 (dd, 1H, *J* = 7.8, 9.0), 4.26 (dd, 1H, *J* = 7.8, 9.0), 3.90-3.86 (m, 1H), 2.91 (dd, 1H, *J* = 8.6, 17.4), 2.64 (dd, 1H, *J* = 8.6, 17.4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 176.2, 140.1, 127.2, 125.8, 121.0, 73.5, 36.8, 35.6; **IR** 1770, 1167, 1017, 783 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_8H_9O_2S$ $[M+H]^+$: 169.03232, found 169.03152.







2-(pyridin-3-yl)butane-1,4-diol (19 mg, 75%). 2-(pyridin-3-yl)prop-2-en-1-ol (20 mg, 0.15 mmol) was hydroformylated. Reduction with $NaBH_4$ (17 mg, 0.45 mmol) and MeOH (3.0 mL) at rt for 2 h was performed instead of oxidation. **^{1}H NMR** (Methanol d-4, 500 MHz) δ 8.46 (s, 1H), 8.41(d, 1H, J = 3.7), 7.80-7.78 (m, 1H), 7.43-7.40 (m, 1H), 3.78-3.72 (m, 2H), 3.55-3.51 (m, 1H), 3.45-3.40 (m, 1H), 3.03-2.99 (m, 1H), 2.10-2.03 (m, 1H), 1.87-1.80 (m, 1H); **^{13}C NMR** (Methanol d-4, 125 MHz) δ 149.0, 146.7, 139.3, 136.3, 123.8, 65.7, 59.1, 42.3, 34.3; **IR** 3260, 2925, 2855, 1427, 1050, 1028, 713 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_9H_{13}NO_2$ $[M+H]^+$: 168.10245, found 168.10230.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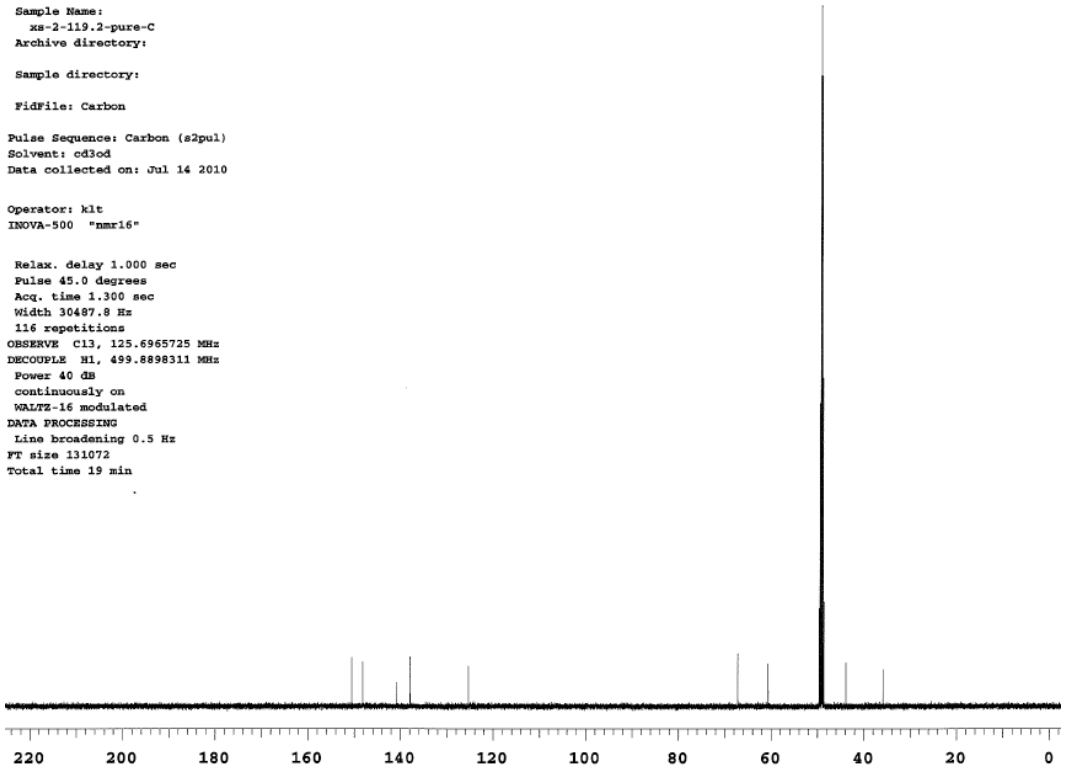
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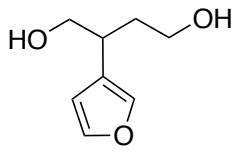
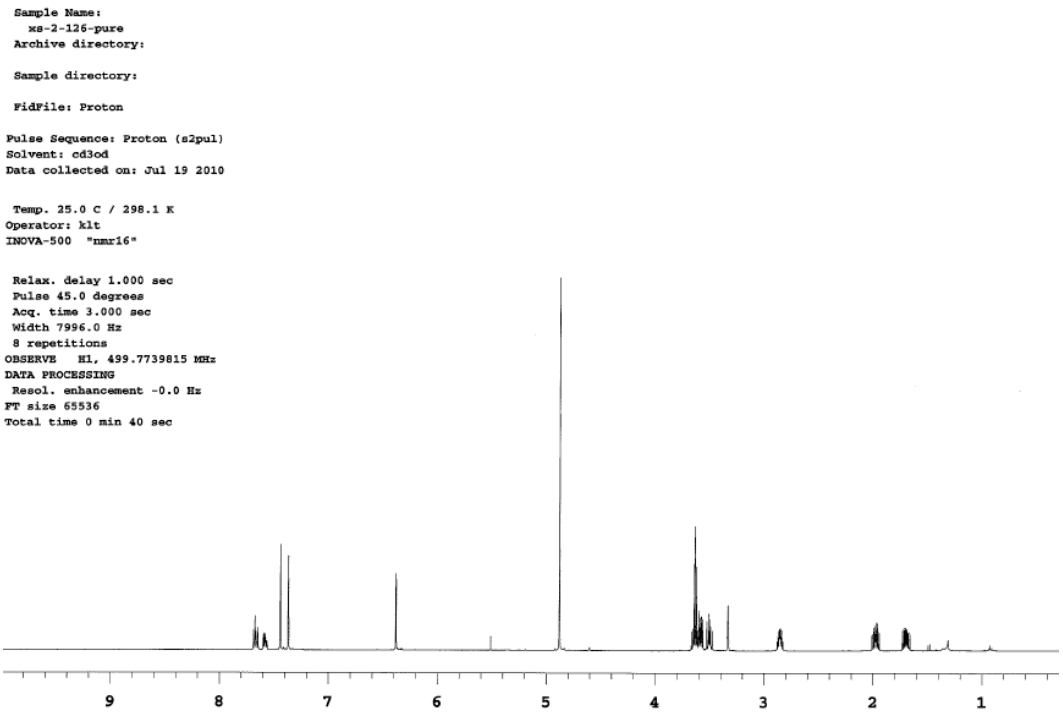
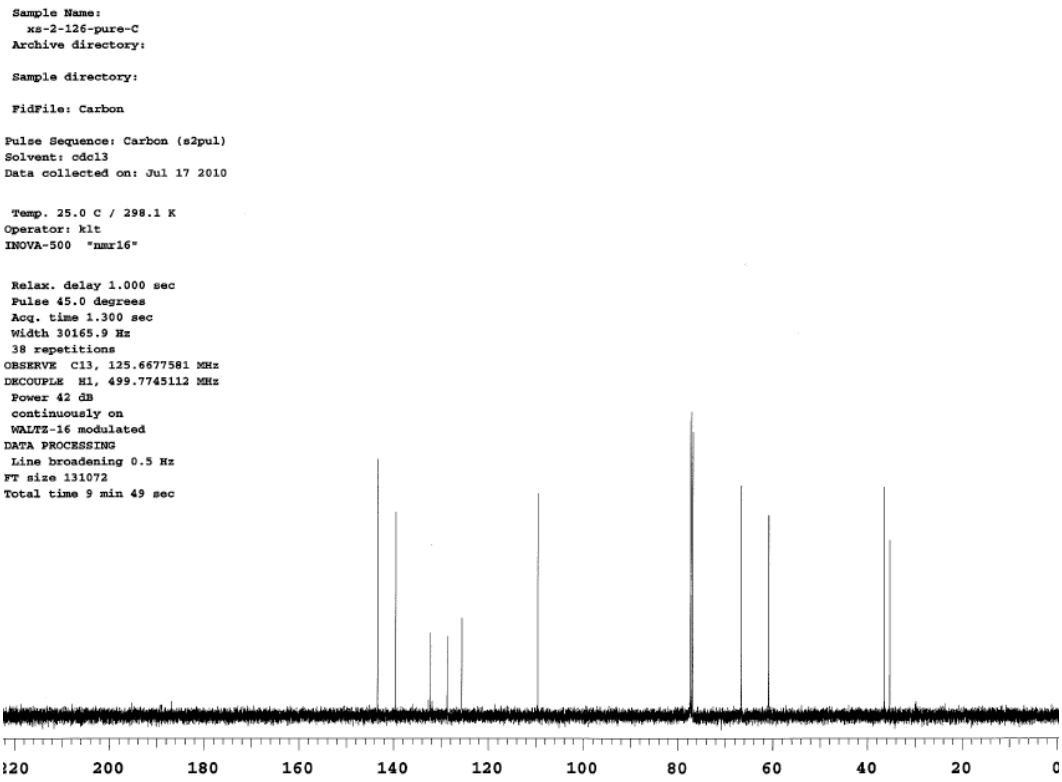
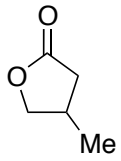


2-(furan-3-yl)butane-1,4-diol (33 mg, 70%). 2-(furan-3-yl)prop-2-en-1-ol (37 mg, 0.30 mmol) was hydroformylated. Reduction with $NaBH_4$ (34 mg, 0.90 mmol) and MeOH (6.0 mL) at rt for 2 h was performed instead of oxidation. **^{1}H NMR** (Methanol d-4, 500 MHz) δ 7.44 (t, 1H, *J* = 1.7), 7.36 (dd, 1H, *J* = 0.7, 1.5), 6.38-6.37 (m, 1H), 3.67-3.56 (m, 3H), 3.53-3.48 (m, 1H), 2.88-2.83 (m, 1H), 2.01-1.94 (m, 1H), 1.73-1.66 (m, 1H); **^{13}C NMR** (Methanol d-4, 125 MHz) δ 142.7, 139.5, 125.8, 109.2, 65.8, 59.5, 35.3, 34.4; **IR** 3334, 2929, 1157, 1025, 874, 786, 724, 601, 542 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_8H_{13}O_3$ $[M+H]^+$: 157.08647, found 157.08586.







4-Methyldihydrofuran-2(3H)-one (37 mg, 62%). Characterization data of this compound was previously reported.[6]

Sample Name:
KF-2-058
Archive directory:

Sample directory:

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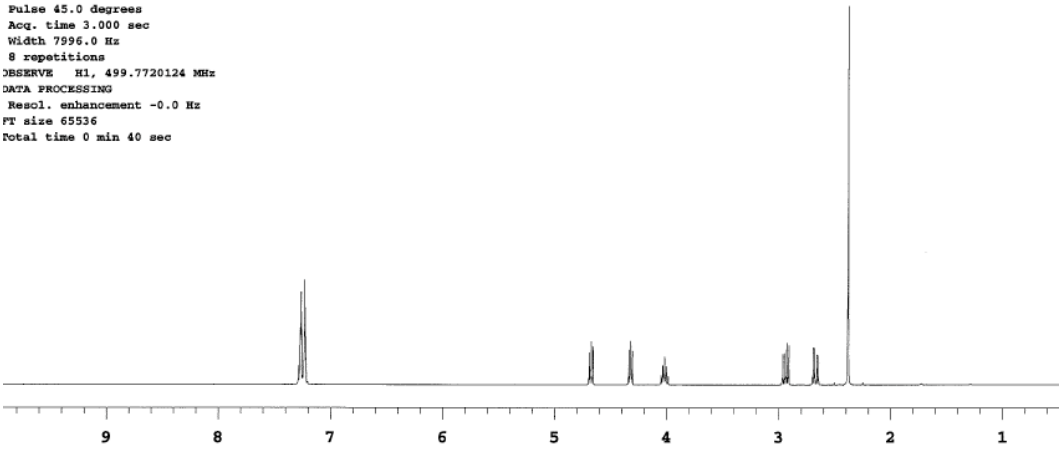

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Solvent: cdcl3
Data collected on: Mar 19 2010

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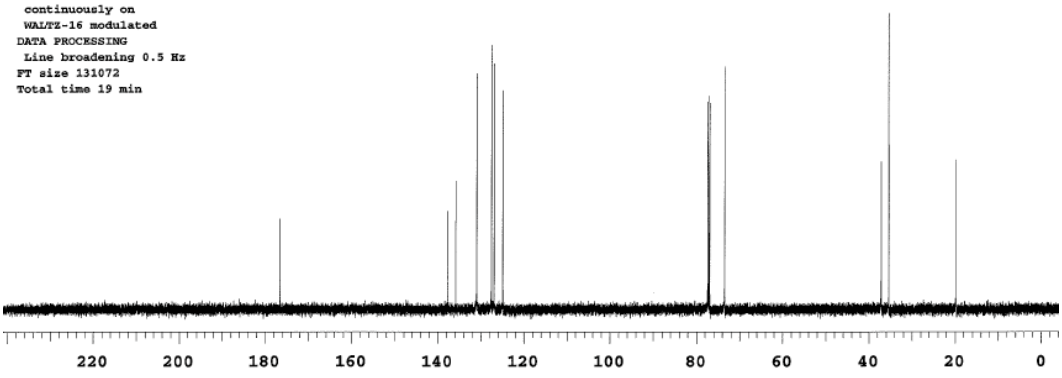
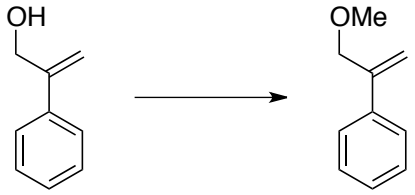
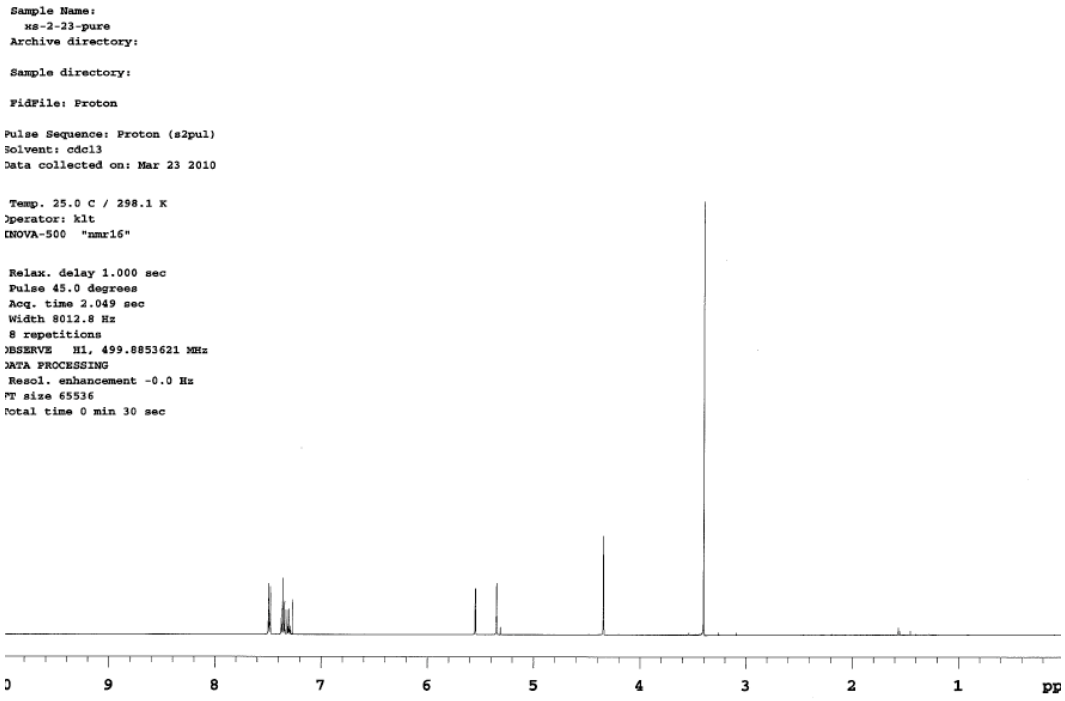


Synthesis of Methyl Ether **1.48**



(3-Methoxyprop-1-en-2-yl)benzene (**1.48**)was synthesized from 2-phenylprop-2-en-1-ol according to literature procedure[7]: To a flame-dried round bottom flask, sodium hydride (36 mg, 1.5 mmol) was added under nitrogen. Iodomethane (110 mL, 1.8 mmol) and anhydrous THF (2 mL) were added and solution was stirred at 45 ℃. A solution of 2-phenylprop-2-en-1-ol (150 mL, 1.2 mmol) in anhydrous THF (1 mL) was added dropwise and reaction was stirred at 45 °C for 30 min. The resulting mixture was allowed to cool to rt and H_2O (1 mL) was added, followed by extraction with Et_2O (3 × 5 mL). Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography (Hex/EtOAc = 30:1) afforded pure product as colorless liquid (156 mg, 88%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.50-7.48 (m, 2H), 7.38-7.27 (m, 3H), 5.55 (t, 1H, *J* = 0.4), 5.35 (m, 1H), 4.34 (d, 2H, *J* = 0.4), 3.40 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 144.2, 138.8, 128.4, 127.8, 126.0, 114.4, 74.6, 57.9; **IR**: 2924, 1121, 1092, 905, 779, 708 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{13}O$ $[M+H]^+$: 149.09664, found: 149.09655.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8 repetitions
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DATA PROCESSING
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FT size 65536
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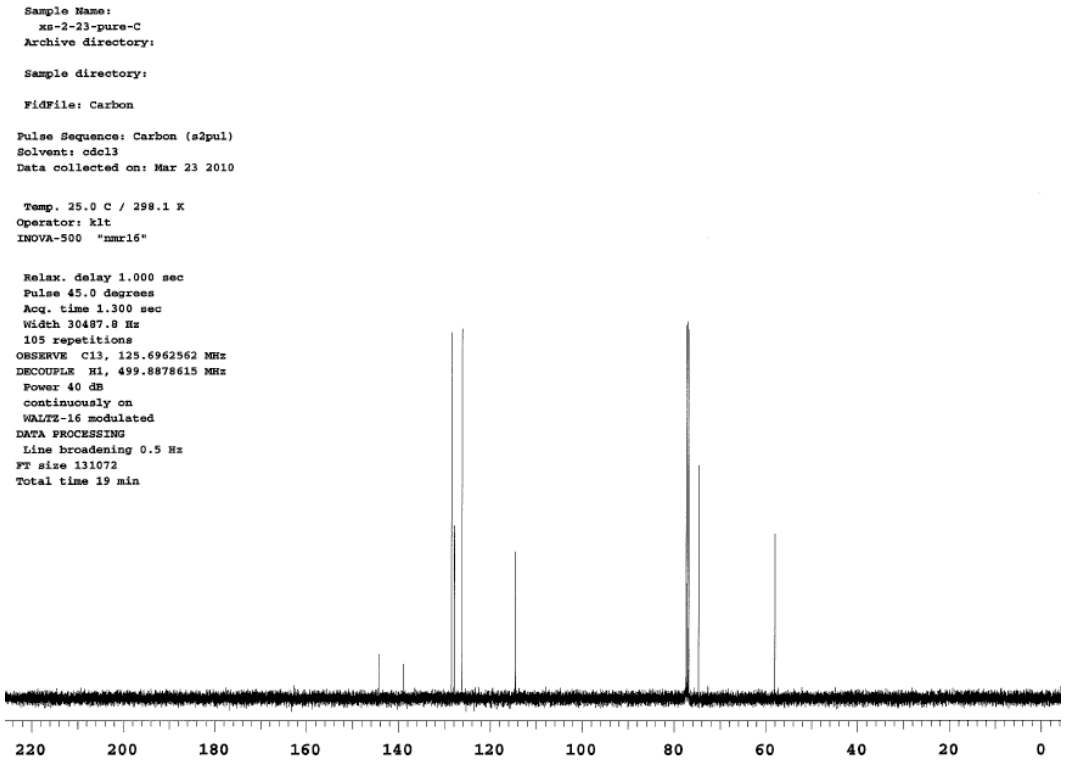
2
1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Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
105 repetitions
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DECOUPLE H1, 499.8878615 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min
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200
180
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140
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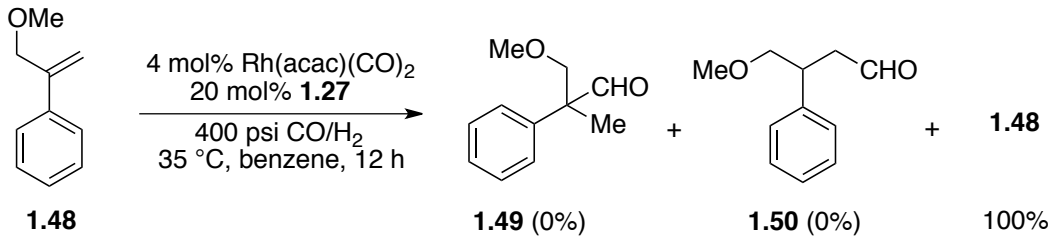
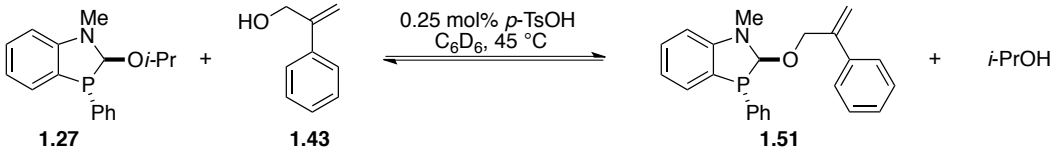
60
40
20
0

Control Reaction of Methyl Ether

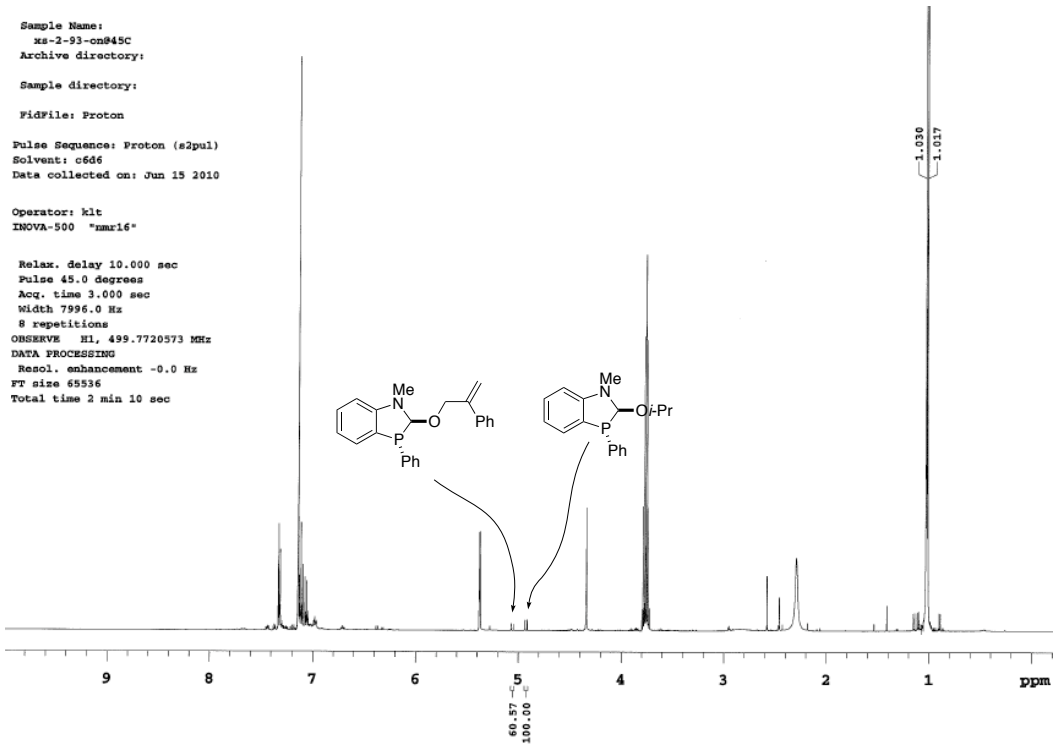


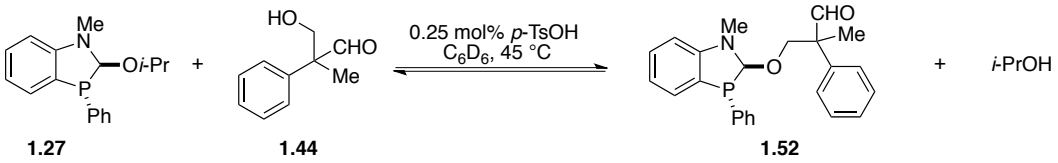
The oven dried glass reaction vial was placed in the Endeavor, and (3-methoxyprop-1-en-2-yl)benzene (89 mg, 0.60 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium(I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol%), ligand **1.27** (34 mg, 0.12 mmol, 20 mol%), *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol, 0.20 mol%) and benzene (to total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 45 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi CO/H_2, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature and pressure of 45 °C and 400 psi CO/H_2 respectively for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction was removed from the Endeavor and concentrated. 1,3,5-Trimethoxybenzene (400 mL of 0.15 M in $CDCl_3$, 0.06 mmol) was added as standard and ^1H NMR showed > 99% substrate and 0% conversion.

Binding Study of Ligand **1.27**



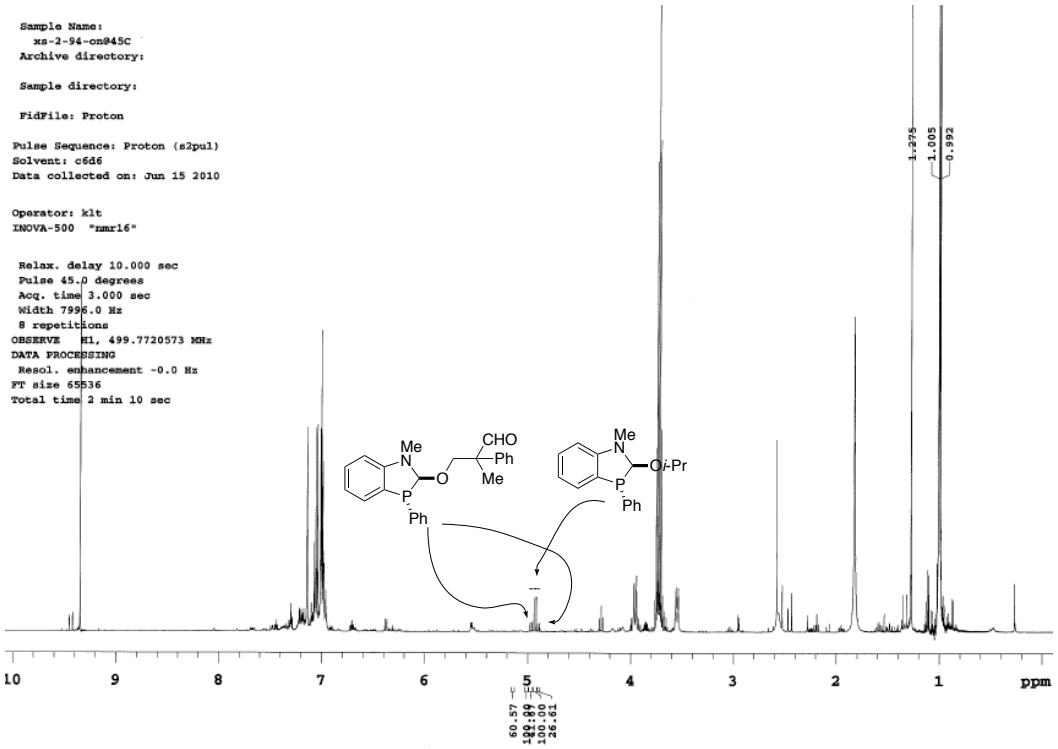
Ligand **1.27** (5.7 mg, 2.0×10^{-2} mmol) was dissolved in benzene d-6 (1 mL) in an NMR tube under N_2. *p*-Toluenesulfonic acid (0.10 mL of 5.0×10^{-4} M in benzene d-6, 5.0×10^{-5} mmol) was added to solution, followed by addition of 2-phenylprop-2-en-1-ol, **1.43** (13 mg, 0.10 mmol) and *i*-PrOH (46 μL, 0.60 mmol). Solution was heated at 45 °C overnight. Analysis of the reaction by ^{1}H NMR showed **1.51**:**1.27** = 38:62, leading to Keq_1= 4.0.

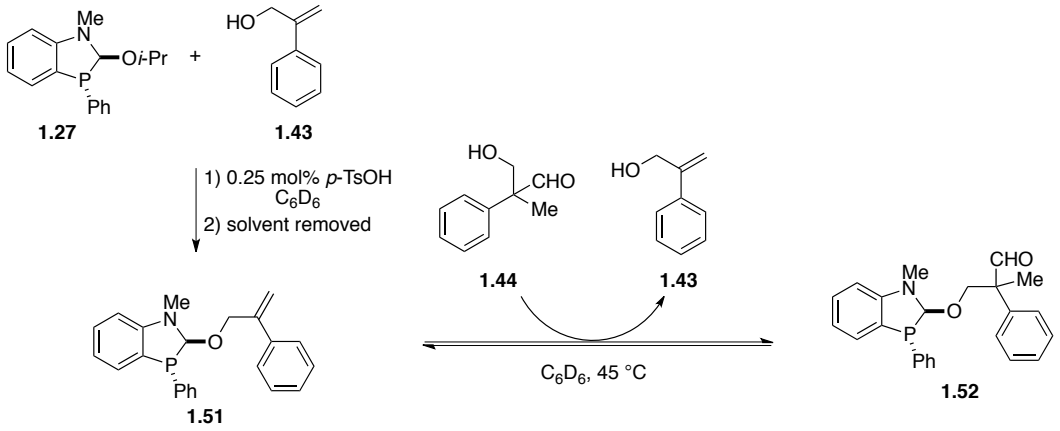




Ligand **1.27** (5.7 mg, 2.0×10^{-2} mmol) was dissolved in benzene-d6 (1 mL) in an NMR tube under N_2. *p*-Toluenesulfonic acid (0.10 mL of 5.0×10^{-4} M in benzene d-6, 5.0×10^{-5} mmol) was added to solution, followed by addition of 3-hydroxy-2-methyl-2-phenylpropanal, **1.44** (16 mg, 0.10 mmol, isolated from hydroformylation) and *i*-PrOH (23 μL, 0.30 mmol). Solution was heated at 45 °C overnight. Analysis of the reaction by ^{1}H NMR showed **1.52**:**1.27** = 41:59.

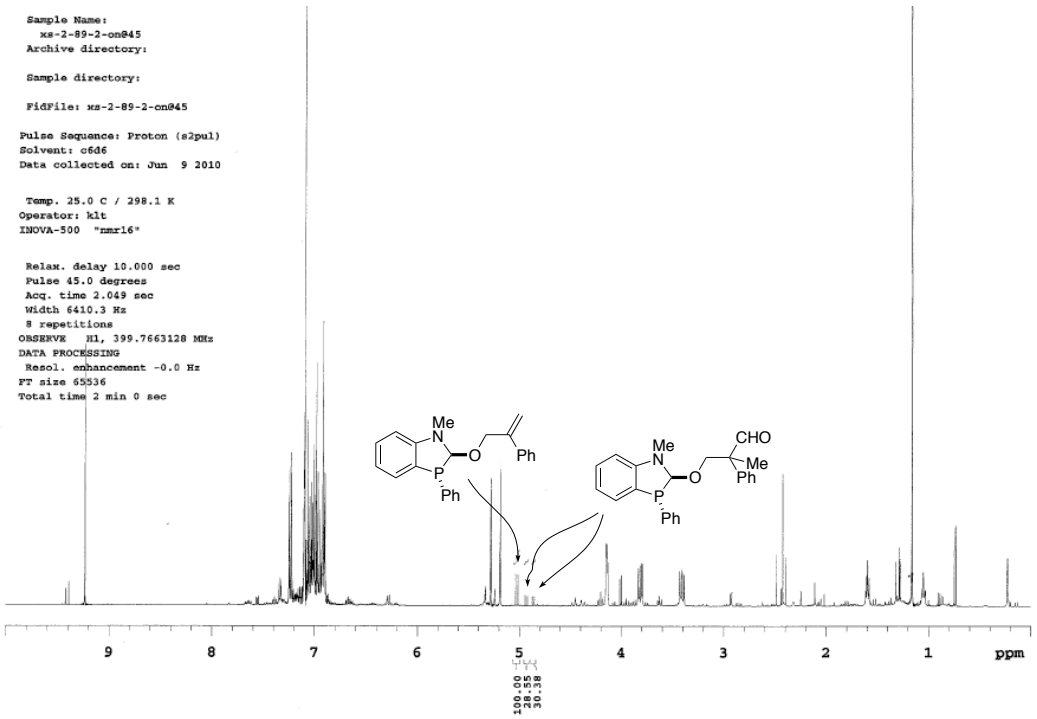
Note: Ignoring minor aldehyde dimerization, Keq_2 was calculated to be 2.3.





Ligand **1.27** (11 mg, 4.0×10^{-2} mmol), 2-phenylprop-2-en-1-ol, **1.43** (13 mg, 0.10 mmol) and *p*-toluenesulfonic acid (0.20 mL of 5.0×10^{-4} M in benzene d-6, 1.0×10^{-4} mmol) were dissolved in benzene d-6 (1 mL) under N_2. Solution was allowed to stand at rt for 10 min, and then solvent was removed under vacuum. The residue was redissolved in benzene d-6 (1 mL), and ^{1}H NMR analysis of solution showed **1.27a** was formed (>99%). 3-hydroxy-2-methyl-2-phenylpropanal, **1.44** (16 mg, 0.10 mmol, isolated from hydroformylation) was added, and mixture was heated at 45 °C overnight. Analysis of the reaction by ^{1}H NMR showed **1.52**:**1.51** = 39:61.

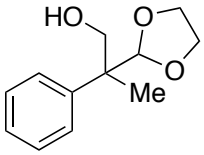
Note: Ignoring minor aldehyde dimerization, Keq_3 was calculated to be 0.57. This result matches the calculated Keq from binding study experiments 1 and 2 (Keq_2 / Keq_1 = Keq_3; 2.3 / 4.0 = 0.58).



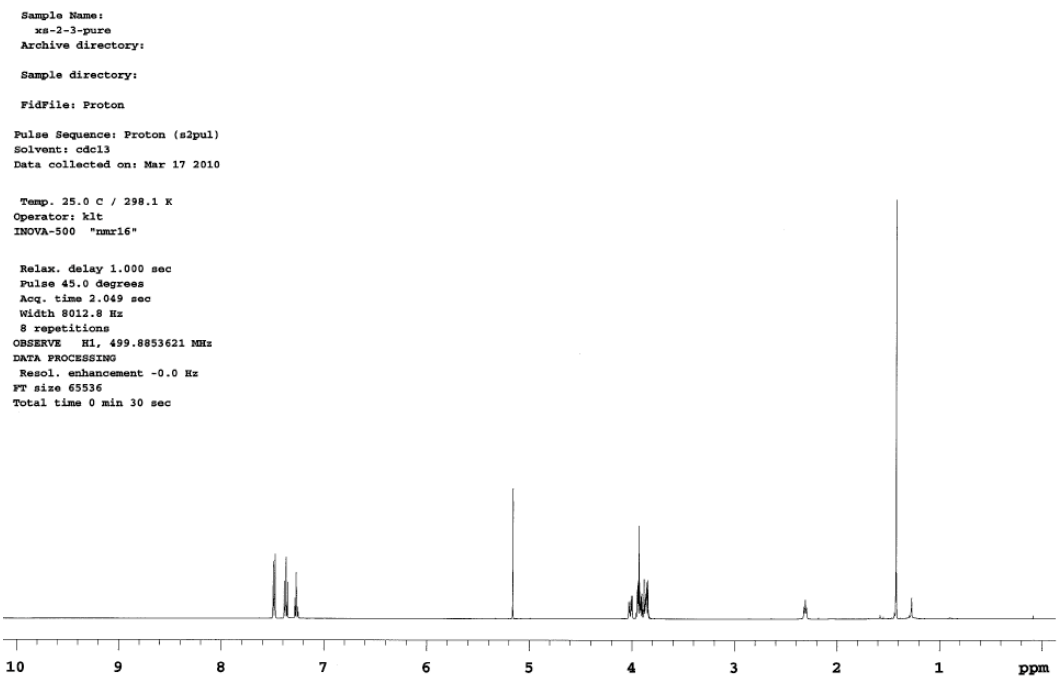
Hydroformylation using Ligand **1.27** and Acetal Protection

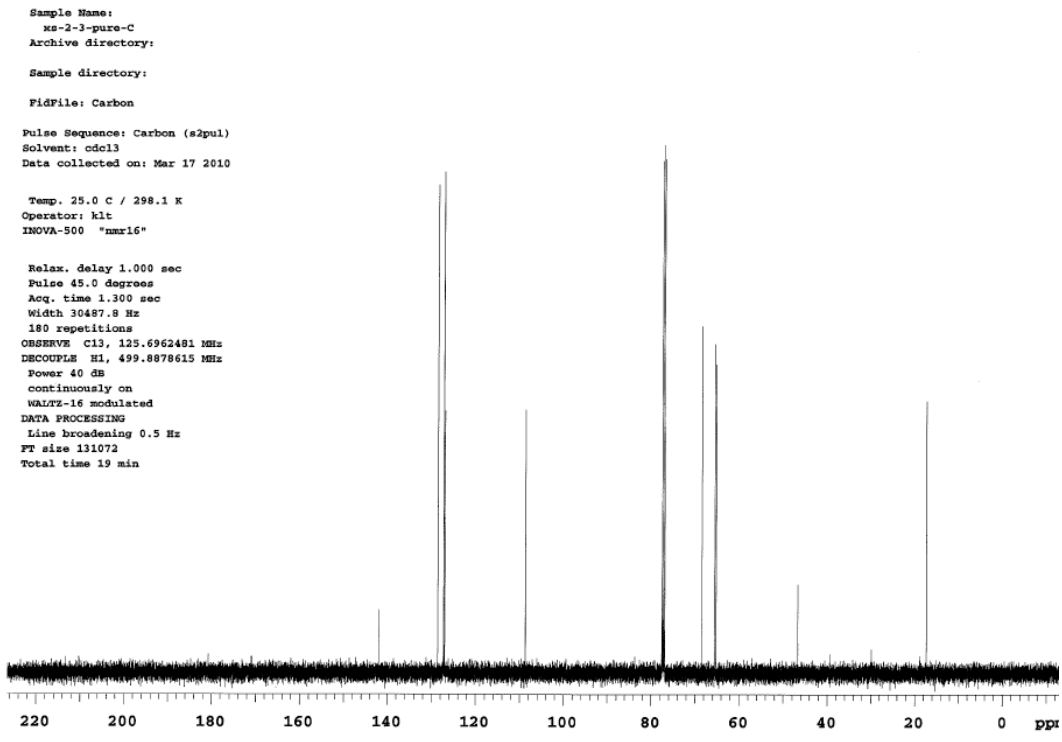
Hydroformylation and Acetal Protection Procedure. The oven dried glass reaction vial was placed in the Endeavor, and 2-phenylprop-2-en-1-ol, **1.43** (80 mg, 0.60 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium(I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol%), ligand **1.27** (34 mg, 0.12 mmol, 20 mol%), *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M, 1.2×10^{-3} mmol, 0.20 mol%) and benzene (to total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 45 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi CO/H_2, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature and pressure of 45 °C and 400 psi CO/H_2 respectively for 12 h. The Endeavor was vented

to ambient pressure and cooled to ambient temperature. The reaction was removed from the Endeavor and concentrated. The residue was redissolved in benzene (0.6 mL). Ethylene glycol (74 μL, 1.3 mmol) and a few crystals of *p*-toluenesulfonic acid were added. The reaction was refluxed for 3 h. The resulting mixture was cooled to room temperature and solvent was removed. Flash column chromatography (Hex/EtOAc = 6/1) afforded the pure product **1.53** as colorless liquid.



2-(1,3-Dioxolan-2-yl)-2-phenylpropan-1-ol (90.2 mg, 72%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.49-7.47 (m, 2H), 7.38-7.35 (m, 2H), 7.28-7.25 (m, 1H), 5.16 (s, 1H), 4.03-3.85 (m, 6H), 2.31 (t, 1H, J = 6.2), 1.42 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 141.8, 128.4, 127.0, 126.8, 108.5, 68.2, 65.3, 65.0, 46.5, 17.1; **IR**: 3458, 2884, 1107, 1028, 767, 699 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{17}O_3$ $[M+H]^+$: 209.11777, found: 209.11798.





VIII. References

(1) Concellon, J. M.; Cuervo, H.; Fernandez-Fano, R. *Tetrahedron* **2001**, 57, 8983.

(2) Gajewski, J. J.; Gee, K. R.; Jurayj, J. *J. Org. Chem*. **1990**, 55, 1813.

(3) Prager, R. H.; Schafer, K.; Hamon, D. P. G.; Massy-Westropp, R. A. *Tetrahedron*, **1995**, 51, 11465.

(4) Arns, S.; Barriault, L. *J. Org. Chem*. **2006**, 71, 1809.

(5) Pei, W.; Mo, J.; Xiao, J. *J. Organomet. Chem*. **2005**, 690, 3546.

(6) Sharma, V.; Kelly, G. T.; Watanabe, C. M. H. *Org. Lett.* **2008**, 10, 4815.

(7) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, 130, 9210.

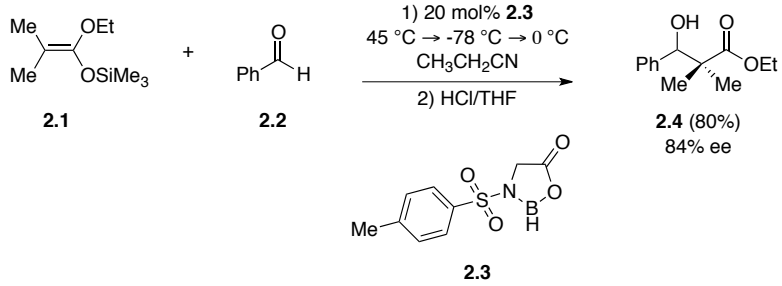
The work presented in this chapter was done in collaboration with Xixi Sun.

Chapter 2: Asymmetric Synthesis of Quaternary Stereogenic Centers

I. Asymmetric Aldol Reactions to form Quaternary Stereogenic Centers

The aldol reaction, one of the most powerful methods for forming C–C bonds, has become a strategically important, reliable transformation that is widely employed in the asymmetric synthesis of complex molecules.[20] However, the development of enantioselective aldol reactions to construct quaternary stereogenic centers represents a continuing challenge in organic chemistry. Catalytic enantioselective aldol reactions with simple ketones are among the most synthetically useful reactions for the formation of chiral alcohols, but the inherent features of this type of reaction make its development rather difficult, in comparison with the catalytic enantioselective aldol reactions of aldehydes. The low reactivities of ketones, relative to aldehydes, and retro-aldol reactions usually lead to low levels of conversion.[21] The development of asymmetric aldol reactions has been led by Lewis-acid catalyzed reactions of silyl enol ethers and their derivatives. The Masamune group demonstrated an application of this strategy in the synthesis of quaternary stereogenic centers from silyl ketene acetal **2.1** using chiral Lewis acid mediator **2.3** to give an 84% ee of quaternary aldol product **2.4** (Figure 2.1).[22]

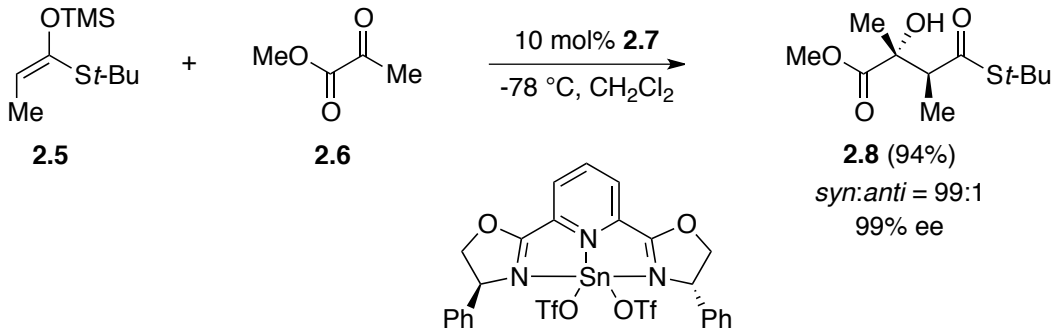
Figure 2.1. Lewis-acid catalyzed enantioselective aldol reaction



[20] Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357.
[21] Ichibakase, *et al. Tetrahedron Letters* **2008**, *49*, 4427.
[22] Masamune, *et al. J. Am. Chem. Soc.* **1991**, *113*, 9365.

In 2000, the Evans group reported that utilization of pybox complex **2.7** in the metal-catalyzed aldol reaction of trisubstituted silyl enol ether **2.5** and pyruvate ester **2.6** afforded essentially enantiopure quaternary aldol adduct **2.8** in 94% yield (Figure 2.2).[23]

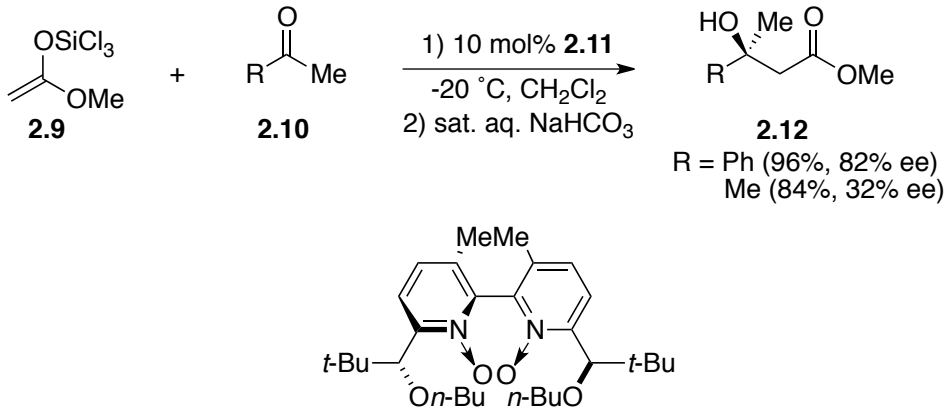
Figure 2.2. Metal-catalyzed aldol enantioselective aldol reactions



Recently, Lewis-base catalyzed enantioselective aldol reactions have attracted considerable attention. The Denmark group developed an asymmetric aldol addition reaction through the application of Lewis base catalysis. In their report, the group showed that addition of methyl trichlorosilyl ketene acetal **2.9** to unactivated ketone **2.10** employing pyridine *N*-oxide **2.11** as the Lewis base led to the formation of tertiary alcohol **2.12** (Figure 2.3).[24] The enantioselectivity was found to be highly dependent on the structure of the ketone acceptor, with aromatic ketones being the most selective.

