Application of Scaffolding Catalysis in Site- and Regioselective Transformations

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APPLICATION OF SCAFFOLDING CATALYSIS IN SITE- AND REGIOSELECTIVE TRANSFORMATIONS

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APPLICATION OF SCAFFOLDING CATALYSIS IN SITE- AND REGIOSELECTIVE TRANSFORMATIONS

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Abstract. Utilization of catalytic directing groups in the regioselective hydroformylation of 1,2-disubstituted olefins and in the site-selective functionalization of 1,2-diols.

Chapter One: Catalytic directing groups for the regioselective hydroformylation of allylic alcohols.

Chapter Two: Scaffolding catalysis as an alternate and more practical solution to the site-selective functionalization of 1,2-diols.

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List of Abbreviations

Ac	acetyl
acac	acetylacetonato
app	apparent
Bn	benzyl
cat.	catalytic
cy	cyclohexyl
DPPBA	*ortho*-diphenylphosphonylbenzoic acid
dr	diastereomeric ratio
ee	enantiomeric ratio
eq	equivalence
GC	gas chromatography
NMR	nuclear magnetic resonance
PMP	*para*-methoxyphenyl
phth	phthalamide
ppm	parts per million
psi	pounds per square inch
PPTS	pyridinium *para*-toluenesulfonate
p-TsOH	*para*-toluenesulfonic acid
rr	regioisomeric ratio
TBDPS	*tert*-butyldiphenyl

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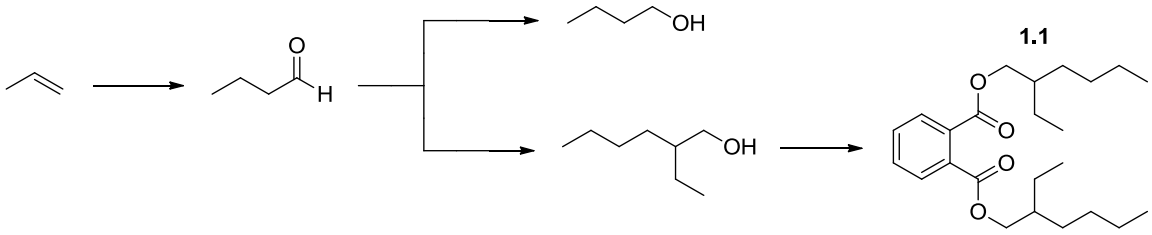
Chapter 1: Catalytic Directing Groups for the Regioselective Hydroformylation of Allylic Alcohols.[1]

I. Background

Hydroformylation, discovered in 1938 by Otto Roelen,[2] is an important industrial process for the synthesis of aldehyde products. It is used to prepare millions of tons of commodity products each year, including detergents and other specialty chemicals. For example, hydroformylation of propene leads to butanal, which can be hydrogenated to form butanol, a common organic solvent; alternatively, butanal can be elaborated to form a phthalate ester **1.1**, which is generally used as a plasticizer (Scheme 1.1).

Scheme 1.1: Examples of Hydroformylation Products.

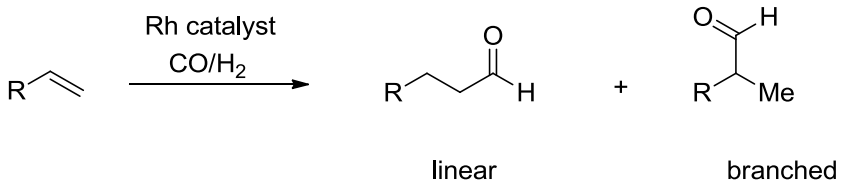


Hydroformylation is especially useful synthetically because it is an atom economical C-C bond forming reaction. The reaction entails the rhodium-catalyzed insertion of carbon monoxide and hydrogen gas across an olefin to form the homologated compound. During the transformation, two potential regioisomers can be formed: the linear and the branched (Scheme 1.2). Typically, the linear isomer is formed preferentially due to steric congestion at the metal center.

[1] The work presented in this chapter has been done in collaboration with Thomas Lightburn and Ka Cheng.
[2] a) Roelen, O. U.S. Patent 2327066, **1943**. b) Roelen, O. *Chem. Abstr.* **1944**, *38*, 5501.

Due to the regioselectivity challenges associated with hydroformylation, its use in organic synthesis has been limited. A great deal of effort has been spent to successfully

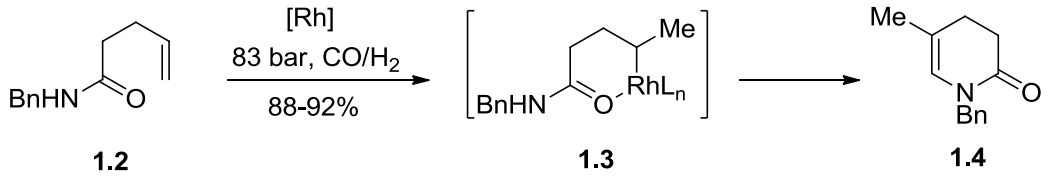
Scheme 1.2: Rhodium-Catalyzed Hydroformylation of Terminal Olefins



develop catalysts that are selective for the formation of the linear isomer.[3] However, fewer solutions have been presented for the selective formation of the branched product. One method relies on the incorporation of an electron-withdrawing group into the olefin.[4] Substrate such as vinyl acetates, vinyl cyanide and vinyl sulfones show a strong preference for the branched isomer due to their stabilization of the formal negative charge developing during hydrometallation. Furthemore, when placed at the optimal distance from the metal, these groups can pre-coordinate to the catalyst and carry out the transformation through chelation control. For example, direction by an amide functionality has been proposed in the literature; the γ-δ unsaturated amide **1.2** was hydroformylated to form exclusively, after cyclization, the benzyl protected methyldihydropyridinone **1.4** (Scheme 1.3).[5]

[3] a) Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavey, J. A.; Powell, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 5535. b) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2066.
[4] a) Devon, T. J.; Phillips, G. W.; Puckette, T. A.; Stavinoha, J. L.; Vanderbilt, J. J. U.S. Patent 4,694,109, **1987.** b) Devon, T. J.; Phillips, G. W.; Puckette, T. A.; Stavinoha, J. L.; Vanderbilt, J. J. *Chem. Abstr.* **1988**, *108*, 7890. c) Yamashita, H.; Roan, B. L.; Sakakura, T.; Tanaka, M. *J. Mol. Catal.* **1993**, *81*, 225.
[5] Ojima, I.; Korda, A.; Shay, W. R. *J. Org. Chem.* **1991**, *56*, 2024.

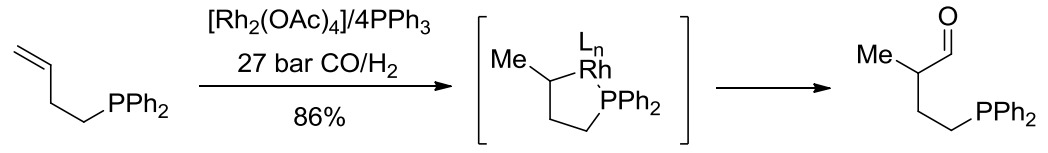
Scheme 1.3: Amide-Directed Hydroformylation of a Terminal Olefin.



1.2 **1.3** **1.4**

A number of phosphorous derivatives have also been used as directing groups for branch-selective hydroformylation. The use of phosphorous functionalities is advantageous because they can act as formal ligands on the metal center, and they are known to be efficient hydroformylation ligands.[1] For example, substrate **1.5** (Scheme 1.4)[6] can undergo hydroformylation in a regioselective fashion to form branched aldehyde **1.7** with a selectivity of >20:1 over the linear isomer. The origin of this regiochemical outcome is based on a transient 5-membered chelate **1.6** after coordination of the biaryl phosphine. Comparing this result to hex-1-ene, the latter is instead hydroformylated under the same conditions to give preferentially the linear aldehyde in a 3:1 ratio. Limitations of the above method include harsh conditions for the removal of the biaryl phosphine group and formation of stoichiometric amounts of byproduct.

Scheme 1.4: Phosphine-Directed Hydroformylation of a Terminal Olefin.



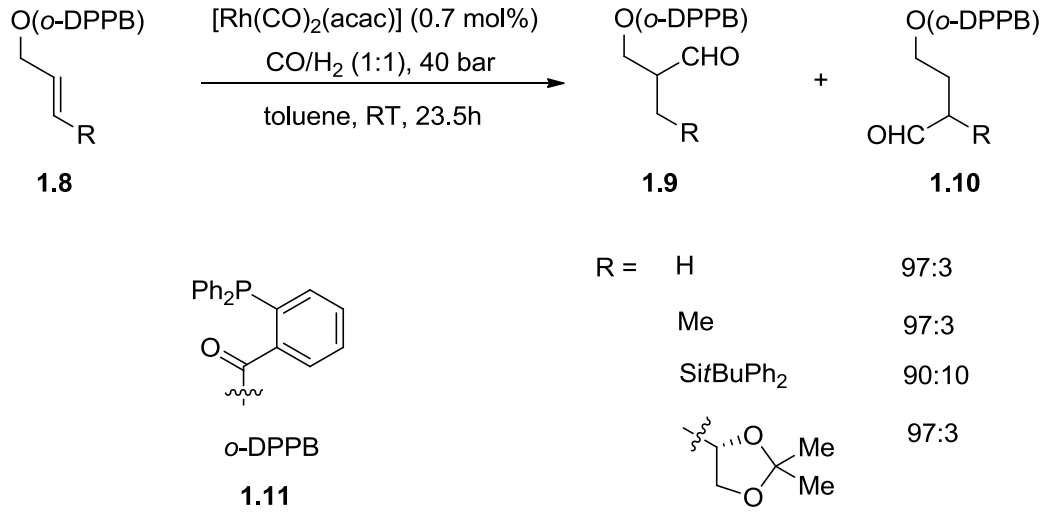
1.5 **1.6** **1.7**

Another phosphorous directing group that can be employed in hydroformylation is the *ortho*-diphenylphosphanylbenzoic acid **1.11** (*o*-DPPBA) (Scheme 1.5). Its utility

[6] Jackson, W. R.; Perlmutter P.; Suh, G.-H. *Chem. Comm.* **1987**, 724.

was shown during the hydroformylation of 1,2-disubstituted unsymmetric alkenes, which usually show low regiochemical control.[7] Subjecting a variety of allylic-*o*-DPPB esters (**1.8)** to hydroformylation afforded regioisomeric aldehyde **1.9** in good yields and regioselectivities (Scheme 1.5);[8] additionally, the *meta* variant of DPPBA, which heralded the work presented in Scheme 1.5, proved to be effective in the course of the total synthesis of phylanthocin.[9] An advantage of this directing group when compared to other phosphines is its ability to form an ester linkage, which allows for an easier introduction and removal from the product. However, like the biarylphosphine directing group in **1.5**, the *o*-DPPBA auxiliary must be used in stoichiometric quantities and it must be removed after the reaction is complete if it is not a desired component of the final product.

Scheme 1.5: Regioselective Hydroformylation of Allylic-*o*-DPPB esters.

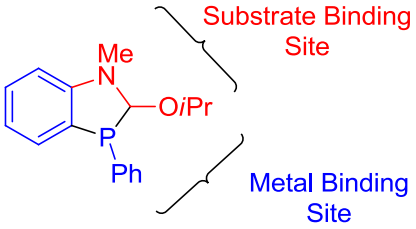


[7] Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264.
[8] Breit, B.; Grunanger, C. U.; Abillard, O. *Eur. J. Org. Chem.* **2007**, 2497.
[9] Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1990**, *55*, 2138.

II. Application of Catalytic Directing Groups in Hydroformylation

To overcome the limitations of using stoichiometric directing groups for the hydroformylation of olefins, the ideal solution would be the use of catalytic amounts of a directing group. In 2008, the Tan[10] group and the Breit[11] group simultaneously reported the use of two phosphorous-based catalyst-directing groups for the branch-selective hydroformylation of terminal and internal olefins. The success of this strategy was based on the ability of the ligands to bind the substrate in a covalent but reversible manner without changing the nature of the substrate. The Breit group developed catalytic directing groups in the form of phosphonites capable of transesterification, and their use was applied for the hydroformylation of homoallylic and bishomoallylic alcohols. For the same purpose, the Tan group instead designed a phosphine-based ligand (**1.12**) (Figure 1.1) that is not limited only to alcohol functionalities but can also bind to substrates containing a diverse set of functional groups, thus making this catalytic directing group more broadly applicable to the hydroformylation process.

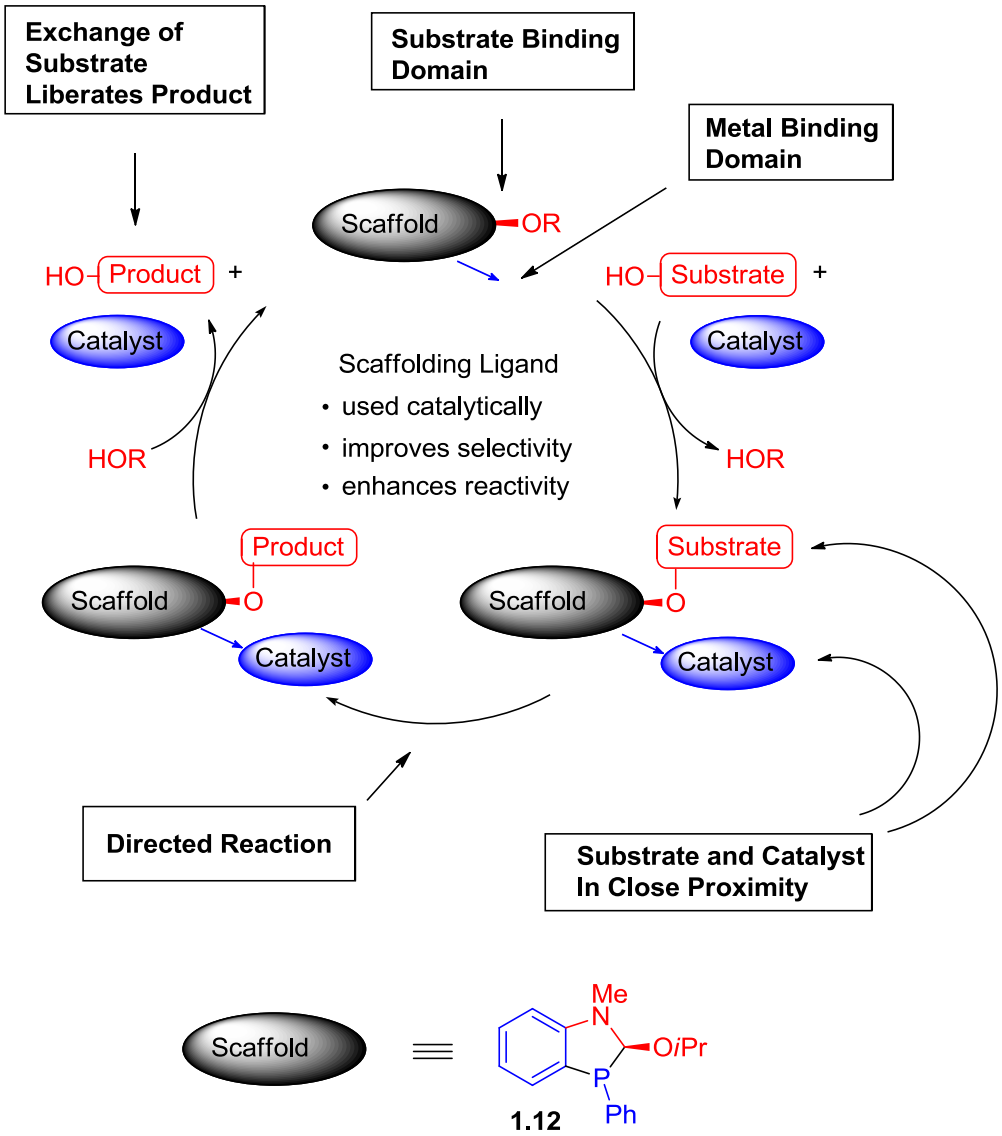
Figure 1.1: Design of the Scaffolding Ligand.