[23] Evans, D. A.; Johnson, J. S. *Acc. Chem. Res.* **2000**, *33*, 325.
[24] Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235.

Figure 2.3. Lewis-base catalyzed aldol reactions

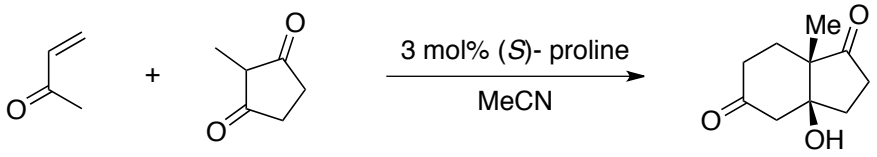


Although the larger number of catalytic enantioselective aldol processes involve the use of enoxysilanes, the direct addition of enolizable ketones and esters to aldehydes and ketones in aldol additions have been documented as well. The classic example in this respect is the proline-catalyzed Robinson annulation reaction for the preparation of the Wieland-Miescher ketone (Figure 2.4).[25] Direct aldolization processes are atom economic, and thus serve as attractive methods for the synthesis of useful polyoxygenated compounds. Recently, emphasis has been placed on the development of chiral organocatalysts for the asymmetric version of this process. Most studies have focused on reactions that produce either β-hydroxy carbonyls or α-alkyl-β-hydroxy carbonyls.[26]

[25] (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3239.; (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.; (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.

[26] (a) List, *et al. J. Am. Chem. Soc.* **2000**, *122*, 2395.; (b) Scott, M. J.; Jarvo, E. R. *Tetrahedron*, **2002**, *58*, 2481.

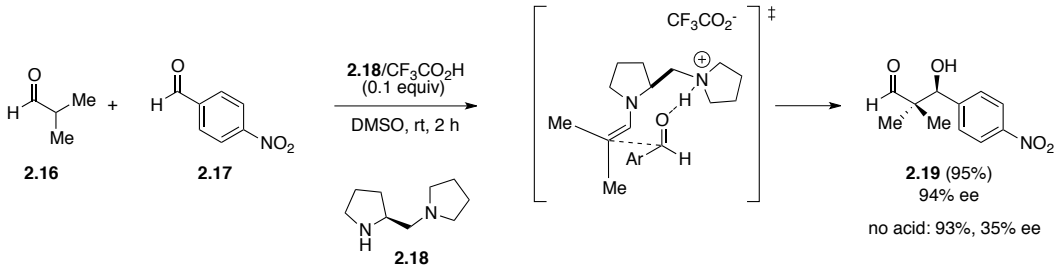
Figure 2.4. Proline-catalyzed Robinson annulation reaction



2.13 **2.14** **2.15** (97%) 93% ee

However, organocatalysts-promoted asymmetric synthesis of α,α-dialkyl-β-hydroxyl carbonyl compounds remains a challenge since low reaction yields and poor enantioselectivities are typically observed. The major reason for this is the general inaccessibility of either the starting α,α-disubstituted aldehydes or their stereochemically defined enolates. A breakthrough was reported by Barbas and co-workers in 2004 and it relies on the use of a chiral diamine organocatalyst (Figure 2.5).[27] The group demonstrated that diamine catalyst **2.18** and an acid additive efficiently catalyzed the aldol reaction of **2.16** and **2.17**. The addition of an acid, in an amount equimolar to the amine, was necessary for improved reactivity and enantioselectivity.

Figure 2.5. Diamine-catalyzed aldol reaction to form quaternary centers

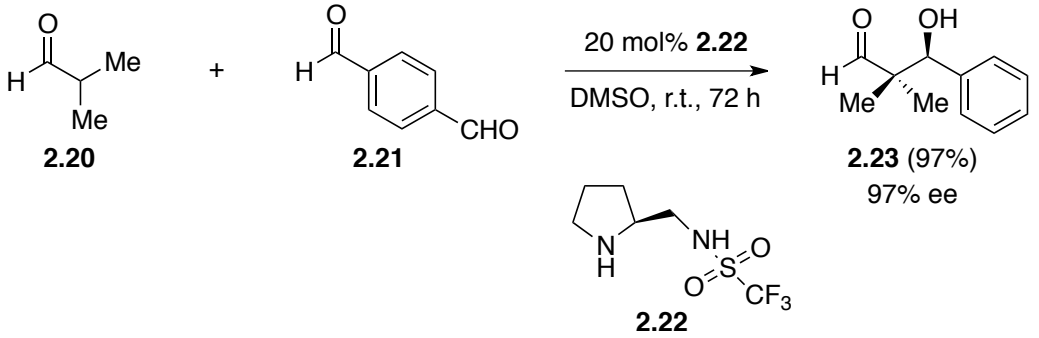


The aldol product was determined to have the *S* configuration by derivatization as the Mosher ester. Thus, **2.18**/CF_3CO_2H catalyzes a *Re*-face attack on the aryl aldehyde via an enamine intermediate, consistent with previously reported L-proline-based

[27] Barbas, *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 2420.

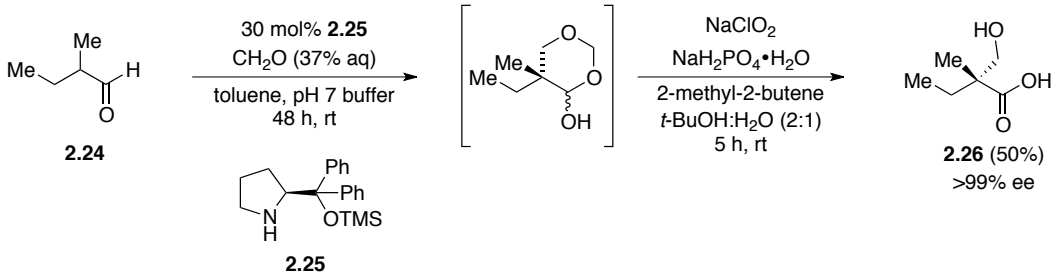
aldol transition states.[28] Inspired by this report, the Wang group reported a direct pyrrolidine sulfonamide promoted asymmetric aldol reaction that occurs with sterically hindered α,α-dialkyl aldehydes to provide quaternary carbon-containing β-hydroxycarbonyl compounds with high levels of enantioselectivity (Figure 2.6).[29]

Figure 2.6. Pyrrolidine sulfonamide catalyzed asymmetric aldol reaction



Another example of organocatalyst-promoted enantioselective synthesis of quaternary stereogenic centers involves the hydroxymethylation of aldehydes, reported by the Boeckman group. In this report, the group employed α,α-diphenylprolinol trimethylsilyl ether **2.25** as the organocatalyst in the hydroxymethylation of **2.24** to give **2.26** in a 50% yield and >99% ee (Figure **2.7**).[30]

Figure 2.7. Hydroxymethylation of aldehydes



The aldol reaction has become one of the most important C–C bond forming

[28] List, *et al. J. Am. Chem. Soc.* **2003**, *125*, 2475.
[29] Wang, *et al. Tet. Lett.* **2005**, *46*, 5077.
[30] Boeckman, R. K.; Miller, J. R. *Organic Letters* **2009**, *11*, 4544.

reactions. Significant progress has been made in the area of asymmetric aldol reactions. However, the development of enantioselective aldol reactions to construct quaternary stereogenic centers is still a challenge and although progress has been made in this respect, more work needs to be done.

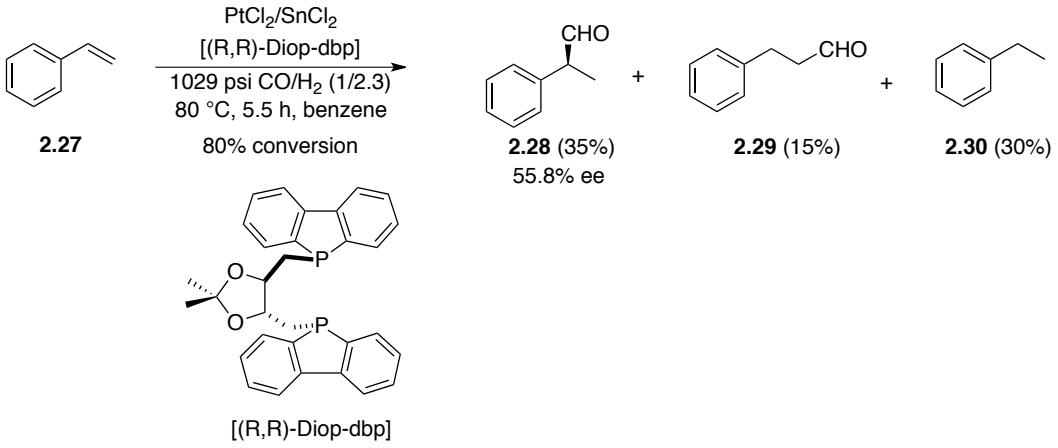
II. Asymmetric Hydroformylation to form Quaternary Carbon Centers

Asymmetric hydroformylation is a powerful methodology for the synthesis of optically active aldehydes in a single step from olefins. Because of the versatility of the aldehyde functional group, a variety of useful chiral compounds such as amines, imines, alcohols, and acids can be easily prepared from chiral aldehydes. [31] Although asymmetric hydroformylation offers great promise to the pharmaceutical and fine-chemical industries, this reaction has not been utilized on a commercial scale because of various technical challenges including low reaction rates at low temperatures, difficulty in controlling regio- and enantioselectivities simultaneously, and limited substrate scope for any single ligand. In 1991, Consiglio and co-workers reported that using a chiral bisphosphine complex of $PtCl_2$ as a catalyst in combination with $SnCl_2$ moderate enantioselectivities could be obtained for the hydroformylation of styrene (Figure 2.8).[32] In spite of the moderate enantioselectivities established with these systems, Pt(II)-catalyzed hydroformylation of arylethenes and some functionalized olefins still suffers from several disadvantages such as low reaction rates, hydrogenation of the substrate, poor regioselectivities and undesirable racemization of the products. Phosphine and phosphite-modified rhodium catalysts have been

[31] (a) Landis, *et al. Acc. Chem. Res.* **2007**, *40*, 1251.; (b) Nozaki, *et al. J. Am. Chem. Soc.* **1997**, *119*, 4413.; (c) Axtell, *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 5834.
[32] Consiglio, *et al. Organometallics* **1991**, *10*, 2046.

shown to give improved reactivity and selectivities, with enantioselectivities of up to 98% ee for styrenes.[33]

Figure 2.8. Enantioselective hydroformylation of styrene using Pt(II) Catalyst

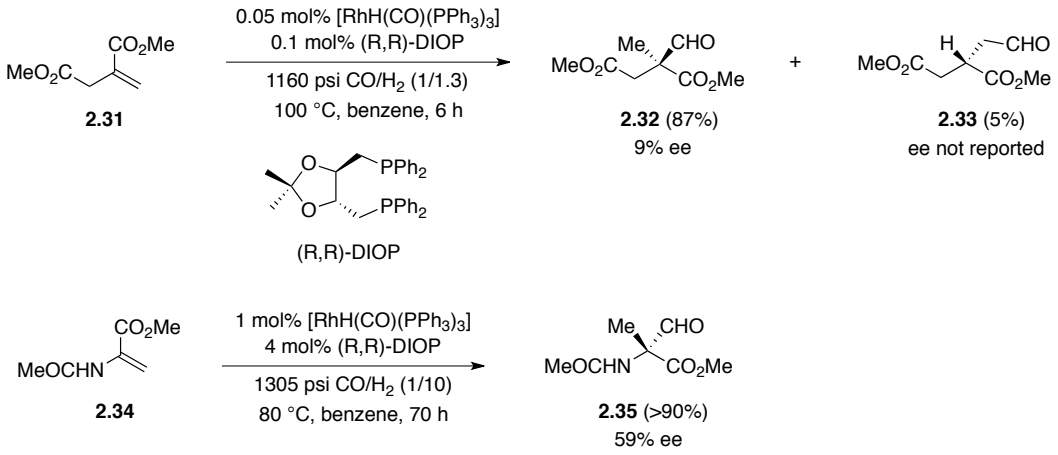


However, the asymmetric hydroformylation of 1,1-disubstituted olefins differs from the classical asymmetric hydroformylation of monosubstituted terminal olefins because the desired product is usually the linear aldehyde. Indeed, the Rh-catalyzed asymmetric hydroformylation of 1,1-methylstyrene using a diphosphite ligand yields the linear aldehyde in moderate enantioselectivities.[34] However, when 1,1-disubstituted olefins containing activating groups such as esters and coordinating groups such as amides are hydroformylated the branched, quaternary aldehyde may be obtained, albeit in low to moderate enantioselectivities. For example, in the Rh-catalyzed hydroformylation of dimethyl itaconate **2.31** using (R,R)-DIOP as ligand, formation of the quaternary aldehyde **2.32** was observed in very low enantioselectivity of 9%. All other unsaturated dicarboxylic esters underwent

[33] Dieguez, *et al. Tetrahedron: Asymmetry*, **2004**, *15*, 2113.
[34] Ojima, I.; Takai, M.; Takahashi, T. Patent WO 078766, 2004.

hydrogenation as the major reaction.[35] Hydroformylation of amino acid, **2.34**, exclusively forms the quaternary aldehyde **2.35** with increased, though moderate, enantioselectivity of 59% (Figure 2.9).[36] The examples illustrated in Figure 2.9 represent the only examples of enantioselective hydroformylation of 1,1-disubstituted olefins to construct quaternary aldehydes.

Figure 2.9. Enantioselective hydroformylation of activated olefins to form quaternary aldehydes



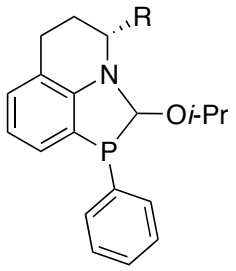
III. Use of First-Generation Chiral Scaffolding Ligand

In an effort to develop a system for practical asymmetric hydroformylation of 1,1-disubstituted olefins and thus, expand the alkene class and substrate scope of asymmetric hydroformylation, we investigated the viability of **2.36** as a chiral scaffolding ligand for such a transformation (Figure 2.10). Because of the efficiency of racemic ligand **1.27** in the hydroformylation of 1,1-disubstituted olefins (see Chapter 1), we posited that a ligand that maintains the scaffolding nature of **1.27** would be ideal. The design of **2.36** arose from preliminary studies conducted in our

[35] Kollar, L.; Consiglio, G.; Pino, P. *Chimia* **1986,** *40*, 428.
[36] Gladiali, *et al. Tetrahedron: Asymmetry* **1990**, *1*, 693.

group involving the exchange reaction of racemic ligand **1.27** and the enantiopure alcohol **2.37**.

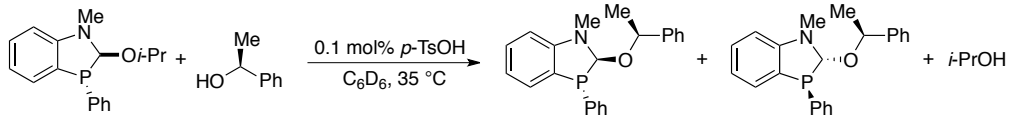
Figure 2.10. First-generation chiral scaffolding ligand



2.36

During the course of the exchange reaction, **2.38** and **2.39** were formed in a 69:31 diastereomeric ratio, suggesting that the two stereogenic centers in **1.27** were epimerizing under the reaction conditions (Figure 2.11). Because a 50:50 diastereomeric mixture of **2.35** and **2.39** was not obtained, it suggested that one diastereomer was thermodynamically more stable than the other and the less stable diastereomer was epimerizing to the more stable one.

Figure 2.11. Exchange reaction of racemic ligand with enantiopure alcohol



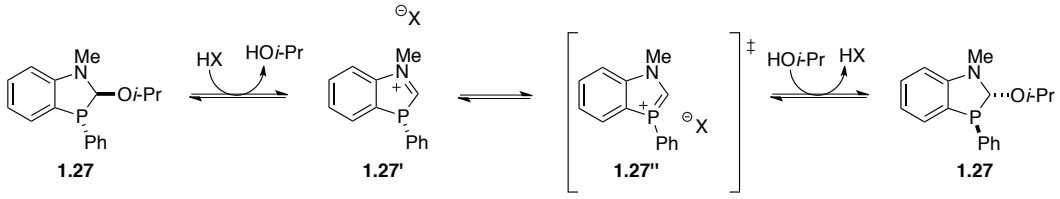
1.27 **2.37** **2.38** **2.39**

cycle	conversion (%)[a]	ratio (**2.38** : **2.39**)[a]
1	71	56 : 44
2	82	62 : 38
3	85	66 : 34
4	95	69 : 31

[a] Calculated by ^{31}P NMR.

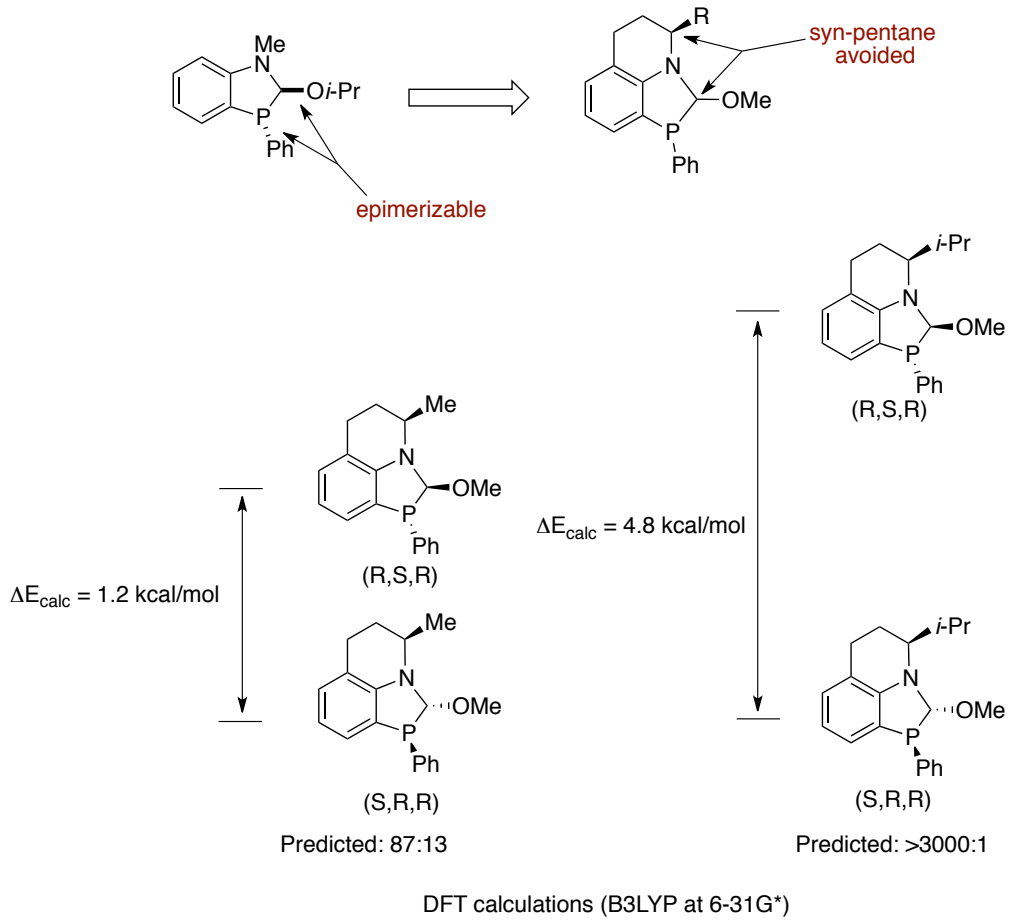
A possible pathway for this epimerization is illustrated in Figure 2.12. The configurational instability of the phosphorous is unusual given the mild exchange conditions. This instability may arise from the fact that iminium ion **1.27′** is a likely intermediate under the acidic exchange conditions. Rehybridization of the phosphorous to sp^2 would generate aromatic transition state **1.27′′** significantly lowering the barrier to inversion. Alternatively, the heterocycle may be ring opening to the secondary phosphine, which epimerizes and then ring closes to reform the heterocycle.

Figure 2.12. Possible pathway of epimerization



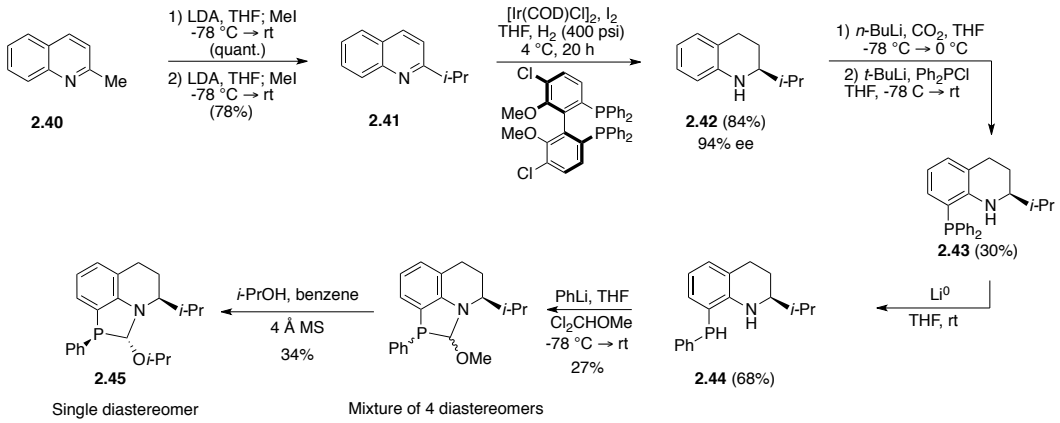
We took advantage of this in the design of a new chiral scaffolding ligand **2.36**. Ligand **2.36** contains an additional stereocenter that is incorporated on the tetrahydroquinoline ring. By incorporating this stereocenter on the tetrahydroquinoline ring, we postulated that thermodynamic gearing would control the conformation of the other two stereocenters even under the exchange conditions. Computational studies suggested that an isopropyl group as the non-epimerizable stereocenter would give a 3000:1 ratio of the most stable diastereomer. In addition, the isopropyl group and C-O bond would have an *anti* relationship in order to minimize any *syn*-pentane-like interactions (Figure 2.13).

Figure 2.13. Rationale for design of first-generation chiral scaffolding ligand



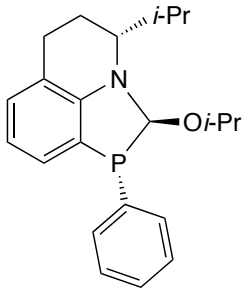
The synthesis of the first-generation chiral ligand is illustrated in Figure 2.14.[7] Starting from commercially available quinaldine, **2.40**, two consecutive alkylations yield 2-isopropylquinoline **2.41**. Asymmetric hydrogenation results in the formation of 2-isopropyl tetrahydroquinoline **2.42**. Kinetic closure of the secondary phosphine **2.44**, obtained after lithium metal reduction of **2.43**, with PhLi and α,α-dichloromethyl methyl ether yields ligand **2.45** as a mixture of four diastereomers, which is equilibrated to a single diastereomer with isopropanol in benzene.

Figure 2.14. Synthesis of first-generation chiral scaffolding ligand

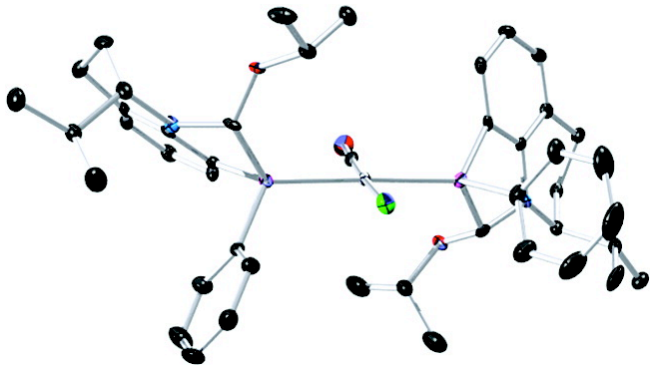


An x-ray crystal structure of **2.45** bound to rhodium shows the *anti* relationship of the three stereocenters relative to each other (Figure 2.15).[37]

Figure 2.15. X-ray crystal structure of 2.45 bound to rhodium



2.45



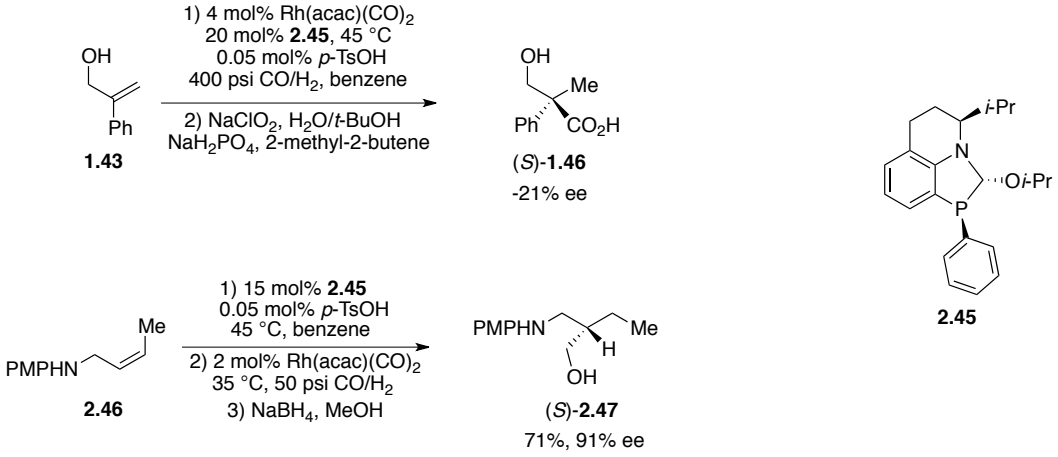
X-ray crystal structure of Rh(**2.45**)$_2$(CO)Cl; (ν_{CO}) = 1979 cm^{-1}

Asymmetric hydroformylation of **1.43** using chiral scaffolding ligand **2.45** gave, after Pinnick oxidation, -21% ee of the acid **1.46** with an *S* configuration. Interestingly, enantioselective hydroformylation of allylic aniline **2.46** employing ligand **2.45** afforded *S*-**2.47** in 91% ee (Figure 2.16).[18] If it is assumed that styrenyl olefin **1.43** and allylic aniline **2.46** have the same facial selectivity, then this

[37] Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757.

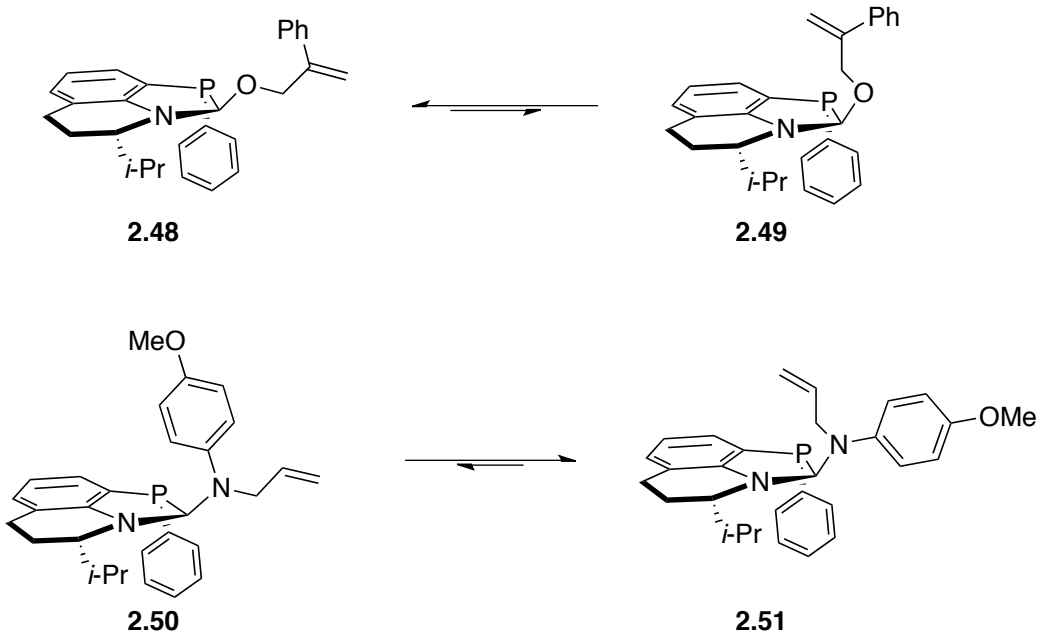
stereochemical outcome would suggest that the formyl group is added to the opposite face of the olefin in **1.43**.

Figure 2.16. Asymmetric hydroformylation using first-generation chiral scaffolding ligand 2.45



We rationalized that this change in the sense of induction may arise from a preference to place the olefin tether away from the heterocycle for allylic alcohols, making **2.48** the favored conformation, whereas in the case of allylic anilines the olefin tether would prefer to reside over the heterocycle with the aryl group pointing out into the free space, making **2.51** the favored conformation (Figure 2.17). This projects the opposite face of the olefin to the phosphorus atom and ultimately the Rh catalyst.

Figure 2.17. Rationale for the stereochemical outcome in the asymmetric hydroformylation of 1.43 and 2.46

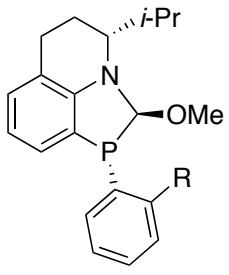


2.48 **2.49**

2.50 **2.51**

Therefore, we hypothesized that installing a substituent at the ortho position of the phenyl ring on phosphorus atom should force the olefin tether to reside over the heterocycle as shown in **2.49** thus, leading to the development of our second generation chiral scaffolding ligands **2.52** (Figure 2.18).

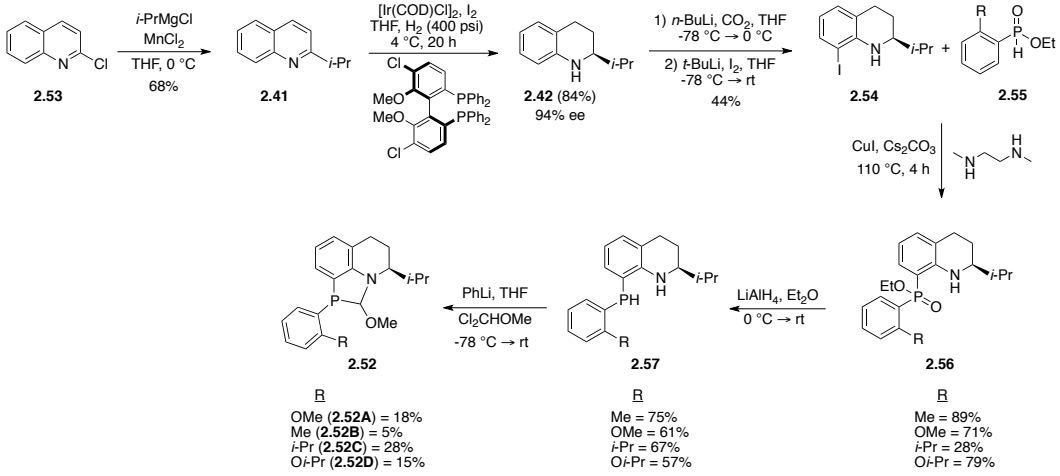
Figure 2.18. Design of second-generation chiral scaffolding ligands



2.52

The synthesis of **2.52** is illustrated in Figure 2.19. This synthesis was modified from the synthesis of the first generation chiral ligand for efficiency and to accommodate derivatization.

Figure 2.19. Synthesis of second-generation chiral scaffolding ligands



Hence, a manganese-catalyzed cross coupling of 2-chloroquinoline with isopropylmagnesium chloride is performed for the synthesis of 2-isopropylquinoline **2.41**. Copper iodide-catalyzed cross coupling of **2.54** with phosphinate **2.55** under Buchwald conditions affords phosphinate ester **2.56**, which is reduced with lithium aluminum hydride to afford the secondary phosphine **2.57**. Kinetic closure then affords the second-generation chiral scaffolding ligand **2.52**.

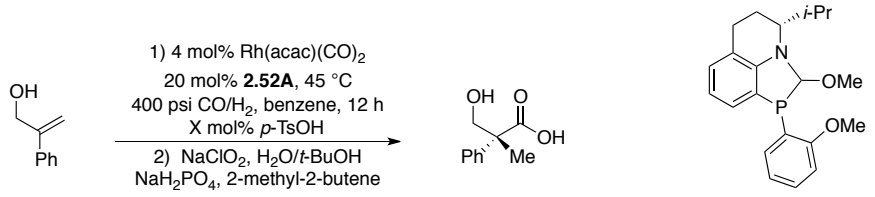
IV. Use of Second-Generation Chiral Scaffolding Ligands

Asymmetric hydroformylation of styrenyl olefin **1.43** was performed with our second-generation chiral scaffolding ligands. It had previously been shown that small amounts of acid is necessary for exchange of racemic ligand **1.27** onto styrenyl olefin **1.43**.[38] Hence, to investigate the efficiency of chiral ligand **2.52A** in the

[38] Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841.

enantioselective hydroformylation of olefin **1.43**, an acid screen was performed. The same reaction conditions employed with racemic ligand **1.27** (4 mol% rhodium catalyst, 20 mol% ligand and 400 psi CO/H_2) were used as a starting point. The amount of acid was varied from 0.05 mol% to 0.20 mol%, and with the exception of the result obtained for 0.10% acid, the isolated yield of the branched product increases slightly with increasing acid loading while the enantioselectivity remains unchanged (Table 2.1). Next, a pressure screen was performed to determine the dependence of the enantioselectivity on pressure. This was done using 0.1 mol% acid since the highest enantioselectivity was obtained with this amount of acid in the acid screen.

Table 2.1. Acid screen with ligand 2.52A



1.43 **1.46** **2.52A**

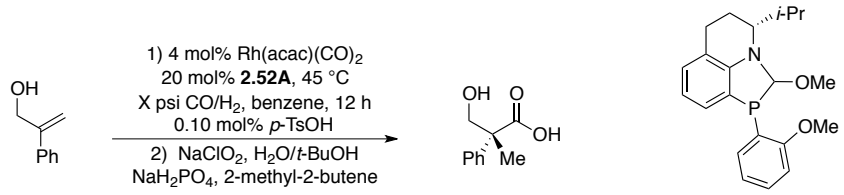
p-TsOH (mol%)	conversion (%)[a]	isolated yield **1.46** (%)	% ee[b]
0.05	-	76	67
0.10	-	37	74
0.15	-	78	69
0.20	-	84	71

-**1.43** and **2.52A** not pre-equilibrated
[a] Conversion not determined
[b] Acid esterified with $TMSCHN_2$ in C_6H_6/MeOH

There is an increase in the isolated yield of the quaternary aldehyde from 67% to 74% when pressure is increased from 50 psi to 100 psi CO/H_2 (Table 2.2). However, the yield of the branched product plateaus at 100 psi of syngas since increasing the

pressure from 100 psi to 300 psi does not improve the isolated yield of the branched product. Furthermore, there is no clear trend in the enantioselectivity of the reaction although the enantioselectivity is highest at lower pressure. This result is in contrast to a report from Landis and co-workers observed in the asymmetric rhodium-catalyzed hydroformylation of styrene. The group disclosed that both regio- and enantioselectivities erode as the syngas pressure is lowered.[39] Based on deuterioformylation studies, which showed that the formation of the Rh-alkyl intermediate that ultimately leads to the major enantiomeric aldehyde is reversible, they explained that it is the CO partial pressure that influences the regio- and enantioselectivities. Thus, the pressure effect on regio- and enantioselectivity arises from a kinetic competition between CO-dependent conversion of one branched rhodium alkyl diastereomer to an acyl and its reversion to a rhodium hydride and styrene.

Table 2.2. Pressure screen with ligand 2.52A



1.43 **1.46** **2.52A**

CO/H_2 (psi)	conversion (%)[a]	isolated yield **1.46** (%)	% ee[b]
50	79	67	75
100	80	74	75
200	86	71	66
300	85	71	68

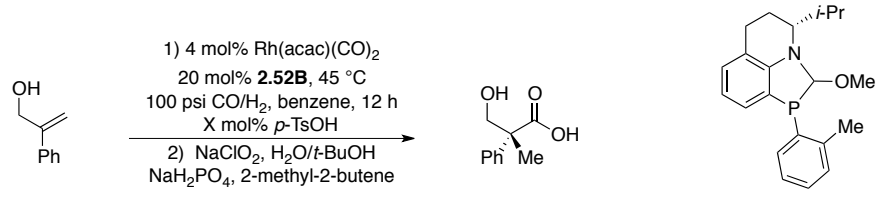
-**1.43** and **2.52A** not pre-equilibrated
[a] Calculated against trimethoxybenzene as internal standard
[b] Acid esterified with $TMSCHN_2$ in C_6H_6/MeOH

[39] Watkins, A. L.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 10306.

The optical rotation of a sample of acid **1.46** obtained from the reactions reported in Table 2.2 was measured to be +16.7 indicating that the stereochemistry at the quaternary carbon is *R*. This is in accordance with literature reports and consistent with our hypothesis.[40]

Next, we investigated the activity of ligand **2.52B** in the enantioselective hydroformylation of **1.43**. This was done to determine the significance, if any, of steric hindrance in the reaction. The results of the acid screening reactions are summarized in **Table 2.3**.

Table 2.3. Acid screen with ligand 2.52B



1.43 **1.46** **2.52B**

p-TsOH (mol%)	conversion (%)[a]	isolated yield **1.46** (%)	% ee[b]
0.05	78	56	76
0.125	70	46	71
0.20	70	44	78

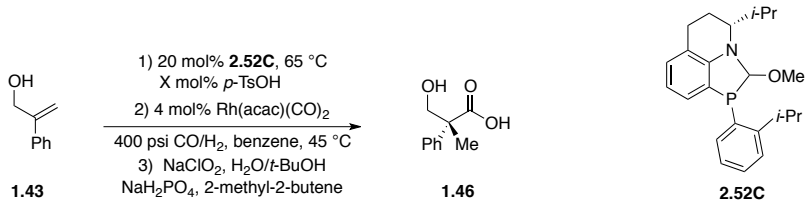
-**1.43** and **2.52B** not pre-equilibrated
[a] Calculated against trimethoxybenzene as internal standard
[b] Acid esterified with $TMSCHN_2$ in C_6H_6/MeOH

As observed in the reactions with ligand **2.52A**, there is no clear trend for the enantioselectivity in this reaction. However, it is evident that lower acid levels give higher yields of the quaternary aldehyde. This may be because higher acid levels lead to decomposition of the ligand. Although the isolated yields of the branched product

[40] (a) Ohkata, *et al. J. Mol. Cat. B: Enzymatic* **2006**, *38*, 1.; (b) Bach, R. D.; Domagala, J. M. *J. Org. Chem.* **1979**, *44*, 2429.; (c) Ohta, *et al. J. Am. Chem. Soc.* **1992**, *114*, 6256.

are lower for ligand **2.52B** compared to ligand **2.52A**, the enantioselectivities are similar. This may suggest that ligand **2.52A** is more selective for the branched pathway compared to ligand **2.52B**. However, enantioselectivity may be dependent on steric encumbrance rather than the methoxy group in ligand **2.52A** providing a second coordination site for the catalyst. We were therefore interested in seeing what effect increasing the size of the substituent on the phenyl ring would have on enantioselectivity. Hence, ligands **2.52C** and **2.52D** were synthesized and analyzed. The results obtained for **2.52C** are summarized in Table 2.4.

Table 2.4. Acid screen with ligand 2.52C



1.43 **1.46** **2.52C**

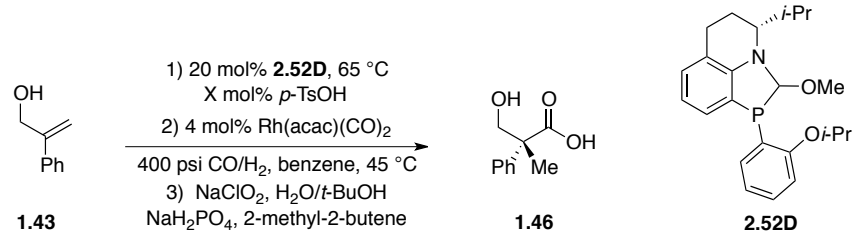
entry	*p*-TsOH (mol%)	conversion (%)[a]	isolated yield **1.46** (%)	% ee[b]
1[c]	0.05	39	-[f]	-[f]
2[d]	0.05	58	13	11
3[e]	1.0	61	12	42

[a] Calculated against trimethoxybenzene as internal standard
[b] Acid esterified with $TMSCHN_2$ in C_6H_6/MeOH
[c] **1.43** and **2.52C** not pre-equilibrated
[d] **1.43** and **2.52C** pre-equilibrated (3 of the 4 ligand diastereomers did not equilibrate)
[e] **1.43** and **2.52C** pre-equilibrated (1 of the 4 ligand diastereomers did not equilibrate)
[f] Isolated yield and ee not determined

The data in Table 2.4 unfortunately did not support our hypothesis, as the enantioselectivities obtained were very low. Very low conversions (39% by ^{1}H NMR) were observed when the reactions were run without pre-exchanging the ligand onto the substrate (Table 2.4, entry 1). Also, no branched aldehyde product or linear lactone product were observed. Although the isolated yields are very low for entries 2 and 3 in Table 2.4, it is evident that more acid increases the enantioselectivity. This is

because at higher acid level of 1.0 mol%, 85% of the ligand was exchanged onto the substrate (Table 2.4, entry 3) compared to only 55% for 0.15 mol% acid (Table 2.4, entry 1). Furthermore, only one of the four ligand diastereomers equilibrated in the case of low acid loading (Table 2.4, entry 2) compared to three in the case of high acid loading (Table 2.4, entry 3). One explanation for these results is that one or more of the ligand diastereomers are active but selective for the opposite enantiomer and thus, erode the enantioselectivity of the reaction. The low yields and enantioselectivities may also be a result of the impure nature of the ligand. Use of ligand **2.52D** did not improve the selectivity of the reaction (Table 2.5). As observed in the case of ligand **2.52C**, low selectivities are obtained and no clear trend is seen for the enantioselectivities. Note this ligand is also impure.

Table 2.5. Acid screen with ligand 2.52D



1.43 **1.46** **2.52D**

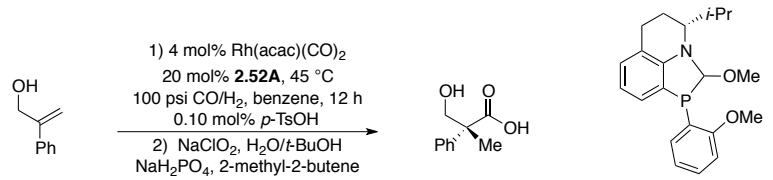
p-TsOH (mol%)	conversion (%)[a]	isolated yield **1.46** (%)	% ee[b]
0.05	53	22	19
0.10	58	9	52
0.15	52	15	26
0.20	49	15	34

-**1.43** and **2.52D** only 20% pre-exchanged. Diastereomers of ligand did not equilibrate
[a] Calculated against trimethoxybenzene as internal standard
[b] Acid esterified with $TMSCHN_2$ in C_6H_6/MeOH

Concerned about these alarming results, we repeated the reaction with ligand **2.52A**. Unfortunately, we observed lower enantioselectivities depending on the

batch of ligand used. For instance, under the same hydroformylation conditions as Table 2.1, and using 0.10 mol% *p*-TsOH, we obtained different enantioselectivities for different batches of chiral ligand **2.52A** (Table 2.6). The optical rotation of the acid product **1.46** was measured for ligand batch 3 (run 1) to be +3.42, supporting an erosion of the ee. It became apparent to us that impurities in these ligands might be causing the mediocre selectivities and batch dependency of enantioselectivity in these reactions. Presumably, erosion of ligand ee could also account for these observations.

Table 2.6. Dependency of enantioselectivity on batch of ligand



1.43 **1.46** **2.52A**

notebook #	ligand batch	run 1 (% ee[b], % yield)	run 2 (% ee[b], % yield)
KF-2-280	1	75, 74	-
KF-3-064/KF-3-067	2	10, 67	12, 60
KF-3-076/KF-3-079	3	40, 63	36, 61
KF-3-104	4	45, 54	-

[a] **1.43** and **2.52A** not pre-equilibrated
[b] Acid esterified with $TMSCHN_2$ in C_6H_6/MeOH

The batch dependency of selectivity on ligands **2.52A-D** may be due to a variety of reasons. It is noteworthy that none of these ligands is pure, even after distillation. All ligands are obtained as a mixture of diastereomers in different amounts and given that one or more of the ligand diastereomers may be active but selective for the opposite enantiomer, enantioselectivity may erode. For instance, when one batch of ligand **2.52A** (KF-2-266, batch 1) is pre-exchanged with **1.43**, there is equilibration to a new peak at -33.8 ppm (86%) with one ligand diastereomer (-32.3 ppm)

remaining. This batch of ligand gave a 74% yield and 75% ee of the branched product (Table 2.2, entry 2). Another batch of the same ligand (KF-3-078, batch 3), after pre-exchange with **1.43**, formed the new peak at -33.8 ppm. However two ligand diastereomers remained (-32.3 ppm and –34.0 ppm). This batch of ligand afforded a 61% yield and 36% ee of the branched product. The first batch of **2.52A** (KF-2-266) also exchanged onto **1.43** at a faster rate than the second batch. These results suggest that the diastereomer at -34.0 ppm may be causing the lower yield and enantioselectivity in the second batch.

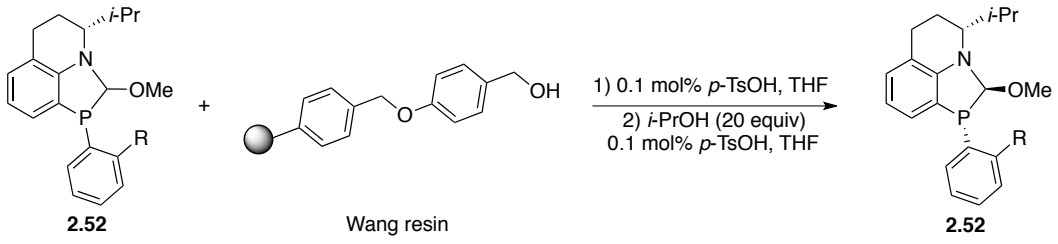
Similar exchange profiles are observed for the other ligands. For instance, one batch of ligand **2.52C** (KF-3-035, batch 2) undergoes exchange with **1.43** to form 55% of a new peak (-35.0 ppm) with three ligand diastereomers (-18.2 ppm, -34.8 ppm, and -36.3 ppm) remaining. This batch of ligand gave the branched product in 13% yield and 11% ee (Table 2.4, entry 2). A second batch of the same ligand (KF-3-036) underwent exchange with 1.43 to give the new peak at -35.1 ppm (85%) with only one ligand diastereomer (-18.2 ppm) remaining. This batch of ligand afforded the branched product in 12% yield and 42% ee. Notably, the exchange reactions for both batches of **2.52C** are slow, which may be one reason for the very low isolated yields. The presence of the other diastereomers in the first batch may be causing the decreased enantioselectivity.

The presence of basic impurities, in addition to other impurities, and varying diastereomer ratio in these ligands may all be contributing in some way to the irreproducibility in the selectivity of the hydroformylation reactions.

V. Ligand Purification with Wang Resin

We investigated the possibility of using a solid support such as Wang resin to equilibrate and purify the ligands. Due to the presence of an alcohol functionality on the resin, exchange of the ligands onto the resin should be feasible. After exchange is complete, any impurity could then be washed off and subsequent cleavage of the resin would yield pure ligand (Figure 2.20).

Figure 2.20. Equilibration of ligand with Wang resin



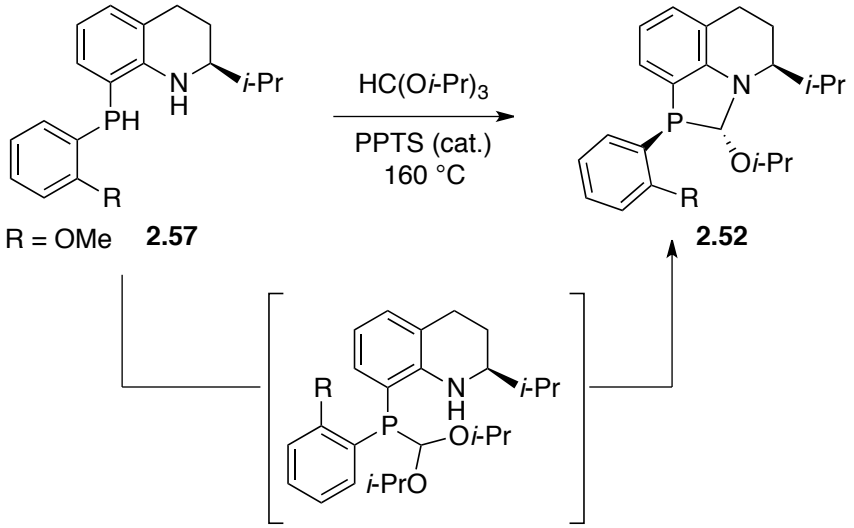
However, no equilibration of the ligand was observed and after cleavage of the resin, the starting impure ligand was recovered in 66%.

VI. Thermodynamic Closure

Because we are able to perform a thermodynamic closure in the final step in the synthesis of racemic ligand **1.27**, we investigated the possibility of such a closure in the synthesis of the chiral ligands. A thermodynamic closure will eliminate basic impurities as well as afford the ligand as a single diastereomer. However, similar thermodynamic conditions as in the synthesis of racemic ligand **1.27** were unsuccessful for the chiral ligands (Figure 2.21). Based on ^{31}P and ^{1}H NMR spectra as well as mass spectroscopy, there is formation of a compound that we believe is the intermediate shown in Figure 2.21. An attempt to force closure by addition of more

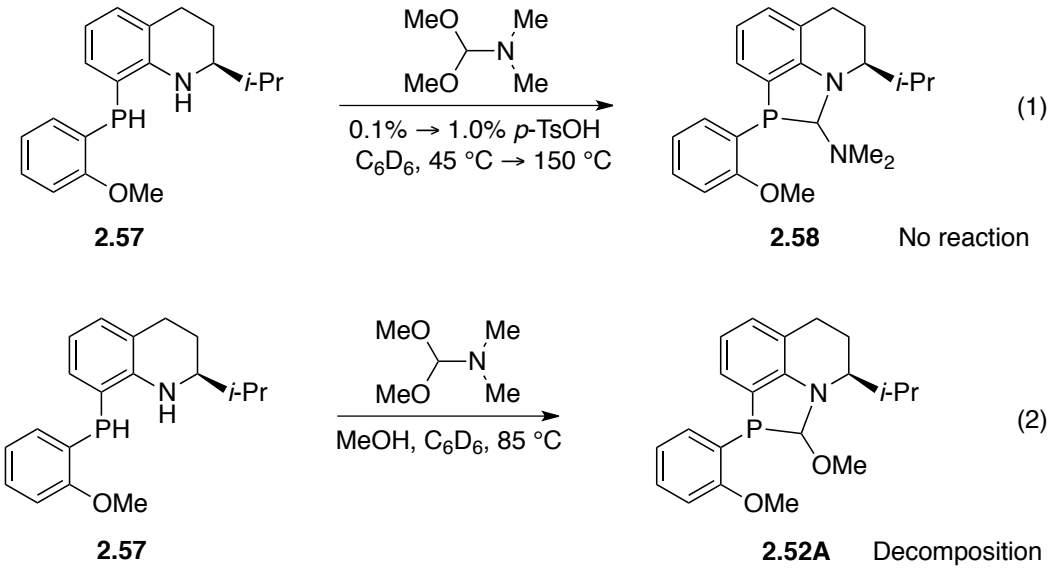
acid (1 equiv. *p*-TsOH) was fruitless. Performing the reaction under microwave conditions (250 °C) was also unproductive and resulted in the formation of various unidentified decomposition products.

Figure 2.21. Thermodynamic closure with triisopropyl orthoformate



Use of *N*,*N*-dimethylformamide dimethyl acetal in either benzene and catalytic amounts of *p*-TsOH (Figure 2.22, eq. 1) or methanol (Figure 2.22, eq. 2) led to no reaction or decomposition of **2.57** respectively.

Figure 2.22. Thermodynamic closure with DMF-dimethyl acetal



VII. Conclusions

The results obtained thus far are encouraging. The increase in enantioselectivities observed with the second-generation chiral ligands seems to support our hypothesis. However, it is apparent that purity of the ligands is crucial for selectivity in the asymmetric hydroformylation reaction. Thus, the need for new purification methods and/or modified ligand synthesis is required. The employment of other chiral ligands for this transformation is also a viable alternative.

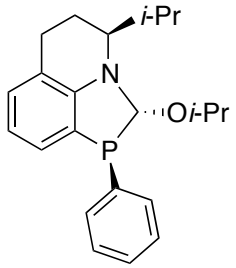
VIII. Experimental

General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an

atmosphere of nitrogen or argon using standard syringes, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). ^{1}H and ^{13}C were performed on either a Varian Unity INOVA 400 MHz or a Varian 500 MHz instrument. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C. Coupling constants are reported in Hz. Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet), br s (broad singlet). All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm^{-1}. HRMS data were generated in Boston College facilities. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Berger Instruments Supercritical Chromatograph equipped with an Alcott auto sampler and a Knauer UV detector with methanol as the modifier. HRMS and X-ray crystal structure data were generated in Boston College facilities. Analytical chiral high-performance liquid chromatography (HPLC) was performed on a Shimadzu-LC-2010A HT Hydroformylation was performed in an Argonaut Technologies Endeavor Catalyst Screening System using 1:1 CO/H_2 supplied by Airgas, Inc.

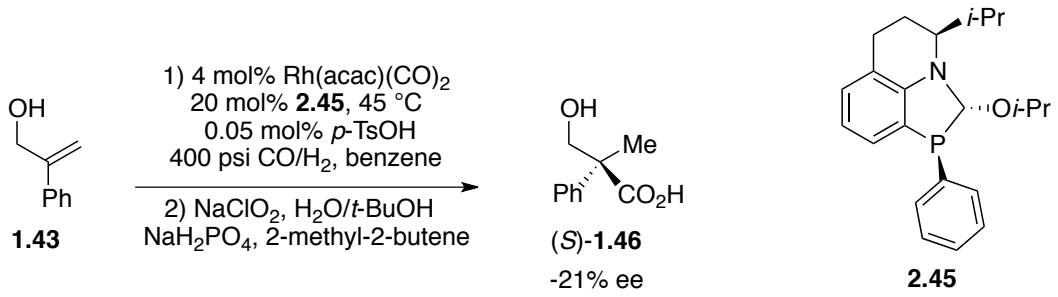
Synthesis and Characterization of First-Generation Chiral Scaffolding Ligand **2.45**



2.45

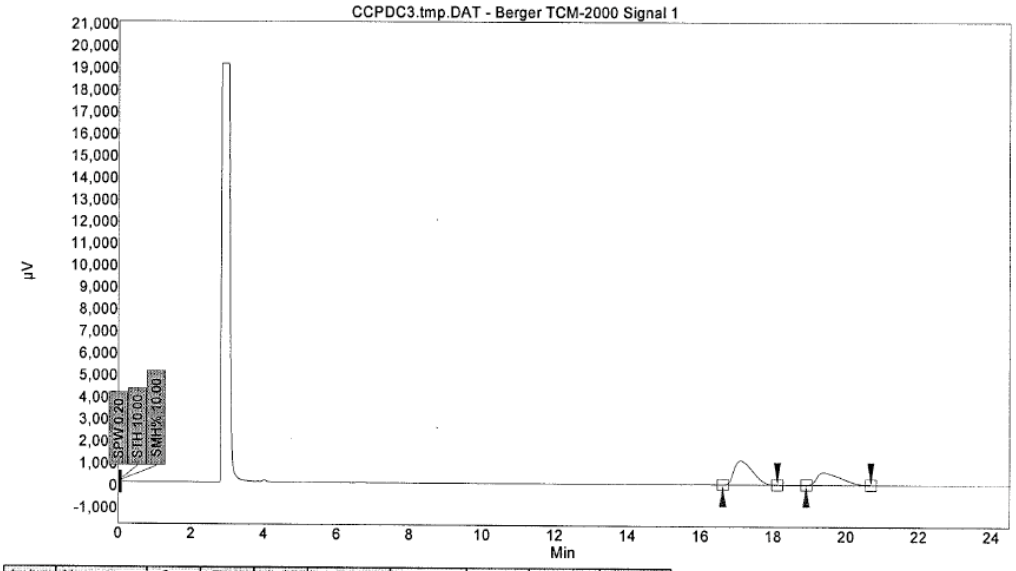
For synthesis and characterization of ligand **2.45** see reference 1.

Asymmetric Hydroformylation Using Ligand **2.45**



An oven dried glass reaction vial was placed in the Endeavor, and 2-phenylprop-2-en-1-ol, **1.43** (20 mg, 0.15 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium(I) (1.6 mg, 6.0×10^{-3} mmol, 4.0 mol%), ligand **2.45** (10.7 mg, 3.0×10^{-2} mmol, 20 mol%), *p*-toluenesulfonic acid (125 μL of 6.0×10^{-4} M in benzene, 7.5×10^{-5} mmol, 0.05 mol%) and benzene (to total volume of 1 mL) was injected, followed by injection of additional benzene (0.5 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 45 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi of CO/H_2, and stirring was re-initiated at 700 rpm. The Endeavor was maintained at a constant temperature of 45 °C and pressure of 400 psi of CO/H_2 for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction mixture was removed from the Endeavor and concentrated. The residue was dissolved in *t*-butanol (0.75 mL) and 2-methyl-2-butene (0.16 mL, 1.5 mmol, 10.0 eq.) followed by addition of a solution of $NaClO_2$ (80%, 68 mg, 0.60 mmol, 4.0 equiv.) and NaH_2PO_4 (72 mg, 0.60 mmol, 4.0 eq.) in H_2O (0.4 mL). The solution was stirred at room temperature overnight. The resulting

mixture was concentrated and redissolved in EtOAc (0.75 mL), followed by addition of 10% HCl (0.18 ml) and brine (0.18 mL). The solution was extracted with EtOAc (3 × 5 mL). Combined organic layers were dried over $MgSO_4$, filtered and solvent was removed. Flash column chromatography was performed to isolate the acid, which was subjected to esterification conditions. To a dried scintillation vial containing the acid and a stir bar under nitrogen was added 1.5 mL each of benzene and methanol. (Trimethylsilyl)diazomethane (358 μL, 2.25 mmol, 15 equiv.) was added dropwise and the resulting solution was stirred for 1 h at room temperature. The reaction was concentrated and purified by preparative TLC. The resulting ester was -21% ee by SFC analysis (AD-H, 1 mL/min, 2.0% MeOH as modifier, 220 nm, 150 psi, 50 °C, t_S = 17.1 min, t_R = 19.4 min).



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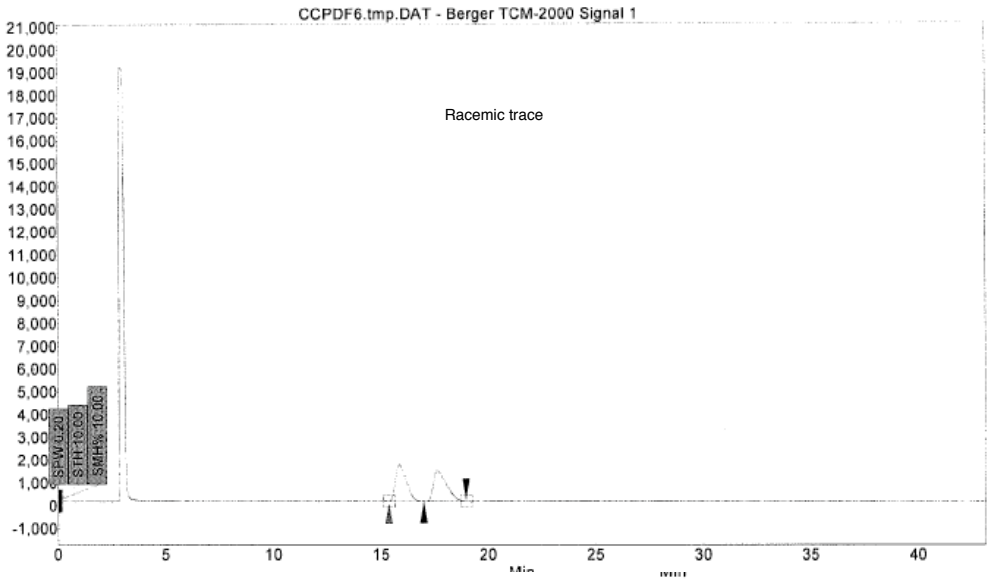
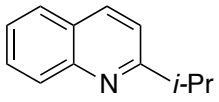
1	UNKNOWN	16.61	17.09	18.11	0.00	60.27	1075.0	623.8	60.273
2	UNKNOWN	18.90	19.37	20.68	0.00	39.73	563.3	411.2	39.727
Total						100.00	1638.3	1035.0	100.000



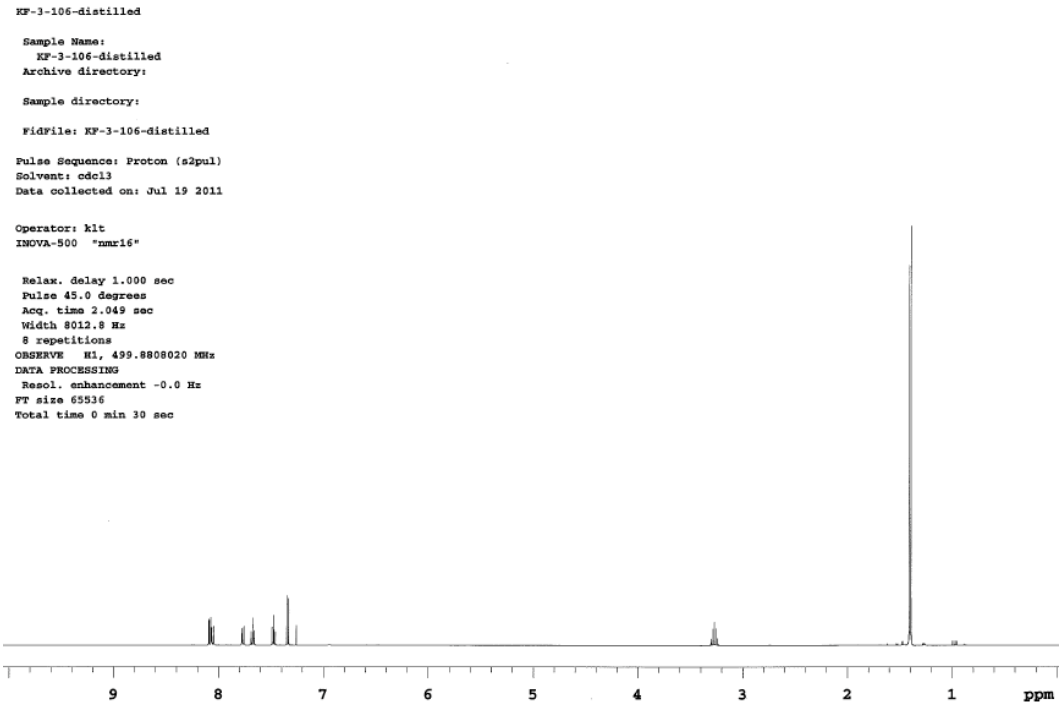
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.37	15.86	16.99	0.00	49.77	1592.8	928.4	49.766
2	UNKNOWN	16.99	17.63	18.97	0.00	50.23	1324.8	937.2	50.234
Total						100.00	2917.5	1865.6	100.000

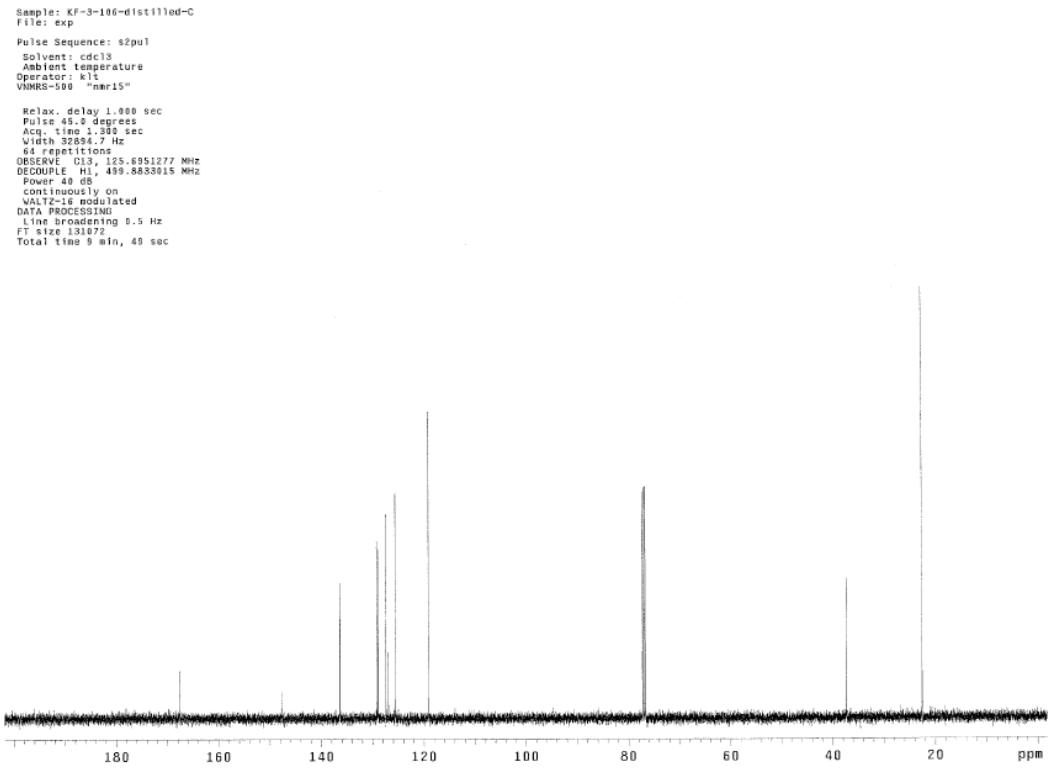
Syntheses of Second-Generation Chiral Scaffolding Ligands

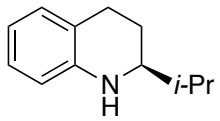


2-Isopropyl quinoline. To a flamed dried 1-L round bottom flask with stir bar and septum was added 2-chloroquinoline (30 g, 183.4 mmol, 1 equiv.) and manganese(II) chloride (1.15 g, 9.17 mmol, 0.05 equiv.). The flask was evacuated three times and purged with nitrogen. THF (460 mL) was added while stirring and the resulting solution was cooled to 0 °C. Isopropylmagnesium chloride (154 mL of 1.79 M in THF, 275.1 mmol, 1.5 equiv.) was added dropwise using a syringe pump. The resulting solution was stirred overnight, allowing to warm to rt gradually. The reaction was quenched with 200 mL of saturated aqueous NH_4Cl, followed by addition of 200 mL of H_2O. The solution was extracted with EtOAc (3 X 200 mL)

and the combined organics was dried over $MgSO_4$ and concentrated under vacuum. The crude residue was distilled at 75 °C @ 0.025 mmHg to afford the title compound as a light yellow oil (21.4 g, 68%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.09-8.05 (dd, 2H, *J* = 8.6, 4.7), 7.78-7.76 (d, 1H, *J* = 8.1), 7.69-7.66 (dtd, 1H, *J* = 8.3, 6.9, 1.5), 7.49-7.46 (dtd, 1H, *J* = 8.1, 6.8, 1.2), 7.35-7.33 (d, 1H, *J* = 8.6), 3.31-3.23 (m, 1H), 1.41-1.39 (d, 1H, *J* = 6.9); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 167.7, 147.7, 136.4, 129.2, 129.0, 127.4, 126.9, 125.6, 119.1, 37.3, 22.5; **IR**: 2962.0, 1600.3, 1502.7, 1426.2, 1086.6, 1038.3, 826.7, 752.5, 618.5, 477.7; **HRMS** (DART-TOF) calcd. for $C_{12}H_{13}N[M+H]^+$: 172.1126, found: 172.1129.

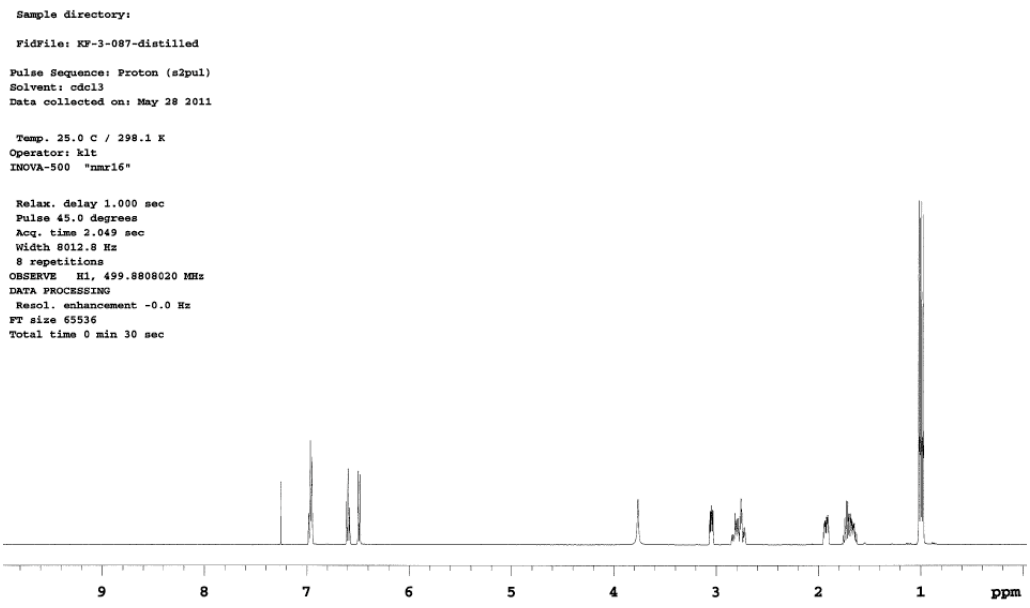


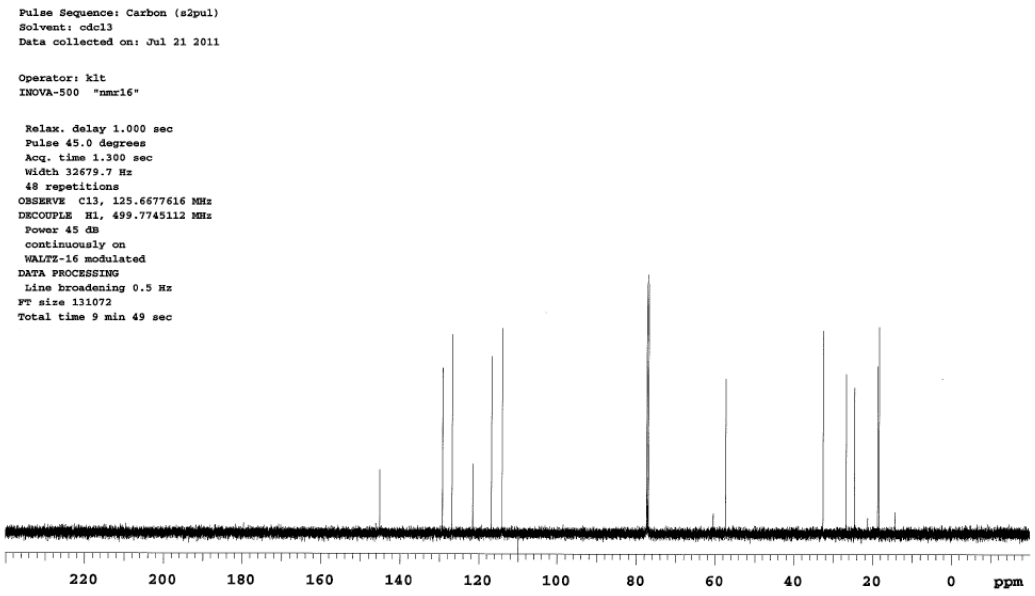


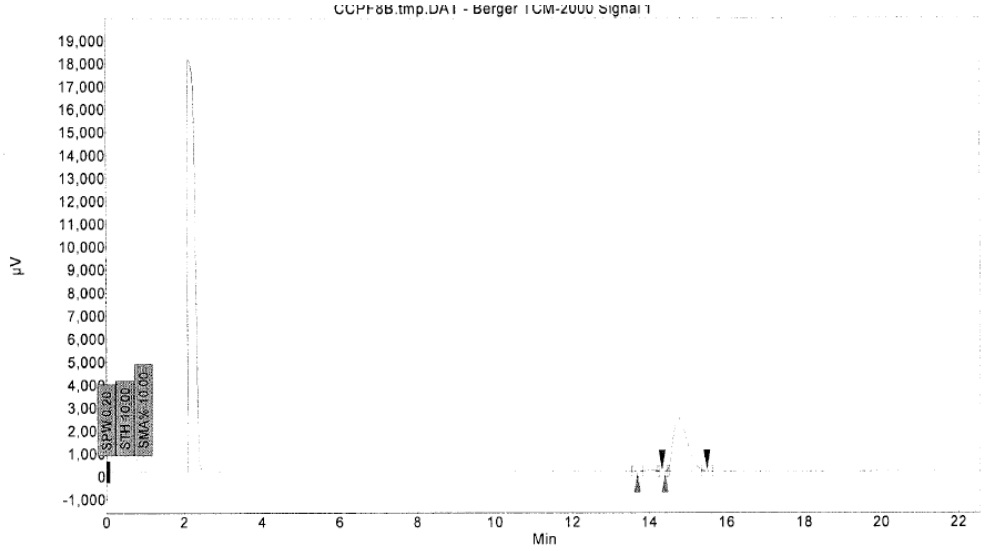


(*S*)-2-Isopropyl-1,2,3,4-tetrahydroquinoline. In a glovebox, $[Ir(COD)Cl]_2$ (82.5 mg, 0.123 mmol, 0.001 equiv.) and (*R*)-(+)-5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl (160 mg, 0.245 mmol, 0.002 equiv.) were dissolved in 10 mL THF. The solution was brought out of the glovebox and was added to a solution of 2-isopropyl quinoline (21 g, 122.7 mmol) and iodine (312 mg, 1.23 mmol, 0.01 equiv.) in THF (150 mL). The solution was added to a parr bomb and cooled to 4 °C (cold room). The system was charged to 400 psi and depressurized 3 times with hydrogen gas. The vessel was pressurized to 400 psi with hydrogen and the reaction was stirred for 20 h. The parr bomb was depressurized. Na_2CO_3 (23.4 g, 92.7 mmol, 1.8 equiv.), and H_2O (282 mL) were added and stirred for 30 minutes.

The mixture was diluted with 200 mL of EtOAc and extracted with H_2O (3 x 100 mL). The combined organics was washed with brine, and dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by distilling at 100 °C @ 0.05 mmHg to yield the title compound as a yellow oil (19.1 g, 89%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.06-7.02 (m, 2H), 6.68 (ddd, 1H, *J* = 8.0, 7.0, 1.0), 6.54 (dd, 1H, *J* = 7.5, 1.0), 3.82 (br s, 1H), 3.14-3.10 (m, 1H), 2.89-2.80 (m, 2H), 2.02-1.97 (m, 1H), 1.81-1.70 (m, 2H), 1.09 (d, 3H, *J* = 7.0), 1.06 (d, 3H, *J* = 7.0); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 145.1, 129.2, 126.8, 121.5, 116.8, 114.0, 57.3, 32.6, 26.7, 24.6, 18.7, 18.3; **IR**: 3415.0, 2956.6, 2870.8, 2842.1, 1606.1, 1483.4, 1308.4, 1273.5, 1253.5, 741.5, 713.9 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{17}N[M+H]^+$: 176.1439, found: 176.1448. The compound was 94% ee by SFC analysis (OD-H, 1% methanol as modifier, 1.5 mL/min, 150 psi. t_R = 12.8 min t_S = 13.6 min).







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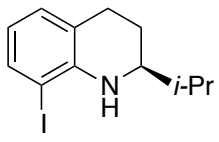
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	13.67	14.00	14.34	0.00	2.41	77.1	24.6	2.415
2	UNKNOWN	14.41	14.75	15.49	0.00	97.59	2334.4	994.3	97.585
Total						100.00	2411.5	1019.0	100.000



(*S*)-8-Iodo-2-isopropyl-1,2,3,4-tetrahydroquinoline. To a flame dried 500 mL three-neck round bottom flask was added THF (250 mL) and (*S*)-2-isopropyl-

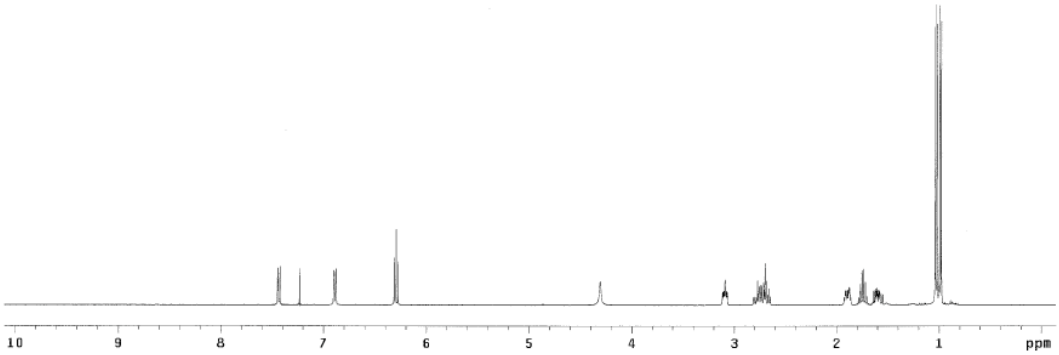
1,2,3,4-tetrahydroquinoline (9.9 g, 56.7 mmol). The solution was cooled to an internal temperature of -78 °C and *n*-BuLi (6.3 mL of 10.0 M, 62.5 mmol, 1.1 equiv.) was added dropwise at a rate that maintained a constant internal temperature of -70 °C. The resulting solution was allowed to warm to 0 °C and CO_2 was bubbled through the solution, resulting in a clearing of the solution and a rise in temperature to 10 °C. The solution was stirred for 45 minutes and concentrated under high vacuum. The resulting foamy residue was dissolved in THF (250 mL) and cooled to -78 °C. To this, *t*-BuLi (53.9 mL of 1.16 M, 62.5 mmol, 1.1 equiv.) was added dropwise at a rate that maintained a constant internal temperature of -70 °C. The solution was allowed to warm to -20 °C by removing from cold bath for 30 minutes then re-cooled to -78 °C. Iodine (15.9 g, 62.5 mmol, 1.1 equiv.) was added as a solution in THF (50 mL). The resulting dark orange solution was allowed to warm slowly overnight to room temperature. The solution was added to 1 M HCl (150 mL) and stirred for 45 minutes. The solution was adjusted to pH 14 with 6 M NaOH, the organic layer was collected, and the aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organics was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography with hexanes (7.5 g, 44%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45-7.43 (d, 1H, *J* = 9), 6.90-6.88 (d, 1H, *J* = 7.2), 6.32-6.28 (t, 1H, *J* = 7.6), 4.31 (bs, 1H), 3.11-3.07 (m, 1H), 2.81-2.65 (m, 2H), 1.93-1.87 (m, 1H), 1.79-1.70 (m, 1H), 1.65-1.55 (m, 1H), 1.04-1.02 (d, 3H, *J* = 6.8), 1.00-0.98 (d, 3H, *J* = 6.9); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 144.1, 136.4, 129.0, 122.4, 117.7, 84.3, 58.0, 32.5, 27.2, 24.5, 18.6, 18.4; **IR**: 2955.9, 1593.9, 1489.6, 1460.4, 1355.0, 1284.7, 1125.7, 1004.7, 925.2, 748.6, 718.7; **HRMS** (DART-TOF) calcd. for $C_{12}H_{16}IN[M+H]^+$: 302.0406, found: 302.0402.

Sample: KF-3-108-2-H
Sample ID: s_20110818_frimponk_44_01
File: /home/walkup/frimponk/KF-3-108-2-H_3_108_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #44, Operator: frimponk
File: KF-3-108-2-H_3_108_01
VNMRS-400 "nmr14"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7662768 MHz
DATA PROCESSING
Resol. enhancement -0.8 Hz
FT size 65536
Total time 0 min, 30 sec

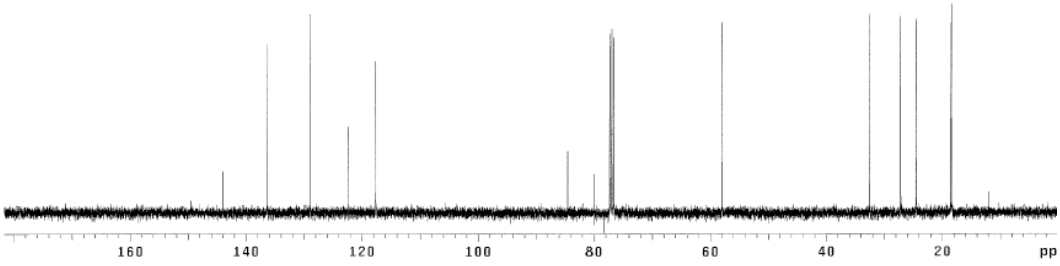


Sample: KF-3-108-2-C
Sample ID: s_20110818_frimponk_44_02
File: /home/walkup/frimponk/KF-3-108-2-C_3_108_01.fid

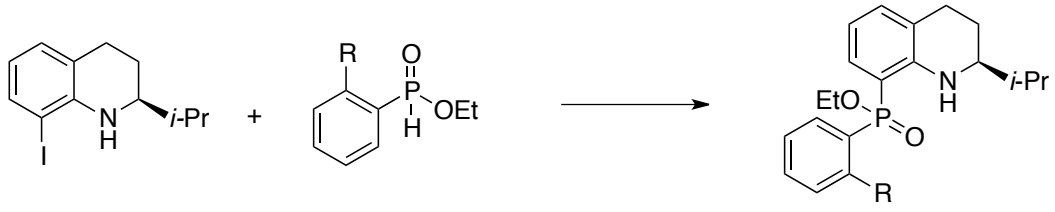
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #44, Operator: frimponk
File: KF-3-108-2-C_3_108_01
VNMRS-400 "nmr14"

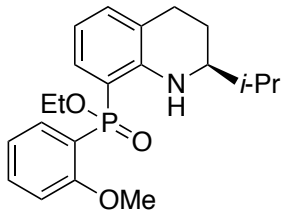
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.301 sec
Width 26595.7 Hz
128 repetitions
OBSERVE C13, 100.5213103 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 4 min, 54 sec



Copper(I)-Catalyzed Cross Coupling Reactions

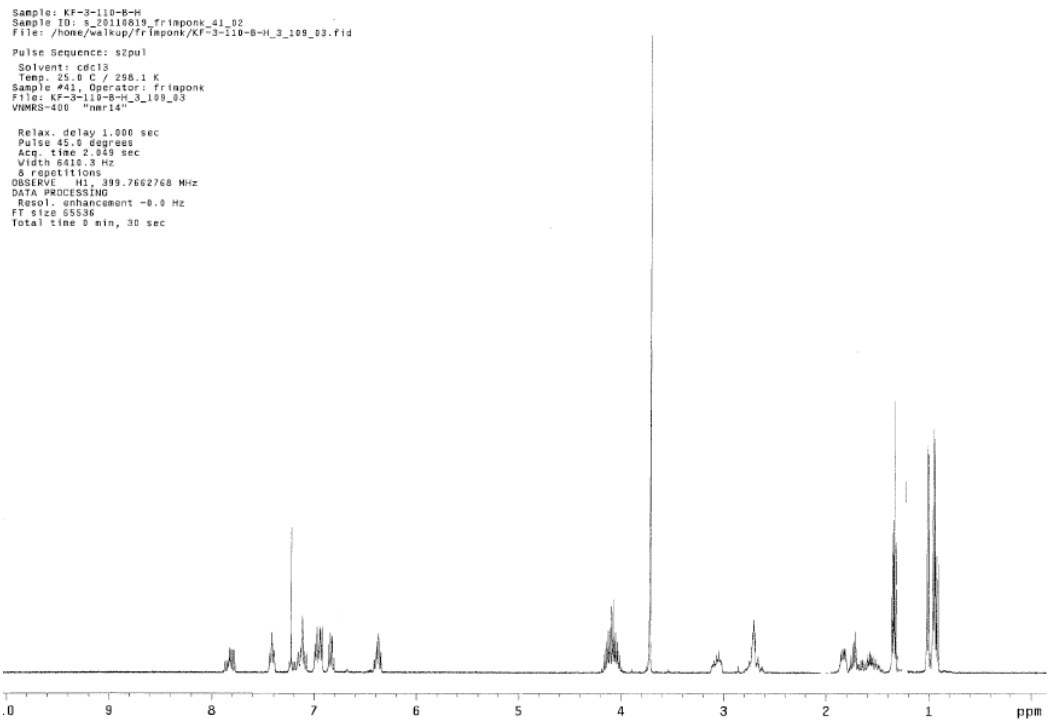


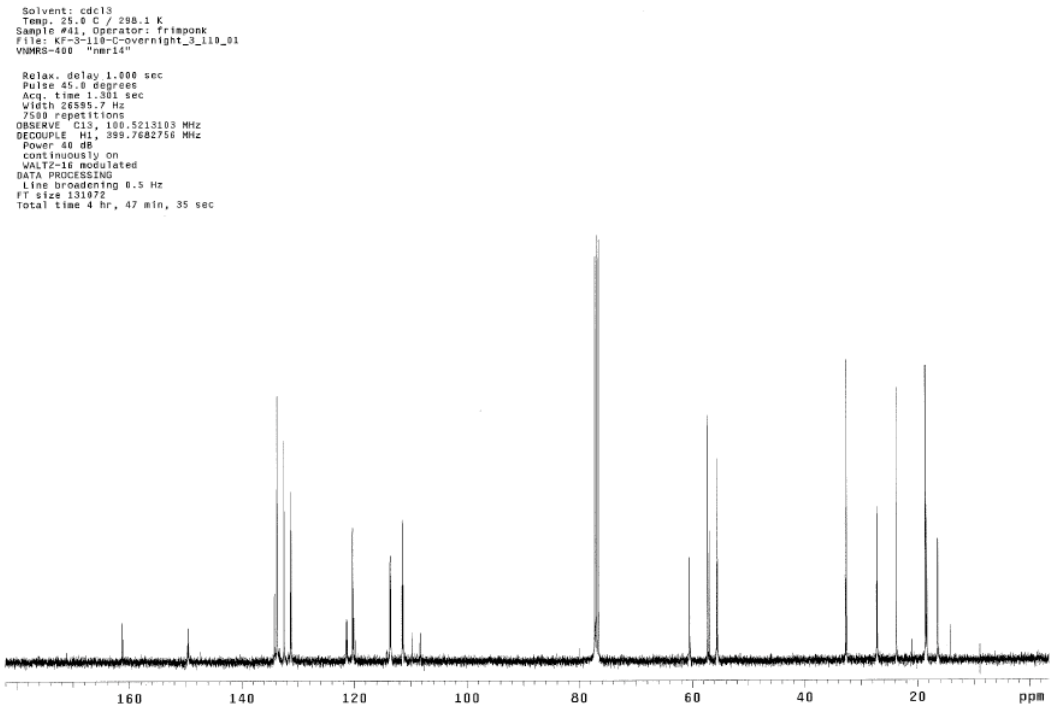
General Procedure. To a flame dried schlenk flask with stir bar was added CuI (0.5 equiv.). The flask was evacuated and refilled with N_2 three times. Toluene (0.25 M) was added, followed by addition of *N,N'*-dimethylethylenediamine (1.5 equiv.) and the corresponding phosphinate (1.5 equiv.). The mixture was stirred for 5 minutes. Cesium carbonate (2 equiv.) was added to the mixture, followed by addition of (*S*)-8-iodo-2-isopropyl-1,2,3,4-tetrahydroquinoline (1.0 equiv.) as a solution in toluene (0.25 M). The resulting reaction mixture was heated at 110 °C for 4 hours. The reaction was allowed to cool to room temperature, diluted with H_2O (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organics was dried over $MgSO_4$ and concentrated under vacuum. Flash column chromatography (hexanes/EtOAc = 90% → 80% → 70%) was performed to give the pure product as a mixture of two diastereomers.

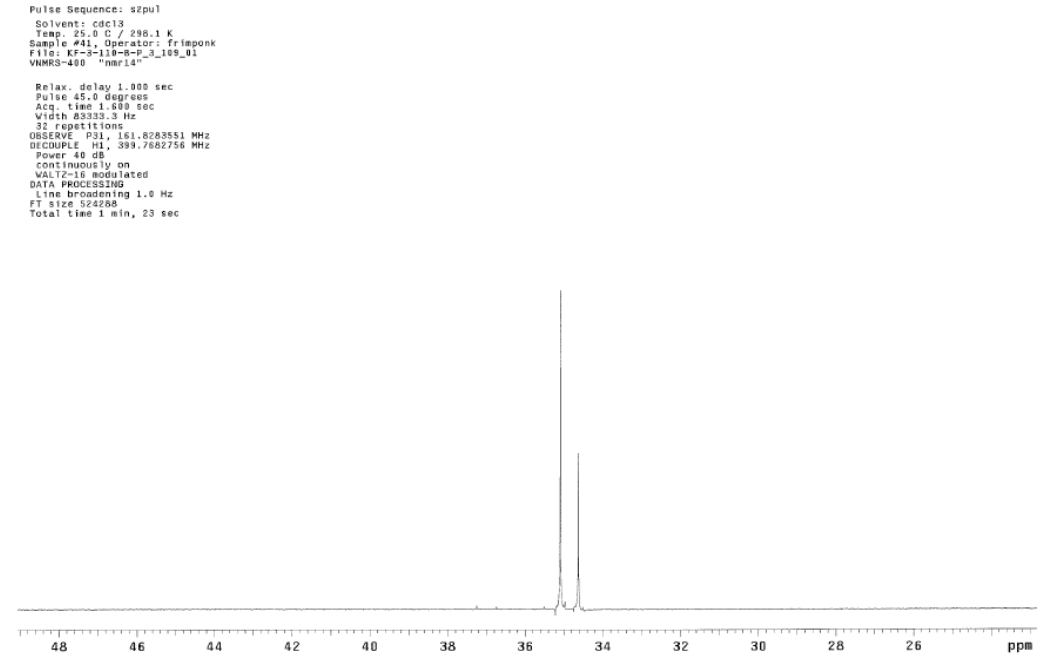


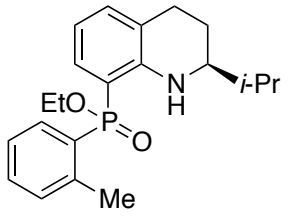
Ethyl((*S*)-2-isopropyl-1,2,3,4-tetrahydroquinolin-8-yl)(2-methoxyphenyl)phosphinate (mixture of two diastereomers). The phosphinate was synthesized from ethyl (2-methoxyphenyl)phosphinate (2.32 g, 11.6

mmol; see below for synthesis) and was obtained as clear oil that solidifies on standing in freezer (2.05 g, 71%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.88-7.78 (m, 1H), 7.44-7.39 (t, 1H, *J* = 8.4), 7.16-7.08 (m, 1H), 7.00-6.93 (m, 2H), 6.82-6.81 (m, 1H), 6.42-6.35 (m, 1H), 4.16-4.00 (m, 2H), 3.72 (s, 3H), 3.12-3.02 (m, 1H), 2.78-2.62 (m, 2H), 1.85-1.45 (m, 3H), 1.36-1.32 (m, 3H), 1.02-1.00 (d, 3H, *J* = 6.9), 0.96-0.94 (d, 3H, *J* = 6.9); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 161.6, 161.2, 149.9, 149.7, 134.4, 134.3, 134.0, 133.9, 132.7, 131.6, 131.5, 131.4, 121.7, 121.6, 120.6, 120.5, 113.9, 113.8, 111.7, 111.6, 111.57, 111.49, 110.0, 109.9, 108.6, 108.5, 60.8, 60.7, 57.5, 57.2, 55.9, 55.7, 33.0, 32.8, 27.5, 27.4, 23.9, 18.9, 18.6, 18.5, 16.7, 16.6; **^{31}P NMR** ($CDCl_3$, 160 MHz) δ 35.1, 34.6; **IR**: 3317.4, 3066.5, 2958.1, 2872.7, 2837.9, 1737.2, 1591.4, 1512.7, 1476.7, 1460.4, 1332.0, 1274.9, 1245.6, 1022.4, 948.1, 825.1, 802.7, 756.7, 738.7, 693.4, 523.4; **HRMS** (DART-TOF) calcd. for $C_{21}H_{28}NO_3P[M+H]^+$: 374.1888, found: 374.1891.