1.12

[10] Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210.
[11] a) Grunanger, C. U; Breit, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 7346. b) Smejkal, T.; Breit, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 311.

Figure 1.2: General Catalytic Cycle for Scaffolding Catalysis.



The phosphine-based ligand consists of an azaphosphole derivative prepared in three steps from commercially available *N*-methylaniline. It is characterized by two independent domains: 1) a substrate binding domain that contains an aniline nitrogen capable of inducing transacetalization with an alcohol substrate, and 2) a metal binding domain that contains an aryl phosphine. These structural specifications allow the ligand

to act as a molecular scaffold that brings the metal catalyst and the substrate into close proximity. This mode of catalysis, which we termed scaffolding catalysis, allows for both acceleration of the reaction as well as control of regiochemistry (Figure 1.2).

The unique substrate binding domain in the form of an orthoformate offers the possibility of bonding to a variety of functionalities, such as alcohols and amine derivatives, which are useful and common groups in subsequent synthetic manipulations. As such, the application of a scaffolding ligand allowed the Tan group to successfully carry out the regioselective hydroformylation of homoallylic alcohols,[10] sulfonamides,[12] and the enantio- and regioselective hydroformylation of PMP-protected amines;[13] the methodology was also extended to the formation of quaternary carbon centers through hydroformylation,[14] a transformation which was considered until recently a formidable challenge in organic synthesis.[15]

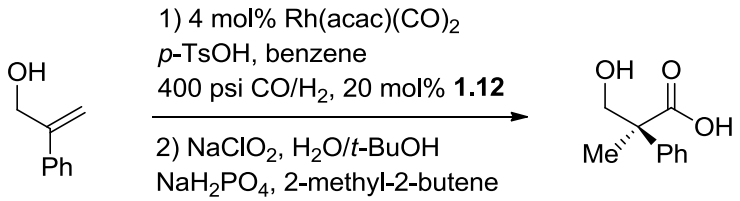
III. Hydroformylation of Allylic Alcohols.

In our latest synthetic efforts, after reporting excellent regioselectivities in the hydroformylation of 1,1-disubstituted olefins furnishing quaternary aldehyde products (Scheme 1.6),[14] we attempted the application of the catalytic system described above for the directed hydroformylation of substrates such as 1,2-di- and trisubstituted olefins. To that end, a variety of allylic alcohol substrates could potentially lead to the formation of

[12] Worthy, A. D.; Gagnon, M. M.; Dombrowski, M. T.; Tan, K. L. *Org. Lett.* **2009**, *11*, 2764.
[13] a) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757. b) Joe, C. L.; Tan, K. L. *J. Org. Chem.* **2011**, *76,* 7590.
[14] Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841.
[15] Dong, V. M.; Yeung, C. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 809.

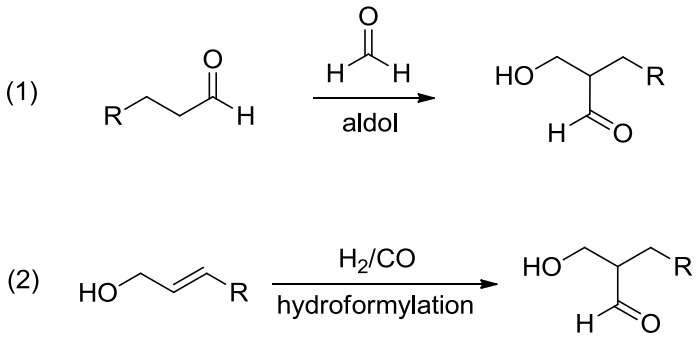
β-hydroxyaldehyde products; this transformation would provide an alternative disconnection to the formaldehyde aldol reaction (Scheme 1.7).

Scheme 1.6: Synthesis of Quaternary Carbon Centers via Hydroformylation.



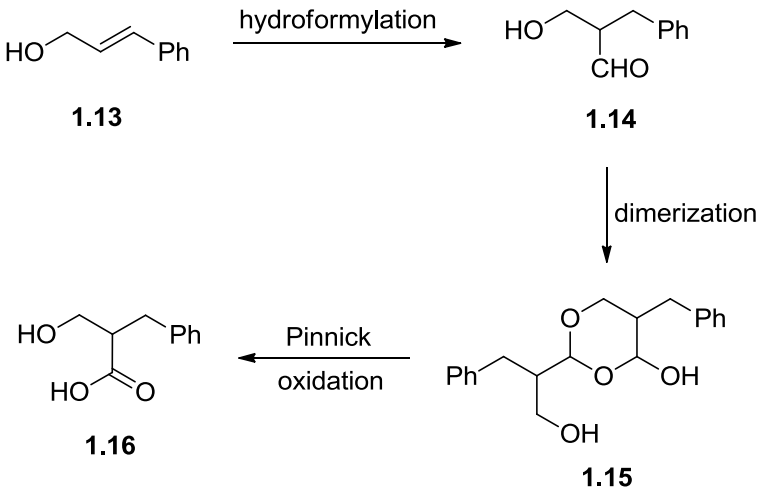
Investigations began with cinnamyl alcohol, a commercially available allylic alcohol. During the optimization of the reaction conditions, it was observed that not all the material after hydroformylation could be accounted for by NMR, which resulted in

Scheme 1.7: Formaldehyde Aldol Reaction and Hydroformylation for the Formation of β-Hydroxyaldehydes.



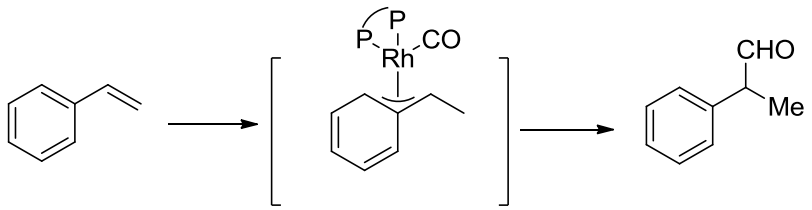
decreased yields and inaccurate regioselectivities. Based on previous experience[14] with the hydroformylation of 1,1-disubstituted olefins, it was found that dimer **1.15** formed during the reaction (Scheme 1.8). Fortunately, a simple Pinnick oxidation converted compound **1.15** to the β-hydroxyacid **1.16**. The use of triphenylphosphine for the hydroformylation of cinnamyl alcohol provided the undesired selectivity in favor of the lactone product **1.17** in a 12:88 ratio and 75% yield (Scheme 1.10). Such selectivity is

Scheme 1.8: Dimerization of the Aldehyde Product after Hydroformylation.



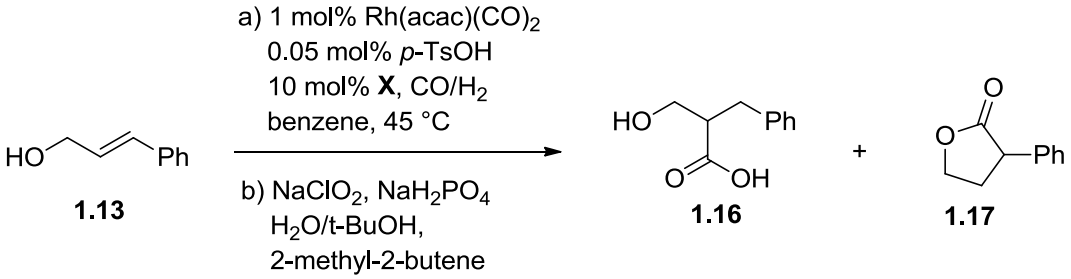
in accordance with other reports of hydroformylation of cinnamyl alcohol yielding the aldehyde α to the aromatic ring;[16] this is due to the fact that rhodium is inclined to form a π-allyl complex with the aromatic ring (Scheme 1.9), thus yielding the branch aldehyde preferentially in the case of styrene-based substrates. Using ligand **1.12**, $Rh(acac)(CO)_2$, and catalytic amounts of *p*-TsOH, it was found that the regioselectivity of the reaction could be completely reversed in favor of **1.16** (Scheme 1.10).

Scheme 1.9: Hydroformylation of Styrene.



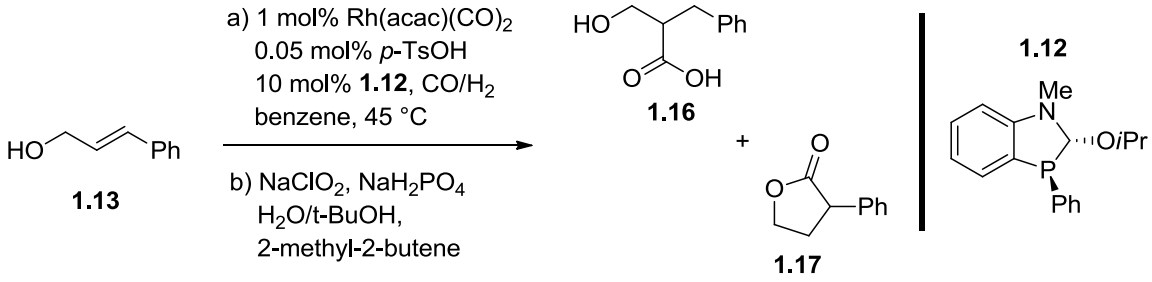
[16] a) Nozaki, K.; Li, W.; Horiuchi, T.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 4611. b) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett.* **2008**, *10*, 4553. c) McDonald, R. I; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027.

Scheme 1.10: Hydroformylation of Cinnamyl Alcohol.



X	regioselectivity (**1.16**:**1.17**)	Yield %
PPh_3	12:88	75
1.12	95:5	83

Table 1.1: Pressure Optimization.



entry	pressure (psi)	regioselectivity (**1.16**:**1.17**)	conversion %
1	50	96:4	85
2	100	95:5	90
3	200	95:5	89
4	400	95:5	88

The optimal conditions for the cinnamyl alcohol substrate were found to be mild. Using 1% $Rh(acac)(CO)_2$, 10% ligand **1.12**, 0.05% *p*-TsOH, 45 ^oC and 100 psi, the expected β-hydroxy acid **1.16** was obtained, upon oxidation, in 83% yield and excellent

regioselectivity (Table 1.1, entry 2).[17] It was found that changing the CO/H_2 pressure showed little effect on the conversion and selectivity.

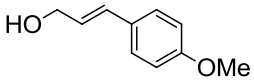
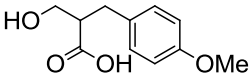
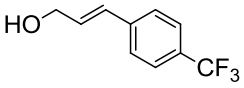
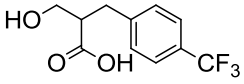
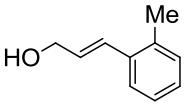
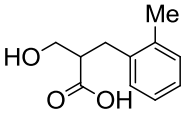
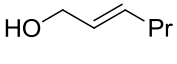
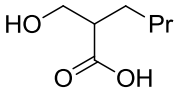
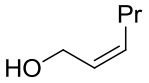
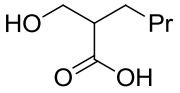
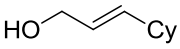
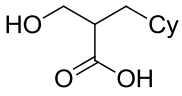
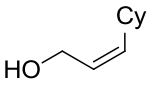
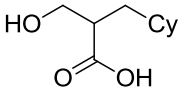
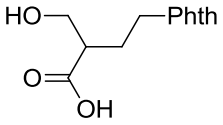
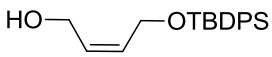
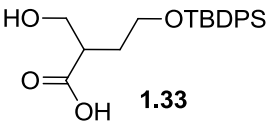
Given the excellent results obtained with the hydroformylation of cinnamyl alcohol, expansion of the substrate scope was investigated. Electronic perturbations and more sterically hindering groups on the aromatic ring afforded the desired products without erosion of regioselectivity (Table 1.2, entries 1-3). Both alkyl substituted *E* and *Z* olefins afforded the desired product with good yields and excellent regioselectivities (Table 1.2, entries 4-7). The reaction was also tolerant of heteroatoms in the form of a phthalamide and a TBDPS ether (Table 1.2, entries 8 and 9). Although phthalamide groups are known directing groups in hydroformylation,[18] the use of catalytic quantities of ligand **1.12** allows for a complete reversal of the inherent regioselectivity of the substrate to afford the γ-aminoacid product.