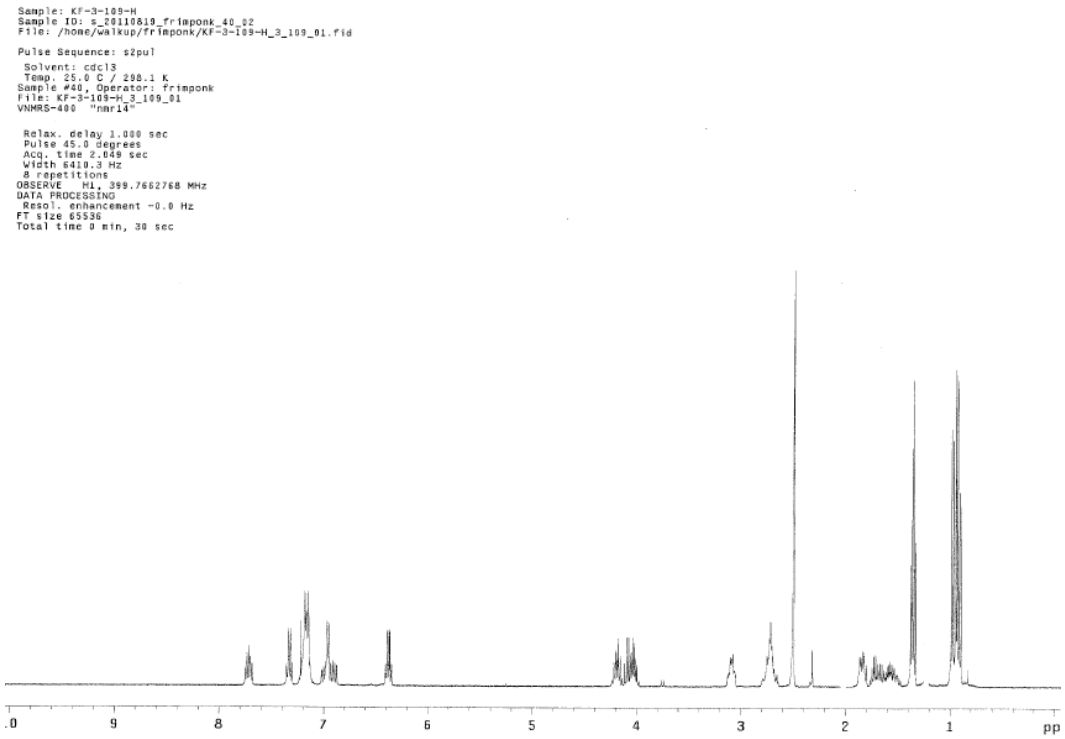


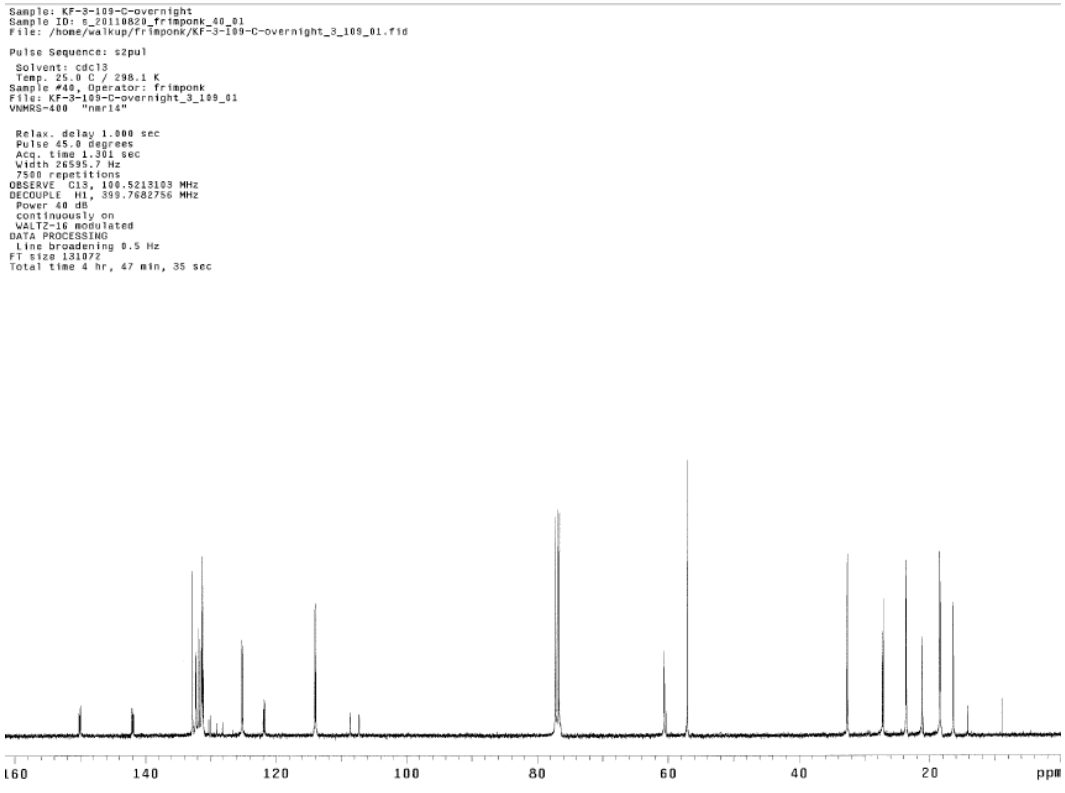

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #41, Operator: frimponk
File: KF-3-110-C-overnight_3_110_01
VNMRS-400 "nmr14"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.301 sec
Width 26585.7 Hz
7580 repetitions
OBSERVE C13, 100.5213103 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 4 hr, 47 min, 35 sec
160
140
120
100
80
60
40
20
ppm

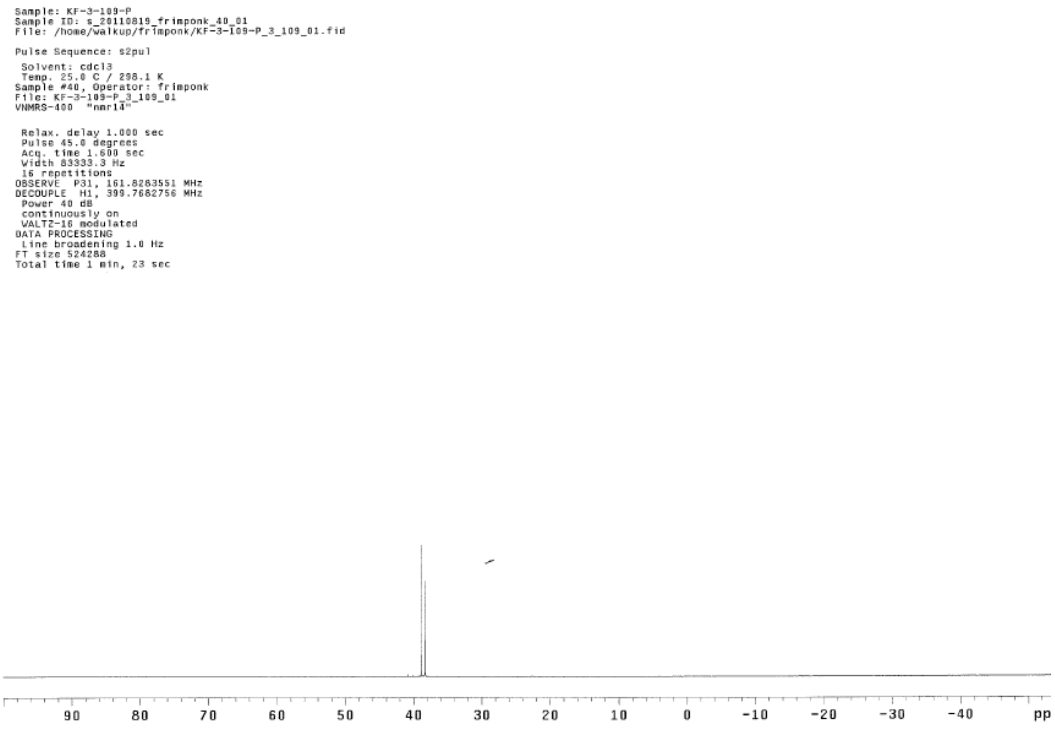

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #41, Operator: frimponk
File: KF-3-110-B-P_3_109_01
VNMRS-400 "nmr14"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 83333.3 Hz
32 repetitions
OBSERVE P31, 161.8283551 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 524288
Total time 1 min, 23 sec
48
46
44
42
40
38
36
34
32
30
28
26
ppm

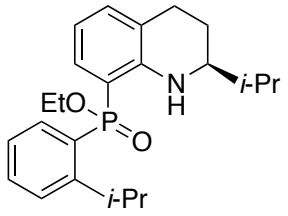


Ethyl ((*S*)-2-isopropyl-1,2,3,4-tetrahydroquinolin-8-yl)(*o*-tolyl)phosphinate (mixture of two diastereomers). The phosphinate was synthesized from ethyl *o*-tolylphosphinate (1.84 g, 9.96 mmol; see below for synthesis) and was obtained as clear oil (2.11 g, 89%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.75-7.68 (m, 1H), 7.36-7.31 (m, 1H), 7.19-7.14 (m, 2H), 7.02-6.88 (m, 2H), 6.41-6.35 (m, 1H), 4.24-4.14 (m, 1H), 4.06-3.98 (m, 1H), 3.13-3.05 (m, 1H), 2.75-2.66 (m, 2H), 2.50 (s, 3H), 1.88-1.80 (m, 1H), 1.75-1.50 (m, 2H), 1.34-1.33 (d, 3H, J = 7.0), 0.99-0.90 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 150.4, 150.3, 150.2, 150.1, 142.3, 142.2, 142.1, 142.0, 133.0, 132.4, 132.0, 131.6, 131.5, 125.4, 125.3, 122.14, 122.05, 122.0, 121.9, 114.2, 114.1, 108.8, 108.7, 107.5, 107.4, 60.8, 60.5, 57.3, 32.9, 32.8, 27.4, 27.3, 23.8, 23.7, 21.4, 21.3, 18.7, 18.6, 18.56, 18.54, 16.6, 16.5 ; **^{31}P NMR** ($CDCl_3$, 160 MHz) δ 38.9, 38.3; **IR**: 3308.5, 2958.4, 2930.7, 2872.2, 1738.2, 1594.0, 1511.3, 1460.0, 1428.0, 1284.3, 1191.5, 1026.3, 945.9, 824.5, 806.7, 752.2, 739.5, 717.1, 691.2, 606.3, 571.3, 536.5, 481.9; **HRMS** (DART-TOF) calcd. for $C_{21}H_{28}NO_2P$ $[M+H]^+$: 358.1936, found: 358.1931.


Sample: KF-3-109-H
Sample ID: s_20110819_frimponk_40_02
File: /home/walkup/frimponk/KF-3-109-H_3_109_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #40, Operator: frimponk
File: KF-3-109-H_3_109_01
VNMRS-400 "nmr14"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7662768 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
.0
9
8
7
6
5
4
3
2
1
pp


Sample: KF-3-109-C-overnight
Sample ID: s_20110820_frimponk_40_01
File: /home/walkup/frimponk/KF-3-109-C-overnight_3_109_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #40, Operator: frimponk
File: KF-3-109-C-overnight_3_109_01
VNMRS-400 "nmr14"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.301 sec
Width 26595.7 Hz
7500 repetitions
OBSERVE C13, 100.5213103 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 4 hr, 47 min, 35 sec
160
140
120
100
80
60
40
20
ppm





Ethyl ((*S*)-2-isopropyl-1,2,3,4-tetrahydroquinolin-8-yl)(2-isopropylphenyl)phosphinate (mixture of two diastereomers). The phosphinate was synthesized from ethyl (2-isopropylphenyl)phosphinate (0.657 g, 3.5 mmol; see below for synthesis) and was obtained as a clear oil (0.744 g, 28%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.79-7.68 (m, 1H), 7.46-7.33 (m, 2H), 7.20-7.13 (m, 2H), 6.98-6.89 (m, 2H), 6.40-6.34 (m, 1H), 4.25-4.17 (m, 1H), 4.07-4.00 (m, 1H), 3.74-3.62 (m, 1H), 3.16-3.04 (m, 1H), 2.82-2.64 (m, 2H), 1.92-1.82 (m, 1H), 1.76-1.48 (m, 2H), 1.39-1.34 (m, 3H), 1.24-1.16 (m, 3H), 0.99-0.86 (m, 9H); **^{31}P NMR** ($CDCl_3$, 160 MHz) δ 36.2, 35.2.

Sample Name:
KF-3-025-column-f4-H
Archive directory:

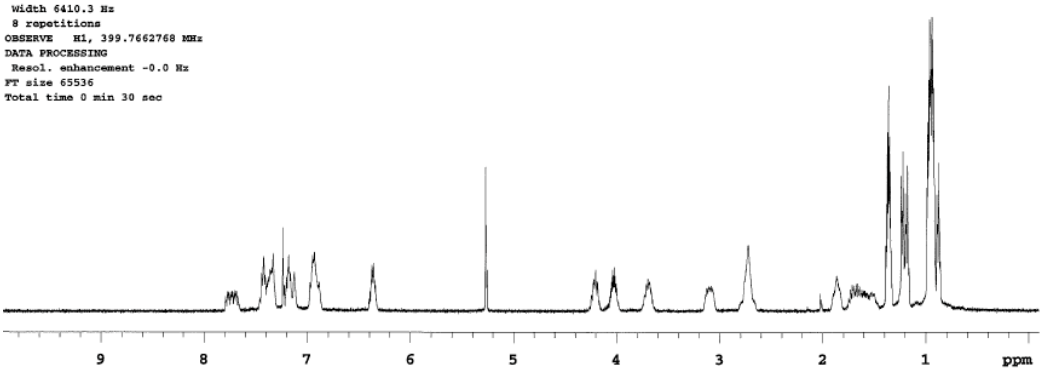
Sample directory:

FidFile: KF-3-025-column-f4-H_3_25_01

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 19 2011

Temp. 25.0 C / 298.1 K
Sample #40, Operator: frimponk
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7662768 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec



Sample Name:
KF-3-025-column-f4-P
Archive directory:

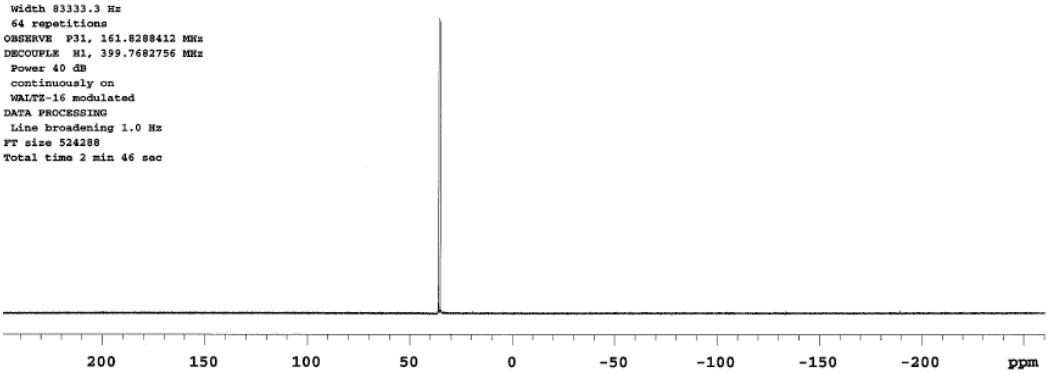
Sample directory:

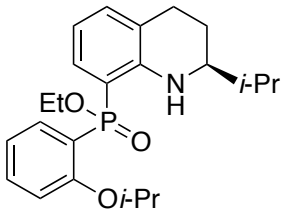
FidFile: KF-3-025-column-f4-P_3_25_01

Pulse Sequence: Phosphorus (s2pul)
Solvent: cdcl3
Data collected on: Mar 19 2011

Temp. 25.0 C / 298.1 K
Sample #40, Operator: frimponk
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 83333.3 Hz
64 repetitions
OBSERVE P31, 161.8288412 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 524288
Total time 2 min 46 sec





Ethyl (2-isopropoxyphenyl)((*S*)-2-isopropyl-1,2,3,4-tetrahydroquinolin-8-yl)phosphinate (mixture of two diastereomers). The phosphinate was synthesized from ethyl (2-isopropoxyphenyl)phosphinate (2.44 g, 10.7 mmol; see below for synthesis) and was obtained as a clear oil that solidifies on standing in freezer (2.26 g, 79%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.01-7.96 (dd, 0.5H, *J* = 13.5, 7.6), 7.93-7.89 (dd, 0.5H, *J* = 13.5, 7.6), 7.41-7.39 (t, 1H, *J* = 7.8), 7.37-7.32 (dd, 0.5H, *J* = 14.4 ,6.6), 7.20-7.01 (d, 1H, *J* = 95.9), 7.17-7.13 (dd, 0.5H, *J* = 15.2, 7.8), 6.97-6.93 (m, 2H), 6.84-6.80 (m, 1H), 6.44-6.40 (m, 0.5H), 6.38-6.35 (m, 0.5H), 4.59-4.52 (m, 1H), 4.16-3.99 (m, 2H), 3.11-3.04 (m, 1H), 2.79-2.62 (m, 2H), 1.86-1.45 (m, 3H), 1.38-1.34 (m, 3H), 1.20-1.19 (d, 3H, *J* = 6.1), 1.05-0.91 (m, 9H); **^{31}P NMR** ($CDCl_3$, 200 MHz) δ 31.5, 31.0.

Sample Name:
KF-3-030-column
Archive directory:

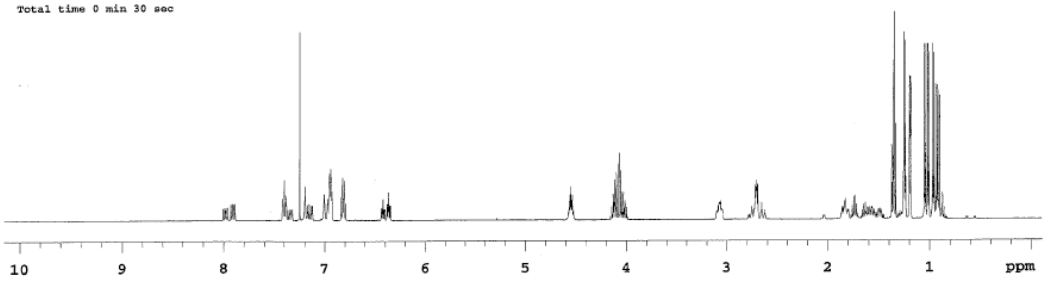
Sample directory:

FidFile: KF-3-030-column-H

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 28 2011

Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8808020 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec



Sample Name:
KF-3-030-column-P
Archive directory:

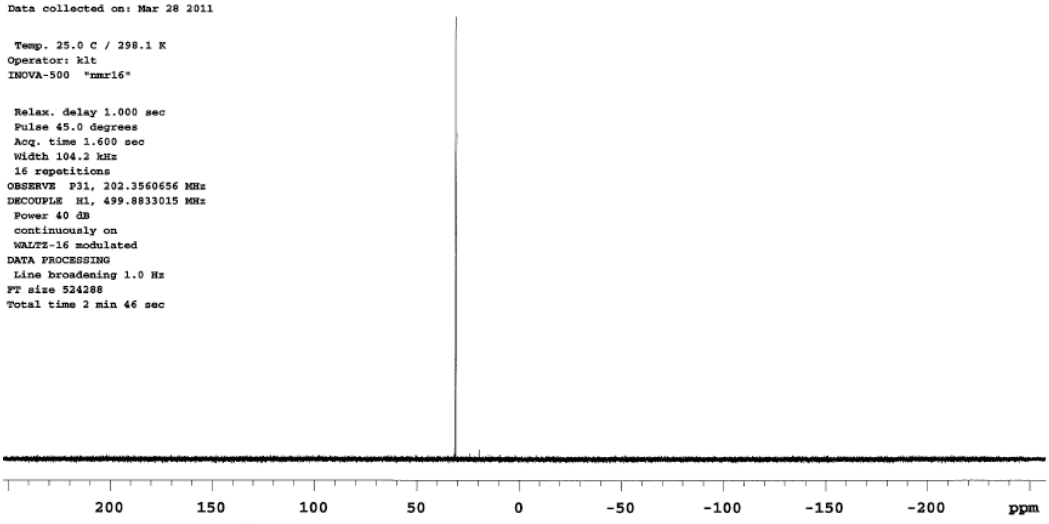
Sample directory:

FidFile: KF-3-030-column-P

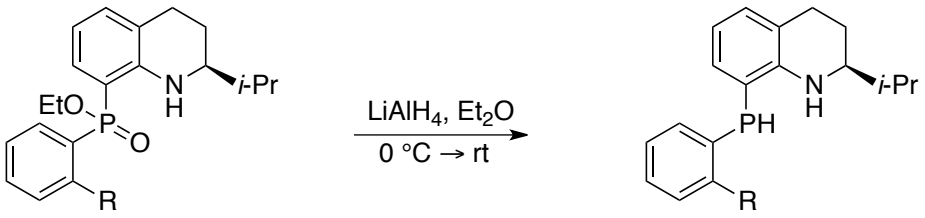
Pulse Sequence: Phosphorus (s2pul)
Solvent: cdcl3
Data collected on: Mar 28 2011

Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"

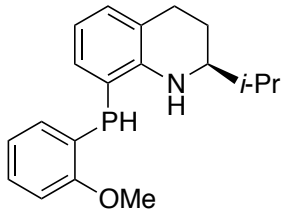
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 104.2 kHz
16 repetitions
OBSERVE P31, 202.3560656 MHz
DECOUPLE H1, 499.8833015 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 524288
Total time 2 min 46 sec



LiAlH$_4$ Reduction

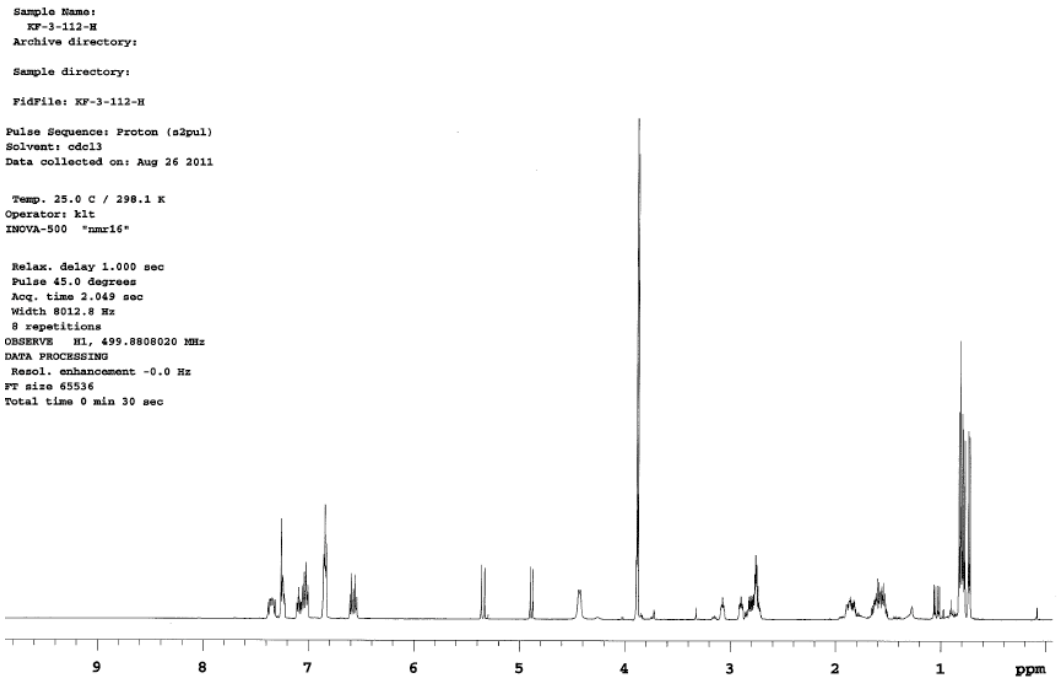


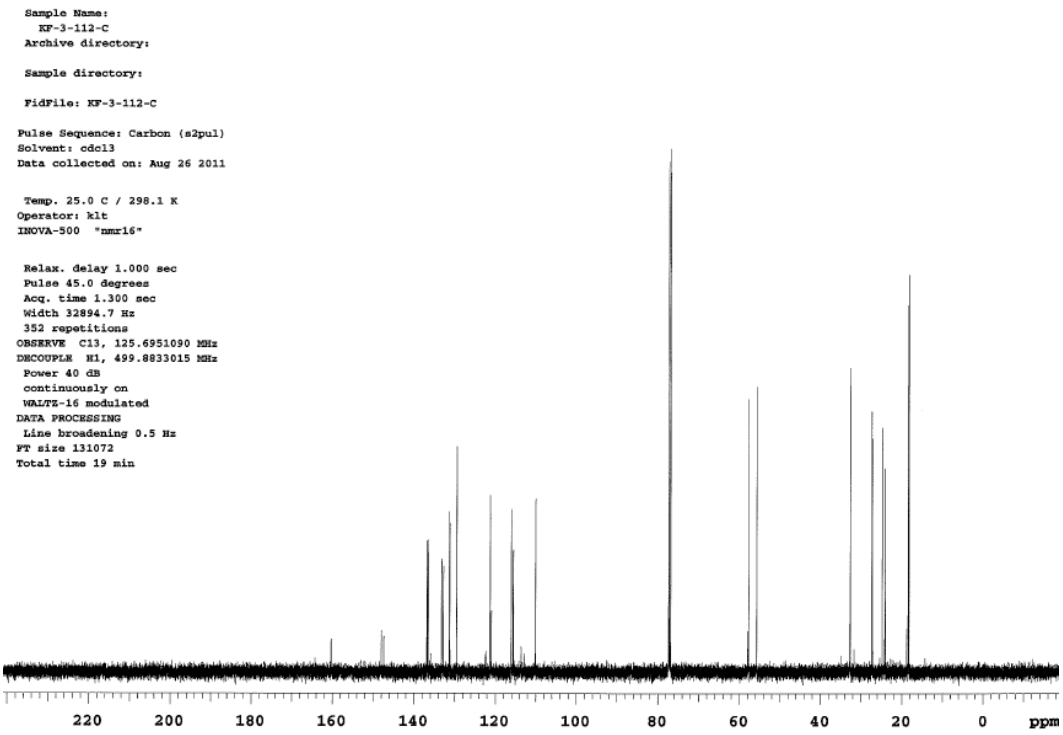
General Procedure. To a flame dried round bottom flask with stir bar was added $LiAlH_4$ (4 equiv.) in a glovebox. To this, Et_2O (0.2 M) was added and cooled to -78 °C. The corresponding phosphinate (1 equiv.) was added dropwise as a solution in Et_2O (0.2 M). The resulting mixture was stirred for 5 minutes at -78 °C and 45 minutes at room temperature. The reaction was quenched with 6 M NaOH (0.18 M), filtered over celite to trap the lithium salts. The filtrate was extracted with CH_2Cl_2 (3 x 100 mL), dried over $MgSO_4$ and concentrated under vacuum. Flash column chromatography (hexanes/EtOAc = 95%) was performed to obtain the pure secondary phosphine (Note: purify over basic alumina because silica gel cleaves the C–P bond; store under inert atmosphere or under vacuum).

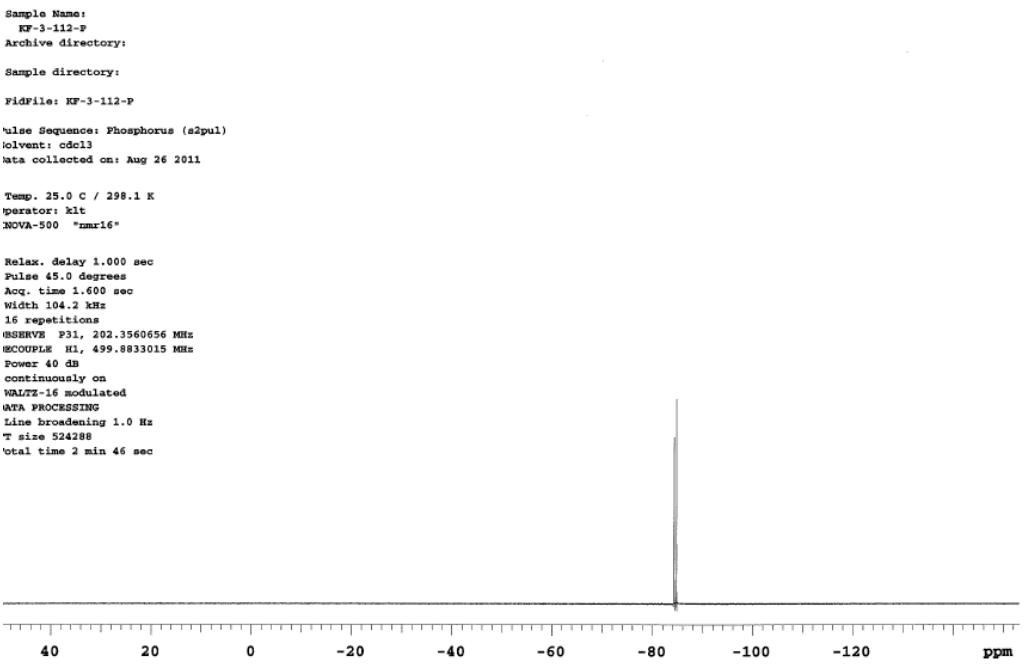


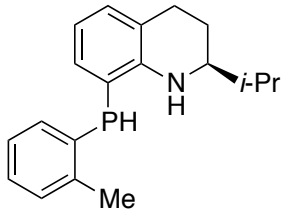
(*S*)-2-Isopropyl-8-((2-methoxyphenyl)phosphino)-1,2,3,4-tetrahydroquinoline (mixture of two diastereomers). The title compound was synthesized from ethyl((*S*)-2-isopropyl-1,2,3,4-tetrahydroquinolin-8-yl)(2-methoxyphenyl)phosphinate (2.00 g, 5.36 mmol) and obtained as a clear oil (1.03 g, 61%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.38-7.32 (m, 1H), 7.26-7.23 (m, 1H), 7.11-

7.01 (m, 2H), 6.85-6.83 (m, 2H), 6.61-6.54 (m, 1H), 5.36-4.87 (dd, 1H, *J* = 230.6, 14.6), 4.43 (bs, 1H), 3.89 (d, 3H, *J* = 5.6), 3.09-3.06 (m, 0.5H), 2.90-2.88 (m, 0.5H), 2.85-2.72 (m, 2H), 1.90-1.81 (m, 1H), 1.66-1.50 (m, 2H), 0.83-0.72 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 160.4, 160.3, 148.1, 148.0, 147.5, 147.4, 136.9, 136.8, 136.7, 136.5, 133.3, 133.2, 132.8, 132.7, 131.4, 131.2, 129.5, 121.3, 121.0, 116.2, 116.1, 116.1, 116.03, 115.7, 115.6, 110.2, 110.1, 57.7, 55.8, 32.7, 32.6, 27.4, 27.2, 24.8, 24.0, 18.4, 18.3, 18.2; **^{31}P NMR** ($CDCl_3$, 200 MHz) δ -84.3, -84.8; **IR**: 3412.9, 3059.6, 3002.9, 2956.3, 2930.1 2870.5, 2834.0, 1586.5, 1574.0, 1490.0, 1456.5, 1430.0, 1236.5, 1208.3, 1074.5, 1041.3, 736.6, 712.3, 548.8; **HRMS** (DART-TOF) calcd. for $C_{19}H_{24}NOP[M+H]^+$: 314.1674, found: 314.1678.

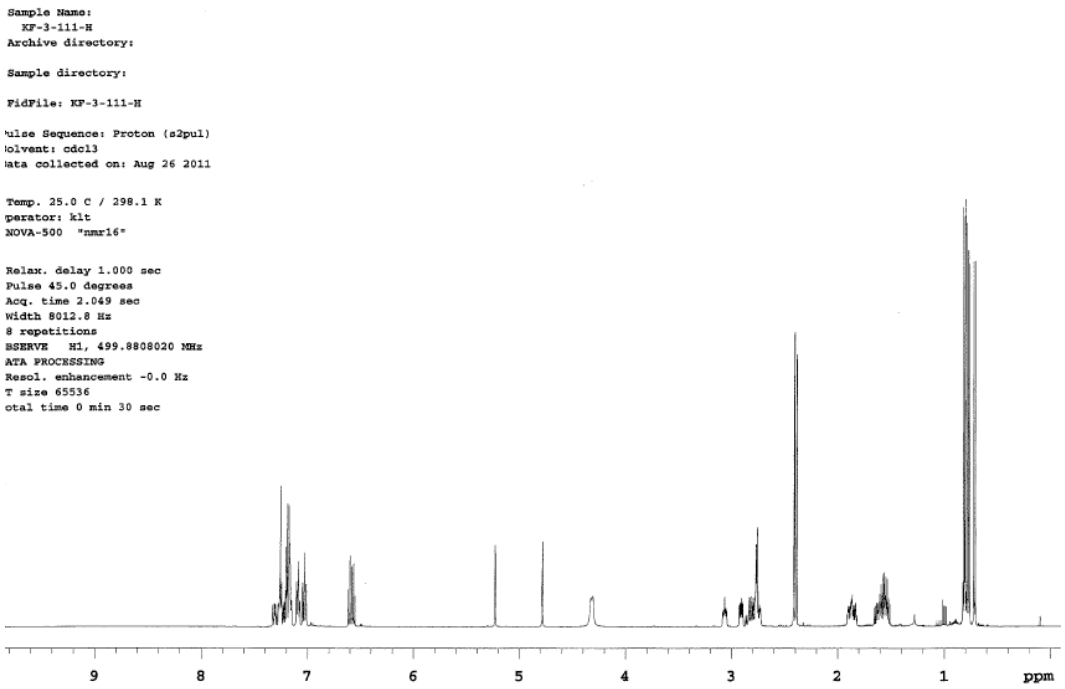


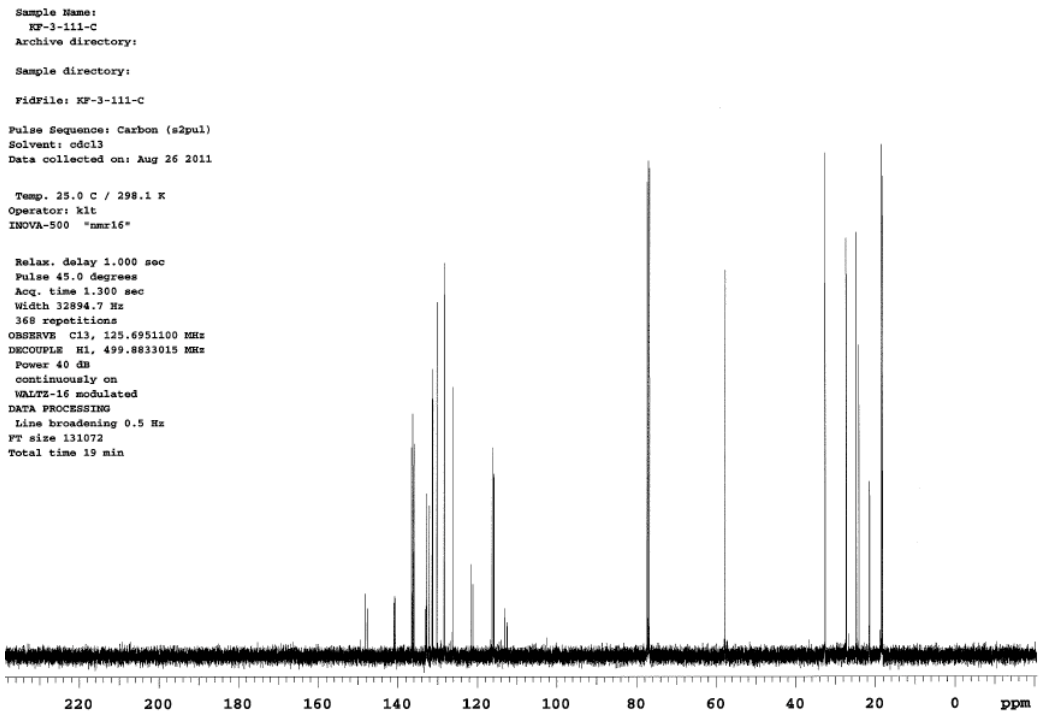

Sample Name:
KF-3-112-C
Archive directory:
Sample directory:
FidFile: KF-3-112-C
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Aug 26 2011
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 32894.7 Hz
352 repetitions
OBSERVE C13, 125.6951090 MHz
DECOUPLE H1, 499.8833015 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min
220
200
180
160
140
120
100
80
60
40
20
0
ppm

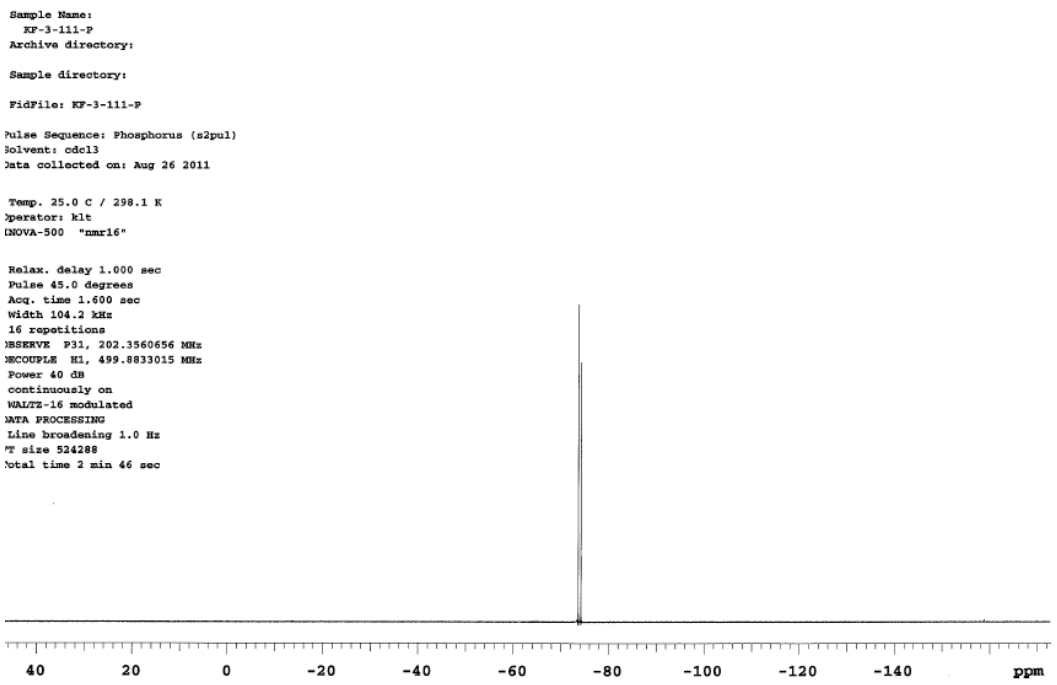

Sample Name:
KF-3-112-P
Archive directory:
Sample directory:
FidFile: KF-3-112-P
ulse Sequence: Phosphorus (s2pul)
olvent: cdcl3
ata collected on: Aug 26 2011
Temp. 25.0 C / 298.1 K
perator: klt
NOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 104.2 kHz
16 repetitions
BSERVE P31, 202.3560656 MHz
ECOUPLE H1, 499.8833015 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
ATA PROCESSING
Line broadening 1.0 Hz
T size 524288
otal time 2 min 46 sec
40
20
0
-20
-40
-60
-80
-100
-120
ppm

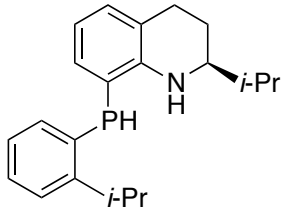


(*S*)-2-Isopropyl-8-(*o*-tolylphosphino)-1,2,3,4-tetrahydroquinoline (mixture of two diastereomers). The title compound was synthesized from ethyl ((*S*)-2-isopropyl-1,2,3,4-tetrahydroquinolin-8-yl)(*o*-tolyl)phosphinate (2.1 g, 5.88 mmol) and obtained as a clear oil (1.32 g, 75%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.33-7.16 (m, 4H), 7.11-7.08 (t, 1H, *J* = 7.6), 7.05-7.02 (t, 1H, *J* = 8.3), 6.62-6.55 (m, 1H), 5.24-4.79 (d, 1H, *J* = 223.8), 4.33 (bs, 1H), 3.08-3.05 (m, 0.5H), 2.93-2.89 (m, 0.5H), 2.86-2.73 (m, 2H), 2.41-2.39 (d, 3H, *J* = 11.3), 1.91-1.82 (m, 1H), 1.66-1.52 (m, 2H), 0.82-0.71 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 148.2 (d, *J* = 4.0), 147.6 (d, *J* = 4.5), 140.9 (d, *J* = 16.1), 140.7 (d, *J* = 15.6), 136.5, 136.3, 136.1, 135.9, 133.1, 132.98, 132.90, 132.8, 132.74, 132.1 (d, *J* = 7.5), 131.4, 131.2, 130.2, 128.4, 128.3, 126.2, 121.6, 121.2, 116.3 (d, *J* = 12.1), 115.9 (d, *J* = 11.5), 113.1 (d, *J* = 9.5), 112.6 (d, *J* = 10), 57.8 (d, *J* = 7.5), 32.7, 32.6, 27.4, 27.2, 24.8, 24.1, 21.6 (d, *J* = 5.0), 21.4 (d, *J* = 5.0), 18.5, 18.2 (d, *J* = 4.5), 18.1; **^{31}P NMR** ($CDCl_3$, 200 MHz) δ -73.6, -74.2; **IR**: 3415.2, 3054.7, 3004.9, 2956.7, 2930.0, 2870.1, 2269.3, 1587.5, 1488.9, 1455.0, 1199.2, 1157.0, 741.3, 521.0; **HRMS** (DART-TOF) calcd. for $C_{19}H_{24}NP[M+H]^+$: 298.1725, found: 298.1717.

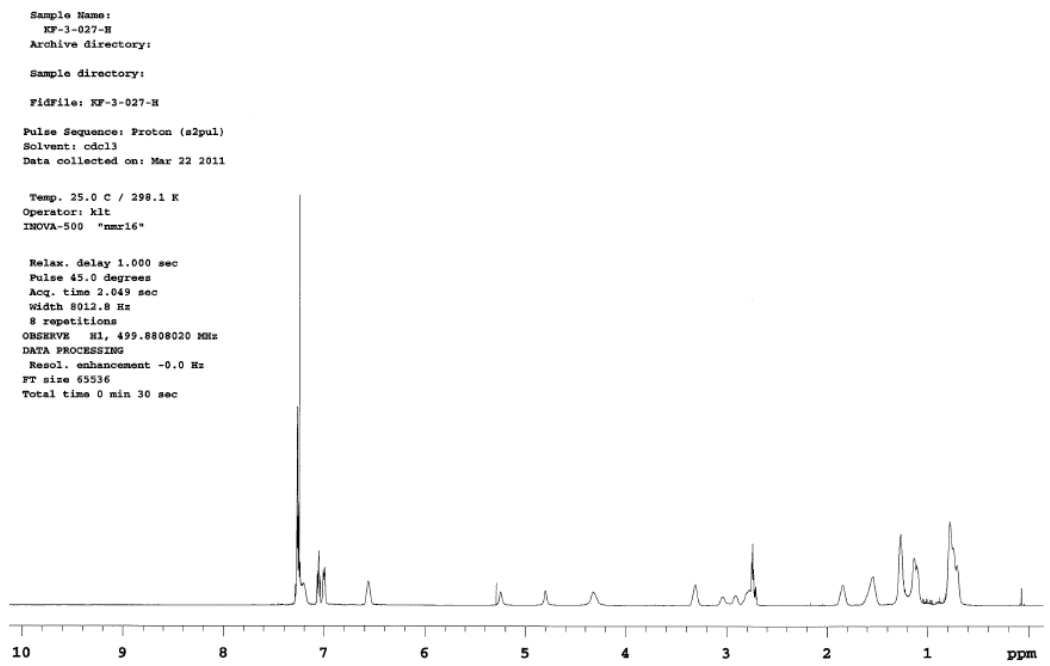

Sample Name:
KF-3-111-H
Archive directory:
Sample directory:
FidFile: KF-3-111-H
ulse Sequence: Proton (s2pul)
olvent: cdcl3
ata collected on: Aug 26 2011
Temp. 25.0 C / 298.1 K
perator: klt
NOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
BSERVE H1, 499.8808020 MHz
ATA PROCESSING
Resol. enhancement -0.0 Hz
T size 65536
otal time 0 min 30 sec
9
8
7
6
5
4
3
2
1
ppm

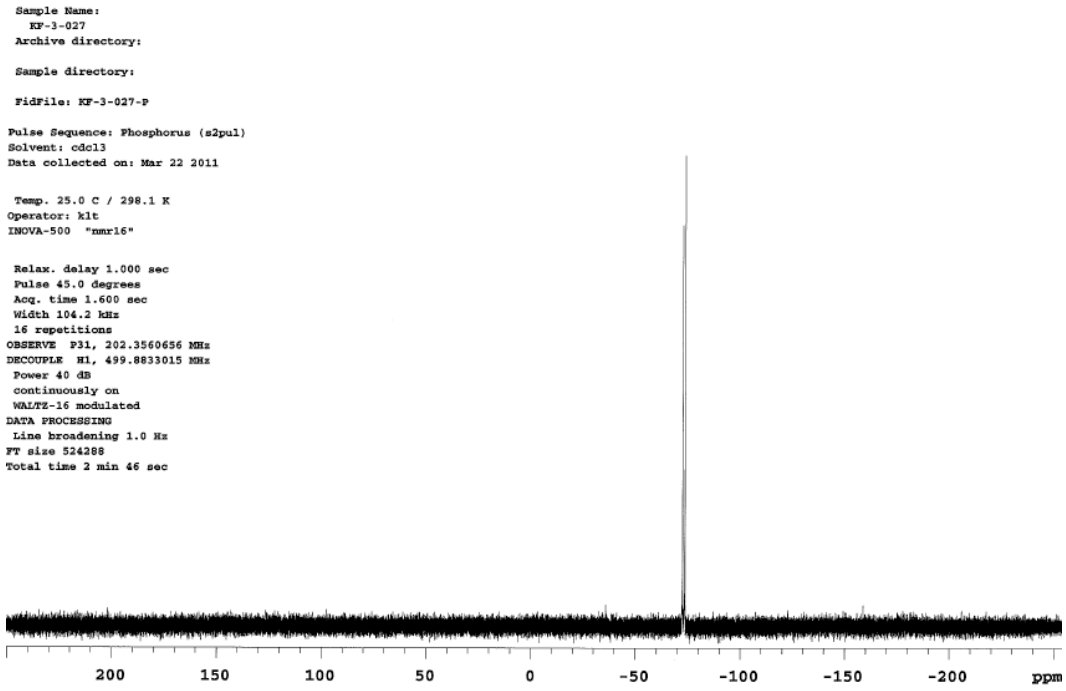

Sample Name:
KF-3-111-C
Archive directory:
Sample directory:
FidFile: KF-3-111-C
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Aug 26 2011
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 32894.7 Hz
368 repetitions
OBSERVE C13, 125.6951100 MHz
DECOUPLE H1, 499.8833015 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min
220
200
180
160
140
120
100
80
60
40
20
0
ppm

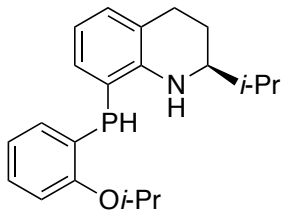




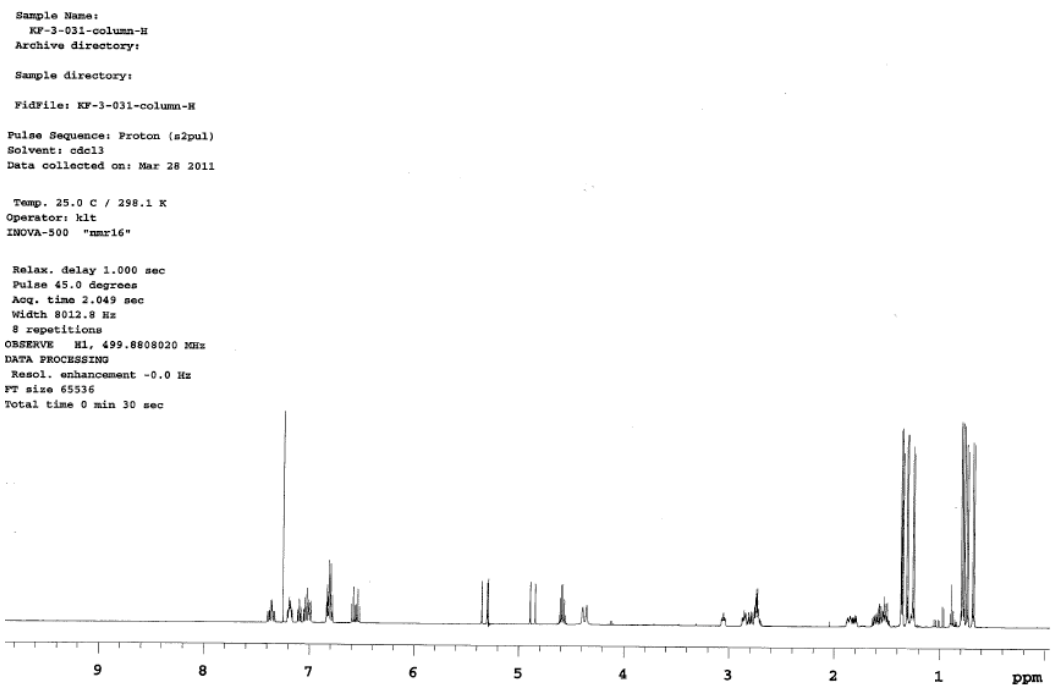
(*S*)-2-Isopropyl-8-((2-isopropylphenyl)phosphino)-1,2,3,4-tetrahydroquinoline (mixture of two diastereomers). The title compound was synthesized from ethyl ((*S*)-2-isopropyl-1,2,3,4-tetrahydroquinolin-8-yl)(2-isopropylphenyl)phosphinate (0.740 g, 1.92 mmol) and was obtained as a clear oil (0.418 g, 67%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.29-7.19 (m, 4H), 7.07-7.04 (m, 1H), 7.01-7.00 (m, 1H), 6.61-6.57 (m, 1H), 5.25-4.80 (d, 1H, J = 224.0), 4.38-4.27 (m, 1H), 3.31-2.70 (m, 4H), 1.85-0.71 (m, 15H); **^{31}P NMR** ($CDCl_3$, 200 MHz) δ -72.4, -73.6.