The application of ligand **1.12** also allows the use of mild conditions in the hydroformylation of trisubstituted olefins, a challenging substrate class. Because they are less reactive than 1,2-disubstituted olefins,[7] the hydroformylation of trisubstituted olefins requires slightly more elevated temperatures in the presence of 20 mol % **1.12**. For example, the hydroformylation of **1.34** was accomplished using 2 mol% $Rh(acac)(CO)_2$, 20% **1.12**, at 55 ^oC and 50 psi to furnish the desired product in 85% yield (Scheme 1.11). Since the insertion of the rhodium hydride into the olefin occurs through a *syn* addition, hydroformylation of both *E*- and *Z*-3-methyloct-2-en-1-ol leads to the formation of single

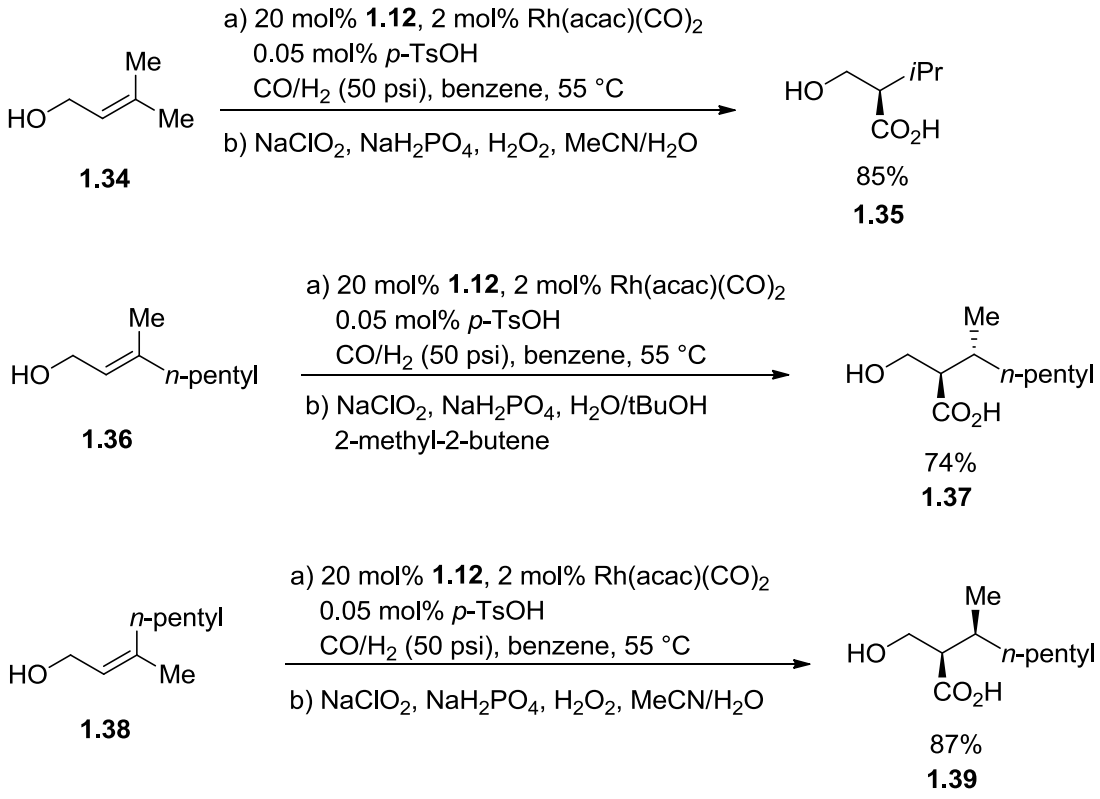
[17] Lightburn, T. E.; De Paolis, O. A.; Cheng, K. H., Tan, K. L. *Org. Lett.* **2011**, *13*, 2686.
[18] a) Zhang, X.; Cao, B.; Yu, S.; Zhang, X. *Angew. Chem. Int. Ed.* **2010**, *35*, 637. b) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027.

diastereomeric products (Scheme 1.11); the *E* olefin forms the *anti* product **1.37**, while the *Z* olefin forms the *syn* product **1.39**.

Table 1.2: Regioselective Hydroformylation of Allylic Alcohols.

entry	substrate	product	regioselectivity	yield
1	 **1.18**	 **1.19**	>95:5	87
2	 **1.20**	 **1.21**	>95:5	62
3	 **1.22**	 **1.23**	94:6	93
4	 **1.24**	 **1.25**	>95:5	81
5	 **1.26**	 **1.25**	>95:5	92
6	 **1.27**	 **1.28**	>95:5	72
7	 **1.29**	 **1.28**	>95:5	82
8	 **1.30**	 **1.31**	88:12	71
9	 **1.32**	 **1.33**	85:15	84

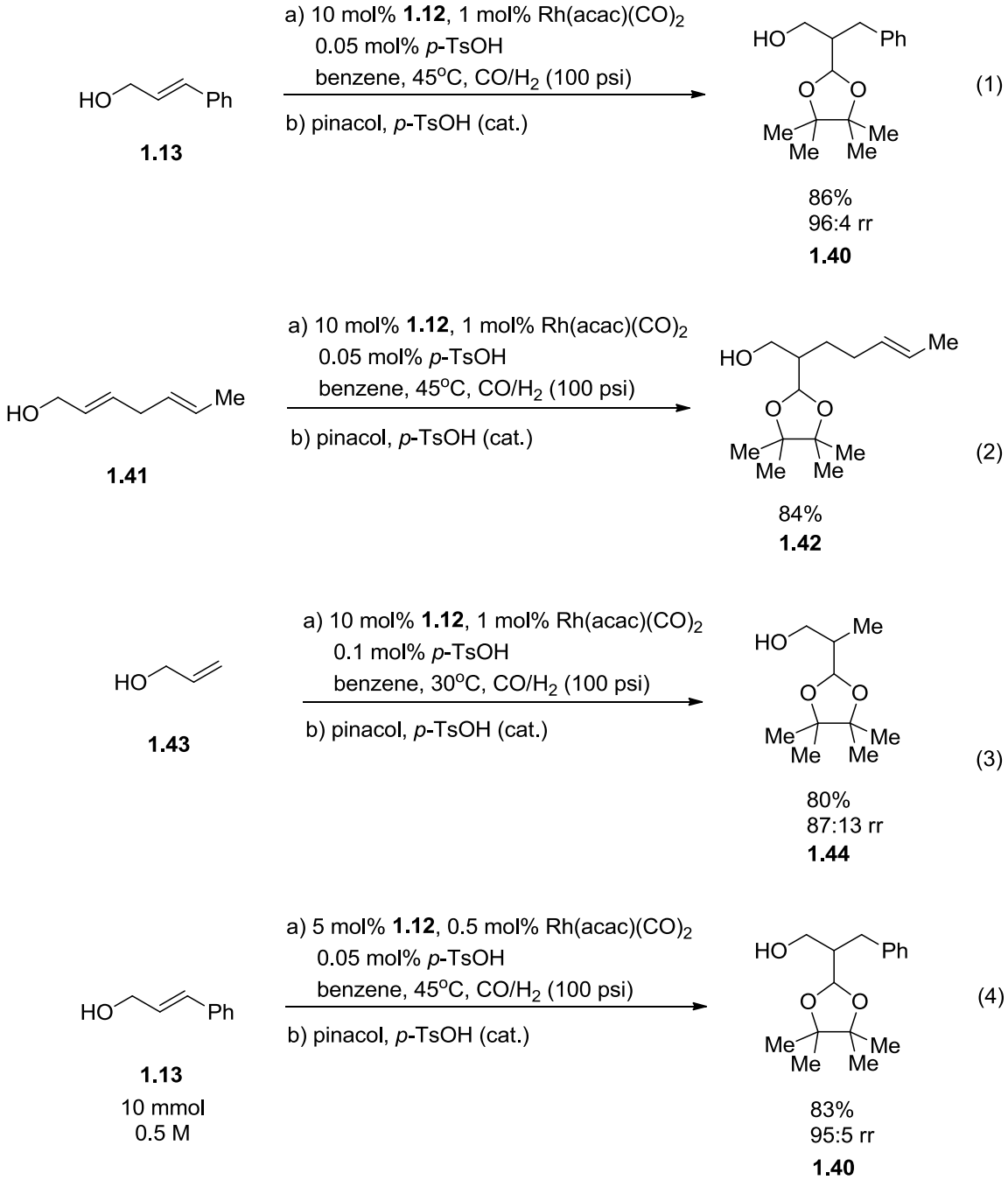
Scheme 1.11: Hydroformylation of Trisubstituted Olefins.



It was also shown that the hydroformylation products could be isolated in the aldehyde oxidation state. The reaction of cinnamyl alcohol and subsequent protection with pinacol affords the acetal in 86% yield (Scheme 1.12, equation 1), with selectivities comparable to those obtained after Pinnick oxidation. Acetal protection also allowed the successful hydroformylation of skip diene **1.41**. Performing a Pinnick oxidation on the mixture directly after hydroformylation of **1.41** led to an unidentifiable mixture of products. It is likely that the unreacted distal olefin is sensitive to the oxidative conditions. Using acetal protection conditions, **1.42** can be isolated in an 84% yield (Scheme 1.12, equation 2). This procedure was also used in the hydroformylation of allyl

alcohol, which formed the desired product in 80% yield and good regioselectivity at 30°C (Scheme 1.12, equation 3).

Scheme 1.12: Acetal Protection of Hydroformylation Products.



In order to showcase the practicality of the method, hydroformylation was performed on a larger scale. On 10 mmol scale, the product could be isolated in 83% yield with no erosion in regioselectivity (Scheme 1.12, equation 4). More importantly, the rhodium loading was reduced to 0.5 mol% and ligand loading was lowered to 5 mol%. The volume efficiency was also improved by increasing the concentration from 0.1M to 0.5M.

IV. Conclusion

The design and synthesis of a phosphine ligand capable of acting as a scaffold for the rhodium catalyst and the olefin substrate has allowed for the resolution of a long-standing problem in regioselective hydroformylation. The concepts of reversible covalent binding and intramolecular activation are at the heart of this new catalytic system and it has quickly become a powerful way of controlling regioselectivity. The hydroformylation of 1,2-di- and trisubstituted olefins can be carried out under mild conditions, and it generates, in the case of trisubstituted olefins, two stereocenters in a stereospecific fashion. The synthetic utility of the reaction was also extended by isolating the hydroformylation products in the aldehyde oxidation state, and by scaling up the reaction while reducing catalyst and ligand loading.

V. Experimental

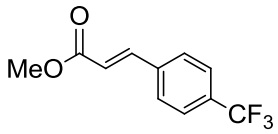
General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Cinnamyl alcohol was purchased from Aldrich Chemical Co. and was dried in a vacuum dessicator with P_2O_5 before use. *Cis*- and *trans*-2-hexen-1-ol were purchased from Aldrich Chemical Co. and used as received. 3-Methyl-2-buten-1-ol and allyl alcohol were purchased from Aldrich Chemical Co. and were distilled from $CaSO_4$ and degassed by three successive freeze-pump-thaw cycles prior to being brought into a drybox for use. Lithium reagents were titrated against *N*-benzyl benzamide in THF at 0 °C. Flash column chromatography was performed using Silicycle SiliaFlash F60 silica gel and ACS grade solvents as received from Fisher Scientific, except for methylene chloride which was distilled using a short path distillation head at ambient pressure (Note: methylene chloride as received contained a greasy yellow residue on evaporation). All experiments were performed in oven- or flame-dried glassware under an atmosphere of nitrogen or argon using standard syringe and cannula techniques, 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 NMR were performed on either a Bruker AS400 400 MHz or a Varian VNMRS 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. Coupling constants are reported in Hz. 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}. High resolution mass spectrometry (HRMS) data was generated in Boston College facilities with DART-TOF as the ionization technique. Hydroformylation was performed in an Argonaut Technologies Endeavor® Catalyst Screening System using 1:1 H_2/CO supplied by Airgas, Inc. Ligand **1.12** was prepared as previously reported by our group.[1]

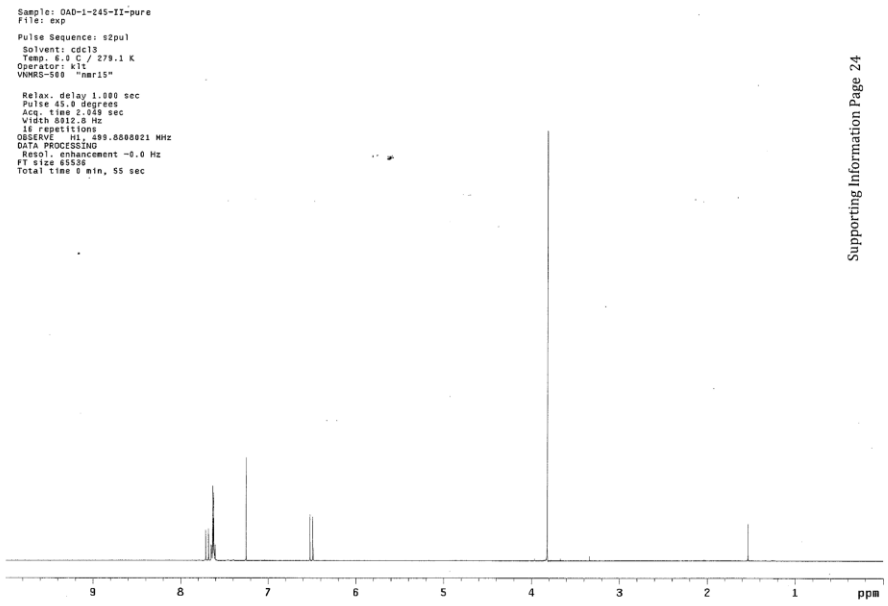
Substrate Syntheses and Characterizations

The following compounds were made according to literature procedures and matched reported spectra: (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol,[2, 3] (*E*)-3-cyclohexylprop-2-en-1-ol,[4, 5] (*Z*)-3-cyclohexylprop-2-en-1-ol,[4, 6] (2*E*,5*E*)-hepta-2,5-dien-1-ol,[7] (*Z*)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-en-1-ol,[8] 4,7-dihydro-1,3,2-dioxathiepine 2-oxide.[9]



(*E*)-Methyl 3-(4-(trifluoromethyl)phenyl)acrylate. To a suspension of sodium hydride (310 mg, 12.6 mmol) in diethyl ether (40 mL) was added methyl-2-(diethoxyphosphoryl) acetate (2.3 mL, 12.6 mmol) in diethyl ether (8 mL) dropwise. After stirring for 1 h at room temperature, 4-(trifluoromethyl)benzaldehyde (1.6 mL, 11.5 mmol) in diethyl ether (2 mL) was added dropwise and the mixture was allowed to stir overnight. The resulting mixture was quenched with ammonium chloride, extracted with diethyl ether (3 x 30 mL) and dried over magnesium sulfate. The crude product was purified on silica gel eluting with 10% ethyl acetate in hexanes to yield 680 mg (24%) of the title compound as a

white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, 1H, *J*= 16), 7.65-7.60 (m, 4H), 6.50 (d, 1H, *J*= 16), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 142.8, 137.7, 131.7 (q, *J*= 32), 128.1, 126.1, 125.7 (q, J= 271), 120.3, 51.7; IR: 2956, 1711, 1318, 1111, 1066 cm^{-1}; HRMS Calcd. for $C_{11}H_{10}F_3O_2$ $[M+H]^+$: 231.0633, Found: 231.0628.