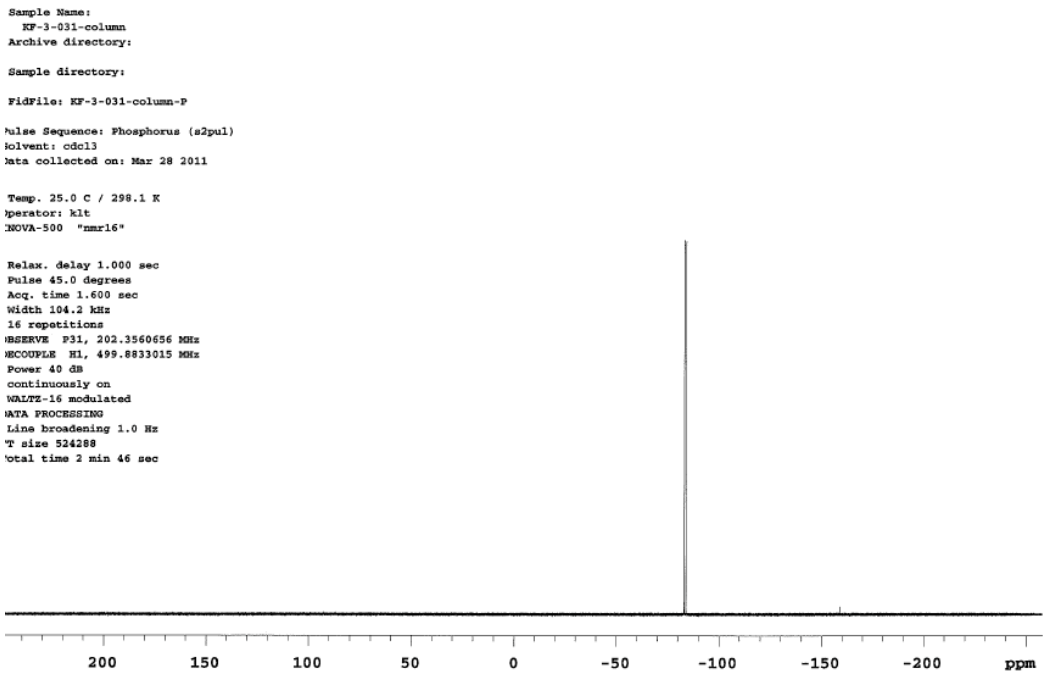

Sample Name:
KF-3-027-H
Archive directory:
Sample directory:
FidFile: KF-3-027-H
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 22 2011
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8808020 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec
10
9
8
7
6
5
4
3
2
1
ppm


Sample Name:
KF-3-027
Archive directory:
Sample directory:
FidFile: KF-3-027-P
Pulse Sequence: Phosphorus (s2pul)
Solvent: cdcl3
Data collected on: Mar 22 2011
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 104.2 kHz
16 repetitions
OBSERVE P31, 202.3560656 MHz
DECOUPLE H1, 499.8833015 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 524288
Total time 2 min 46 sec
200
150
100
50
0
-50
-100
-150
-200
ppm

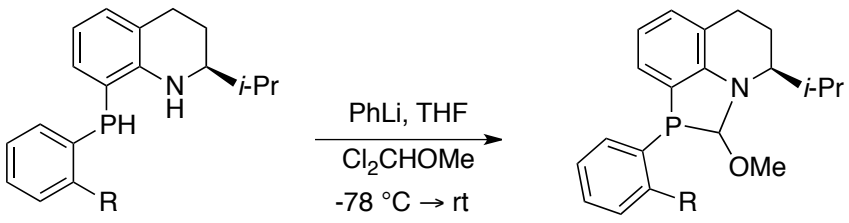

N
H
i-Pr
PH
Oi-Pr

(*S*)-8-((2-Isopropoxyphenyl)phosphino)-2-isopropyl-1,2,3,4-tetrahydroquinoline (mixture of two diastereomers). The title compound was synthesized from ethyl (2-isopropoxyphenyl)((*S*)-2-isopropyl-1,2,3,4-tetrahydroquinolin-8-yl)phosphinate (2.26 g, 5.63 mmol) and was obtained as a clear oil (1.1 g, 57%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.40-7.33 (m, 1H), 7.21-7.17 (m, 1H), 7.11-6.99 (m, 2H), 6.84-6.78 (m, 2H), 6.60-6.52 (m, 1H), 5.35-4.84 (dd, 1H, J = 229.9, 26.4), 4.63-4.55 (m, 1H), 4.39-4.36 (d, 1H, J = 18.3), 3.07-3.03 (m, 0.5H), 2.88-2.84 (m, 0.5H), 2.82-2.69 (m, 2H), 1.89-1.78 (m, 1H), 1.64-1.48 (m, 2H), 1.36-1.24 (m, 6H), 0.80-0.67 (m, 6H); **^{31}P NMR** ($CDCl_3$, 200 MHz) δ -83.1, -83.9.



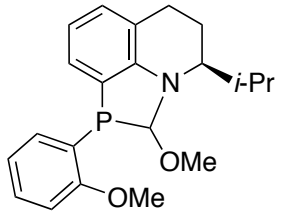


Kinetic Closure

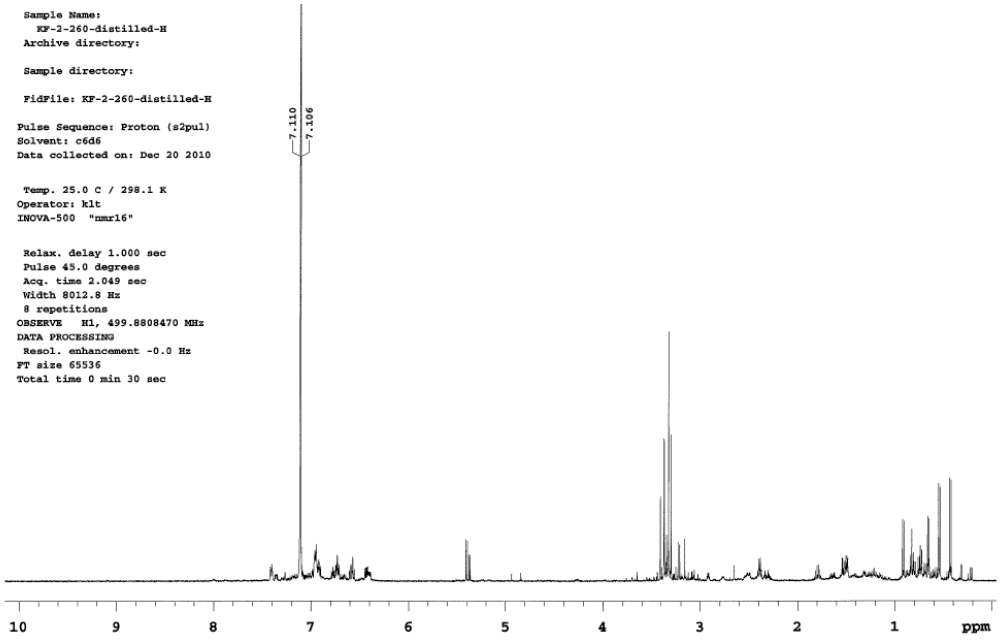


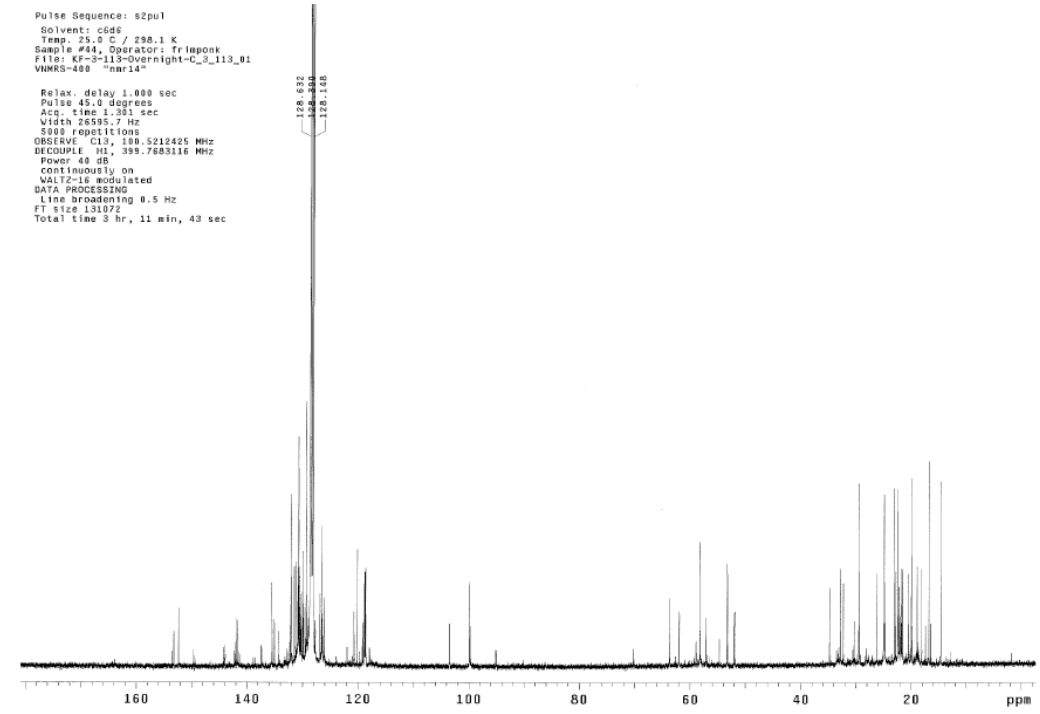
General Procedure. To a flame dried round bottom flask was added the corresponding phosphine as a solution in THF (0.13 M). The solution was cooled to −78 °C and PhLi (2.1 equiv.) was added dropwise. After stirring for 30 minutes the flask was transferred to an ice water bath and stirred for an additional 30 min. The dianion solution was added via syringe pump over 1 hour to a solution of dichloromethyl methylether (1.1 equiv.) in THF (0.03 M) at 0 °C. The reaction was stirred for 150 minutes and the solvent was removed under high vacuum. The resulting residue was brought into a glovebox and extracted with pentane. The

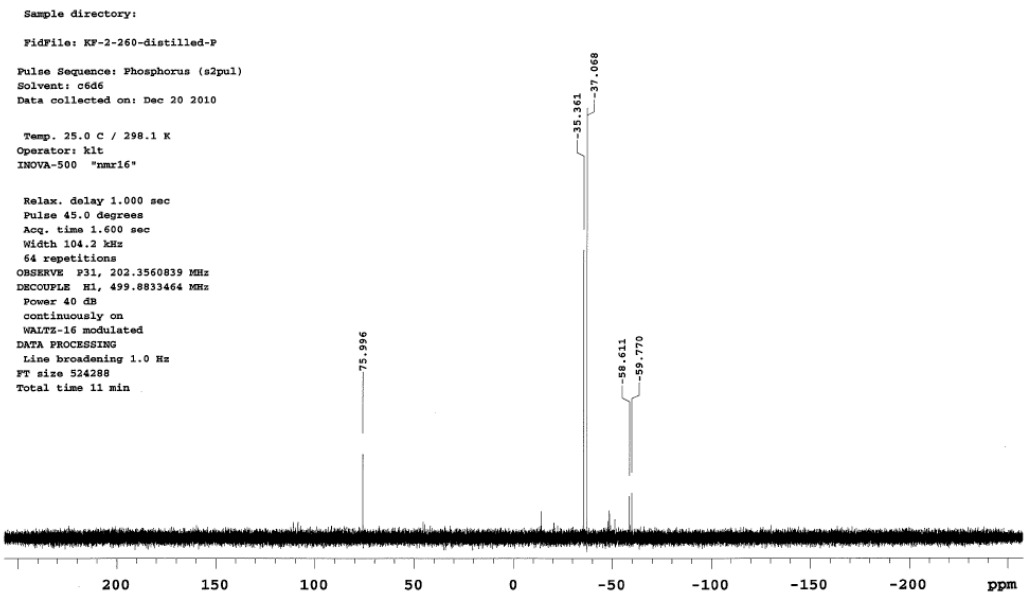
pentane extract was filtered through glass fiber filter paper. The crude mixture was distilled to give the ligand (Note: ligand is stored in glovebox after distillation).

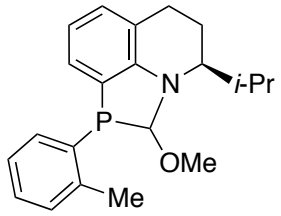


(4*S*)-4-Isopropyl-2-methoxy-1-(2-methoxyphenyl)-2,4,5,6-tetrahydro-1*H*-[1,3]azaphospholo[4,5,1-*ij*]quinoline. The ligand was synthesized from (*S*)-2-Isopropyl-8-((2-methoxyphenyl)phosphino)-1,2,3,4-tetrahydroquinoline (1.03 g, 3.29 mmol) and was obtained as a mixture of four diastereomers that was distilled at 150 °C @ 0.05 mmHg to afford the ligand as a yellow oil (0.206 g, 18%). After distillation the ligand was obtained as a mixture of two diastereomers. ^{31}P NMR shows some impurities. **^{31}P NMR** (C_6D_6, 200 MHz) δ -32.4, -34.1; **IR**: 3293.0, 3056.3, 2957.5, 2870.4, 1744.2, 1722.2, 1678.5, 1583.2, 1455.1, 1062.9, 744.6; **HRMS** (DART-TOF) calcd. for $C_{21}H_{26}NO_2P[M+H]^+$: 340.1830, found: 340.1829.

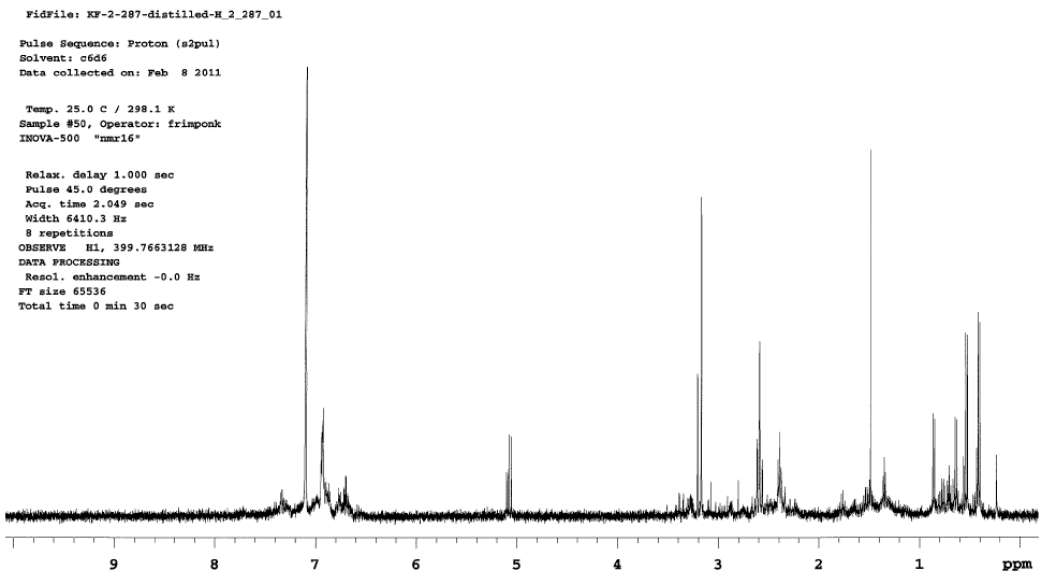

Sample Name:
KF-2-260-distilled-H
Archive directory:
Sample directory:
FidFile: KF-2-260-distilled-H
Pulse Sequence: Proton (s2pul)
Solvent: c6d6
Data collected on: Dec 20 2010
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8808470 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec
7.110
7.106
10
9
8
7
6
5
4
3
2
1
ppm


Pulse Sequence: s2pul
Solvent: c6d6
Temp. 25.0 C / 298.1 K
Sample #44, Operator: frimponk
File: KF-3-113-Overnight-C_3_113_01
VNMRS-400 "nmr14"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.381 sec
Width 26595.7 Hz
5000 repetitions
OBSERVE C13, 100.5212425 MHz
DECOUPLE H1, 399.7683116 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 3 hr, 11 min, 43 sec
128.632
128.390
128.148
160
140
120
100
80
60
40
20
ppm





(4*S*)-4-Isopropyl-2-methoxy-1-(*o*-tolyl)-2,4,5,6-tetrahydro-1*H*-[1,3]azaphospholo[4,5,1-*ij*]quinoline. The ligand was synthesized from (*S*)-2-Isopropyl-8-(*o*-tolylphosphino)-1,2,3,4-tetrahydroquinoline (2.17 g, 7.30 mmol) and was obtained as a mixture of four diastereomers that was distilled at 150 °C @ 0.025 mmHg to afford the ligand as a yellow oil (0.131 g, 5%). After distillation the ligand was obtained as a mixture of 2 diastereomers. ^{31}P NMR shows some impurities. **^{31}P NMR** (C_6D_6 160 MHz) δ -33.6, -34.1; **IR**: 3293.0, 3056.3, 2957.5, 2870.4, 1744.2, 1722.2, 1678.5, 1583.2, 1455.1, 1062.9, 744.6; **HRMS** (DART-TOF) calcd. for $C_{21}H_{26}NOP[M+H]^+$: 356.1779, found: 356.1776.


FidFile: KF-2-287-distilled-H_2_287_01
Pulse Sequence: Proton (s2pul)
Solvent: c6d6
Data collected on: Feb 8 2011
Temp. 25.0 C / 298.1 K
Sample #50, Operator: frimponk
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7663128 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec
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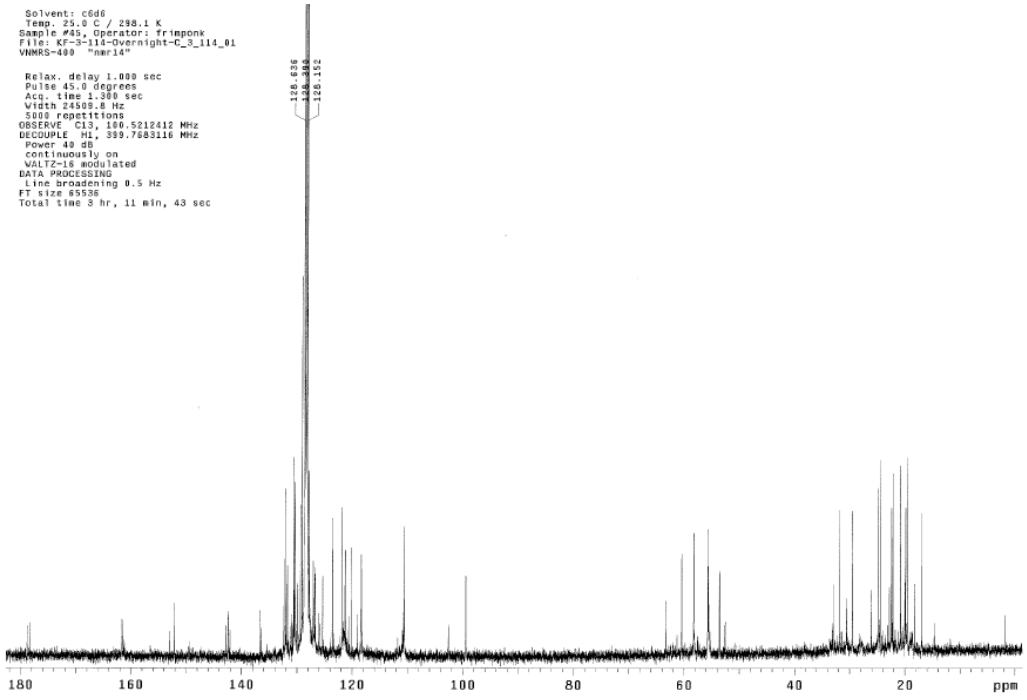
8
7
6
5
4
3
2
1
ppm


Solvent: c6d6
Temp. 25.0 C / 298.1 K
Sample #45, Operator: frimponk
File: KF-3-114-Overnight-C_3_114_01
VNMRS-400 "nmr14"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5212412 MHz
DECOUPLE H1, 399.7683116 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 11 min, 43 sec
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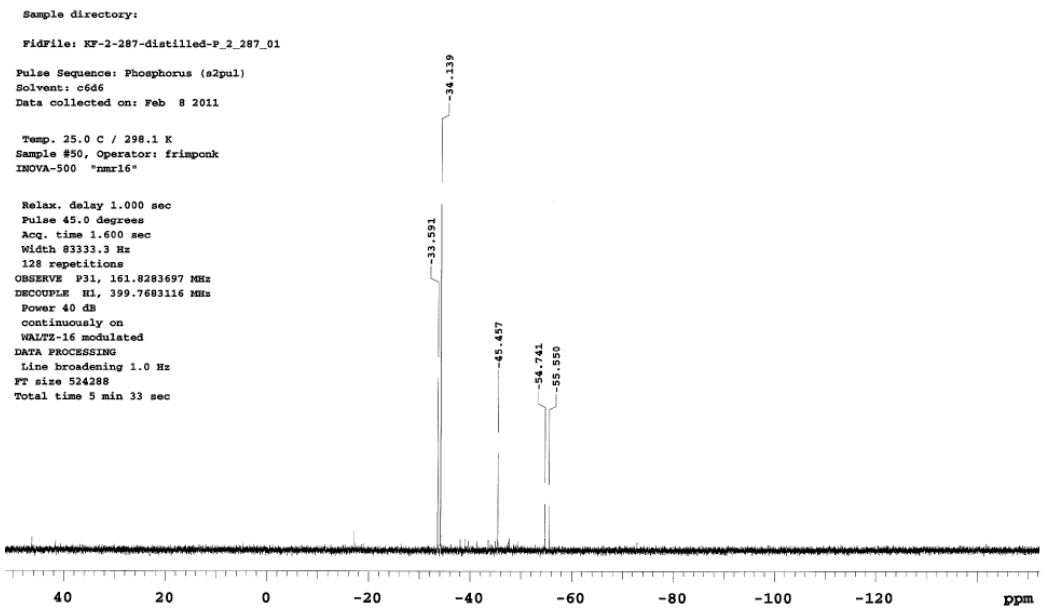
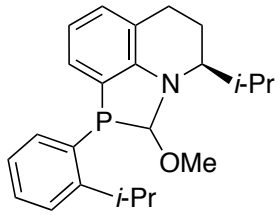
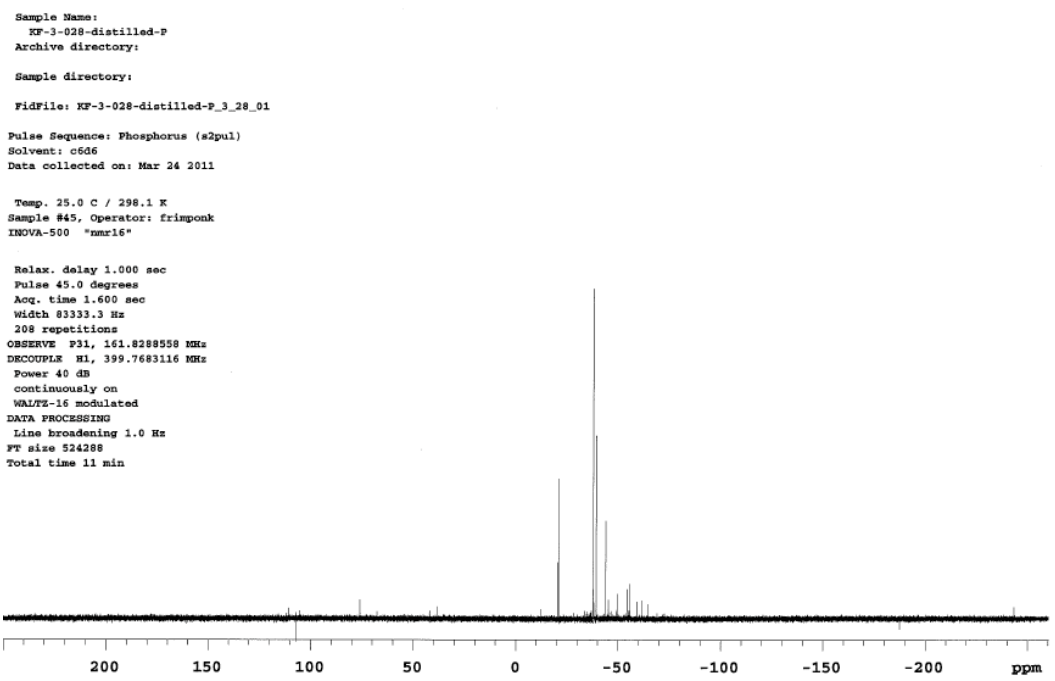
128.369
128.152
180
160
140
120
100
80
60
40
20
ppm





(4*S*)-4-Isopropyl-1-(2-isopropylphenyl)-2-methoxy-2,4,5,6-tetrahydro-1*H*-[1,3]azaphospholo[4,5,1-*ij*]quinoline. The ligand was synthesized from (*S*)-2-isopropyl-8-((2-isopropylphenyl)phosphino)-1,2,3,4-tetrahydroquinoline (0.416 g, 1.28 mmol) and was obtained as a mixture of four diastereomers that was distilled at 150 °C @ 0.025 mmHg to afford the ligand as a yellow oil (0.13 g, 28%). After distillation the ligand was obtained as a mixture of 4 diastereomers. ^{31}P NMR shows some impurities. **^{31}P NMR** (C_6D_6 160 MHz) δ -20.6, -21.3, -37.9, -39.3.


Sample Name:
KF-3-028-distilled-P
Archive directory:
Sample directory:
FidFile: KF-3-028-distilled-P_3_28_01
Pulse Sequence: Phosphorus (s2pul)
Solvent: c6d6
Data collected on: Mar 24 2011
Temp. 25.0 C / 298.1 K
Sample #45, Operator: frimponk
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 83333.3 Hz
208 repetitions
OBSERVE P31, 161.8288558 MHz
DECOUPLE H1, 399.7683116 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 524288
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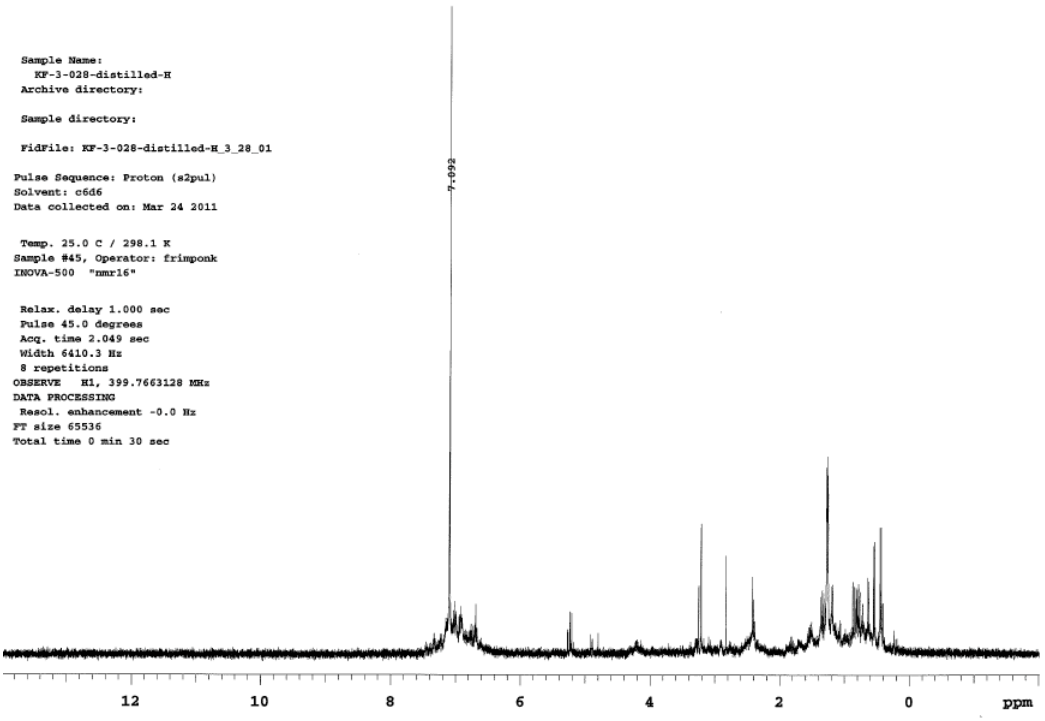
150
100
50
0
-50
-100
-150
-200
ppm


Sample Name:
KF-3-028-distilled-H
Archive directory:
Sample directory:
FidFile: KF-3-028-distilled-H_3_28_01
Pulse Sequence: Proton (s2pul)
Solvent: c6d6
Data collected on: Mar 24 2011
Temp. 25.0 C / 298.1 K
Sample #45, Operator: frimponk
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7663128 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec
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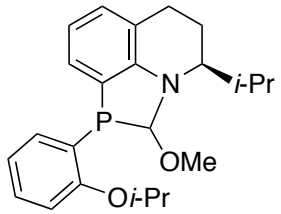
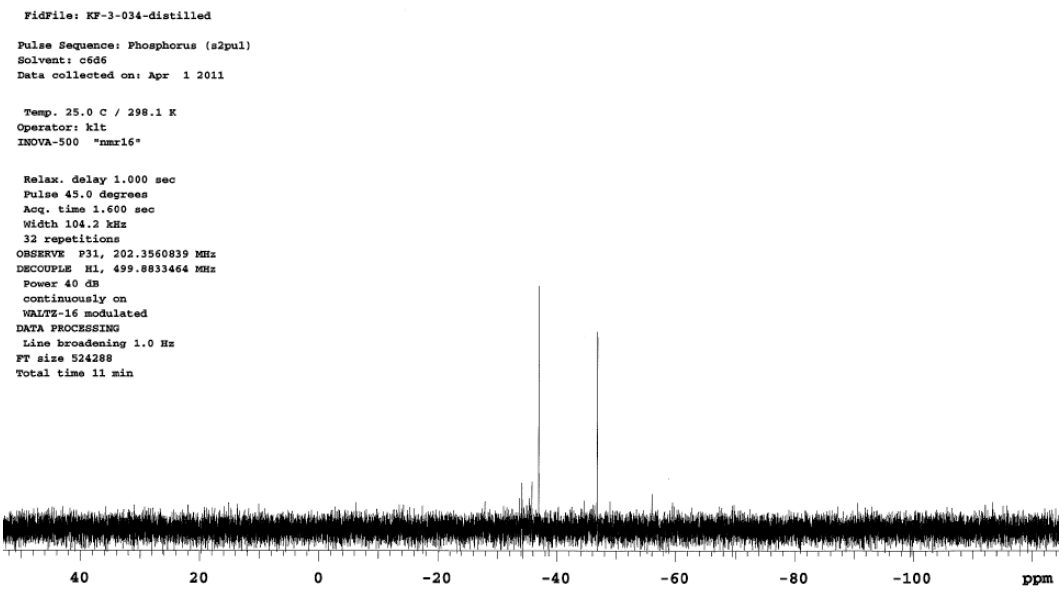
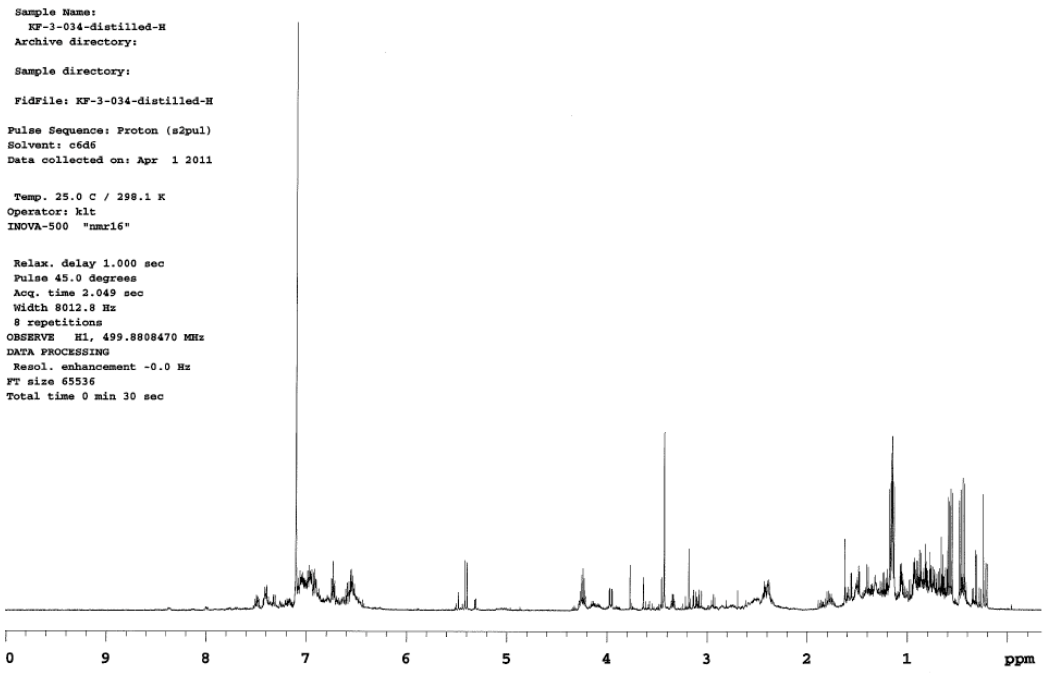
12
10
8
6
4
2
0
ppm

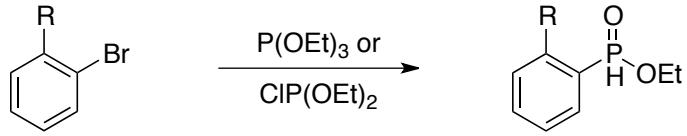


(4*S*)-1-(2-Isopropoxyphenyl)-4-isopropyl-2-methoxy-2,4,5,6-tetrahydro-1*H*-[1,3]azaphospholo[4,5,1-*ij*]quinoline. The ligand was synthesized from (*S*)-8-((2-isopropoxyphenyl)phosphino)-2-isopropyl-1,2,3,4-tetrahydroquinoline (0.88 g, 2.58 mmol) and was obtained as a mixture of four diastereomers that was distilled at 200 °C @ 0.025 mmHg to afford the ligand as a yellow oil (0.15 g, 15%). After distillation the ligand was obtained as a mixture of 3 diastereomers. ^{31}P NMR shows some impurities. **^{31}P NMR** (C_6D_6 200 MHz) δ -34.1, -35.8, -36.9.



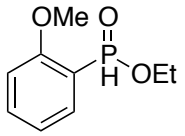


Synthesis of Phosphinates

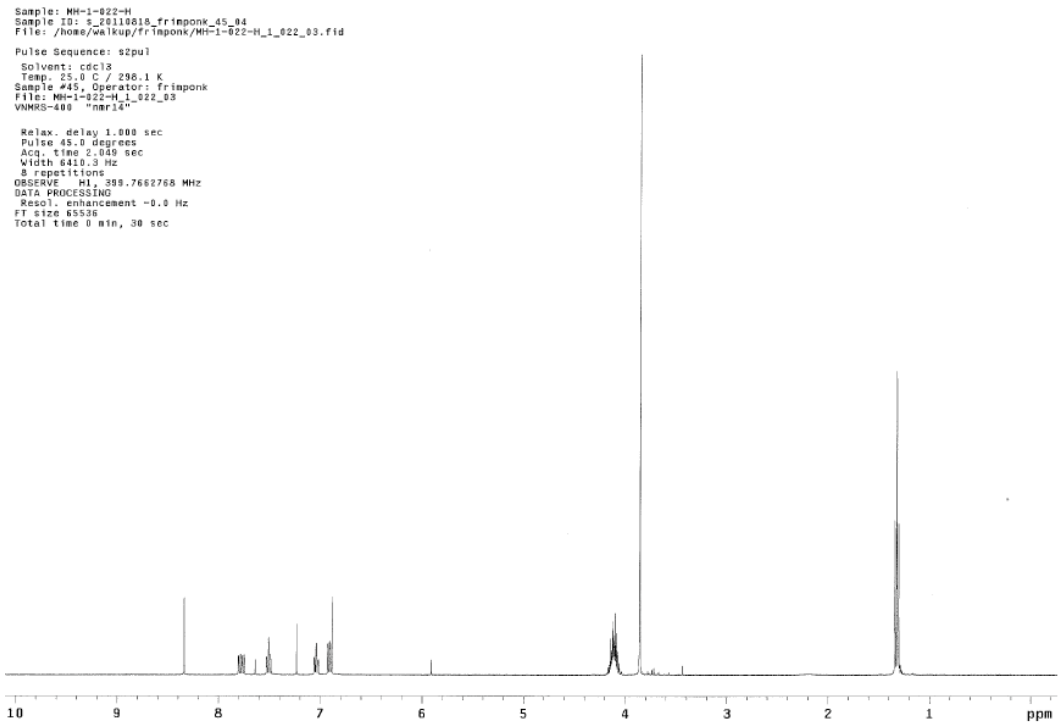


General Procedure.[2] To a flame dried round bottom flask with stir bar was added the corresponding bromobenzene (1 equiv.). To this, Et_2O (0.7 M) was added and the solution was cooled to -78 °C. *t*-BuLi (1.1 equiv.) was added dropwise and the resulting mixture was stirred for 30 minutes at -78 °C. To this mixture was added triethyl phosphite (1.1 equiv.) as a solution in Et_2O (0.7 M) or diethyl chlorophosphite (1.1 equiv.) dropwise. The resulting reaction mixture was allowed to stir overnight while warming to room temperature. The mixture was quenched with 6 N HCl (1.2 equiv.), diluted with H_2O and extracted with $CHCl_3$ (3 x 100 mL). The combined organics was dried over $MgSO_4$ and concentrated under vacuum to afford

the phosphinate. The crude phosphinate was purified by flash column chromatography (CH_2Cl_2:MeOH = 98:2).



Ethyl (2-methoxyphenyl)phosphinate. The phosphinate was synthesized from 1-bromo-2-methoxybenzene (3.33 mL, 26.73 mmol) and triethyl phosphite (5.04 mL, 29.4 mmol) and was obtained as clear liquid (1.2 g, 22%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.34-6.89 (d, 1H, *J* = 580.8), 7.81-7.75 (dd, 1H, *J* = 14.5, 7.4), 7.53-7.49 (t, 1H, *J* = 8.4), 7.06-7.02 (td, 1H, *J* = 7.4), 6.93-6.91 (d, 1H, *J* = 8.4), 4.14-4.07 (m, 2H), 3.86 (s, 3H), 1.34-1.30 (t, 3H, *J* = 8.8); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 161.3 (d, *J* = 4), 134.8, 133.2, 120.8 (d, *J* = 13.0), 117.9 (d, *J* = 132.3), 110.8 (d, *J* = 6.9), 62.1 (d, *J* = 6.5), 55.7, 16.4 (d, *J* = 6.5); **^{31}P NMR** ($CDCl_3$, 160 MHz) δ 20.9; **IR**: 3466.5, 2982.1, 2940.5, 2840.7, 2372.4, 1591.5, 1479.1, 1438.8, 1277.1, 1220.9, 1182.0, 1163.3, 1040.5, 1018.2, 940.7, 799.3, 758.2, 548.9, 468.4; **HRMS** (DART-TOF) calcd. for $C_9H_{13}O_3P[M+H]^+$: 201.0681, found: 201.0687.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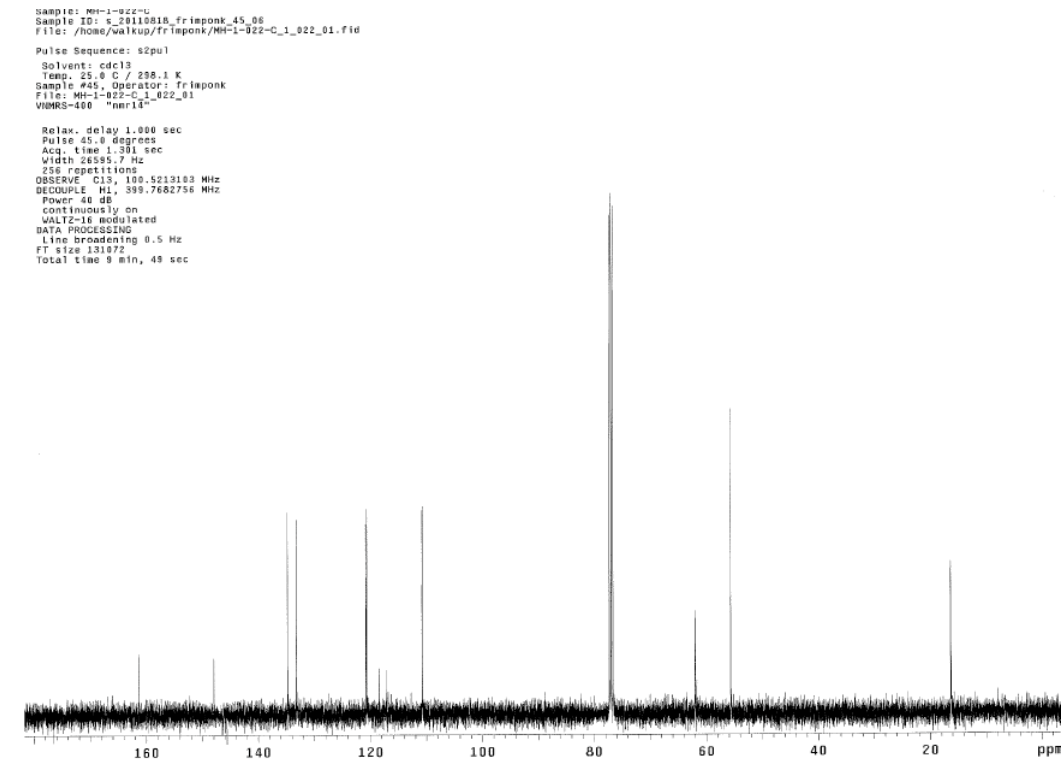
Sample ID: s_20110818_frimponk_45_04
File: /home/walkup/frimponk/MH-1-022-H_1_022_03.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #45, Operator: frimponk
File: MH-1-022-H_1_022_03
VNMRS-400 "nmr14"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7682768 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
10
9
8
7
6
5
4
3
2
1
ppm


Sample: MH-1-022-C
Sample ID: s_20110818_frimponk_45_06
File: /home/walkup/frimponk/MH-1-022-C_1_022_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #45, Operator: frimponk
File: MH-1-022-C_1_022_01
VNMRS-400 "nmr14"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.301 sec
Width 26595.7 Hz
256 repetitions
OBSERVE C13, 100.5213103 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 9 min, 48 sec
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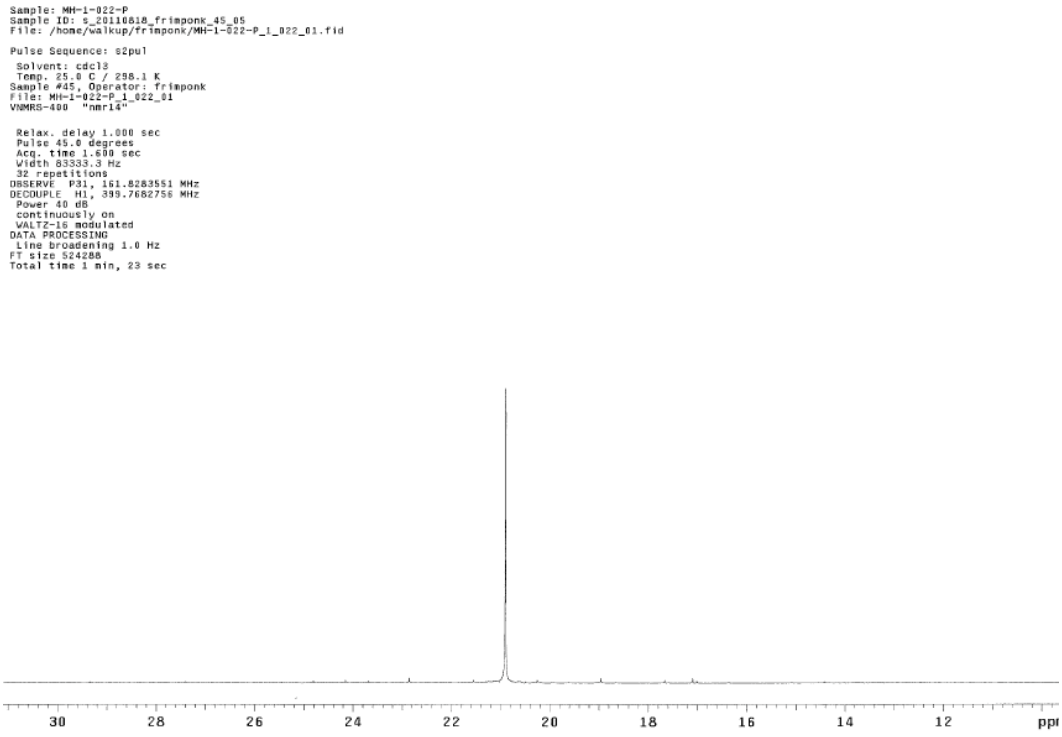
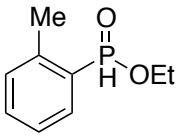
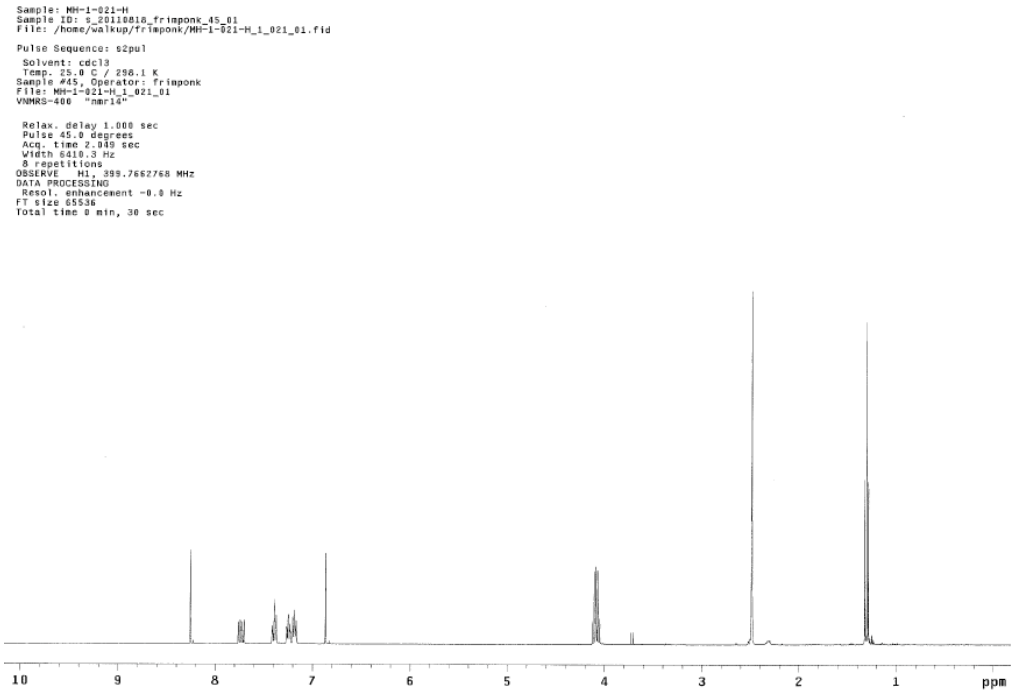
140
120
100
80
60
40
20
ppm

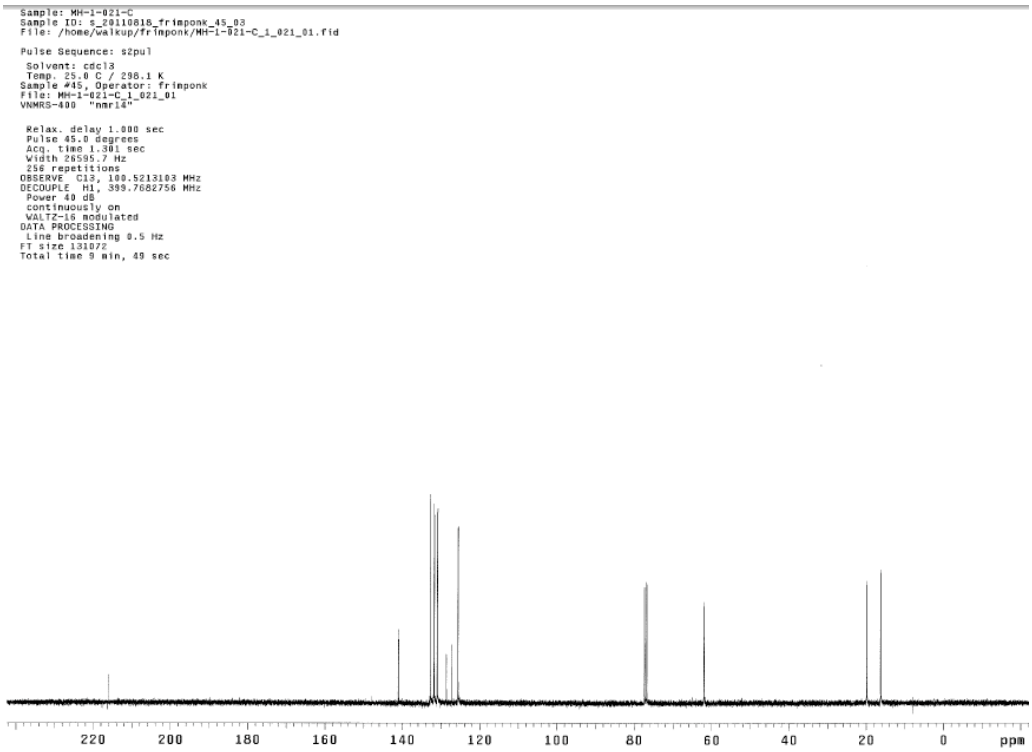


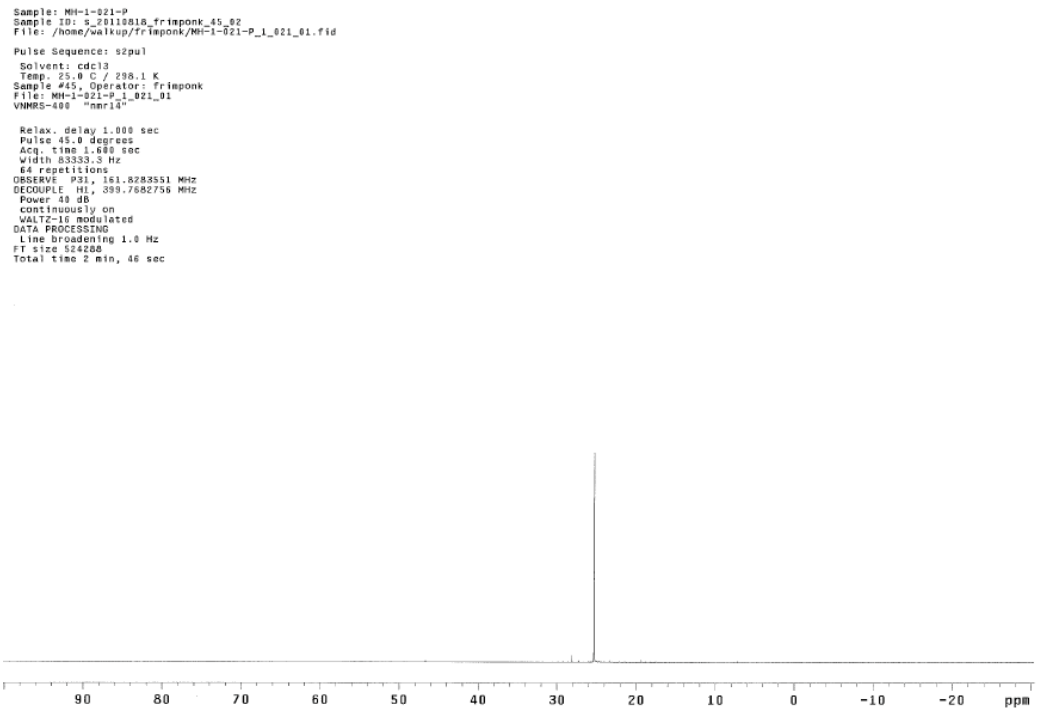


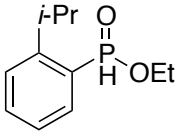
Ethyl *o*-tolylphosphinate. The phosphinate was synthesized from 1-bromo-2-methylbenzene (18.1 mL, 150.0 mmol) and triethyl phosphite (17.1 mL, 145.8 mmol) and was obtained as clear liquid (3.24 g, 11%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.26-6.87 (d, 1H, *J* = 554.9), 7.76-7.70 (dd, 1H, *J* = 15.9, 6.9), 7.41-7.37 (t, 1H, *J* = 7.4), 7.269-7.231 (t, 1H, *J* = 7.4), 7.230-7.168 (t, 1H, *J* = 6.8), 4.13-4.05 (m, 2H), 2.49 (s, 3H), 1.32-1.29 (t, 3H, *J* = 8.0); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 141.0 (d, *J* = 11.0), 132.9 (d, *J* = 2.8), 131.9 (d, *J* = 13.0), 131.1 (d, *J* = 11.8), 128.7-127.4 (d, *J* = 131.5), 125.7 (d, *J* = 14.2), 62.0 (d, *J* = 6.5), 19.8 (d, *J* = 6.9), 16.2 (d, *J* = 6.9); **^{31}P NMR** ($CDCl_3$, 160 MHz) δ 25.3; **IR**: 3478.4, 2981.4, 2345.8, 1595.2, 1476.5, 1390.4,

1281.1, 1222.5, 1161.8, 1087.9, 1035.9, 935.2, 807.3, 751.5, 563.4, 482.0; **HRMS** (DART-TOF) calcd. for $C_9H_{13}O_2P[M+H]^+$: 185.0731, found: 185.0739.

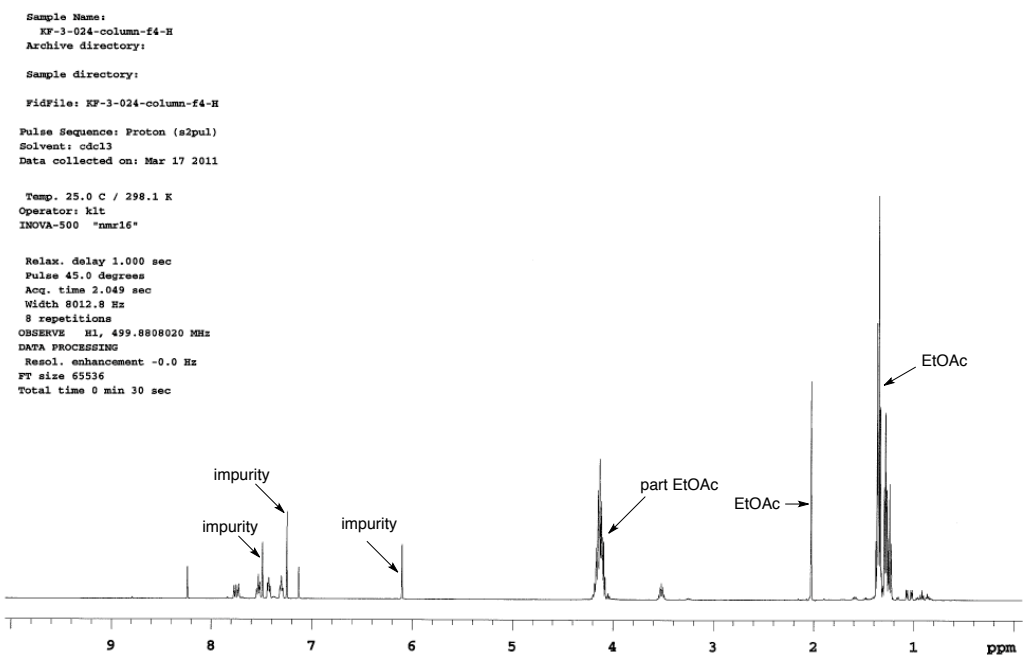








Ethyl (2-isopropylphenyl)phosphinate. The phosphinate was synthesized from 1-bromo-2-isopropylbenzene (9.8 g, 49.2 mmol) and diethyl chlorophosphite (8.5 mL, 59.1 mmol) and was obtained as clear liquid (6.4 g, 62%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.24-7.13 (d, 1H, *J* = 554.1), 7.78-7.72 (dd, 1H, *J* = 16.6, 7.8), 7.55-7.52 (m, 1H), 7.44-7.42 (t, 1H, *J* = 6.8), 7.32-7.29 (m, 1H), 4.19-4.08 (m, 2H), 3.58-3.49 (m, 1H), 1.30-1.23 (m, 9H); **^{31}P NMR** ($CDCl_3$, 200 MHz) δ 26.6.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Sample directory:
FidFile: KF-3-024-column-f4-H
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 17 2011
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr16"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8808020 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 30 sec
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impurity
impurity
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EtOAc
9
8
7
6
5
4
3
2
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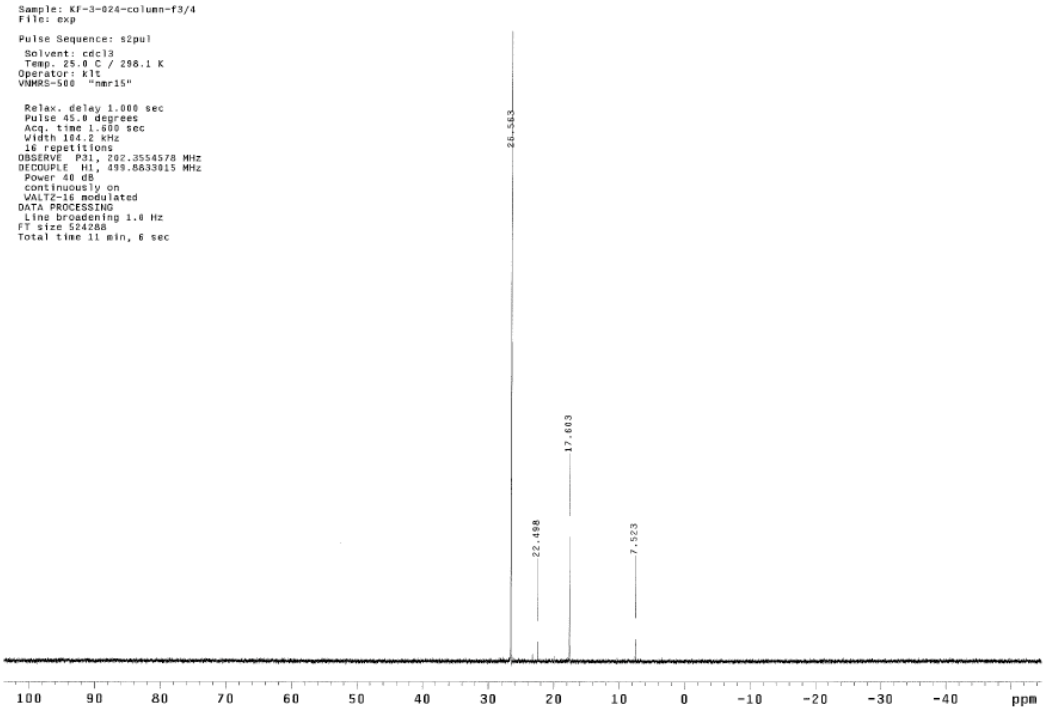
ppm


Sample: KF-3-024-column-f3/4
File: exp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
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Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
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16 repetitions
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DECOUPLE H1, 499.8833015 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 524288
Total time 11 min, 6 sec
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17.603
22.498
7.523
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70
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30
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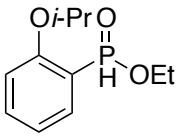
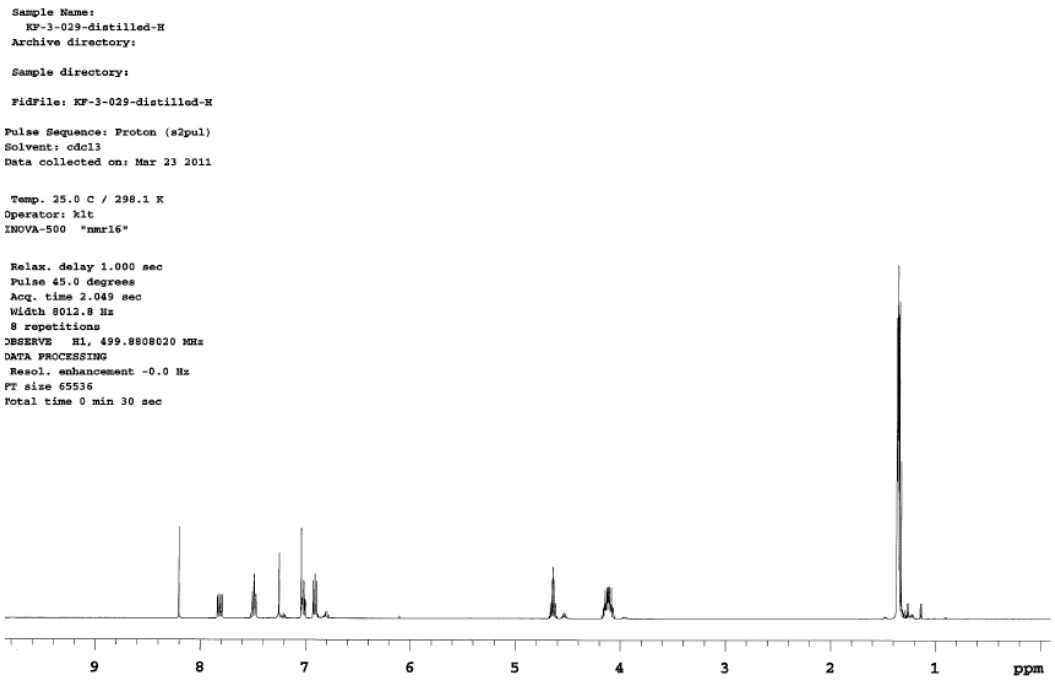
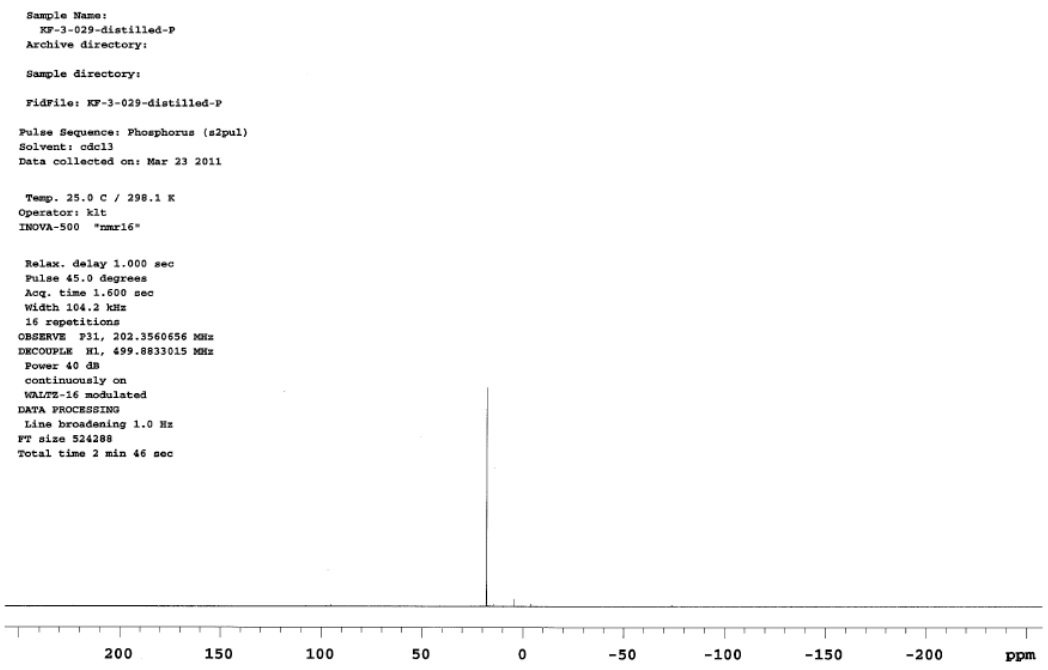
10
0
-10
-20
-30
-40
ppm



Ethyl (2-isopropoxyphenyl)phosphinate. The phosphinate was synthesized from 1-bromo-2-isopropoxybenzene (5.00 g, 23.2 mmol) and diethyl chlorophosphite (3.66 mL, 25.5 mmol) and was obtained as clear liquid (4.61 g, 87%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.20-7.04 (d, 1H, *J* = 580.4), 7.84-7.79 (dd, 1H, *J* = 14.2, 7.6), 7.50-7.47 (t, 1H, 8.1), 7.03-7.00 (t, 1H, *J* = 7.4), 6.93-6.90 (dd, 1H, *J* = 8.3, 6.6), 4.68-4.61 (m, 1H), 4.18-4.05 (m, 2H), 1.37-1.33 (m, 9H); **^{31}P NMR** ($CDCl_3$, 200 MHz) δ 18.0.





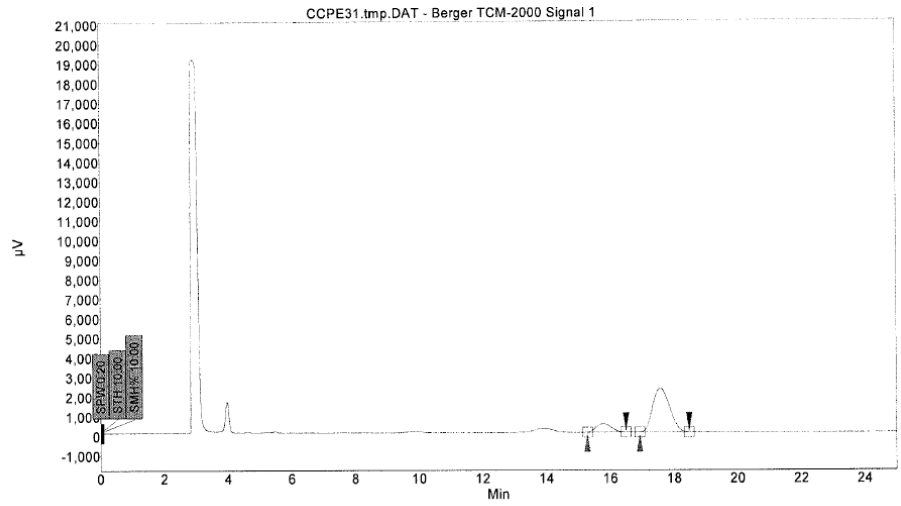
Hydroformylation with Second-Generation Chiral Ligands

General Procedure. An oven dried glass reaction vial was placed in the Endeavor, and 2-phenylprop-2-en-1-ol, **1.43** (20 mg, 0.15 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium(I) (1.6 mg, 6.0×10^{-3} mmol, 4.0 mol%), ligand **2.52** (3.0×10^{-2} mmol, 20 mol%), *p*-toluenesulfonic acid and benzene (to total volume of 1 mL) was injected, followed by injection of additional benzene (0.5 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 45 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with X psi of CO/H_2, and stirring was re-initiated at 700 rpm. The Endeavor was maintained at a constant temperature of 45 °C and pressure of X psi of CO/H_2 for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction mixture

was removed from the Endeavor and concentrated. The residue was dissolved in *t*-butanol (0.75 mL) and 2-methyl-2-butene (0.16 mL, 1.5 mmol, 10.0 eq.) followed by addition of a solution of $NaClO_2$ (80%, 68 mg, 0.60 mmol, 4.0 equiv.) and NaH_2PO_4 (72 mg, 0.60 mmol, 4.0 eq.) in H_2O (0.4 mL). The solution was stirred at room temperature overnight. The resulting mixture was concentrated and redissolved in EtOAc (0.75 mL), followed by addition of 10% HCl (0.18 ml) and brine (0.18 mL). The solution was extracted with EtOAc (3 × 5 mL). Combined organic layers were dried over $MgSO_4$, filtered and solvent was removed. Flash column chromatography was performed to isolate the acid, which was subjected to esterification conditions. To a dried scintillation vial containing the acid and a stir bar under nitrogen was added 1.5 mL each of benzene and methanol. (Trimethylsilyl)diazomethane (358 μL, 2.25 mmol, 15 equiv.) was added dropwise and the resulting solution was stirred for 1 h at room temperature. The reaction was concentrated and purified by preparative TLC and analyzed by SFC (AD-H, 1 mL/min, 2.0% MeOH as modifier, 220 nm, 150 psi, 50 °C).

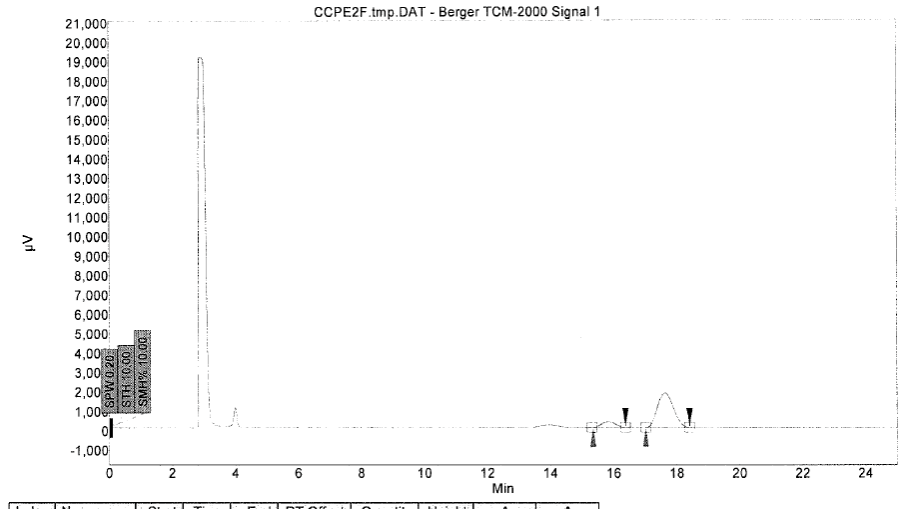
Acid Screen Using Ligand **2.52A**

Table 2.1, Entry 1: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (132 μL of 5.69×10^{-4} M in benzene, 7.5 x 10^{-5} mmol, 0.05 mol%) at 400 psi CO/H_2. The branched product was isolated in 76% yield and 67% ee.



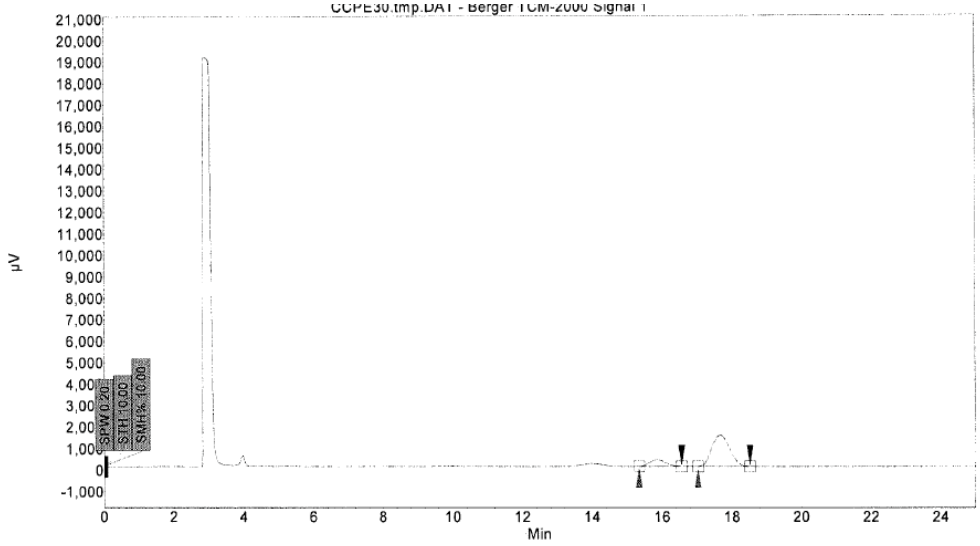
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	15.28	15.78	16.49	0.00	14.43	430.9	230.2	14.430
2	UNKNOWN	16.92	17.56	18.47	0.00	85.57	2217.9	1365.1	85.570
Total						100.00	2648.8	1595.3	100.000

Table 2.1, Entry 2: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (264 μL of 5.69 × 10^{-4} M in benzene, 1.5 x 10^{-4} mmol, 0.10 mol%) at 400 psi CO/H_2. The branched product was isolated in 37% yield and 74% ee.



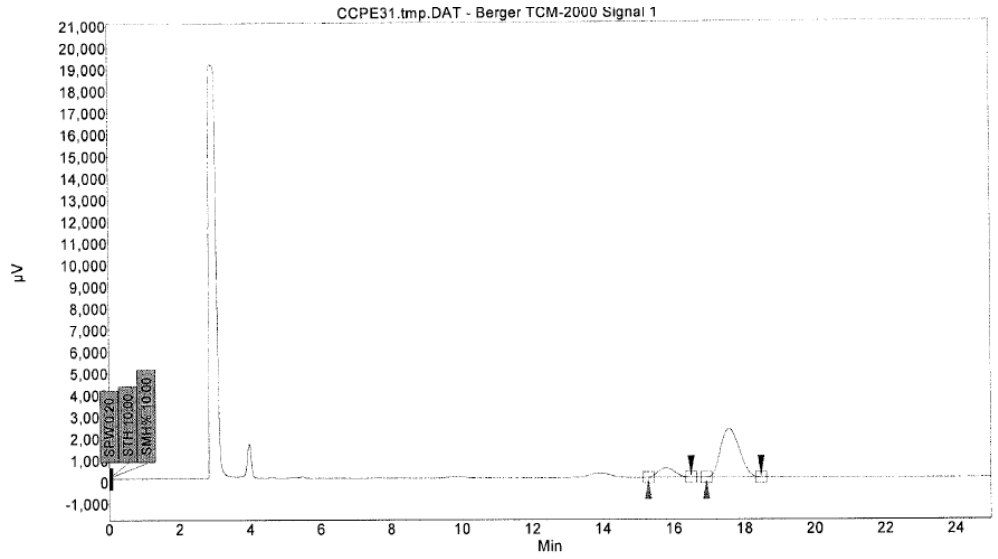
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	15.34	15.82	16.36	0.00	12.93	302.0	154.0	12.933
2	UNKNOWN	17.01	17.62	18.40	0.00	87.07	1770.3	1036.6	87.067
Total						100.00	2072.3	1190.6	100.000

Table 2.1, Entry 3: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (396 μL of 5.69 × 10^{-4} M in benzene, 2.25 x 10^{-4} mmol, 0.15 mol%) at 400 psi CO/H_2. The branched product was isolated in 78% yield and 69% ee.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	15.34	15.86	16.55	0.00	15.77	300.5	160.1	15.774
2	UNKNOWN	17.02	17.67	18.52	0.00	84.23	1440.6	854.6	84.226
Total						100.00	1741.2	1014.7	100.000

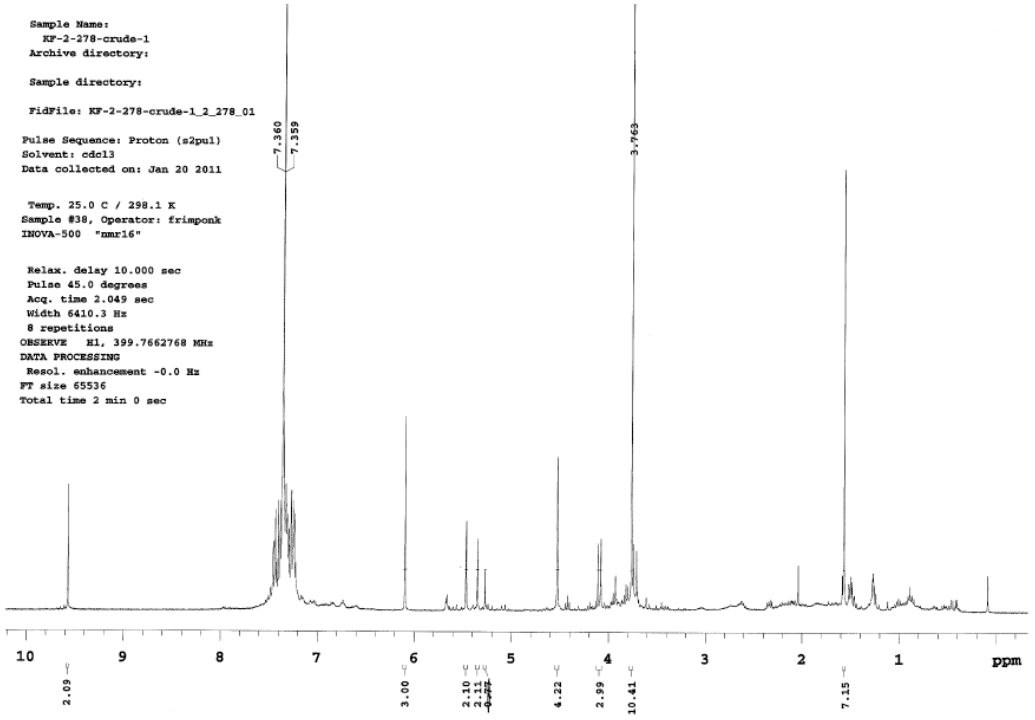
Table 2.1, Entry 4: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (528 μL of 5.69 × 10^{-4} M in benzene, 3.0 x 10^{-4} mmol, 0.20 mol%) at 400 psi CO/H_2. The branched product was isolated in 84% yield and 71% ee.

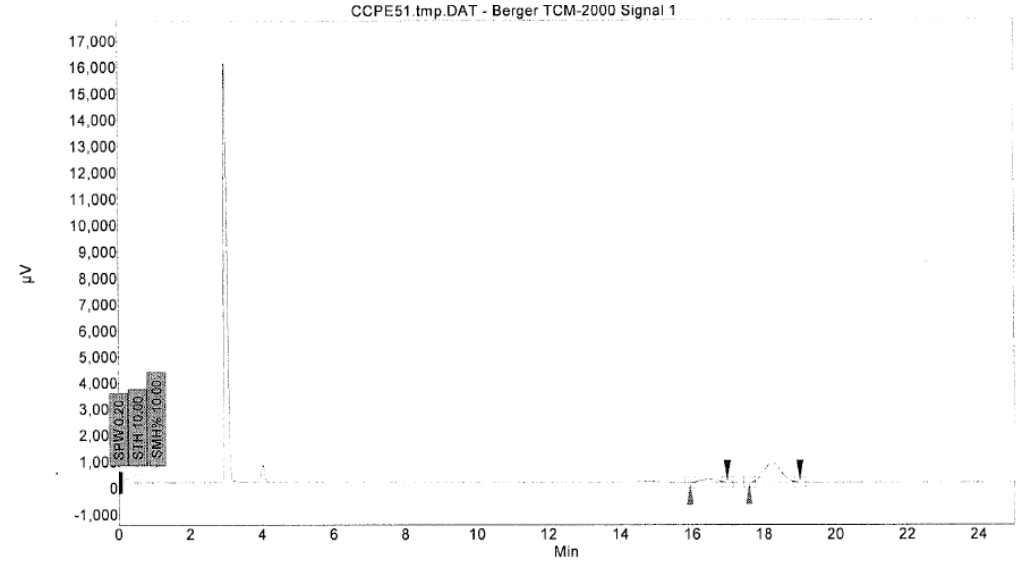


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.28	15.78	16.49	0.00	14.43	430.9	230.2	14.430
2	UNKNOWN	16.92	17.56	18.47	0.00	85.57	2217.9	1365.1	85.570
Total						100.00	2648.8	1595.3	100.000

Pressure Screen Using Ligand **2.52A**

Table 2.2, Entry 1: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (264 µL of 5.69×10^{-4} M in benzene, 1.5×10^{-4} mmol, 0.10 mol%) at 50 psi CO/H_2. Analysis of the crude reaction mixture showed a 79% conversion by ^1H NMR. The branched product was isolated in 67% yield and 75% ee.

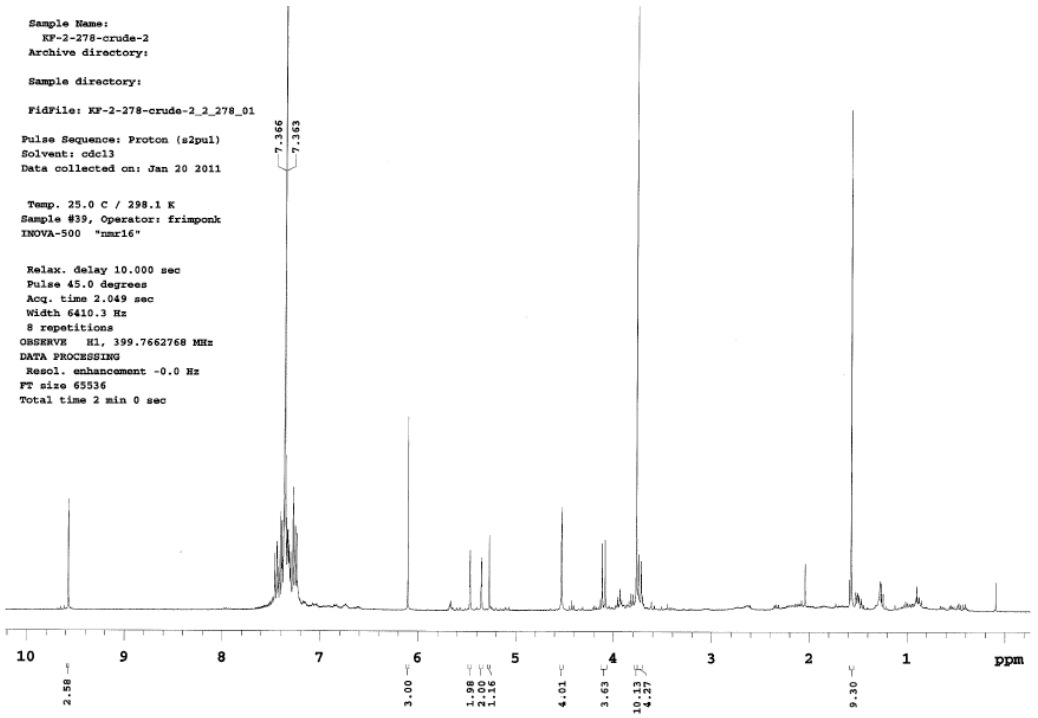


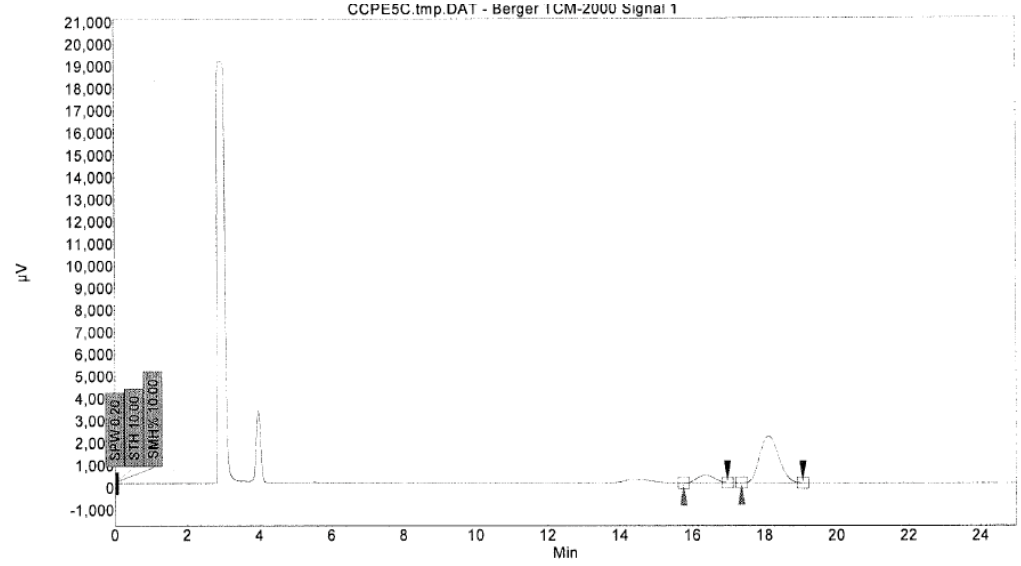


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	15.94	16.45	16.97	0.00	12.74	118.0	59.7	12.737
2	UNKNOWN	17.59	18.25	19.00	0.00	87.26	721.0	409.3	87.263
Total						100.00	838.9	469.0	100.000

Table 2.2, Entry 2: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (264 μL of 5.69×10^{-4} M in benzene, 1.5 x 10^{-4} mmol, 0.10

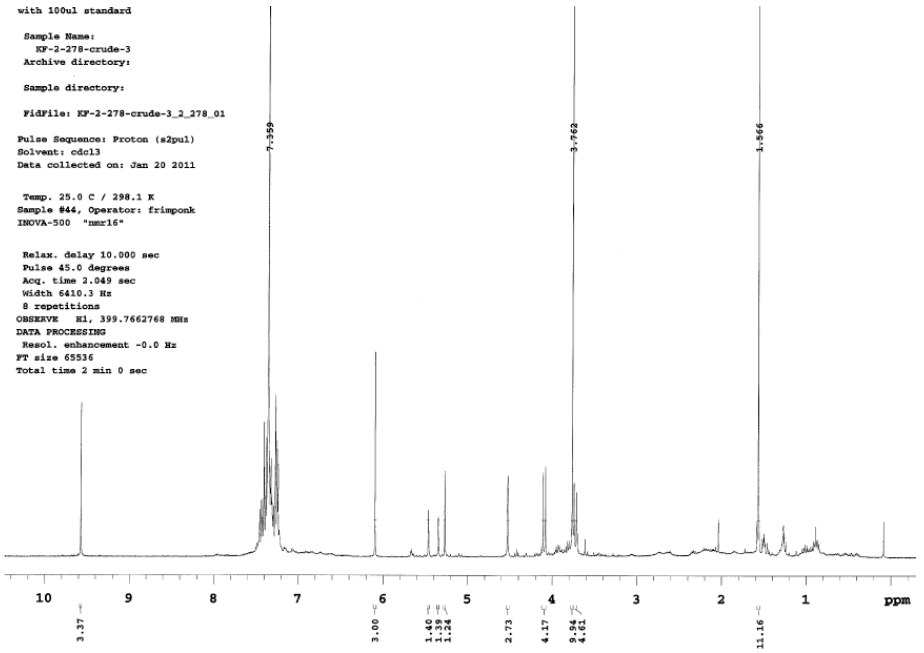
mol%) at 100 psi CO/H_2. Analysis of the crude reaction mixture showed an 80% conversion by ^1H NMR. The branched product was isolated in 74% yield and 75% ee.

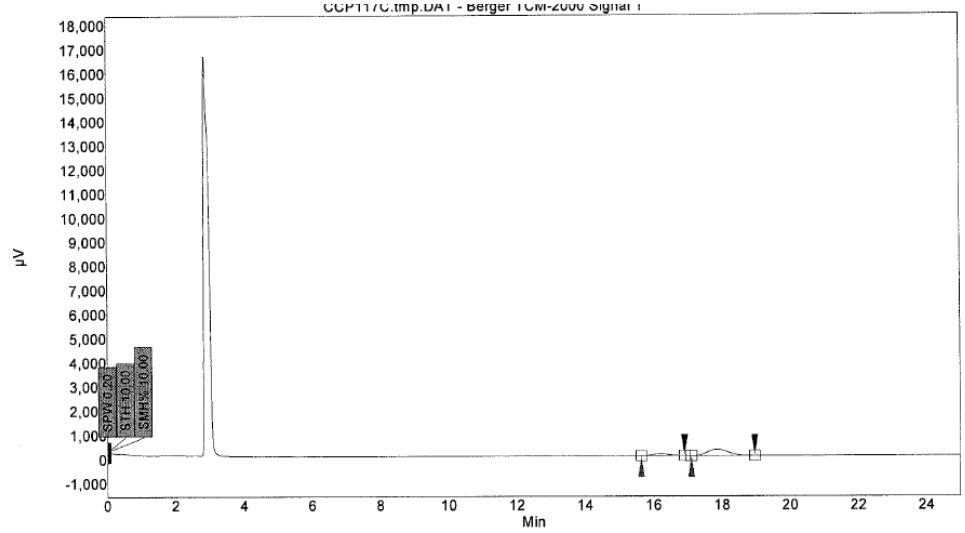




Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.76	16.36	16.98	0.00	12.55	334.4	182.7	12.549
2	UNKNOWN	17.37	18.11	19.06	0.00	87.45	2090.2	1273.3	87.451
Total						100.00	2424.6	1456.0	100.000

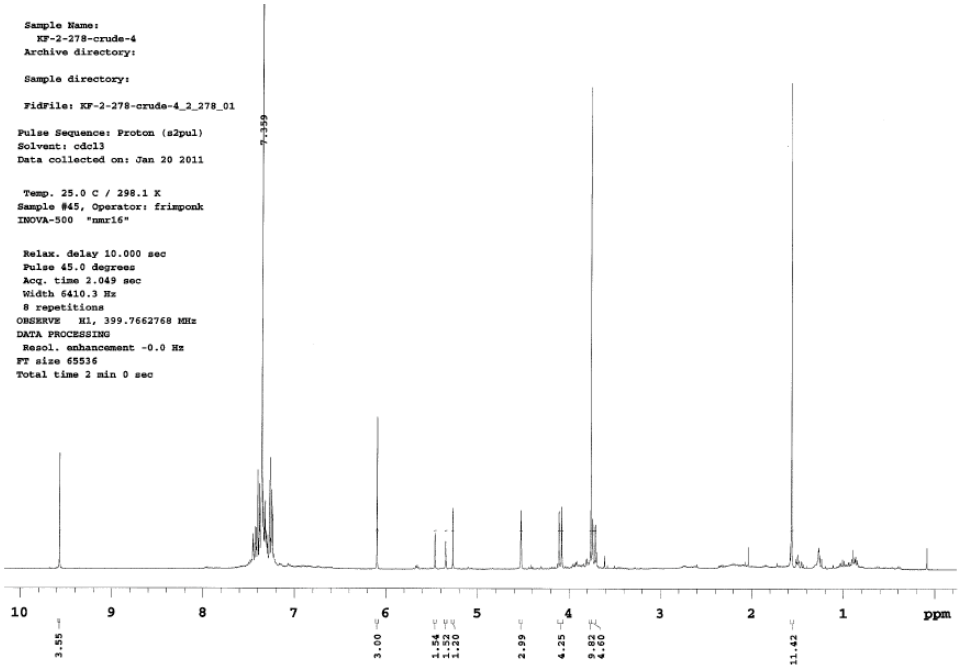
Table 2.2, Entry 3: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (264 μL of 5.69 × 10^{-4} M in benzene, 1.5 x 10^{-4} mmol, 0.10 mol%) at 200 psi CO/H_2. Analysis of the crude reaction mixture showed an 86% conversion by ^1H NMR. The branched product was isolated in 71% yield and 66% ee.