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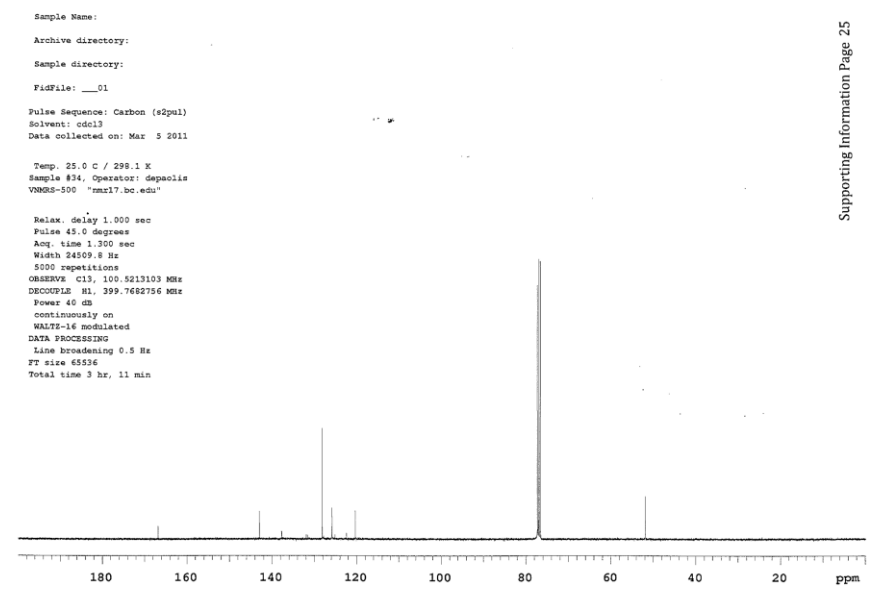

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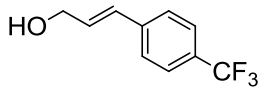

(*E*)-3-(4-(Trifluoromethyl)phenyl)prop-2-en-1-ol (1.20). A suspension of lithium aluminum hydride (318 mg, 8.40 mmol) in diethyl ether (8 mL) was cooled to 0 °C. Aluminum trichloride (511 mg, 2.80 mmol) in diethyl ether (4 mL) was added slowly. The mixture was allowed to warm to room temperature and was stirred for an additional 30 min. (*E*)-methyl 3-(4-(trifluoromethyl)phenyl)acrylate (680 mg, 2.8 mmol) in diethyl ether (8 mL) was added dropwise and allowed to stir for 30 min. The reaction mixture was quenched with 15% aqueous sodium hydroxide and then acidified with 1M hydrochloric acid. The aqueous layer was extracted with diethyl ether (3 x 20 mL), washed with brine and dried over magnesium sulfate. The crude product was purified on silica gel eluting with 20% ethyl acetate in hexanes to yield 420 mg (70 %) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, 2H, *J*= 8.2), 7.46 (d, 2H, *J*= 8.2), 6.65 (d, 1H, *J*= 16), 6.44 (dt, 1H, *J*=16.0, 5.4), 4.35 (d, 2H, *J*= 5.4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.2, 131.2, 129.4 (q, *J*= 32.7), 129.2, 126.5, 125.5 (q, *J*= 3.8), 124.1 (q, *J*= 271), 63.2; IR: 2374, 2937, 1337, 1123, 856 cm^{-1}; HRMS Calcd. for $C_{10}H_8F_3$ $[M\text{-}H_2O+H]^+$: 185.0578, Found: 185.0588.

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Solvent: cdcl3
Data collected on: Mar  7 2011

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Sample #34, Operator: depaolis
VNMRS-500  "nmr17.bc.edu"

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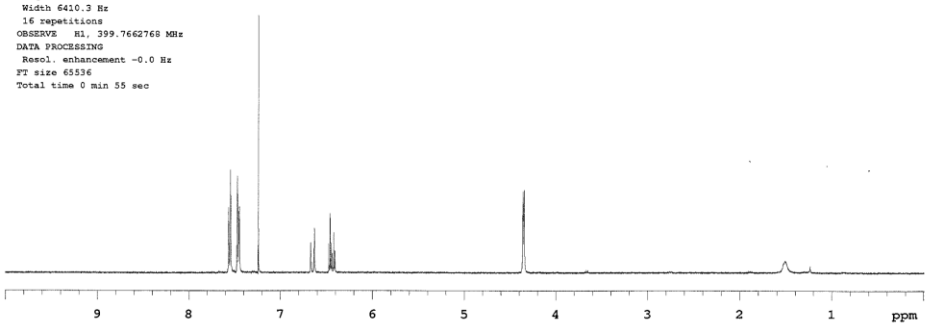

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at	1.300	in	n
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fb	17000	hs	nn
bs	64	PROCESSING	
d1	1.000	lb	0.50
nt	512	fn	not used
ct	512	DISPLAY	
TRANSMITTER		sp	-13.5
tn	C13	wp	20115.4
sfrq	100.532	rfl	1700.2
tof	1028.1	rfp	0
tpwr	57	rp	-150.0
pw	4.650	lp	0
DECOUPLER		PLOT	
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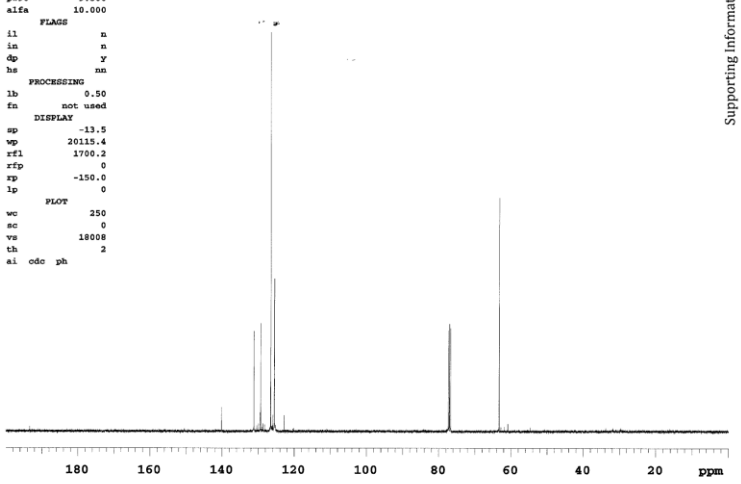
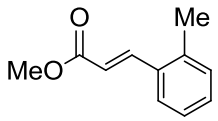
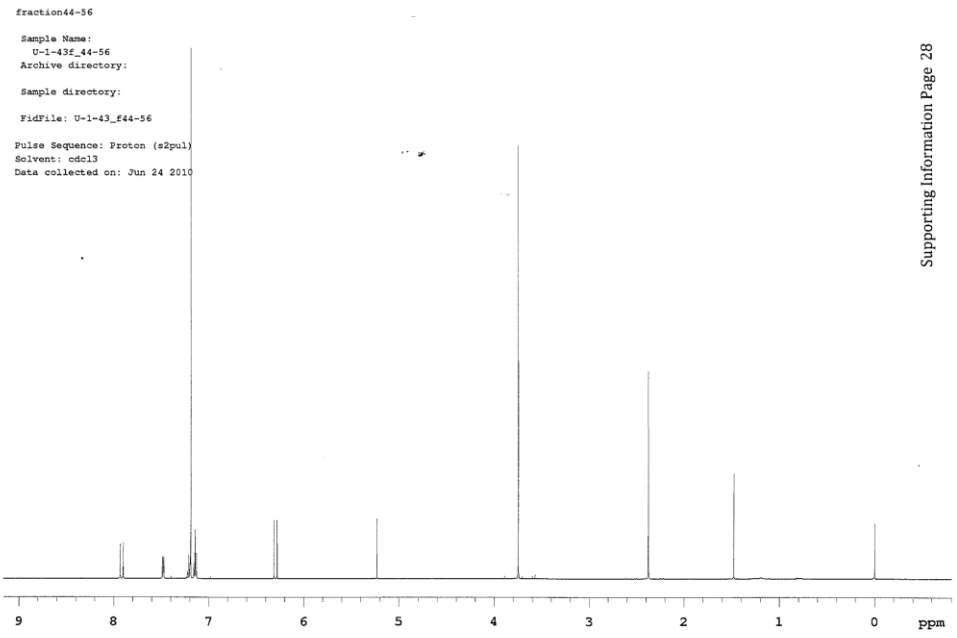
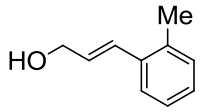




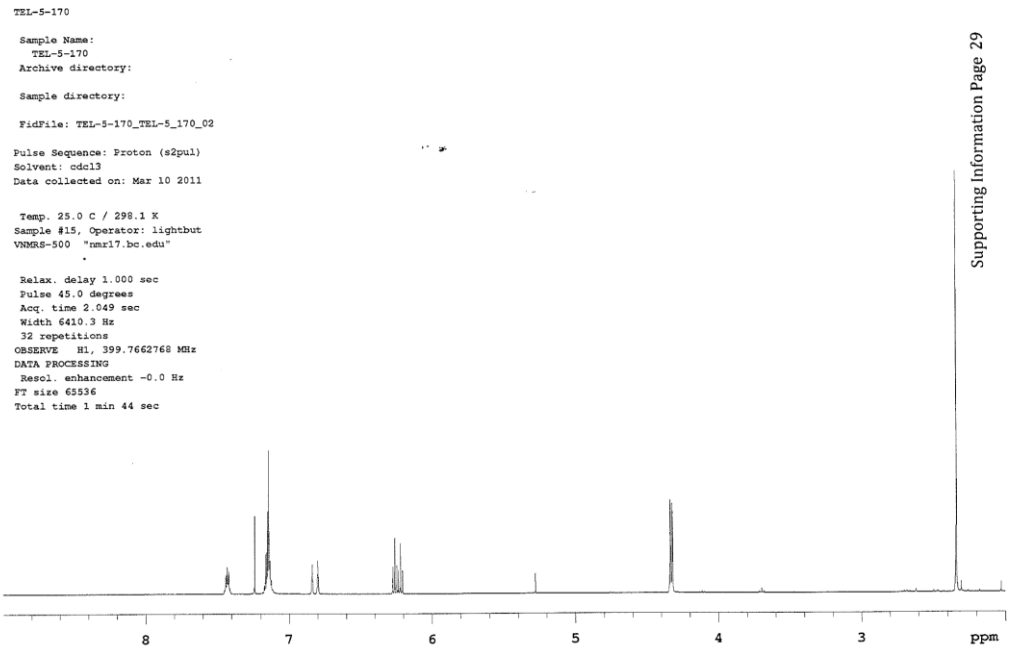
(*E*)-Methyl 3-(*o*-tolyl)acrylate. To a suspension of sodium hydride (247 mg, 10.3 mmol) in *N*,*N*-dimethylformamide (4.1 mL) at 0 °C was added methyl diethylphosphonoacetate (1.89 mL, 10.3 mmol) dropwise. The reaction was warmed to room temperature for 15 min and re-cooled to 0 °C. *o*-Tolualdehyde (1.35 g, 11.3 mmol) in *N*,*N*-dimethylformamide (3.6 mL) was added and the reaction was stirred for 20 h. The reaction was cooled to 0 °C, quenched with water (200 mL), extracted with ethyl acetate (3 x 50 mL), dried over anhydrous magnesium sulfate and concentrated. Purification on silica gel eluting with 10% ethyl acetate in hexanes yielded 850 mg (43%) of a clear oil whose spectra matched those reported in the literature.[10]

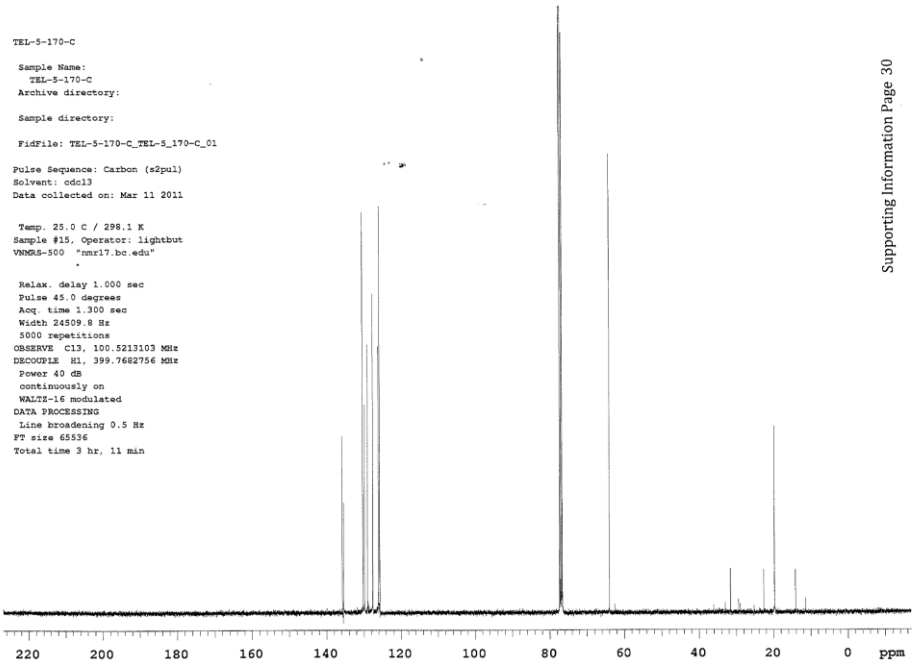


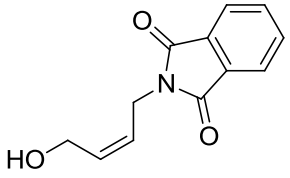


(*E*)-3-(*o*-Tolyl)prop-2-en-1-ol (1.22). A 25 mL flask was charged with lithium aluminum hydride (499 mg, 13.1 mmol) and diethyl ether (13 mL). The suspension was cooled to 0°C in an ice water bath and aluminum trichloride (561 mg, 4.2 mmol) was added and the reaction was stirred for 30 min. (*E*)-methyl-3-(*o*-tolyl)acrylate (850 mg, 4.80 mmol) was added as a solution in diethyl ether (13 mL) and the reaction was stirred for 30 min. The reaction was carefully quenched with 1M NaOH and then acidified with 1M HCl. Brine was added and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate and

concentrated. Purification on silica gel eluting with 25% ethyl acetate in hexanes yielded 317 mg (44%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46-7.40 (m, 1H), 7.18-7.11 (m, 3H), 6.82 (dt, 1H, *J*= 15.6, 1.6), 6.24 (dt, 1H, *J*= 15.6, 6.0), 4.33 (dd, 2H, *J*= 5.6, 1.6), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.7, 135.5, 130.3, 129.8, 129.0, 127.6, 126.1, 125.7, 64.0, 19.8; IR: 3372 (br), 3021, 2924, 2861, 1723, 1677, 1485, 1460, 968, 747 cm^{-1}; HRMS Calcd. for $C_{10}H_{11}$ $[M-H_2O+H]^+$: 131.0861, Found: 131.0859.

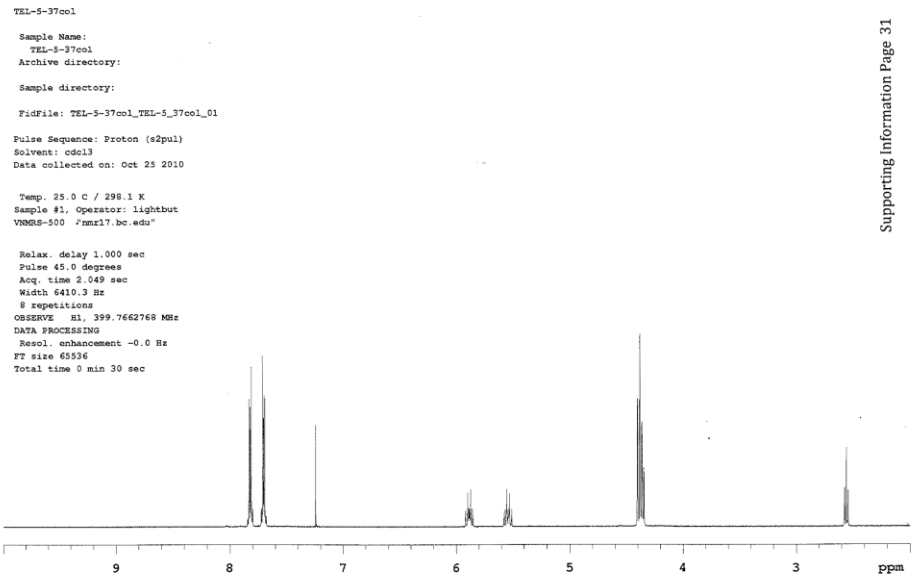


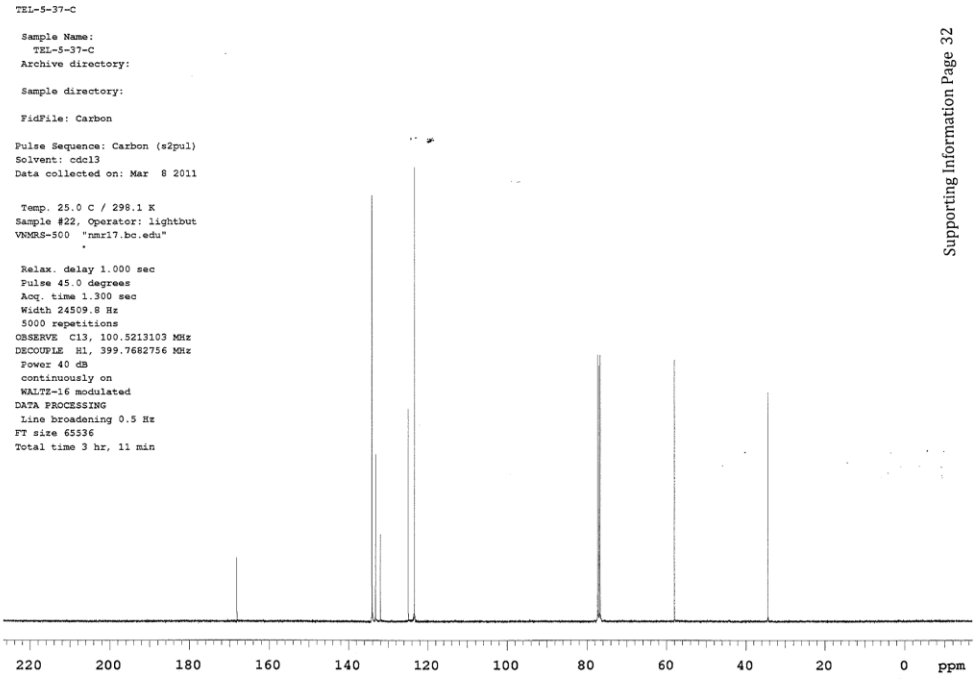




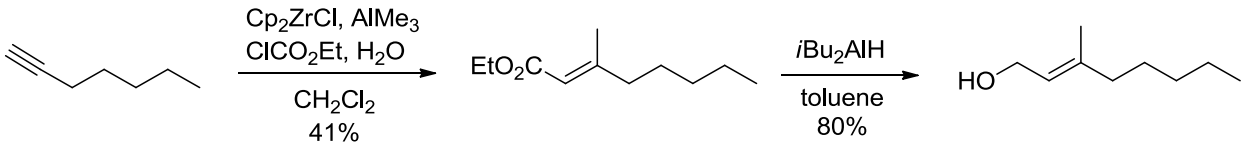
(*Z*)-2-(4-Hydroxybut-2-en-1-yl)isoindoline-1,3-dione (1.30). To a 100 mL flask was added 4,7-dihydro-1,3,2-dioxathiepine 2-oxide[9] (2.99 g, 22.3 mmol), dimethylformamide (12 mL), and potassium phthalamide (3.54 g, 19.1 mmol) and the suspension was heated to 100 °C for 1 h. The reaction was cooled and quenched by careful addition of water (32 mL). The aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organics were washed with water. Purification on silica gel eluting with 35% ethyl acetate in hexane afforded 2.06 g (42%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85-7.79 (m, 2H), 7.73-7.67 (m, 2H), 5.92-5.85 (m, 1H), 5.58-5.50

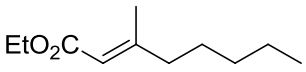
(m, 1H), 4.41-4.34 (m, 4H), 2.56 (t, 1H, *J*= 6.4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 134.1, 133.2, 132.0, 124.9, 123.4, 58.0, 34.4; IR: 3458 (br), 2922, 1770, 1706, 1393, 1325, 716 cm^{-1}; HRMS Calcd. for $C_{12}H_{12}NO_3$ $[M+H]^+$: 218.0817, Found: 218.0825.





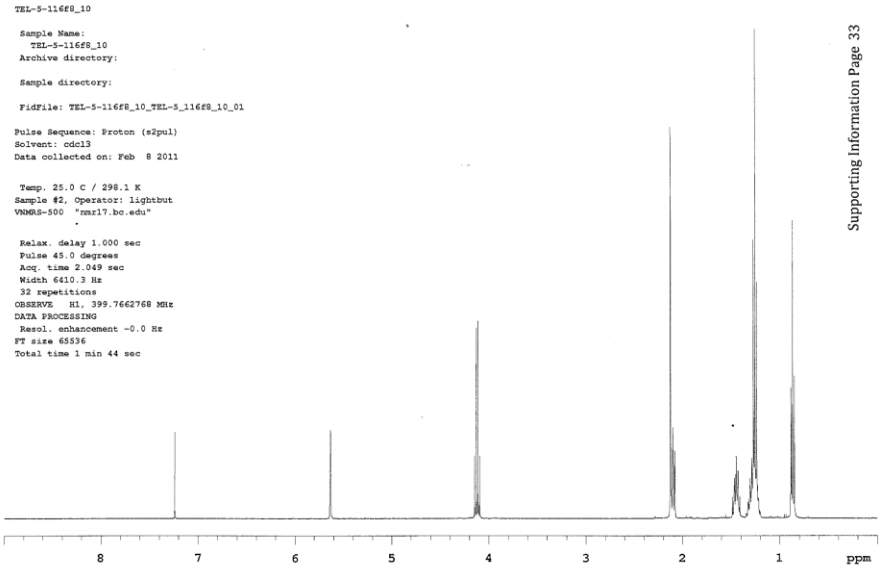
Synthesis of Substrate **1.36**





(*E*)-Ethyl 3-methyloct-2-enoate. To a flame dried 250 mL flask was added zirconocene dichloride (584 mg, 2.00 mmol). Methylene chloride (40 mL) and hexane (15 mL) were added and the reaction was cooled to -30 °C. Trimethyl aluminum (2.97 mL, 31.0 mmol) was added and the reaction was stirred at -30 °C for 10 min. Water (270 uL, 15.0 mmol)

was added dropwise and the reaction was stirred for 10 min. Hept-1-yne (1.31 mL, 10.0 mmol) was added as a solution in methylene chloride (15 mL) and the reaction was stirred for 15 min. Ethyl chloroformate (1.15 mL, 12.0 mmol) was added and the reaction was stirred for 30 min. allowing the reaction to warm to -10 °C. The reaction was allowed to warm to room temperature and a saturated aqueous solution of potassium carbonate (3.1 mL) was added slowly. The reaction was stirred for 15 min., anhydrous magnesium sulfate (6.0 g) was added and the solution was filtered. The solid was rinsed with diethyl ether (30 mL). The combined organic layers were concentrated and purified on silica gel eluting with a gradient of 2-10% ethyl acetate in hexanes, affording 760 mg (41%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.63 (s, 1H), 4.12 (q, 2H, *J*= 7.4), 2.14-2.07 (m, 5H), 1.50-1.40 (m, 2H), 1.35-1.19 (m, 7H), 0.87 (t, 3H, *J*= 7.1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 160.3, 115.4, 59.4, 40.9, 31.3, 27.0, 22.4, 18.7, 14.3, 13.9; IR: 2957, 2931, 2860, 1715, 1648, 1460, 1220, 1144, 1111, 1041, 868 cm^{-1}; HRMS Calcd. for $C_{11}H_{21}O_2$ $[M+H]^+$: 185.1542, Found: 185.1539.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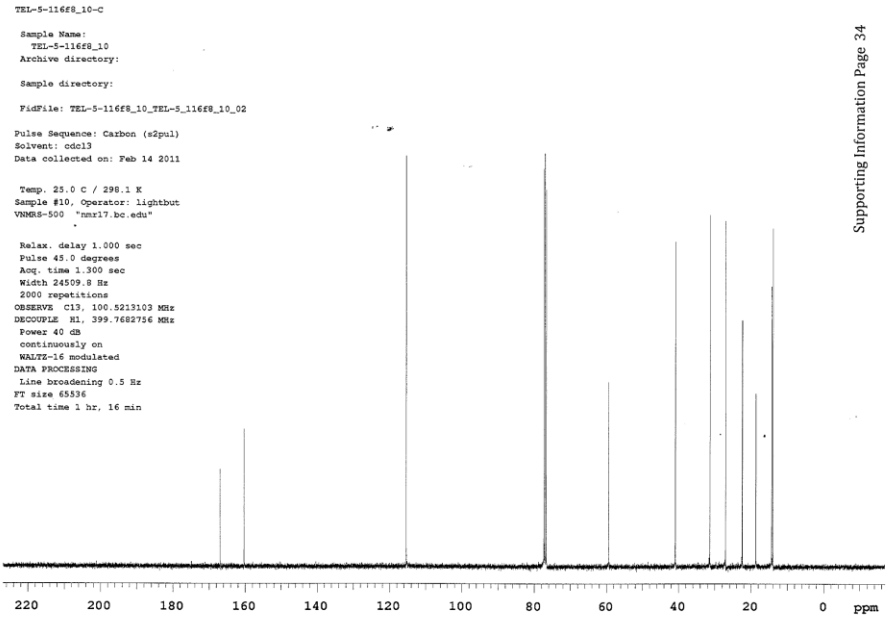
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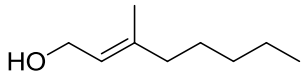
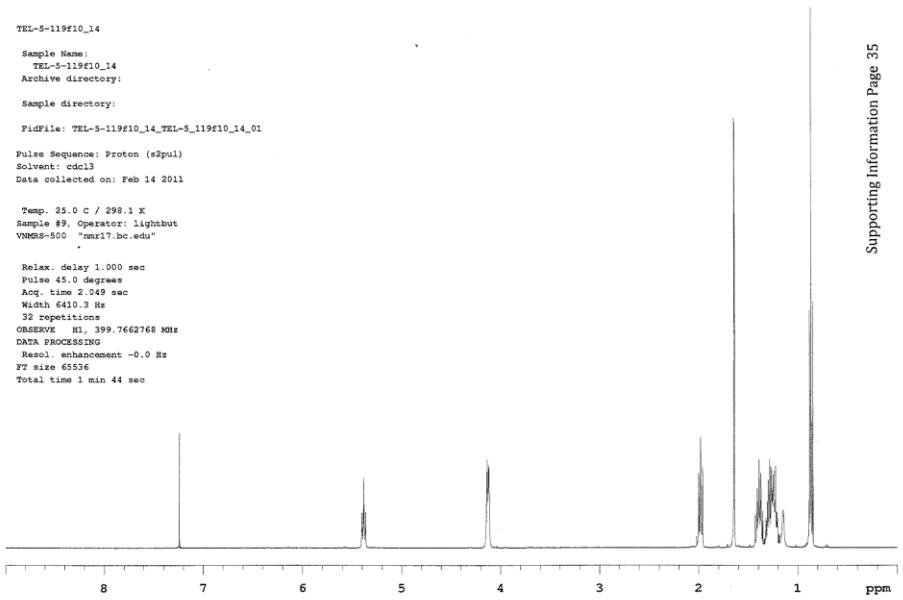


(*E*)-3-Methyloct-2-en-1-ol (1.36). To a dry 50 ml flask was added (*E*)-ethyl 3-methyloct-2-enoate (760 mg, 4.12 mmol) in toluene (9 mL). The solution was cooled to 0 °C and DIBAL-H (1.62 mL, 9.10 mmol) was added dropwise as a solution in toluene (4 mL). The reaction was stirred overnight, allowing the reaction to warm to room temperature. The reaction was poured onto aqueous HCl (1M, 20 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL), dried over anhydrous magnesium sulfate and purified on silica gel, eluting with a gradient of 10-20% ethyl acetate in hexanes, resulting in 469 mg (80%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.42-5.35 (m, 1H), 4.16-4.10 (m, 2H), 1.98 (t, 2H, *J*= 7.6), 1.64 (s, 3H), 1.44-1.12 (m, 7H), 0.87 (t, 3H, *J*= 7.1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.2, 123.0, 59.4, 39.5, 31.5, 27.3, 22.5, 16.1, 14.0; IR: 3415 (br), 2957, 2926, 2858, 1669, 1458, 1379, 998 cm^{-1}; HRMS Calcd. for C_9H_{17} $[M-H_2O+H]^+$: 125.1330, Found: 125.1330.