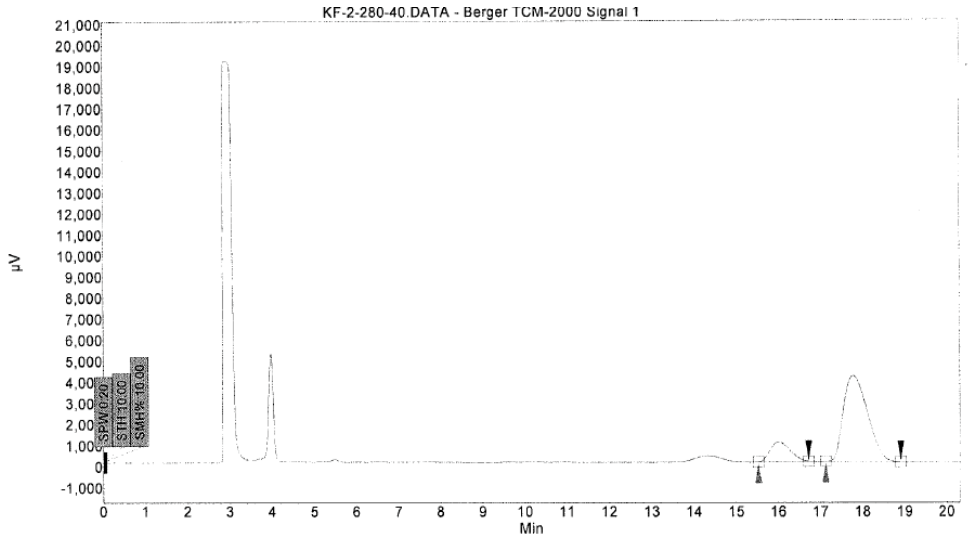




Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	15.64	16.22	16.90	0.00	19.28	71.0	42.8	19.281
2	UNKNOWN	17.10	17.86	18.96	0.00	80.72	255.3	179.2	80.719
Total						100.00	326.3	222.0	100.000

Table 2.2, Entry 4: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (264 μL of 5.69 × 10^{-4} M in benzene, 1.5 x 10^{-4} mmol, 0.10 mol%) at 300 psi CO/H_2. Analysis of the crude reaction mixture showed an 85% conversion by ^{1}H NMR. The branched product was isolated in 71% yield and 68% ee.

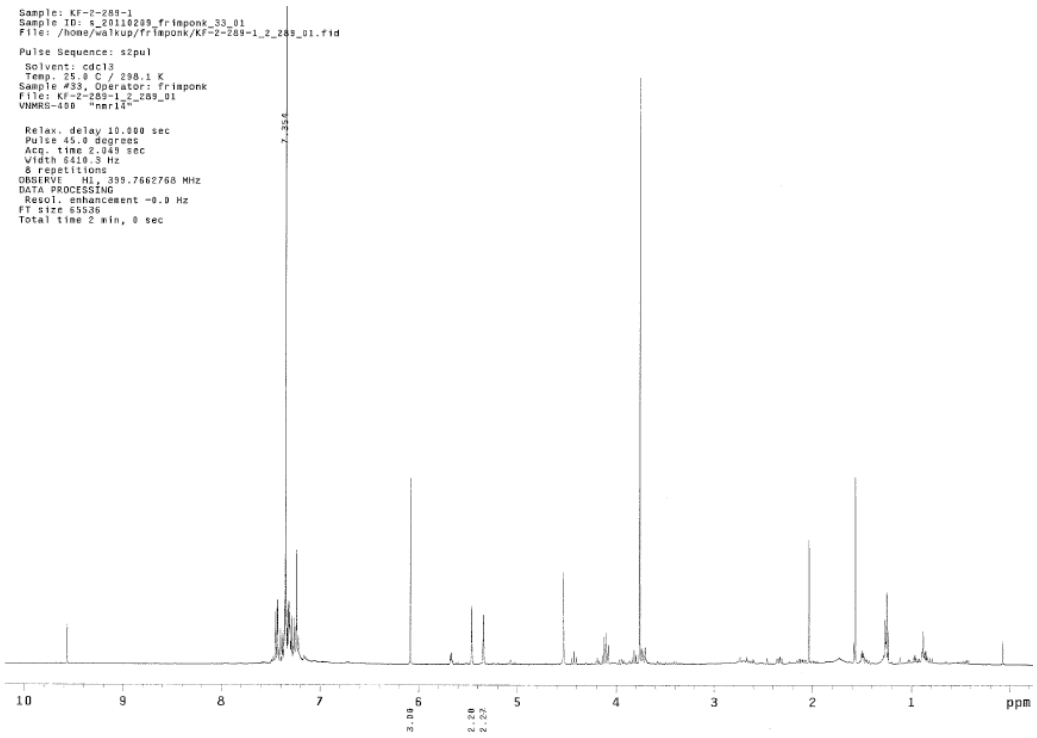


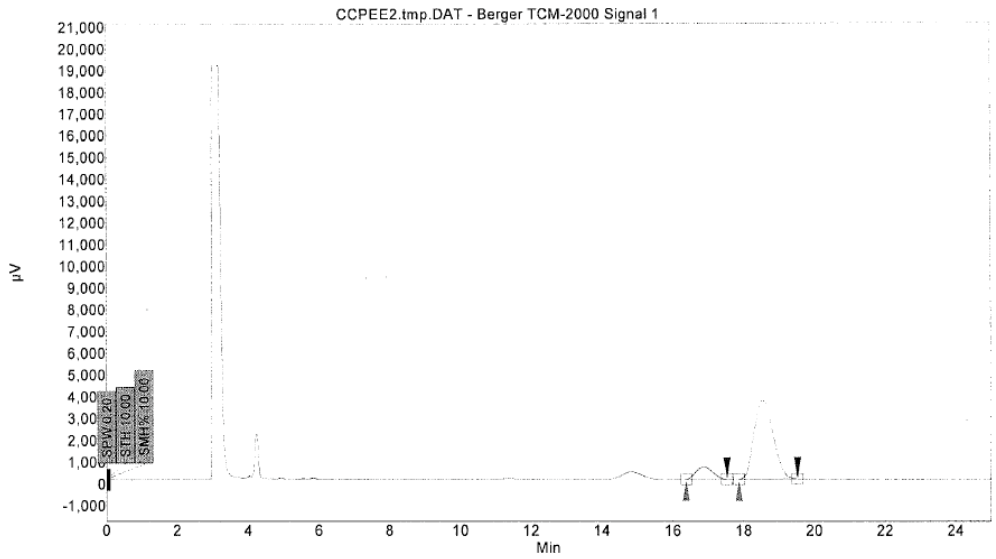


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	15.52	16.00	16.71	0.00	15.98	935.2	511.7	15.980
2	UNKNOWN	17.12	17.77	18.90	0.00	84.02	4056.8	2690.6	84.020
Total						100.00	4992.0	3202.3	100.000

Acid Screen Using Ligand **2.52B**

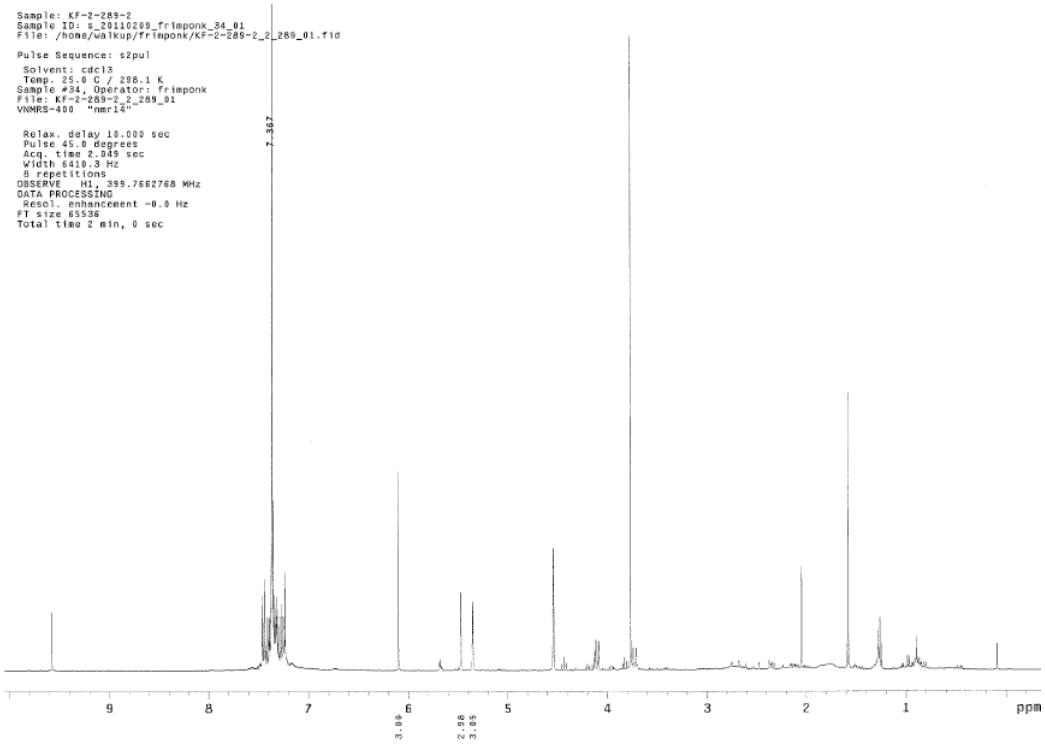
Table 2.3, Entry 1: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (132 μL of 5.69 × 10^{-4} M in benzene, 7.5 x 10^{-5} mmol, 0.05 mol%) at 100 psi CO/H_2. Analysis of the crude reaction mixture showed a 78% conversion by ^1H NMR. The branched product was isolated in 56% yield and 76% ee.

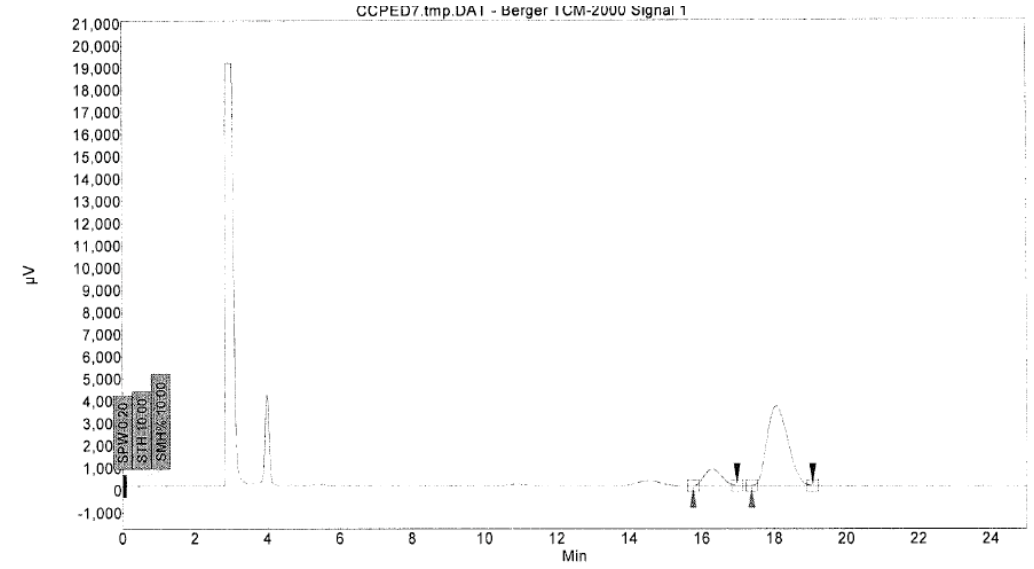




Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	16.37	16.89	17.53	0.00	12.02	564.8	306.5	12.024
2	UNKNOWN	17.86	18.53	19.51	0.00	87.98	3602.5	2242.5	87.976
Total						100.00	4167.2	2549.0	100.000

Table 2.3, Entry 2: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (330 µL of 5.69×10^{-4} M in benzene, 1.9 x 10^{-4} mmol, 0.125 mol%) at 100 psi CO/H_2. Analysis of the crude reaction mixture showed a 70% conversion by ^1H NMR. The branched product was isolated in 46% yield and 71% ee.

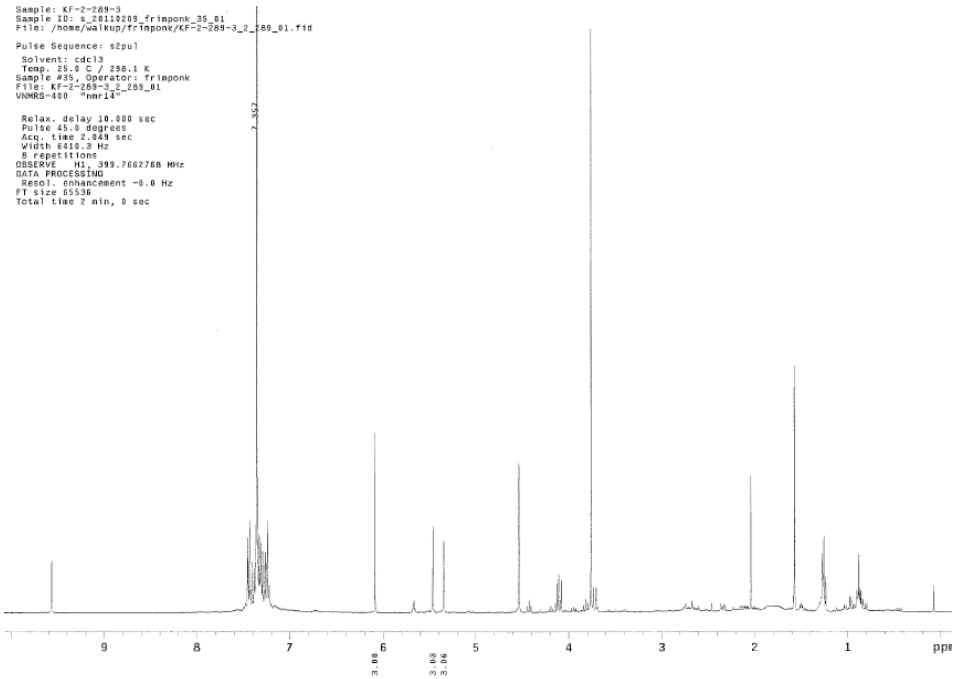


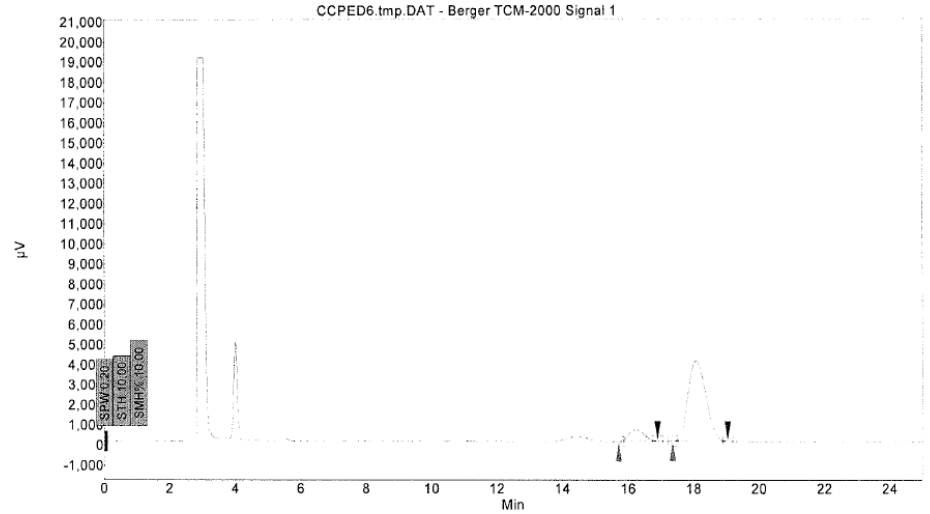


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.76	16.30	16.97	0.00	14.62	745.6	403.8	14.620
2	UNKNOWN	17.37	18.06	19.06	0.00	85.38	3557.4	2358.1	85.380
Total						100.00	4303.1	2761.9	100.000

Table 2.3, Entry 3: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (528 µL of 5.69 × 10^{-4} M in benzene, 3.0 x 10^{-4} mmol, 0.20

mol%) at 100 psi CO/H_2. Analysis of the crude reaction mixture showed a 70% conversion by ^1H NMR. The branched product was isolated in 44% yield and 78% ee.





Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.71	16.24	16.90	0.00	11.09	580.1	313.4	11.094
2	UNKNOWN	17.36	18.06	19.03	0.00	88.91	3993.3	2511.7	88.906
Total						100.00	4573.4	2825.2	100.000

Acid Screen Using Ligand **2.52C**

Table 2.4, Entry 1: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (132 μL of 5.69 × 10^{-4} M in benzene, 7.5 x 10^{-5} mmol, 0.05 mol%) at 400 psi CO/H_2. Analysis of the crude reaction mixture showed a 30% conversion by ^1H NMR. Isolated yield and enantioselectivity were not determined.

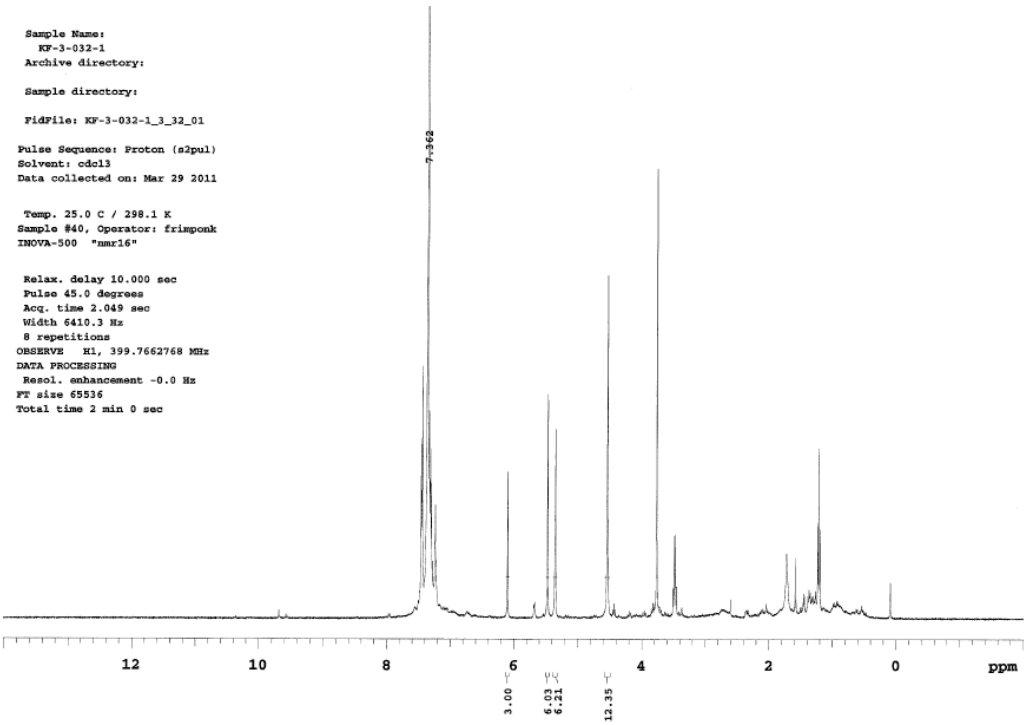
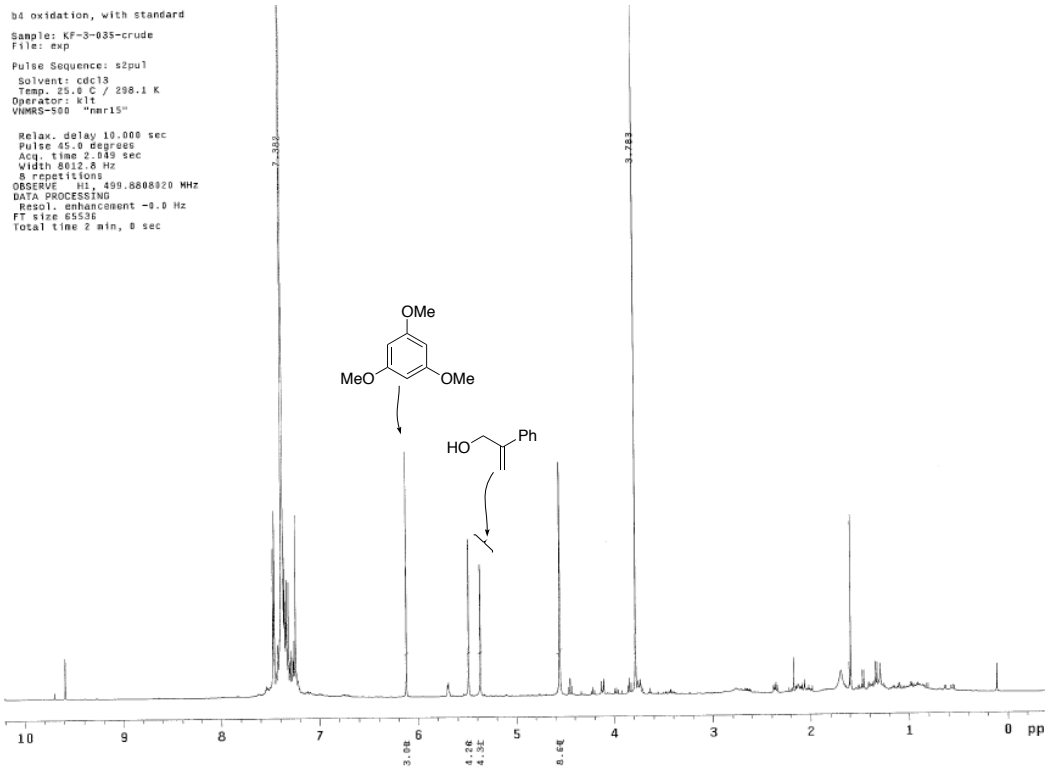
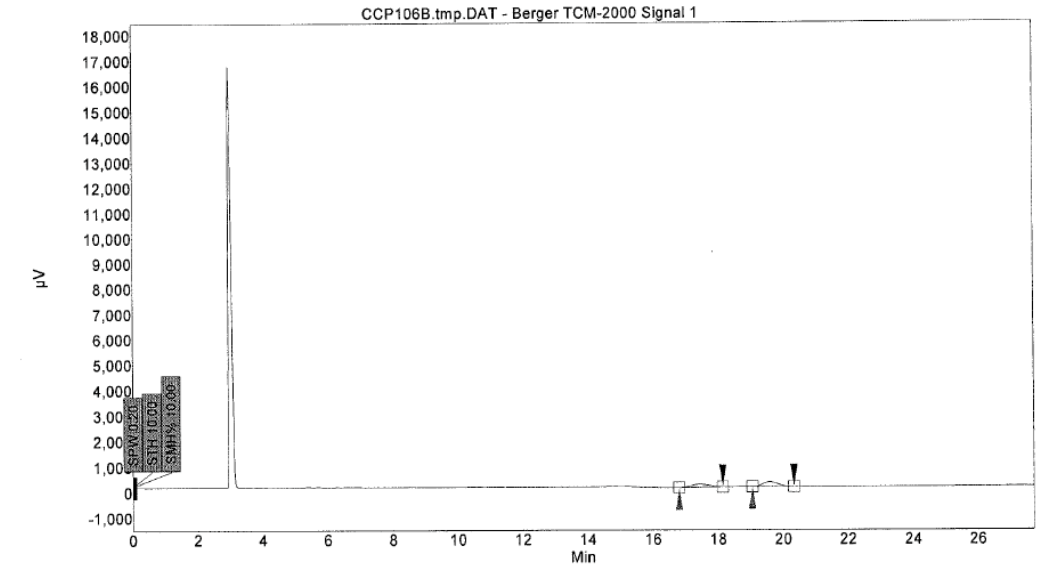


Table 2.4, Entry 2: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (132 μL of 5.69 × 10^{-4} M in benzene, 7.5 x 10^{-5} mmol, 0.05 mol%) at 400 psi CO/H_2. Analysis of the crude reaction mixture showed a 58% conversion by ^1H NMR. The branched product was isolated in 13% yield and 11% ee.

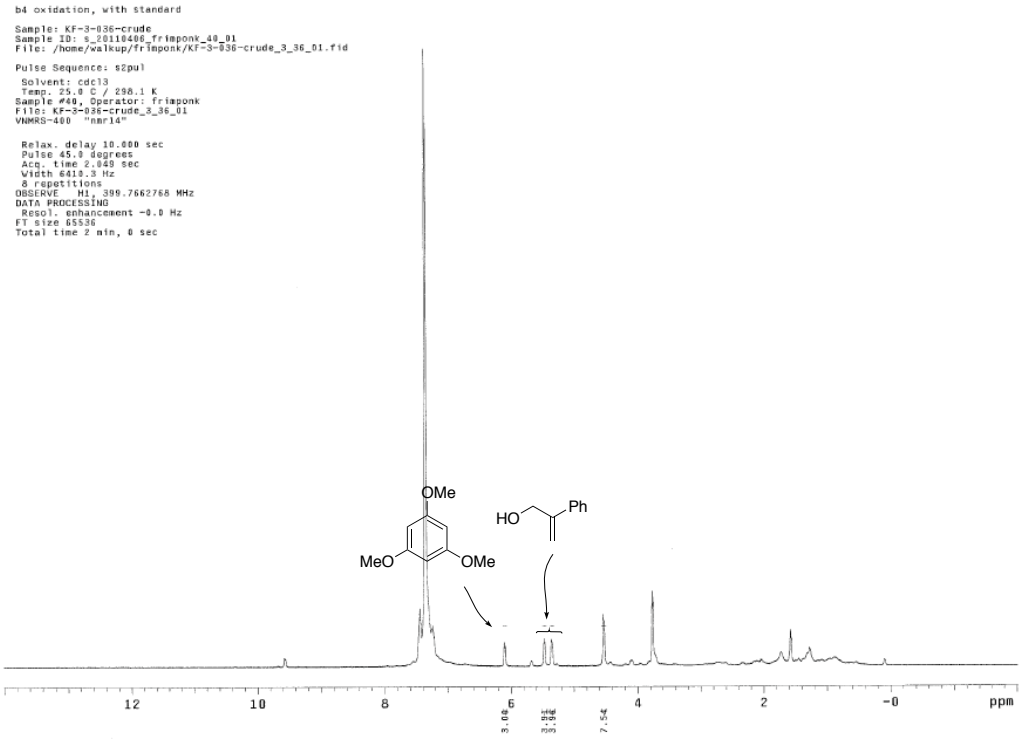


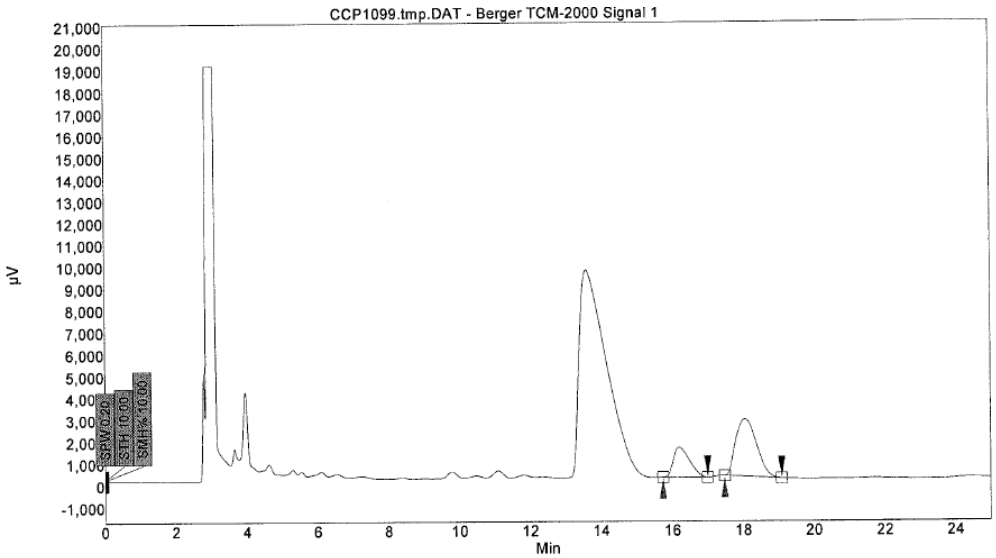


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	16.80	17.44	18.14	0.00	44.67	116.4	73.9	44.671
2	UNKNOWN	19.05	19.57	20.32	0.00	55.33	175.7	91.5	55.329
Total						100.00	292.1	165.4	100.000

Table 2.4, Entry 3: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (2.64 mL of 5.69 × 10^{-4} M in benzene, 1.5 x 10^{-3} mmol, 1.0

mol%) at 400 psi CO/H_2. Analysis of the crude reaction mixture showed a 61% conversion by ^1H NMR. The branched product was isolated in 12% yield and 42% ee.

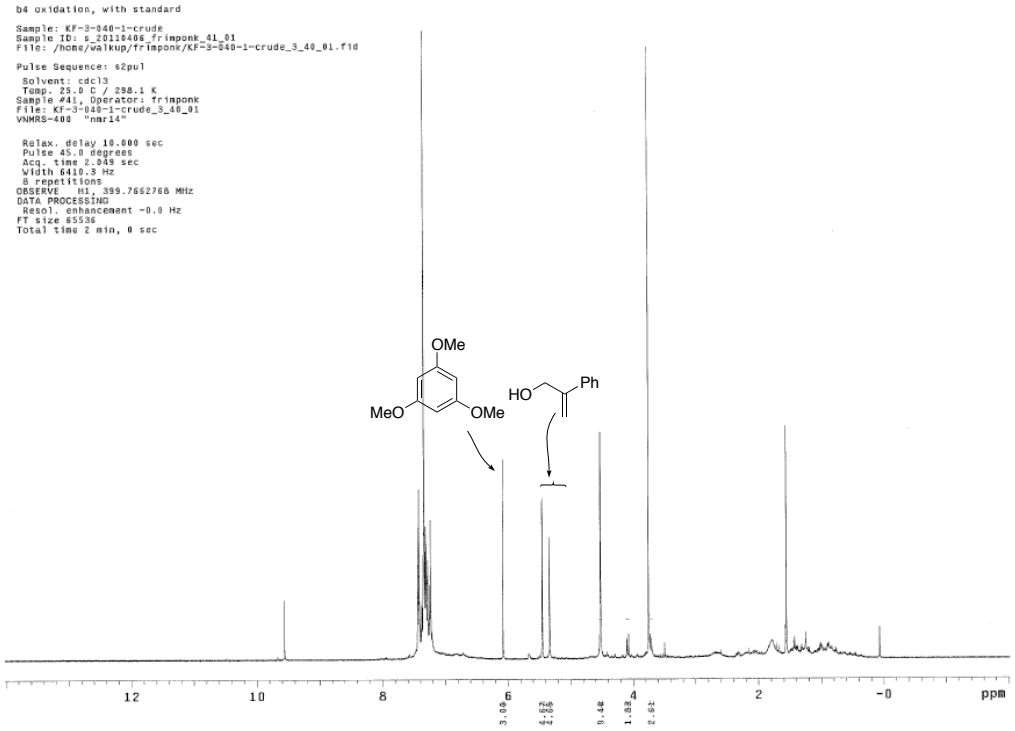


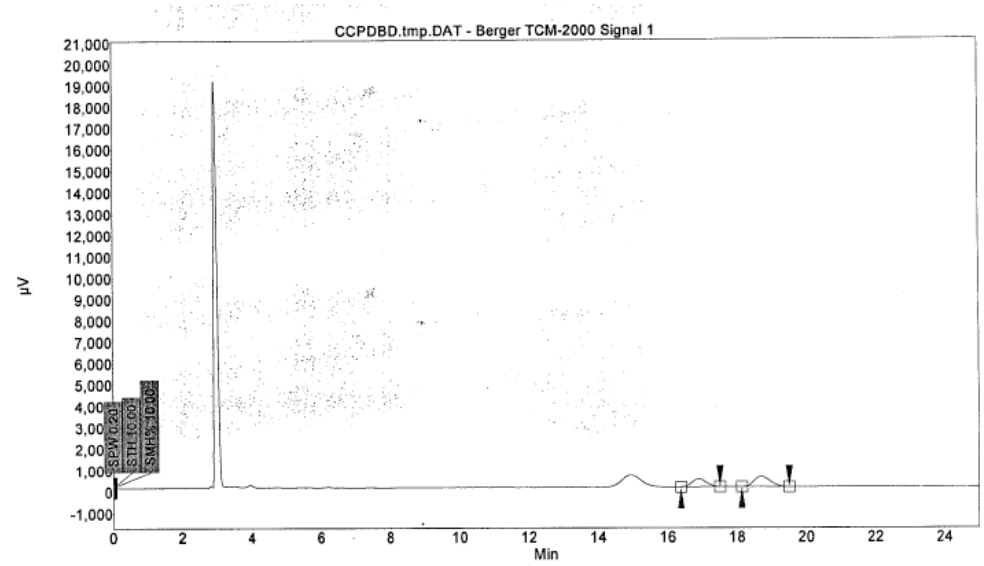


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.74	16.19	16.99	0.00	28.89	1378.3	718.9	28.893
2	UNKNOWN	17.47	18.04	19.08	0.00	71.11	2618.6	1769.3	71.107
Total						100.00	3996.9	2488.3	100.000

Acid Screen Using Ligand **2.52D**

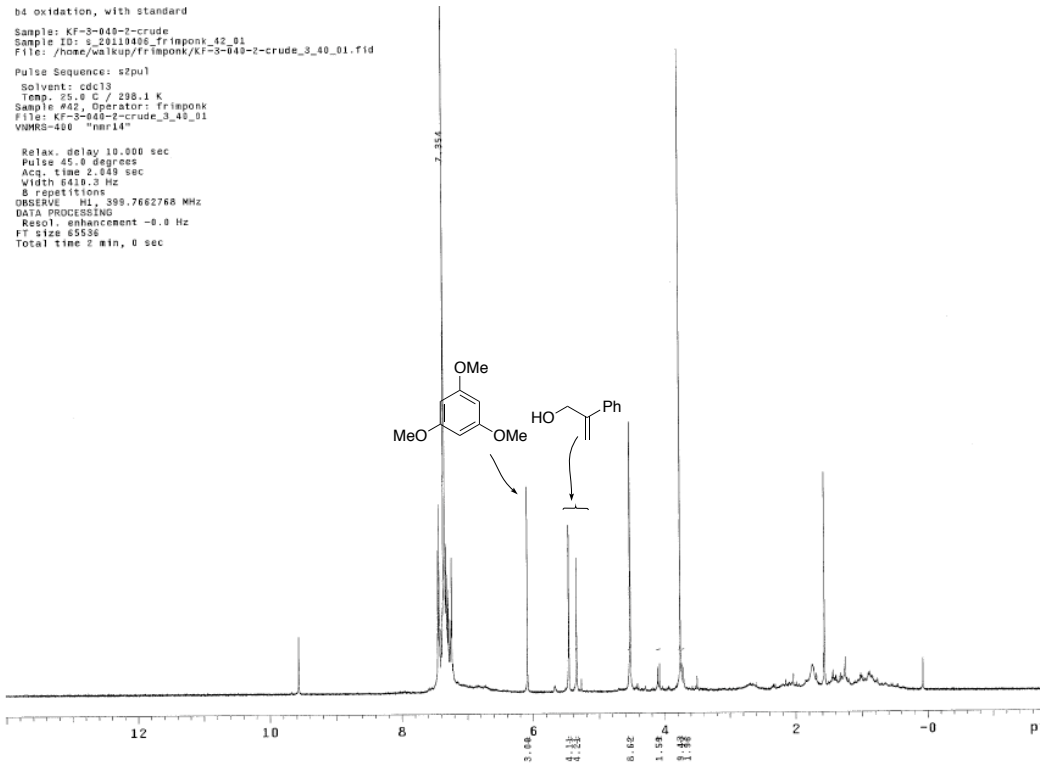
Table 2.5, Entry 1: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (132 μL of 5.69 × 10^{-4} M in benzene, 7.5 x 10^{-5} mmol, 0.05 mol%) at 400 psi CO/H_2. Analysis of the crude reaction mixture showed a 53% conversion by ^1H NMR. The branched product was isolated in 22% yield and 19% ee.

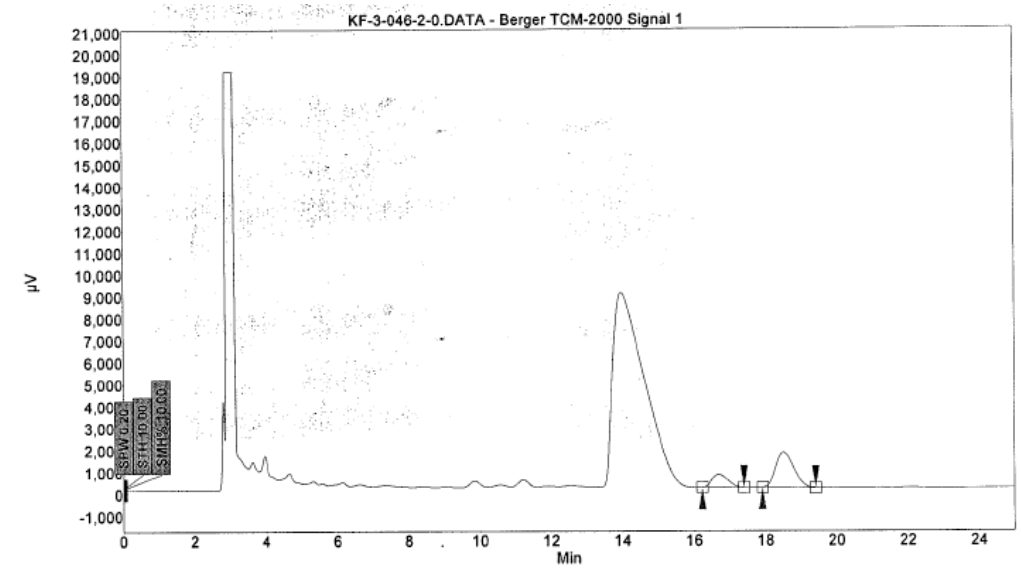




Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	16.38	16.89	17.50	0.00	40.36	357.1	168.1	40.362
2	UNKNOWN	18.13	18.69	19.50	0.00	59.64	468.7	248.3	59.638
Total						100.00	825.7	416.4	100.000

Table 2.5, Entry 2: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (264 μL of 5.69×10^{-4} M in benzene, 1.5×10^{-4} mmol, 0.10 mol%) at 400 psi CO/H_2. Analysis of the crude reaction mixture showed a 58% conversion by ^1H NMR. The branched product was isolated in 9% yield and 52% ee.

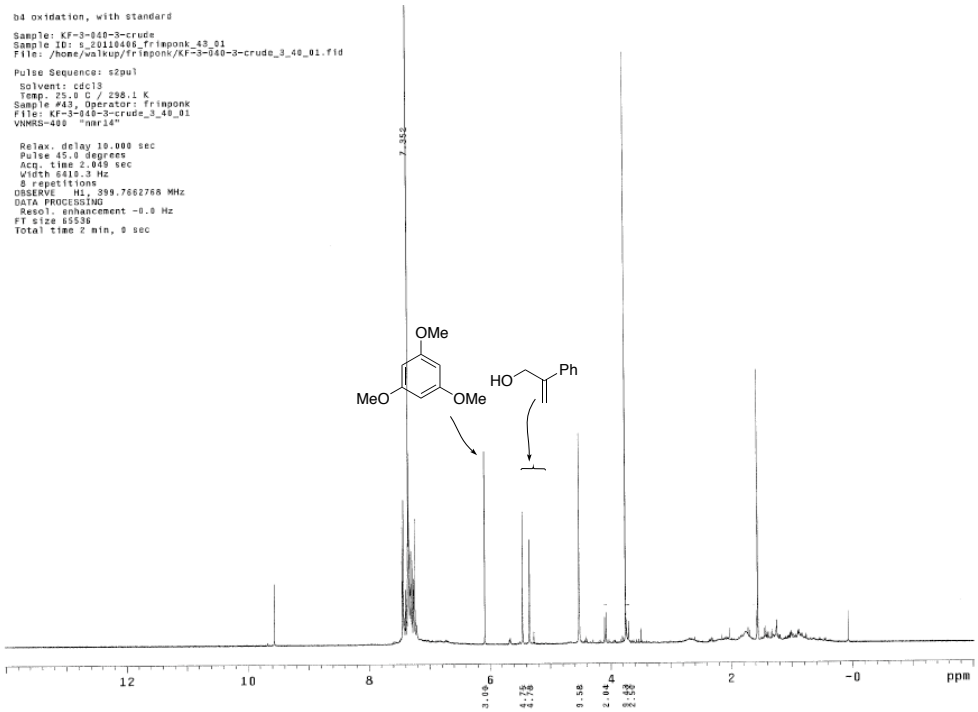


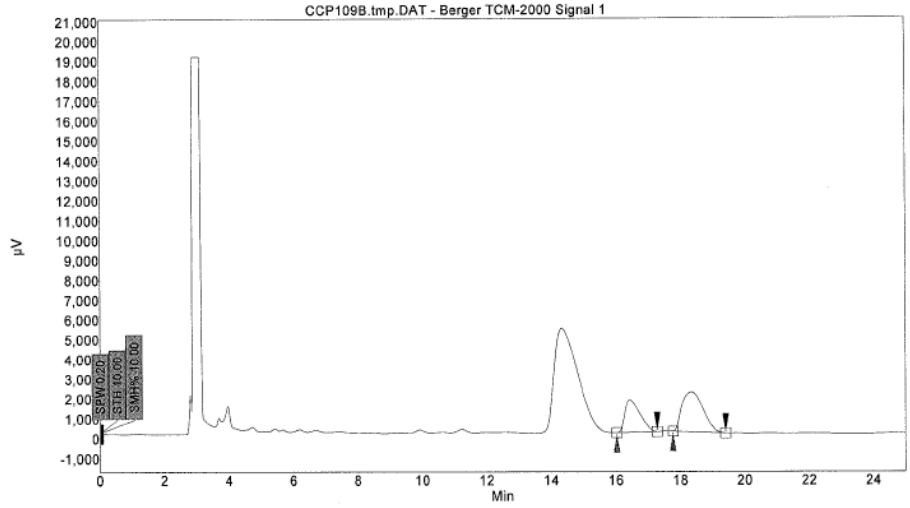


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[μV]	[μV.Min]	[%]
1	UNKNOWN	16.23	16.69	17.39	0.00	24.23	585.3	299.0	24.227
2	UNKNOWN	17.91	18.50	19.41	0.00	75.77	1597.0	935.0	75.773
Total						100.00	2182.2	1234.0	100.000

Table 2.5, Entry 3: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (396 μL of 5.69×10^{-4} M in benzene, 2.25×10^{-4} mmol, 0.15

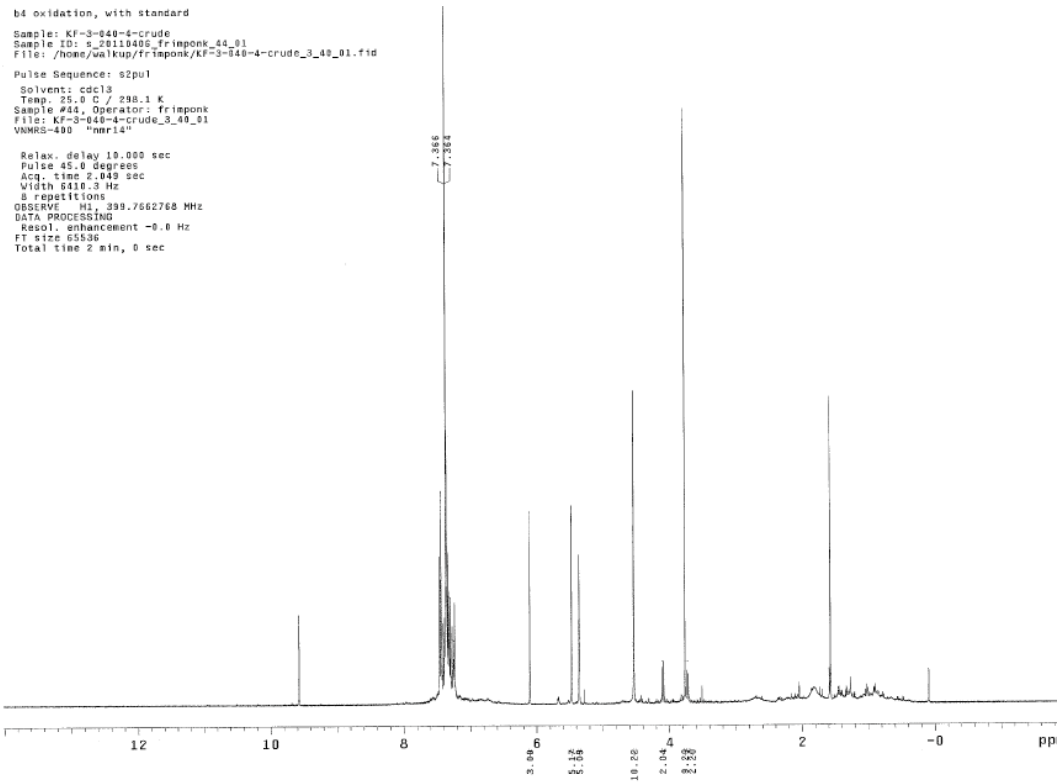
mol%) at 400 psi CO/H_2. Analysis of the crude reaction mixture showed a 52% conversion by ^1H NMR. The branched product was isolated in 15% yield and 26% ee.