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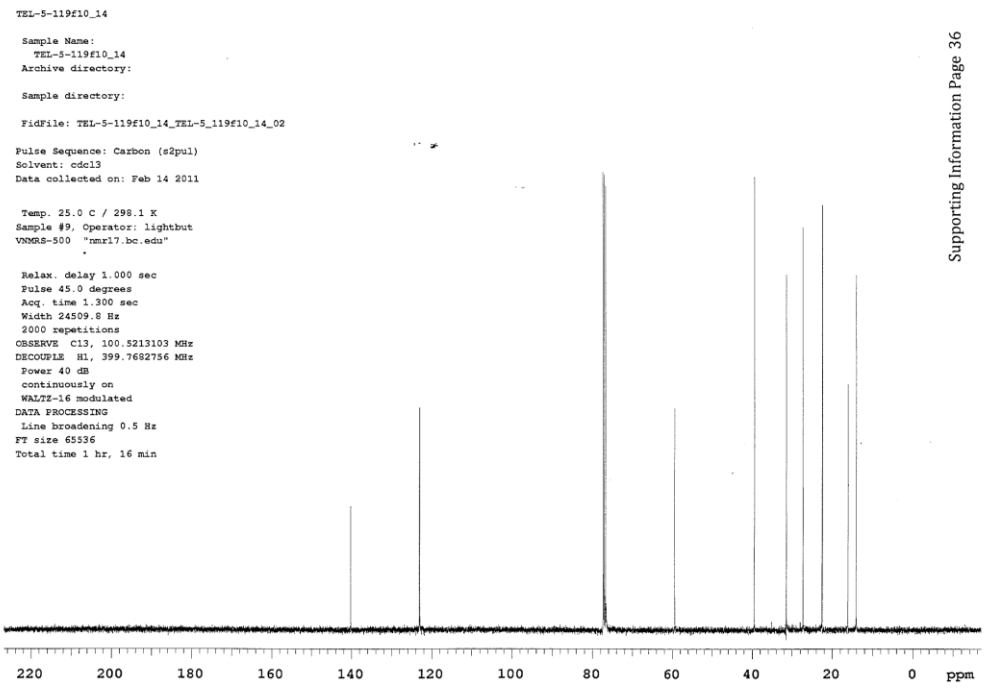

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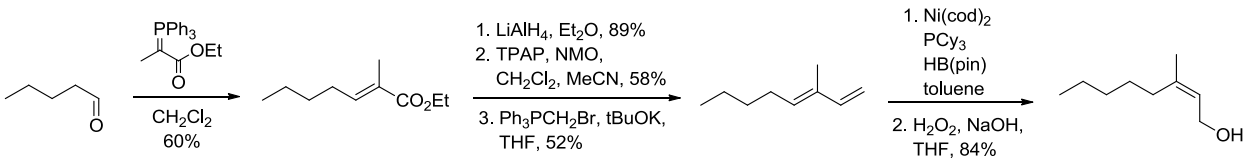
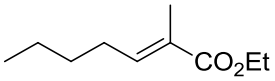
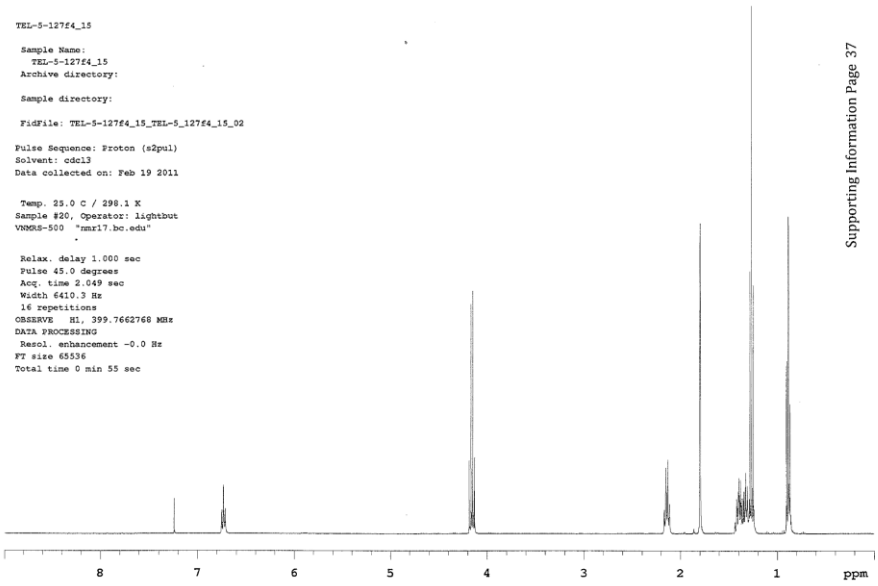
Synthesis of Substrate **1.38**

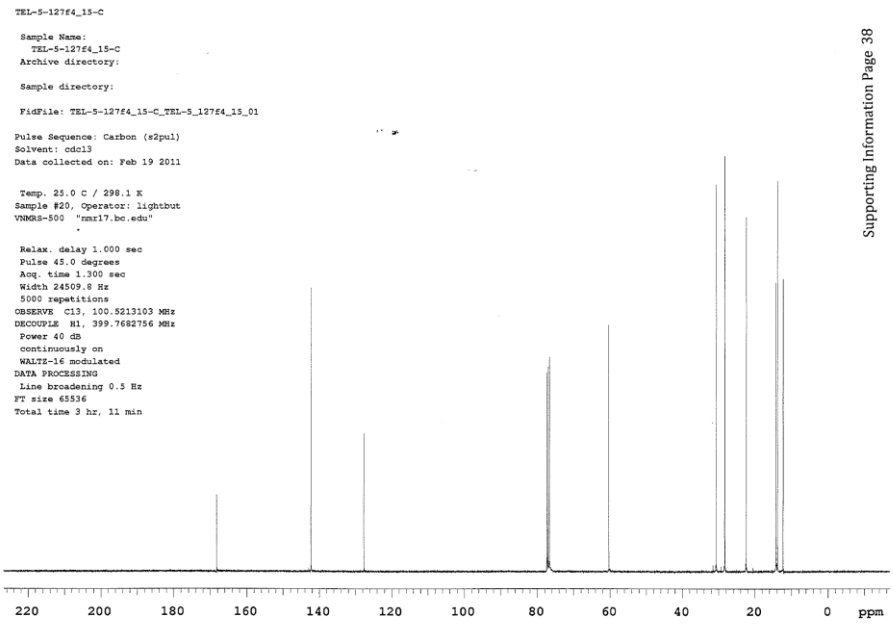


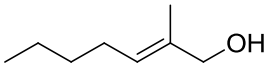


(*E*)-Ethyl 2-methylhept-2-enoate. In a drybox, (carbethoxyethylidene)-triphenylphosphorane (5.0 g, 13.8 mmol) was weighed into a dry 250 mL flask. The flask was brought out of the dry box and placed under a nitrogen atmosphere. Methylene chloride (42 mL) was added and valeraldehyde (1.34 mL, 12.5 mmol) was added dropwise. The solution was stirred at room temperature for 4 h. The reaction was concentrate to a slurry on a rotary evaporator and diluted with diethyl ether (60 mL). This suspension was filtered through a pad of silica gel, the silica gel was rinsed with diethyl ether (30 mL), and the combined organic solutions were again concentrated to a slurry. Again, diethyl ether was added (60 mL) and the suspension was filtered though a pad of silica gel, rinsing with diethyl ether (30 mL). The solution was concentrated and purified on silica gel eluting with a gradient of 2-4% ethyl acetate in hexane, resulting in 1.27 g (60%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.73 (dt, 1H, *J*= 6.1, 1.4), 4.16 (q, 2H, *J*= 7.2), 2.18-2.10 (m, 2H), 1.81-1.78 (m, 3H), 1.44-1.22 (m, 7H), 0.88 (t, 3H, *J*= 7.0); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 142.3, 127.6, 60.3,

30.7, 28.3, 22.4, 14.2, 13.8, 12.3; IR: 2958, 2930, 1708, 1650, 1260, 1142, 1095, 745 cm^{-1}; HRMS Calcd. for $C_{10}H_{19}O_2$ $[M+H]^+$: 171.1385, Found: 171.1394.

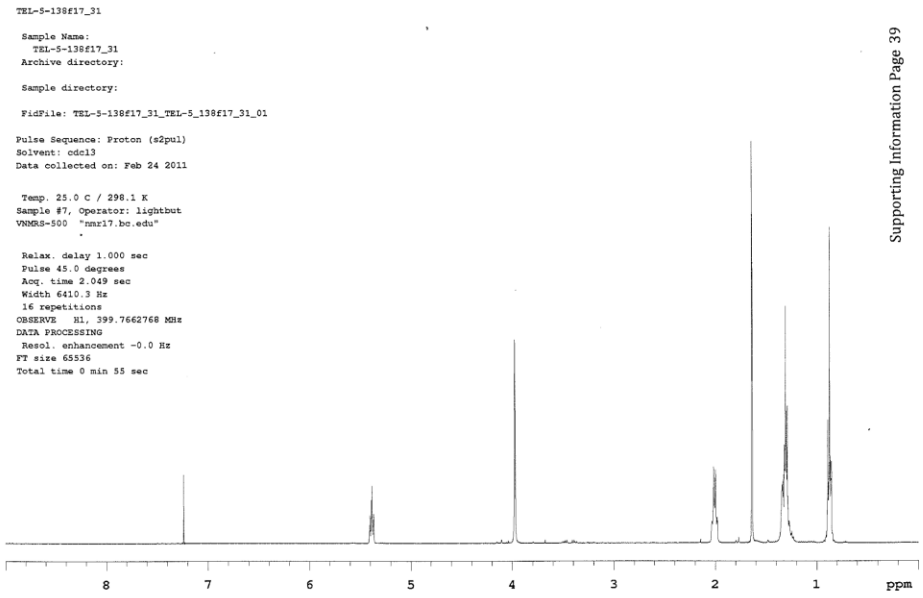


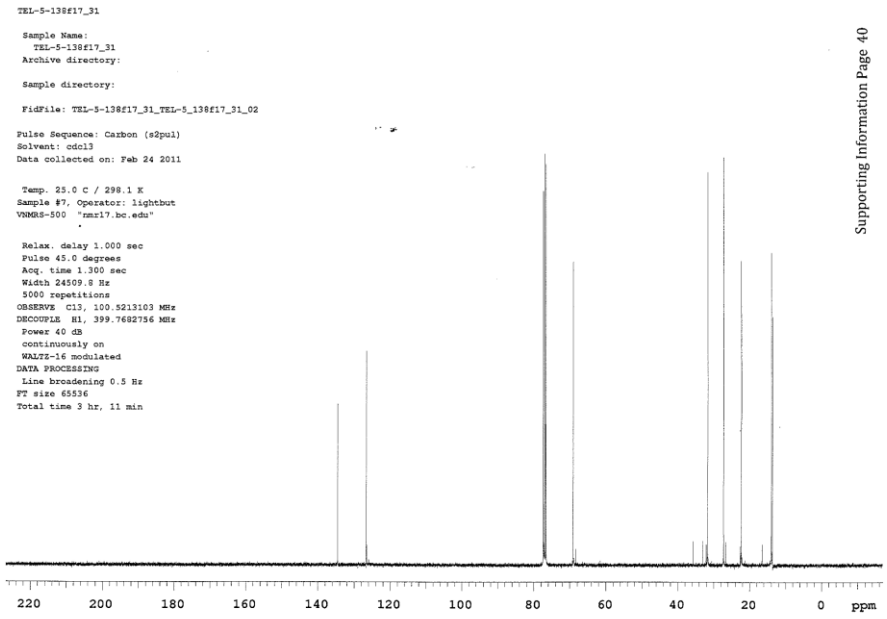


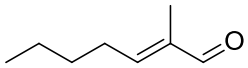


(*E*)-2-Methylhept-2-en-1-ol. A solution of (*E*)-ethyl 2-methylhept-2-enoate (1.23 g, 7.23 mmol) in diethyl ether (5 mL) was added to a suspension of lithium aluminum hydride (302 mg, 7.95 mmol) in diethyl ether (15 mL) at 0 °C. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction was quenched by careful addition of water. 10% aqueous sulfuric acid (10 mL) was added and the aqueous layer was extracted with diethyl ether (3 x 60 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. The residue was purified on silica gel, eluting with a gradient of 10-15% ethyl acetate in hexane, resulting in 823 mg (89%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.42-5.36 (m,

1H), 3.97 (s, 2H), 2.05-1.97 (m, 2H), 1.64 (s, 3H), 1.38-1.22 (m, 5H), 0.87 (t, 3H, *J*= 7.2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.5, 126.6, 69.0, 31.6, 27.2, 22.3, 13.9, 13.6; IR: 3316 (br), 2957, 2924, 2858, 1457, 1378, 1011 cm^{-1}; HRMS Calcd. for C_8H_{15} [M-H_2O+H]$^+$: 111.1174, Found: 111.1170.

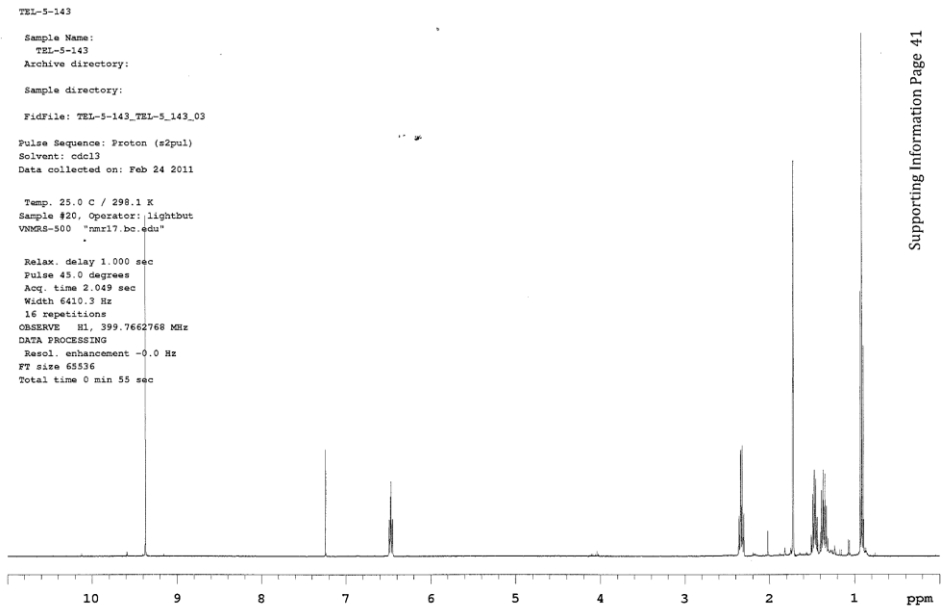


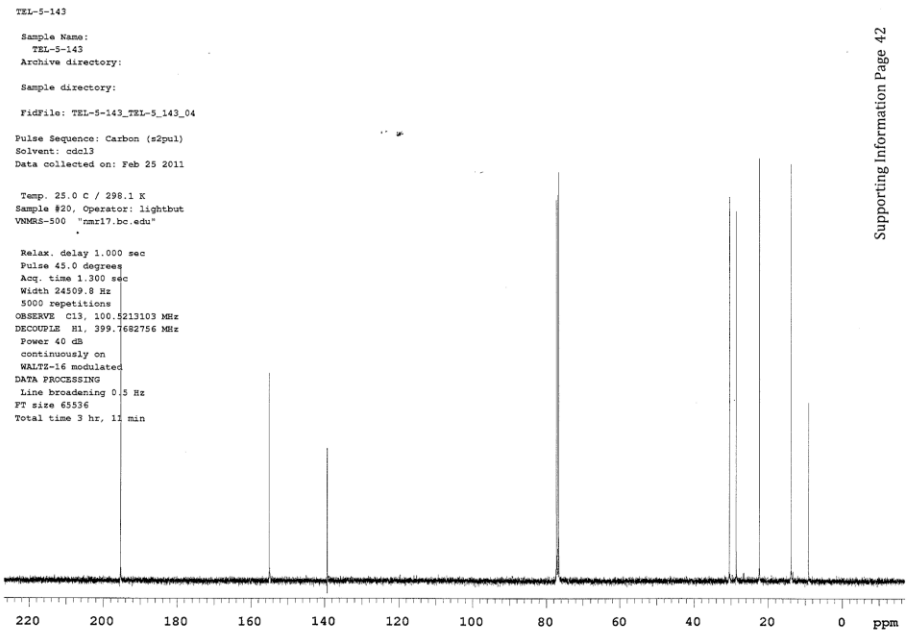


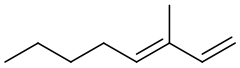


(*E*)-2-Methylhept-2-enal. A 100 mL flask with stir bar and 3Å mol. sieves was flame dried under vacuum and cooled under a nitrogen atmosphere. *N*-Methylmorpholine-*N*-oxide (66 mg, 0.19 mmol) was added, followed by methylene chloride (21 mL) and acetonitrile (2 mL). (*E*)-2-methylhept-2-en-1-ol (801 mg, 6.24 mmol) was added as a solution in methylene chloride (3 mL). The reaction was stirred for 25 min. and tetrapropylammonium perruthenate (66 mg, 0.19 mmol) was added. The reaction was stirred for 4 h and concentrated to a black slurry. The crude mixture was suspended in ethyl acetate/hexanes (1:1) and filtered through a plug of silica gel. The solution was concentrated by rotary evaporation with a 10 °C water bath to yield 454 mg (58%) of the title compound and was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ

9.38 (s, 1H), 6.50-6.44 (m, 1H), 2.37-2.29 (m, 2H), 1.74-1.71 (m, 3H), 1.51-1.42 (m, 2H), 1.41-1.31 (m, 2H), 0.91 (t, 3H, *J*= 7.2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.4, 155.0, 139.3, 30.5, 28.7, 22.4, 13.8, 9.1; IR: 2958, 2931, 2862, 1687, 1644, 1280 cm^{-1}; HRMS Calcd. for $C_8H_{15}O_2$ $[M+H]^+$: 127.1123, Found: 127.1119.

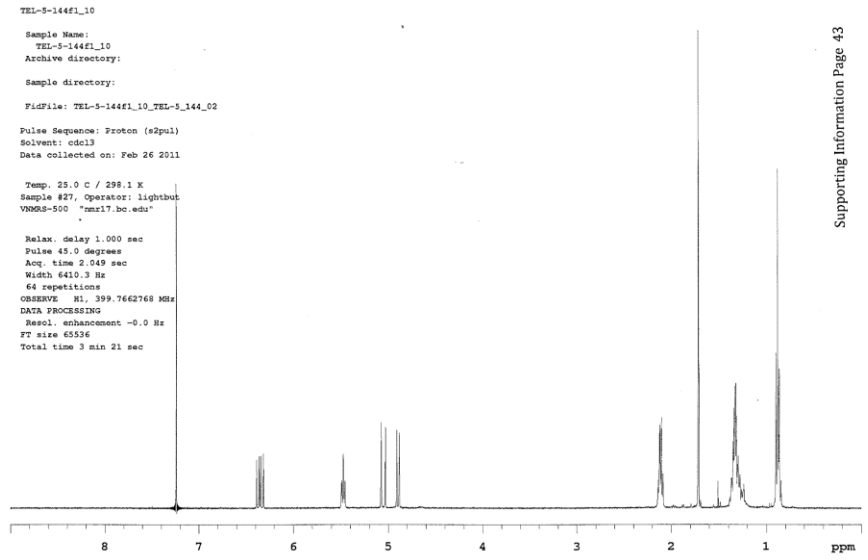






(*E*)-3-Methylocta-1,3-diene. In a dry box a 100 mL flask was charged with methyl triphenylphosphonium bromide (1.38 g, 3.87 mmol) and potassium *tert*-butoxide (434 mg, 3.87 mmol). The flask was brought out of the dry box and placed under a nitrogen atmosphere. The flask was cooled in an ice water bath and tetrahydrofuran (10 mL) was added. The resulting yellow solution was stirred for 10 min. at which time the flask was allowed to warm to room temperature and the reaction was stirred for an additional 30 min. The reaction was re-cooled in an ice water bath and (*E*)-2-methylhept-2-enal (444 mg, 3.52 mmol) was added dropwise as a solution in tetrahydrofuran (1 mL). The reaction was stirred for 15 min., the cold bath was removed, and stirring continued for an

additional 2 hours. The reaction was concentrated to a slurry on a rotary evaporator with a 10 °C water bath. Diethyl ether (50 mL) was added and the suspension was filtered through silica gel, rinsing with diethyl ether (25 mL). The solution was again concentrated to a slurry in the same fashion and pentane (50 mL) was added. This suspension was filtered through silica gel. Careful concentration (rotary evaporation with a 10 °C water bath) was followed by purification on silica gel using pentane as eluent, affording 225 mg (52%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.35 (dd, 1H, *J*= 17.4, 10.6), 5.50-5.44 (m, 1H), 5.30 (d, 1H, *J*= 17.4), 4.90 (d, 1H, *J*= 10.6), 2.16-2.08 (m, 2H), 1.72 (s, 3H), 1.40-1.22 (m, 4H), 0.88 (t, 3H, *J*= 7.0); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.6, 133.8, 133.5, 110.2, 31.6, 27.9, 22.4, 13.9, 11.6; IR: 2957, 2927, 2859, 1680, 1459, 1379, 989, 891 cm^{-1}; HRMS Calcd. for C_9H_{17} $[M+H]^+$: 125.1330, Found: 125.1336.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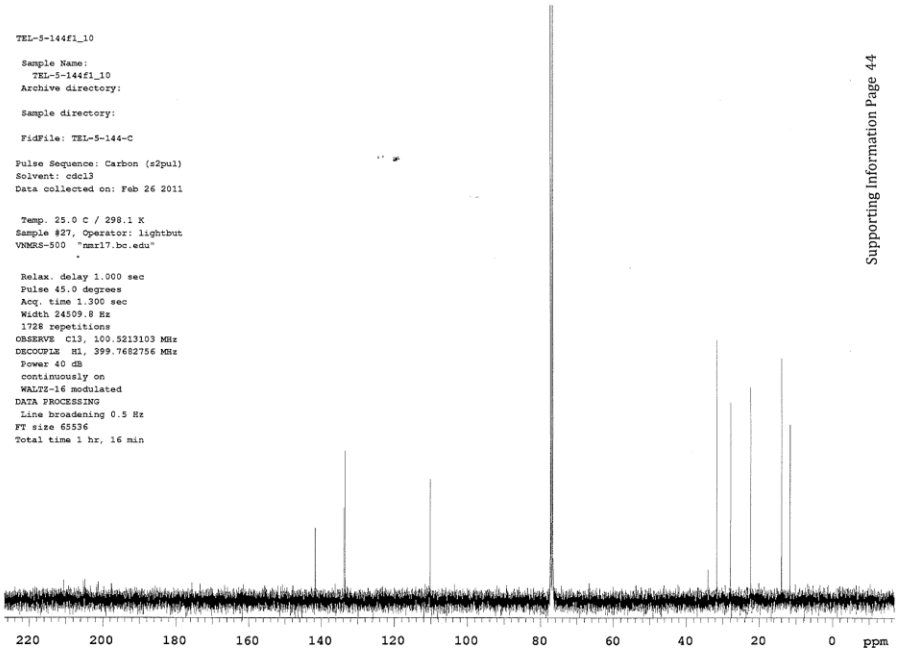
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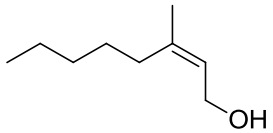
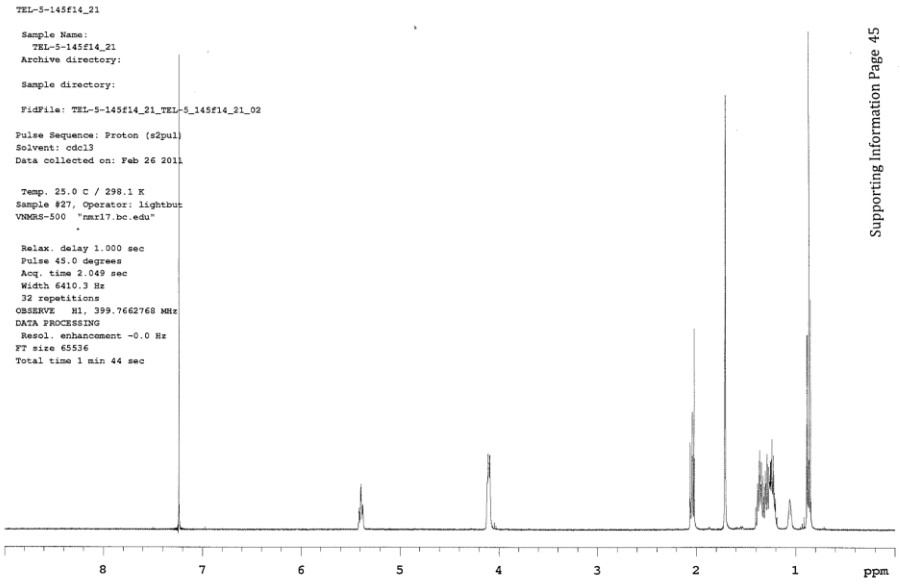


(*Z*)-3-Methyloct-2-en-1-ol (1.38). In a dry box bis(cyclooctadiene)nickel (0) (11.5 mg, 0.042 mmol) and tricyclohexylphosphine (11.8 mg, 0.042 mmol) were added to a 25 mL flask. Toluene (6 mL) and pinacolborane (226 mg, 1.76 mmol) were added, followed by (*E*)-3-methylocta-1,3-diene (208 mg, 1.68 mmol) as a solution in toluene (1 mL). The reaction was brought out of the dry box and was stirred for 4 h under an atmosphere of argon. The reaction was cooled in an ice water bath, tetrahydrofuran (7 mL) was added, followed by aqueous sodium hydroxide (3M, 2 mL) and cold 35% aqueous hydrogen peroxide (2 mL). The reaction was stirred for 3 h while warming to room temperature with the warming of the ice water bath. The reaction was re-cooled in an ice water bath and was quenched with careful addition of saturated aqueous sodium thiosulfate (2 mL) (Caution: Delayed exotherm!). The reaction was diluted with water (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organics were dried over anhydrous magnesium sulfate and concentrated. Purification on silica gel eluting with 10% ethyl acetate in hexane afforded 200 mg (84%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.42-5.36 (m, 1H), 4.14-4.08 (m, 2H), 2.07-2.01 (m, 2H), 1.73-1.70 (m, 3H), 1.41-1.18 (m, 6H), 1.06 (br s, 1H), 0.87 (t, 3H, *J*= 7.0); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.6, 123.9, 59.1, 31.8, 31.6, 27.9, 23.4, 22.5, 14.1; IR: 3315, 2957, 2928, 2858, 1448, 1377, 999 cm^{-1}; HRMS Calcd. for C_9H_{17} $[M-H_2O+H]^+$: 125.1330, Found: 125.1331.



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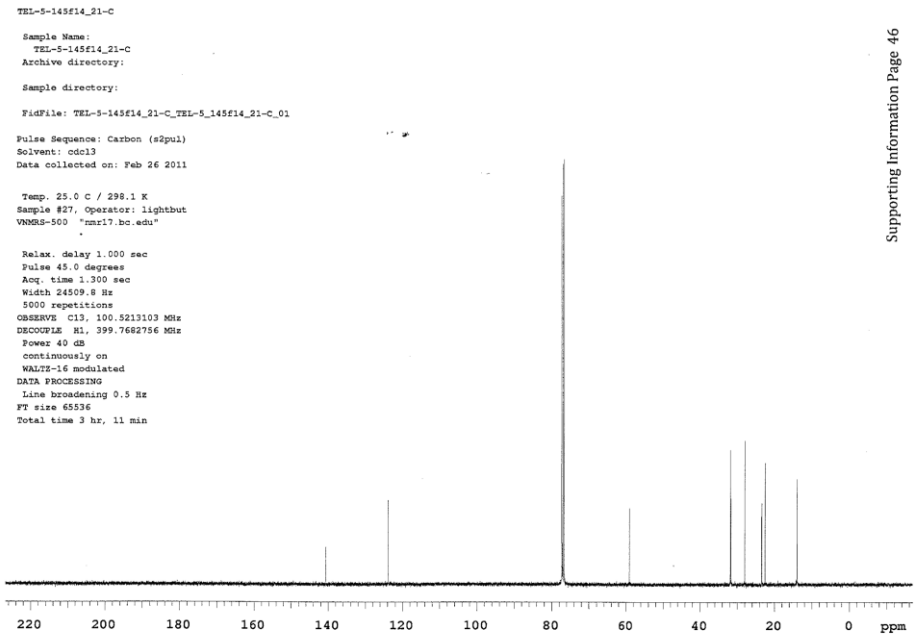

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Branch Selective Hydroformylation Using Ligand **1.12**

Hydroformylation General Procedure A. An oven dried glass reaction vial containing substrate (0.60 mmol) was placed in the Endeavor. The Endeavor was sealed and purged with nitrogen (4 x 100 psi). In a dry box a solution of dicarbonylacetylacetonato rhodium (I) (1 mol %, 1.5 mg, 0.006 mmol), ligand **1.12** (10 mol %, 17.1 mg, 0.06 mmol), a solution of anhydrous *p*-toluene sulfonic acid (0.05 mol %, 527 μL, 5.69 x 10^{-4} M in benzene) and benzene (6 mL) were combined in a syringe. This solution was taken out of the dry box and injected into the Endeavor. The Endeavor was purged with nitrogen (1 x 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 100 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at 45 °C and 100 psi H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature.

Hydroformylation General Procedure B. An oven dried glass reaction vial containing substrate (0.20 mmol) was placed in the Endeavor. The Endeavor was sealed and purged with nitrogen (4 x 100 psi). In a dry box a solution of dicarbonylacetylacetonato rhodium (I) (1 mol %, 0.52 mg, 0.002 mmol), ligand **1.12** (10 mol %, 5.7 mg, 0.02 mmol), a solution of anhydrous *p*-toluene sulfonic acid (0.05 mol %, 175 μL, 5.69 x 10^{-4} M in benzene) and benzene (2 mL) were combined in a syringe. This solution was taken out of the dry box and injected into the Endeavor. The Endeavor was purged with nitrogen (1 x 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 100 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at 45 °C and 100 psi H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature.