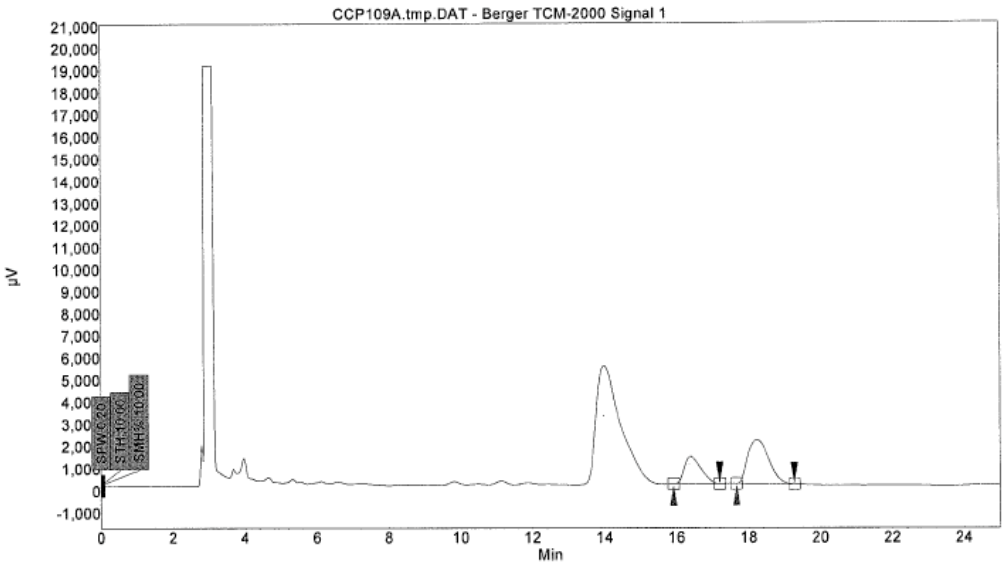




Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	16.03	16.43	17.28	0.00	37.00	1629.8	888.4	36.998
2	UNKNOWN	17.77	18.34	19.40	0.00	63.00	2005.0	1512.8	63.002
Total						100.00	3634.8	2401.2	100.000

Table 2.5, Entry 4: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using *p*-toluenesulfonic acid (528 μL of 5.69 × 10^{-4} M in benzene, 3.0 x 10^{-4} mmol, 0.20 mol%) at 400 psi CO/H_2. Analysis of the crude reaction mixture showed a 49% conversion by ^1H NMR. The branched product was isolated in 15% yield and 34% ee.



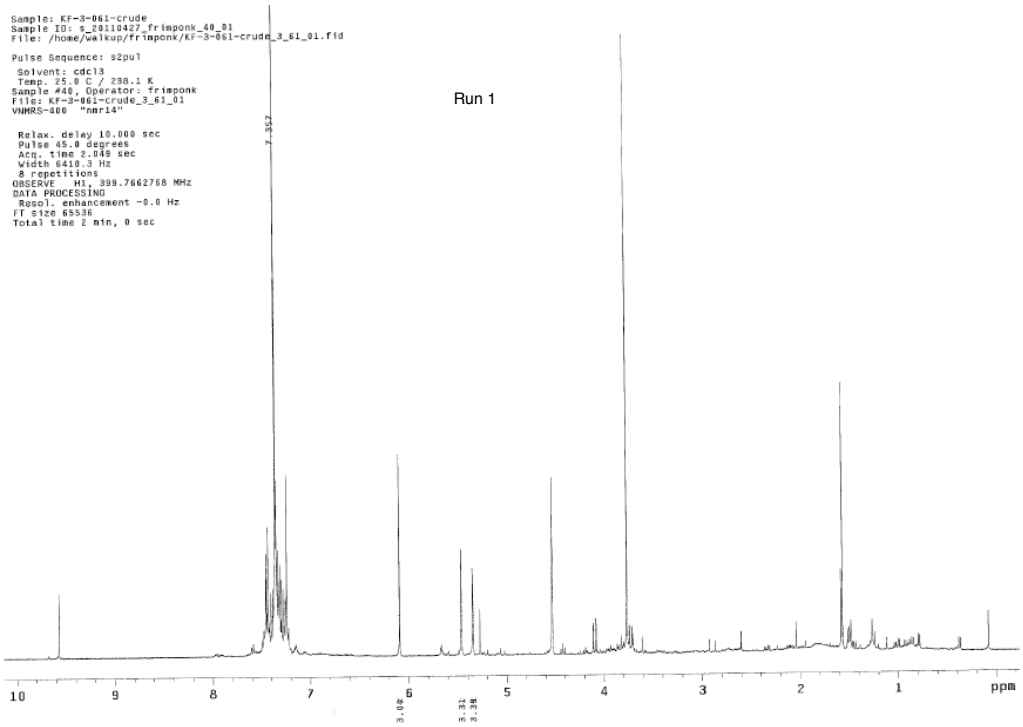


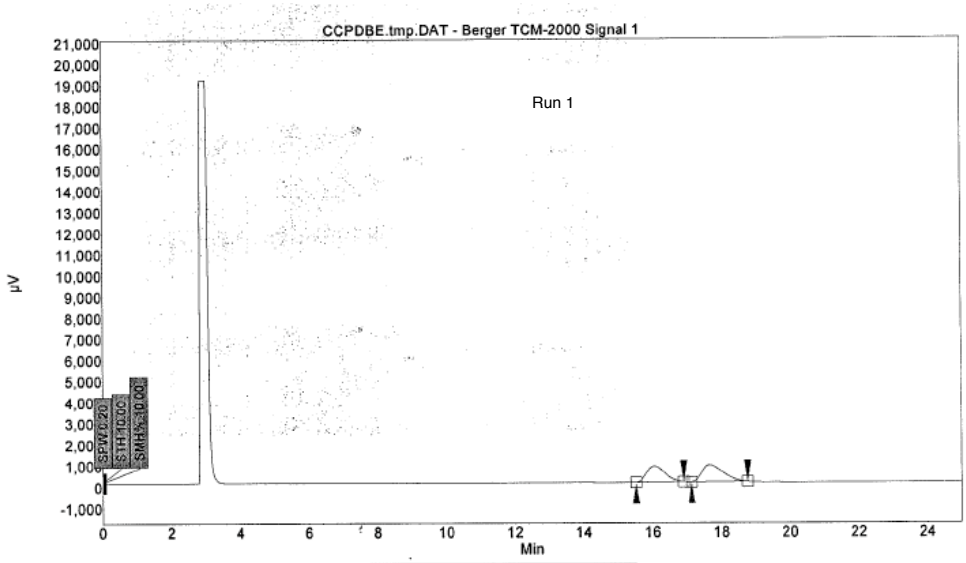
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.91	16.38	17.19	0.00	33.17	1235.1	660.3	33.167
2	UNKNOWN	17.66	18.22	19.27	0.00	66.83	1985.3	1330.4	66.833
Total						100.00	3220.3	1990.7	100.000

Dependency of Enantioselectivity on Batch of Ligand

Table 2.6, Entry 1: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using ligand **2.52A** (10.7 mg, 0.030 mmol, 20 mol%), and *p*-toluenesulfonic acid (264 µL of 5.69 × 10^{-4} M in benzene, 1.5 x 10^{-4} mmol, 0.10 mol%) at 45 °C, and 100 psi CO/H_2. Analysis of the crude reaction mixture showed an 80% conversion by ^1H NMR. The branched product was isolated in 74% yield and 75% ee (see Table 2.2, entry 2).

Table 2.6, Entry 2: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using ligand **2.52A** (10.7 mg, 0.030 mmol, 20 mol%), and *p*-toluenesulfonic acid (264 µL of 5.69 × 10^{-4} M in benzene, 1.5 x 10^{-4} mmol, 0.10 mol%) at 45 °C, and 100 psi CO/H_2. The isolated yield of the branched product was 67% (10% ee) for run 1 and 60% (12% ee) for run 2.





Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.51	16.05	16.90	0.00	44.84	742.8	454.5	44.839
2	UNKNOWN	17.13	17.65	18.76	0.00	55.16	785.2	559.2	55.161
Total						100.00	1528.0	1013.7	100.000

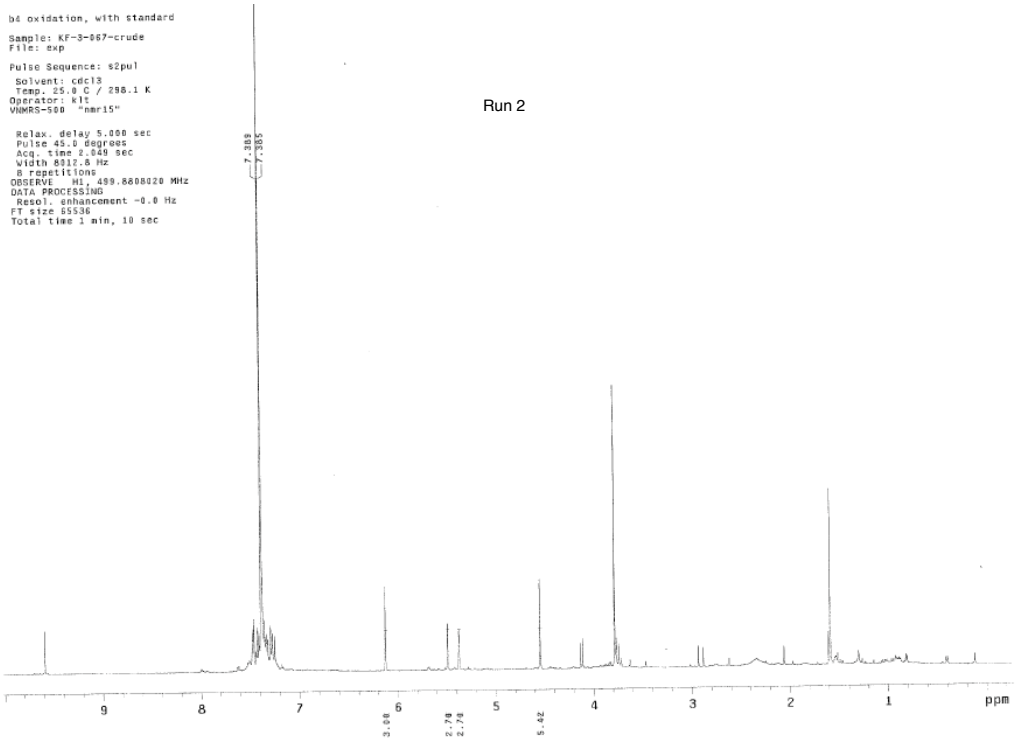
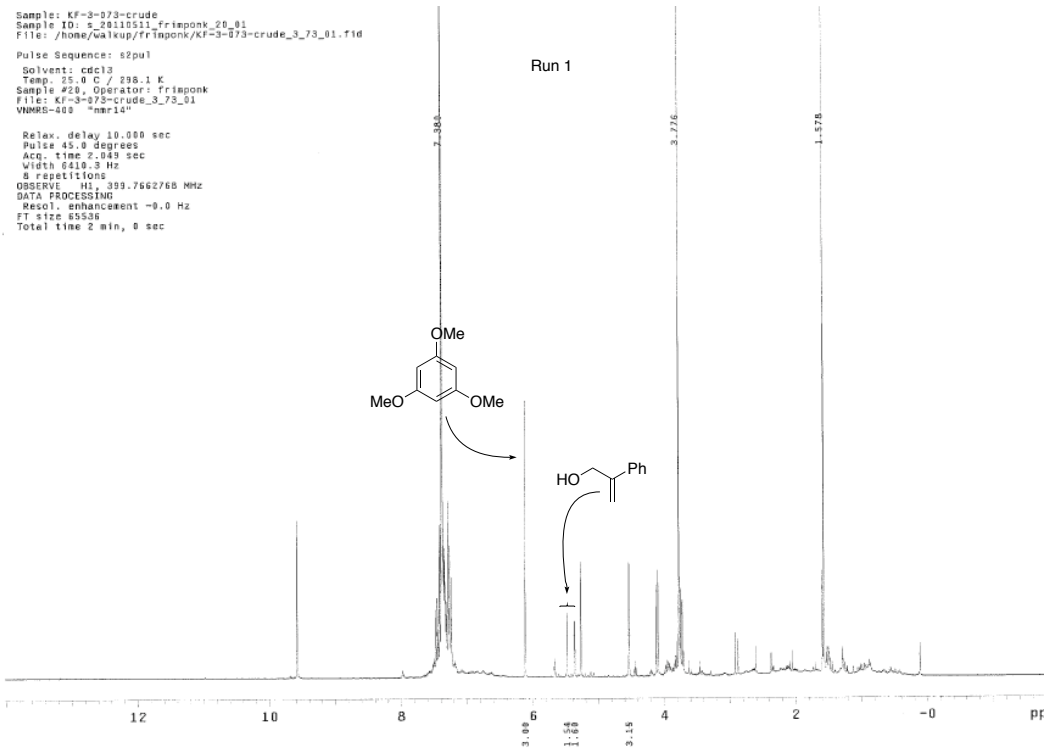
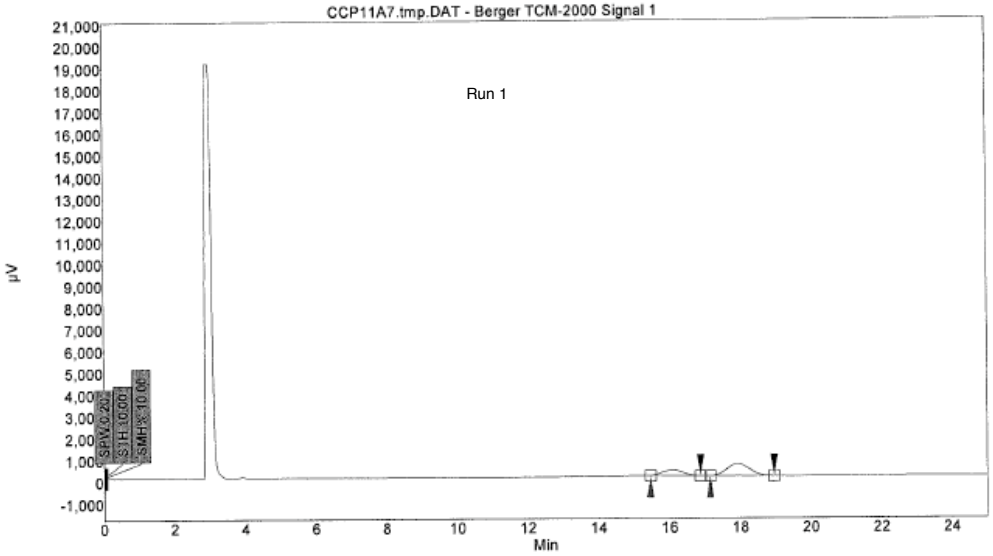
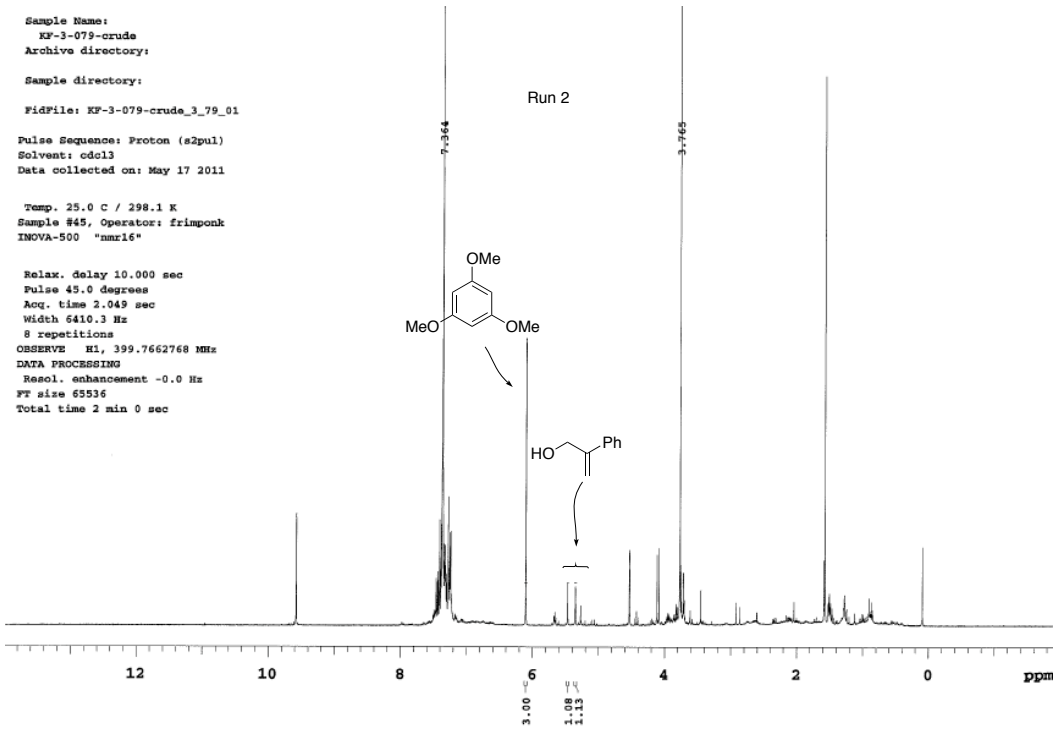


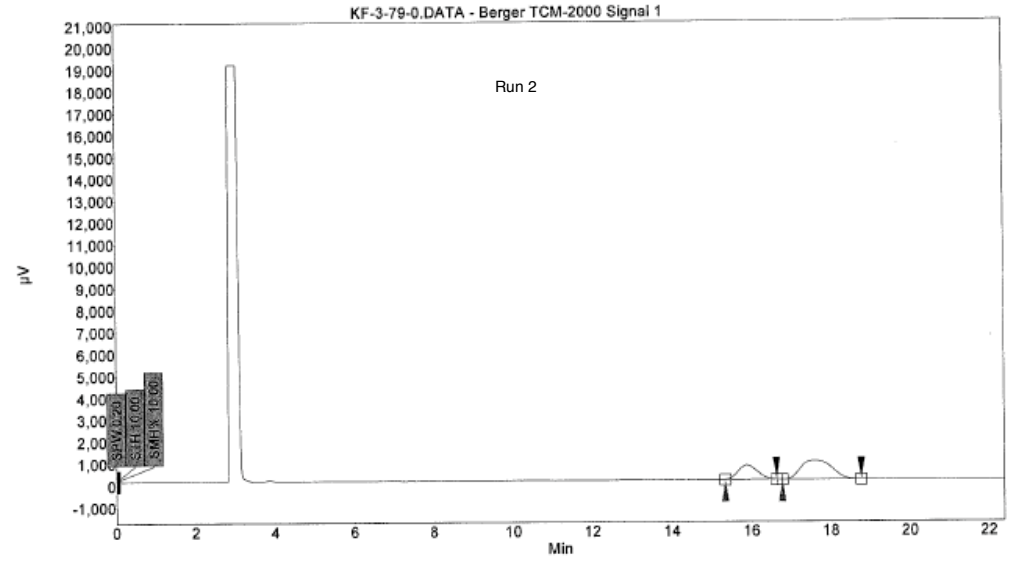
Table 2.6, Entry 3: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using ligand **2.52A** (10.7 mg, 0.030 mmol, 20 mol%), and *p*-toluenesulfonic acid (264 μL of 5.69 × 10^{-4} M in benzene, 1.5 x 10^{-4} mmol, 0.10 mol%) at 45 °C, and 100 psi CO/H_2. The isolated yield of the branched product was 63% (40% ee) for run 1 and 61% (36% ee) for run 2.





Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.45	16.08	16.87	0.00	30.15	271.2	178.0	30.149
2	UNKNOWN	17.14	17.92	18.95	0.00	69.85	553.4	412.3	69.851
Total						100.00	824.6	590.3	100.000

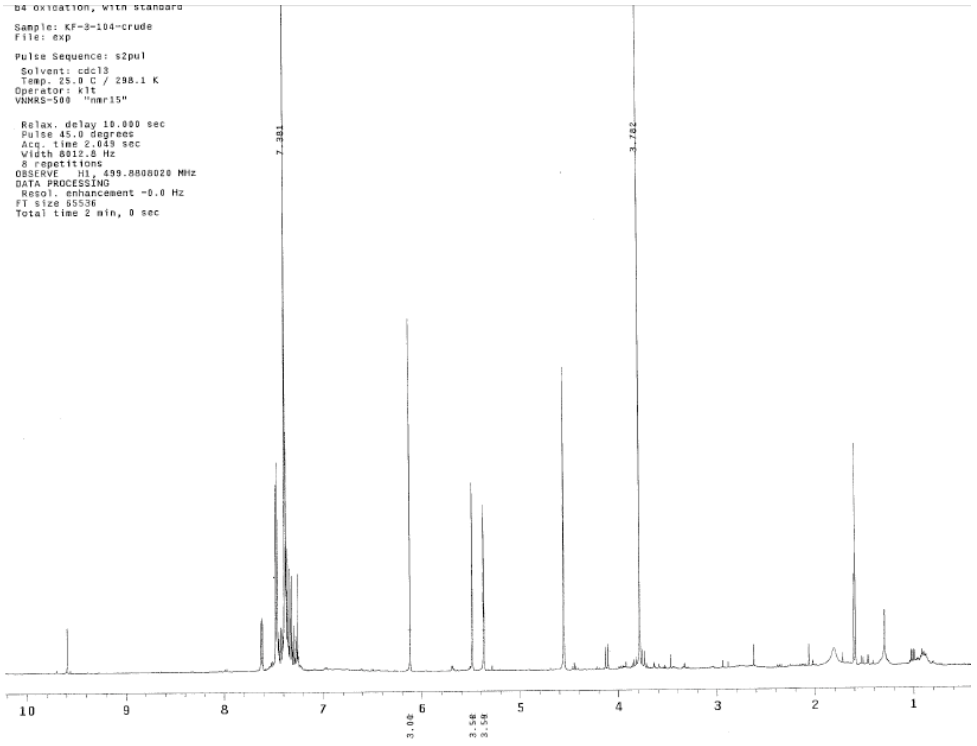


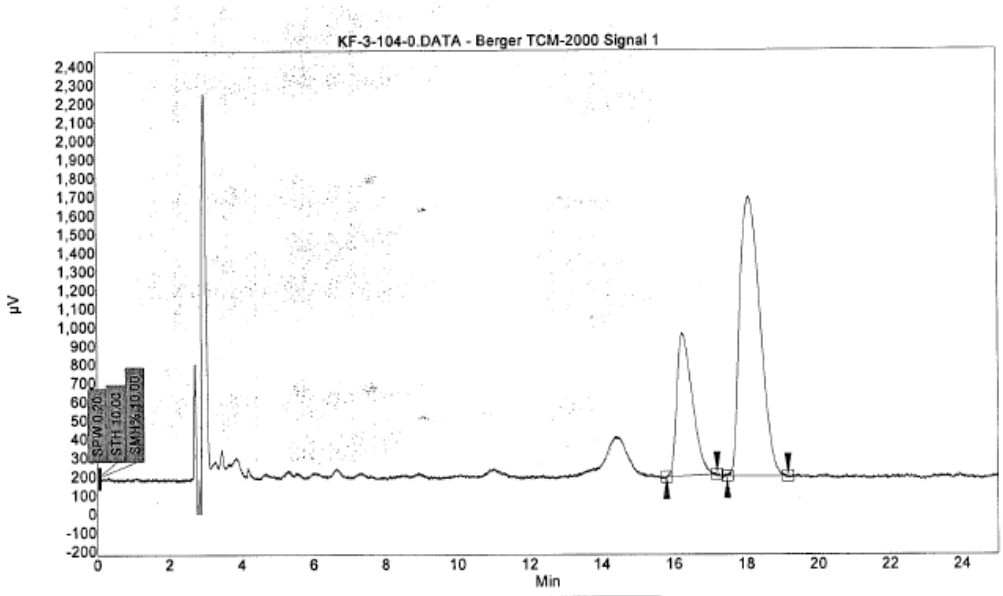


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.34	15.88	16.62	0.00	32.00	651.6	359.4	31.999
2	UNKNOWN	16.78	17.58	18.77	0.00	68.00	850.4	763.7	68.001
Total						100.00	1502.1	1123.1	100.000

Table 2.6, Entry 4: 2-Phenylprop-2-en-1-ol (**1.43**) was hydroformylated using ligand **2.52A** (10.7 mg, 0.030 mmol, 20 mol%), and *p*-toluenesulfonic acid (264 µL

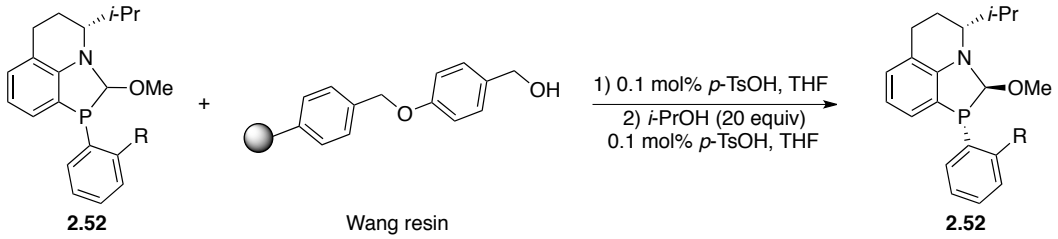
of 5.69 × 10^{-4} M in benzene, 1.5 x 10^{-4} mmol, 0.10 mol%) at 45 °C, and 100 psi CO/H_2. The isolated yield of the branched product was 54% (45% ee).



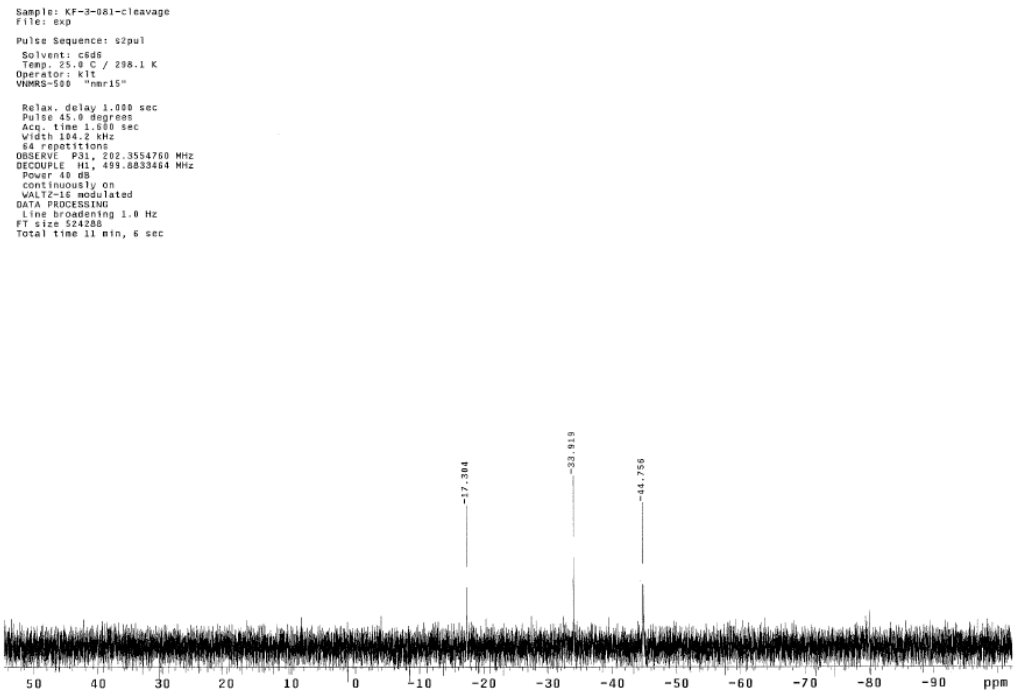


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	15.79	16.24	17.19	0.00	27.89	766.0	375.1	27.894
2	UNKNOWN	17.47	18.10	19.15	0.00	72.11	1497.1	969.7	72.106
Total						100.00	2263.1	1344.9	100.000

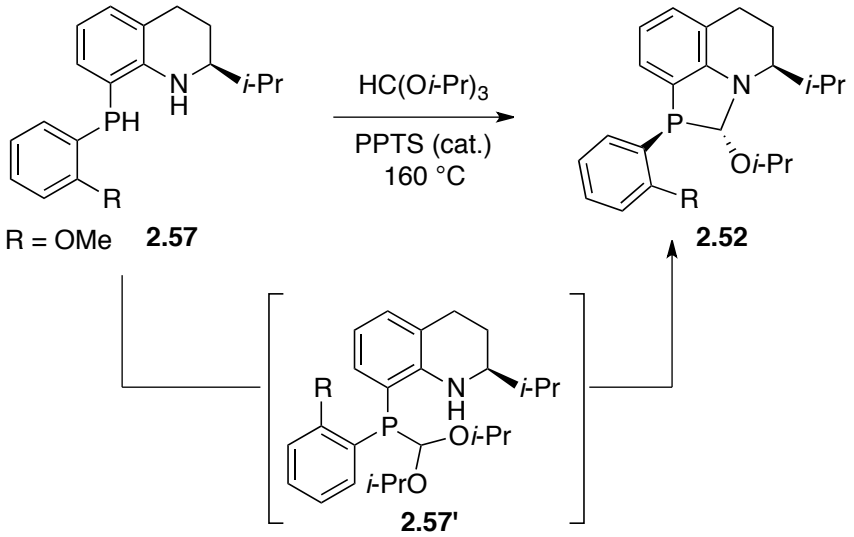
Ligand Purification with Wang Resin



To a scintillation vial with a stir bar was added ligand **2.52D** (50 mg, 0.130 mmol), *p*-TsOH (228 μL of 5.69 x 10^{-4} M, 1.3 x 10^{-4} mmol, 0.1 mol%) and THF (4 mL) in glovebox. This mixture was added to a scintillation vial containing Wang resin (300 mg, 0.391 mmol) that was swollen in 3 mL of THF for 15 minutes. The resulting mixture was stirred for 48 hours and filtered. The residue was put in a scintillation vial and 4 mL of THF was added. To this was added *i*-PrOH (200 μL, 2.60 mmol), and *p*-TsOH (228 μL of 5.69 x 10^{-4} M, 1.3 x 10^{-4} mmol). The resulting mixture was stirred for 2 days, filtered and concentrated. Analysis of the filtrate by ^{31}P NMR showed no equilibration of the diastereomers, with 66% recovery of the impure starting ligand.

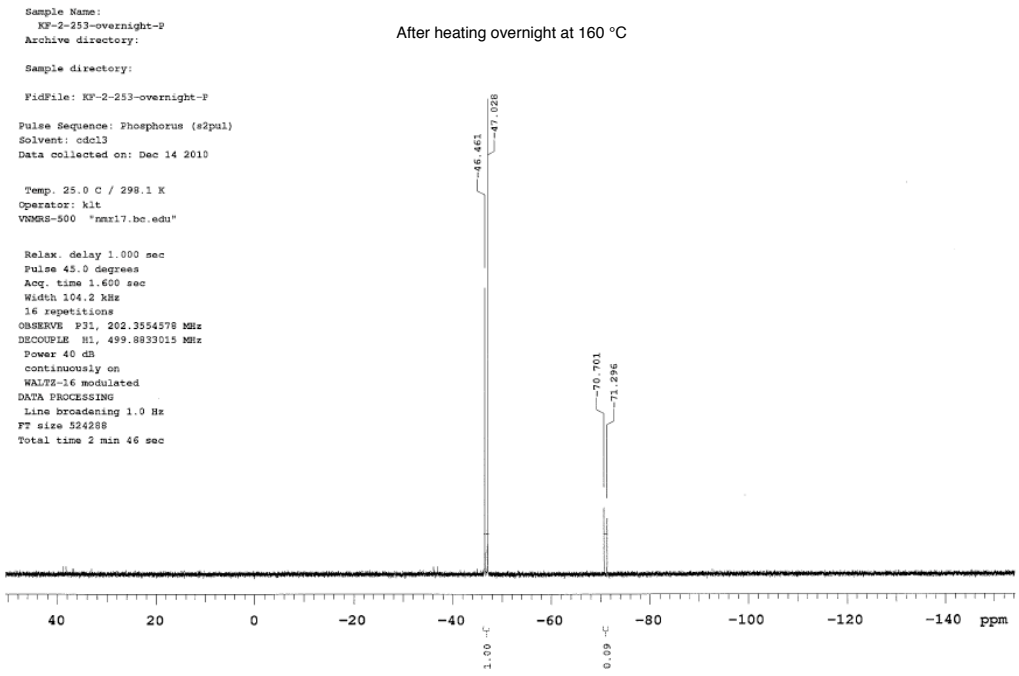


Thermodynamic Closure with Triisopropyl orthoformate

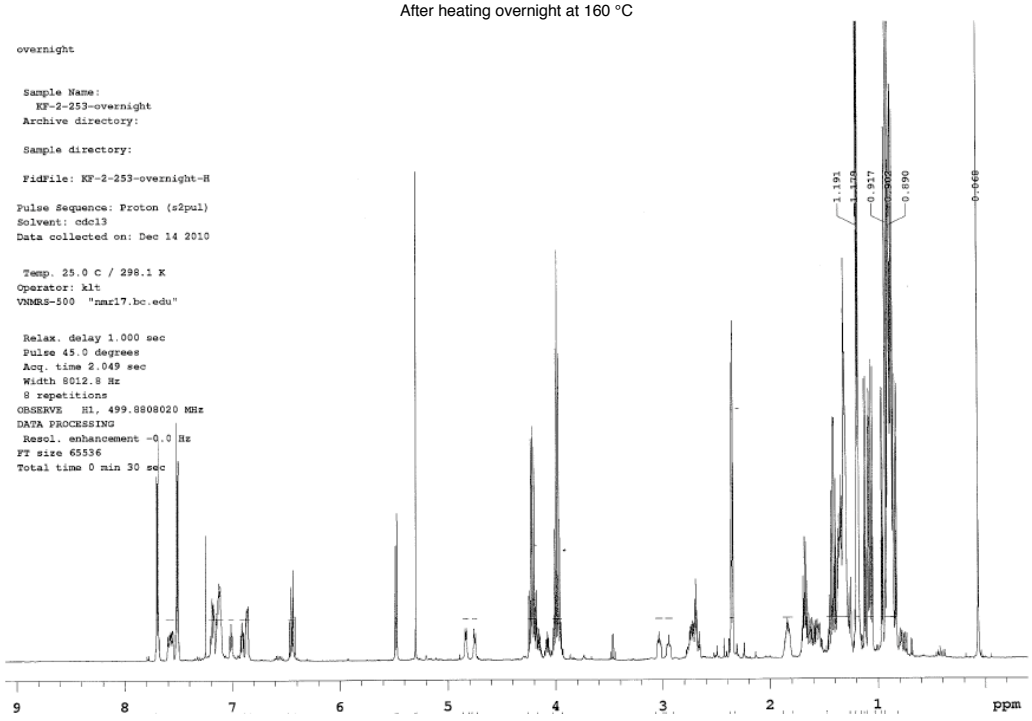


To a flame dried 2-neck round bottom flask with stir bar and reflux condenser was added phosphine **2.57** (587 mg, 1.97 mmol), pyridinium *p*-toluenesulfonic acid (25 mg, 0.099 mmol, 0.05 equiv.), and triisopropyl orthoformate (10 mL, 0.2 M). The resulting mixture was heated overnight at 160 °C. Analysis of an aliquot by ^{31}P NMR

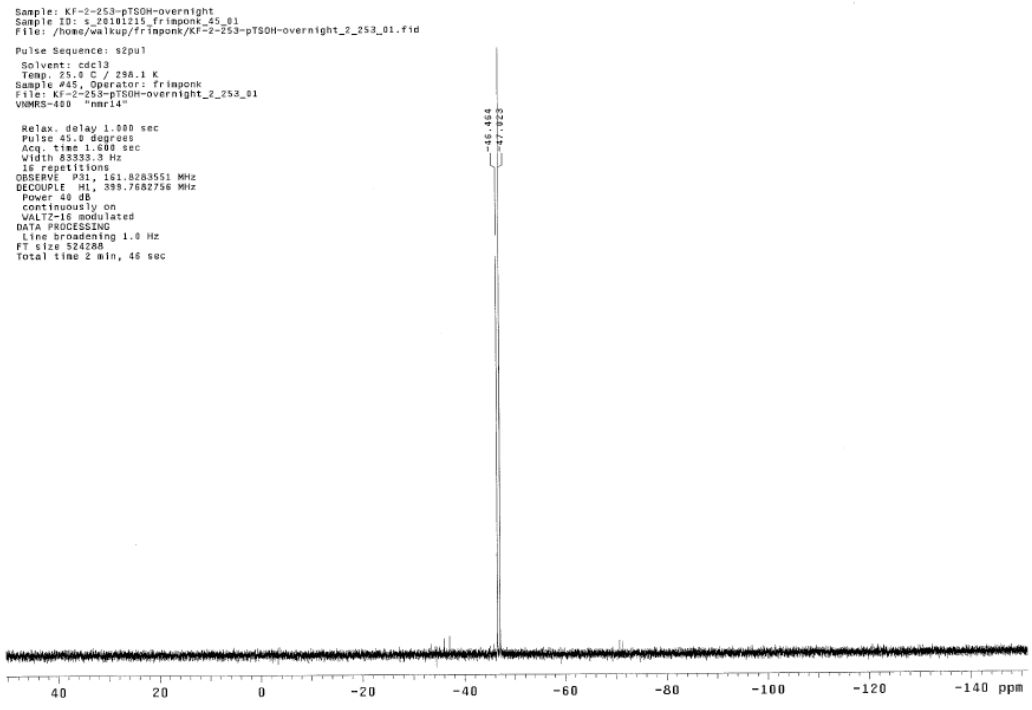
showed 8% of **2.57** and 92% of two diastereomers at -46.46 ppm and -47.03 ppm, identified by mass spectrometry (443.2598), ^{31}P NMR and ^{1}H NMR to be **2.57'**. To force closure, *p*-TsOH (3.5 mL of 5.69 x 10^{-4} M, 1.99 mmol, 1.0 equiv.) was added and stirred at 160 °C. Analysis of an aliquot after 16 hours showed only the 2 diastereomers at -46.46 ppm and -47.03 ppm by ^{31}P NMR. The reaction mixture was concentrated under vacuum. To the residue was added dimethyl acetamide (3 mL) and subjected to the following microwave conditions: P = 103 W, temperature = 250 °C, pressure = 108 psi. Analysis of the resulting reaction mixture by ^{31}P NMR showed formation of various unidentified decomposition products.



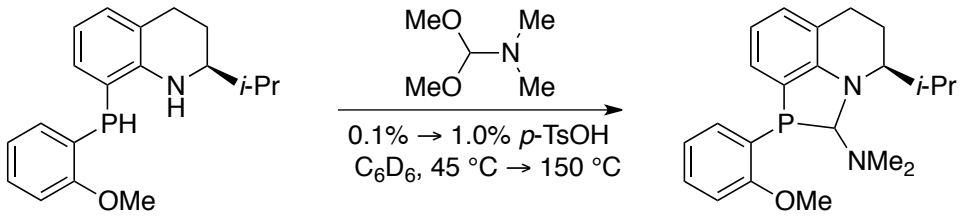
After heating overnight at 160 °C



After adding *p*-TsOH and heating at 160 °C for 16 h

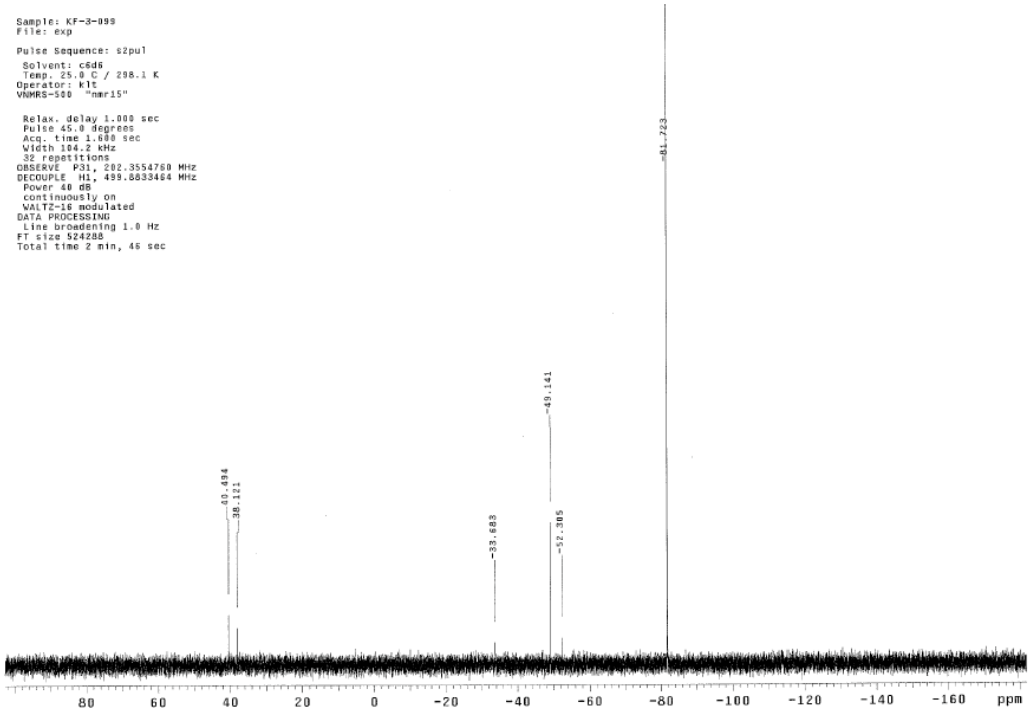


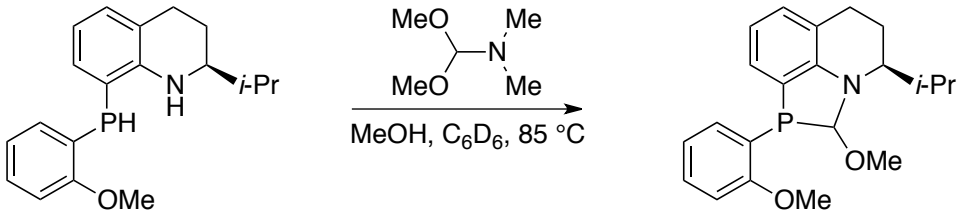
Thermodynamic Closure with DMF-dimethyl acetal



2.57 **2.58**

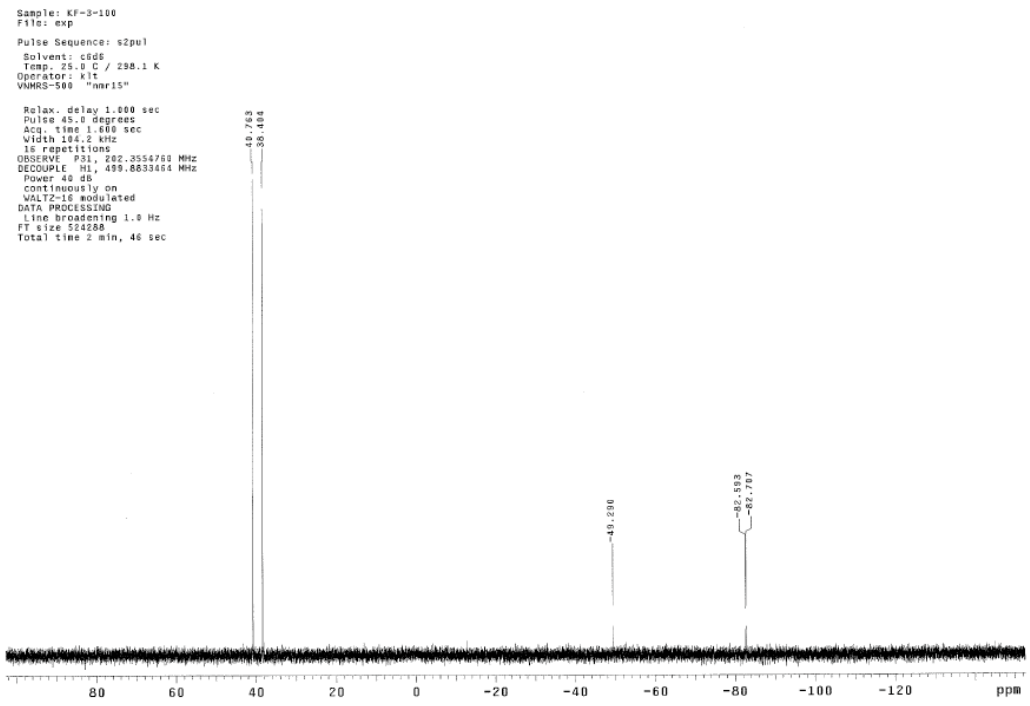
To an NMR tube in a glovebox was added DMF-dimethyl acetal (40.0 μL, 0.255 mmol, 5.00 equiv.) and **2.57** (16.0 mg, 0.0510 mmol) dissolved in benzene-d_6 (600 μL). The reaction mixture was heated at 45 °C for 1 hour. There was no conversion by ^{31}P NMR. The temperature was increased to 85 °C and heated overnight. ^{31}P NMR showed 2% conversion to two diastereomers at -49.5 ppm and -52.1 ppm. The temperature was raised to 100 °C and heated for 1 hour, with no observance of ligand peaks. *p*-TsOH (89.6 μL, 5.10 x 10^{-5} mmol, 1.00 x 10^{-3} equiv.) was added and the resulting mixture was heated at 100 °C for 2 hours. ^{31}P NMR showed no improvement. Additional *p*-TsOH (807 μL, 4.59 x 10^{-4} mmol, 9.00 x 10^{-3} equiv.) was added and the reaction was heated at 150 °C. ^{31}P NMR showed 86% of **2.57** remaining. Methanol (200 μL) was added and the reaction was heated at 85 °C for 2 hours. Analysis by ^{31}P NMR showed 82% of **2.57** remaining. The reaction temperature was maintained at 85 °C overnight and analysis by ^{31}P NMR showed some decomposition with no conversion to ligand.





2.57 **2.52A**

To an NMR tube in a glovebox was added DMF-dimethyl acetal (31.0 μL, 0.233 mmol, 5.00 equiv.), **2.57** (14.6 mg, 0.0466 mmol), 200 μL MeOH and benzene-d_6 (400 μL). The mixture was heated at 85 °C for 2 hours. Analysis by ^{31}P NMR showed 2.5% conversion to ligand (-33.9 ppm), 8% conversion to the unidentified diastereomers at -49.3 ppm and -52.5 ppm, 5% conversion to decomposed products (40.8 ppm and 38.5 ppm). The mixture was maintained at 85 °C overnight and analysis showed complete decomposition.



IX. References

1) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757.

2) Petnehazy, I.; Jaszay, Z. M.; Szabo, A.; Everaert, K. *Synthetic Communications* **2003**, *33*, 1665.