Hydroformylation General Procedure C. An oven dried glass reaction vial containing substrate (0.60 mmol) was placed in the Endeavor. The Endeavor was sealed and purged with nitrogen (4 x 100 psi). In a dry box a solution of dicarbonylacetylacetonato rhodium (I) (2 mol %, 3.0 mg, 0.012 mmol), ligand **1.12** (20 mol %, 34.2 mg, 0.12 mmol), a solution of anhydrous *p*-toluene sulfonic acid (0.02 mol %, 211 μL, 5.69 x 10^{-4} M in benzene) and benzene (6 mL) were combined in a syringe. This solution was taken out of the dry box and injected into the Endeavor. The Endeavor was purged with nitrogen (1 x 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 55 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 50 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at 55 °C and 50 psi H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature.

Hydroformylation General Procedure D. An oven dried glass reaction vial containing substrate (0.20 mmol) was placed in the Endeavor. The Endeavor was sealed and purged with nitrogen (4 x 100 psi). In a dry box a solution of dicarbonylacetylacetonato rhodium (I) (2 mol %, 1.5 mg, 0.004 mmol), ligand **1.12** (20 mol %, 11.4 mg, 0.04 mmol), a solution of anhydrous *p*-toluene sulfonic acid (0.02 mol %, 70 μL, 5.69 x 10^{-4} M in

benzene) and benzene (2 mL) were combined in a syringe. This solution was taken out of the dry box and injected into the Endeavor. The Endeavor was purged with nitrogen (1 x 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 55 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 50 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at 55 °C and 50 psi H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature.

Hydroformylation General Procedure E. An oven dried glass reaction vial containing substrate (0.60 mmol) was placed in the Endeavor. The Endeavor was sealed and purged with nitrogen (4 x 100 psi). In a dry box a solution of dicarbonylacetylacetonato rhodium (I) (2 mol %, 3.1 mg, 0.012 mmol), triphenylphosphine (4 mol %, 6.3 mg, 0.024 mmol) and benzene (6 mL) were combined in a syringe. This solution was taken out of the dry box and injected into the Endeavor. The Endeavor was purged with nitrogen (1 x 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 100 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at 45 °C and 100 psi H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature.

Pinnick Oxidation General Procedures

Pinnick Oxidation General Procedure F. The crude hydroformylation reaction mixture was concentrated on a rotary evaporator in a glass scintillation vial, a magnetic stir bar

added, and *t*BuOH (3 mL), 2-methyl-2-butene (636 μL, 6.0 mmol), and a solution of sodium phosphate (288 mg, 2.4 mmol) and sodium chlorite (tech. grade (80%), 272 mg, 2.4 mmol) in water (3 mL) was added dropwise. The reaction was stirred vigorously for 6 hours. Saturated aqueous sodium chloride (1 mL) and 1M aqueous hydrogen chloride (1 mL) were added and the aqueous layer was extracted with dichloromethane (5 x 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was analyzed by NMR to determine the regioselectivity of the reaction. Purification on silica gel (1-5% MeOH in CH_2Cl_2) afforded pure carboxylic acid products.

Note: An impurity, presumably arising from the use of 2-methyl-2-butene as an HOCl scavenger, has a very similar polarity on silica gel as the desired carboxylic acid products. This impurity is not seen when Pinnick Oxidation General Procedure G is followed.

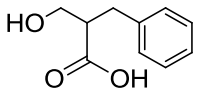
Pinnick Oxidation General Procedure G. The crude hydroformylation reaction mixture was concentrated on a rotary evaporator in a glass scintillation vial, a magnetic stir bar added, and acetonitrile (1.5 mL), water (1.5 mL), sodium phosphate (288 mg, 2.40 mmol), and 35% aqueous H_2O_2 (240 μL, 2.46 mmol) were added to the vial. The reaction was cooled in a water bath to 10 °C and a solution of sodium chlorite (tech. grade 80%, 272 mg, 2.4 mmol) in water (1.5 mL) was added dropwise. The reaction was stirred for 3 hours, warming to room temperature with the water bath. Sodium sulfite (spatula tip) was added to quench the reaction and 1M aqueous hydrogen chloride (6 mL)

was added. The reaction was extracted with methylene chloride (5 x 20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was analyzed by NMR spectroscopy to determine the regioselectivity of the reaction. Purification on silica gel (1-5% MeOH in CH_2Cl_2) afforded pure carboxylic acid products.

Pinacol Acetal Protection General Procedure

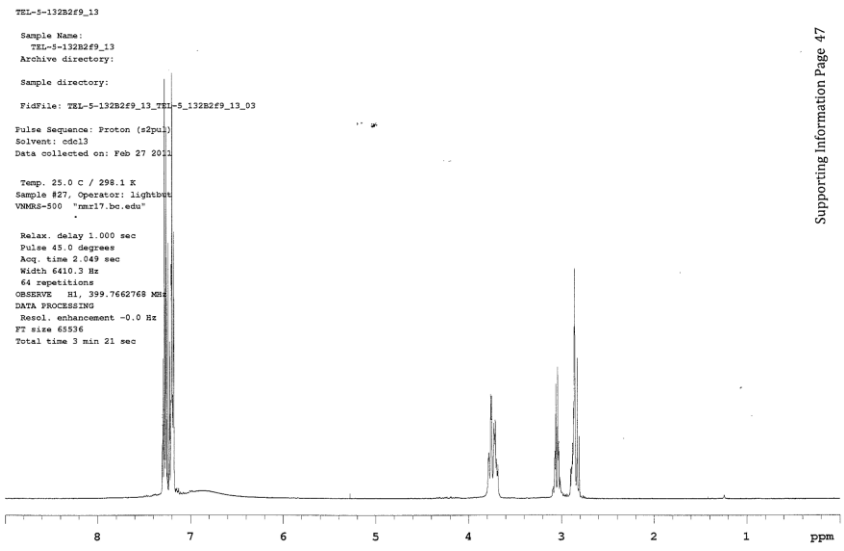
Pinacol Acetal Protection General Procedure H. The crude hydroformylation reaction mixture was transferred to a glass scintillation vial using 1 mL of benzene to rinse out the reaction vial. Pinacol (300 mg, 2.50 mmol) and a catalytic amount of *p*-toluene sulfonic acid (~10 mg) were added and the vials were sealed with rubber septa and black electrical tape and placed under a nitrogen atmosphere. The vials were placed on a sand bath at 80 °C and were stirred for 90 minutes. The reactions were cooled, concentrated, and analyzed by NMR to determine the regioselectivity of the reaction. Purification on silica gel eluting with a gradient of 5-20% ethyl acetate in hexane afforded pure acetal products.

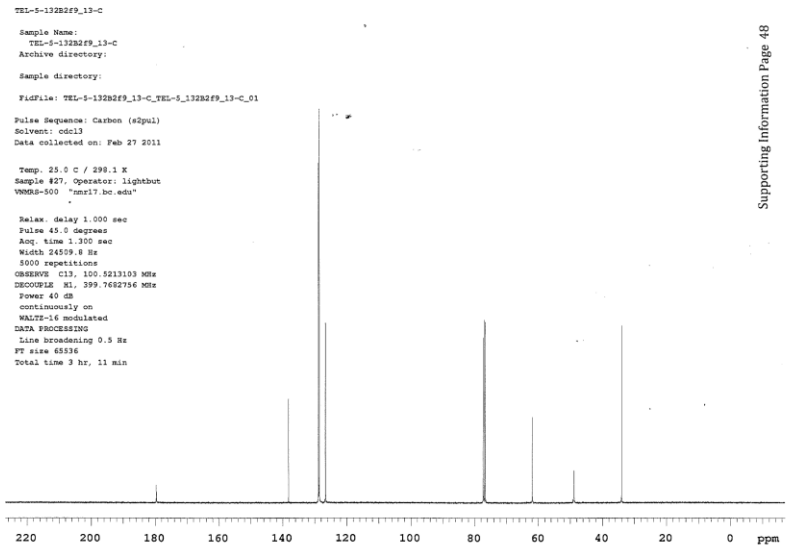
Product Syntheses and Characterization

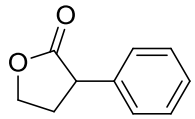


2-Benzyl-3-hydroxypropanoic acid (1.16). Hydroformylation of cinnamyl alcohol was performed following General Procedure B and oxidation following General Procedure G. Analysis of the crude oxidation showed a regioselectivity of 95:5. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a

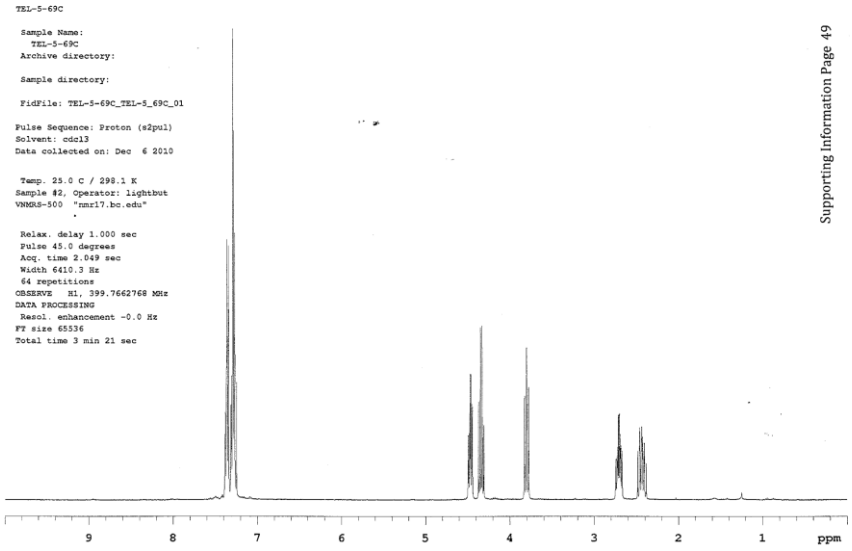
white solid (29.8 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.17 (m, 5H), 3.81-3.67 (m, 2H), 3.11-2.99 (m, 1H), 2.91-2.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.6, 138.2, 128.9, 128.7, 126.6, 61.9, 48.8, 34.0; IR: 3061, 3028, 2945, 1709, 1244, 1199, 1030, 742, 700 cm^{-1}; HRMS Calcd. for $C_{10}H_{13}O_3$ $[M+H]^+$: 181.0865, Found: 181.0861.







3-Phenyldihydrofuran-2(3*H*)-one (1.17). Hydroformylation of cinnamyl alcohol was performed following General Procedure E and oxidation following General Procedure F afforded the title compound in sufficient quantity for analysis. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.33 (m, 2H), 7.32-7.26 (m, 3H), 4.47 (app dt, 1H, *J*= 8.9, 3.3), 4.34 (app dt, 1H, *J*= 8.9, 6.6), 3.80 (app t, 1H, *J*= 9.6), 2.76-2.38 (m, 1H), 2.49-2.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.3, 136.6, 128.9, 127.9, 127.6, 66.5, 45.5, 31.6; IR: 3063, 3031, 2990, 2913, 2251, 1762, 1498, 1453, 1372, 1147, 1023, 908, 728, 696, 554 cm^{-1}; HRMS Calcd. for $C_{10}H_{11}O_2$ $[M+H]^+$: 163.0759, Found: 163.0760.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Sample directory:
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Solvent: cdcl3
Data collected on: Dec 6 2010
Temp. 25.0 C / 298.1 K
Sample #2, Operator: lightbut
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Pulse 45.0 degrees
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64 repetitions
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DATA PROCESSING
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FT size 65536
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2
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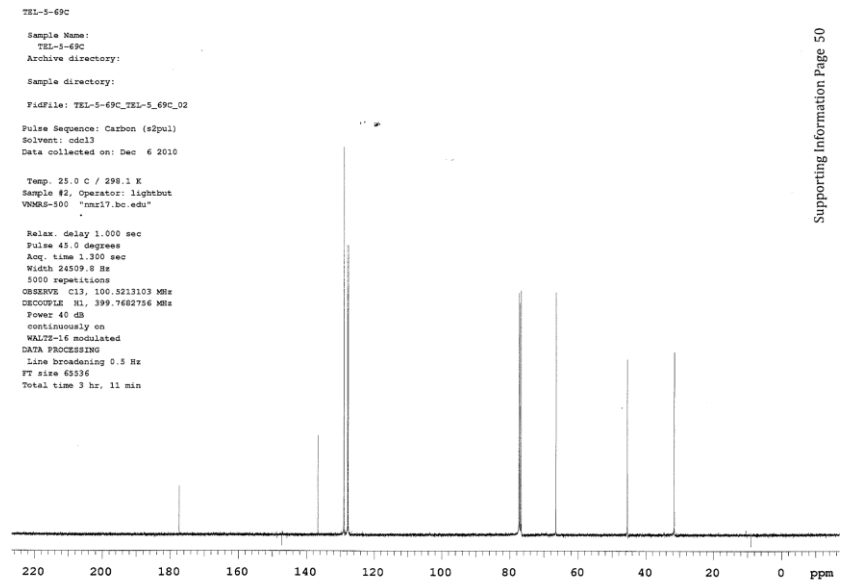
ppm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Solvent: cdcl3
Data collected on: Dec 6 2010
Temp. 25.0 C / 298.1 K
Sample #2, Operator: lightbut
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Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5213103 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
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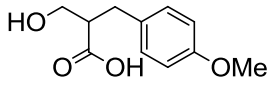
ppm



3-Hydroxy-2-(4-methoxybenzyl)propanoic acid (1.19). Hydroformylation of (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol was performed following General Procedure A [except pressure (50 psi) and acid loading (0.012 mol % *p*-TsOH)] and oxidation following General Procedure F. Analysis of the crude oxidation showed a regioselectivity of >95:5. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound (109 mg, 87%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (d, 2H, *J*= 8.5), 6.81 (d, 2H, *J*= 8.5), 3.76 (s, 3H), 3.74-3.68 (m, 2H), 2.99-2.96 (m, 1H), 2.85-2.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.7, 158.3, 130.1, 129.9, 113.9, 61.9, 55.2, 49.0, 33.2; IR: 2933, 1706, 1512, 1244, 1030 cm^{-1}; HRMS Calcd. for $C_{11}H_{15}O_4$ $[M+H]^+$: 211.0970, Found: 211.0979.

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Archive directory:

Sample directory:

FidFile: OAD-2-155-pure

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Solvent: cdcl3
Data collected on: Feb 27 2011

Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500  "rmr17.bc.edu"

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Pulse 45.0 degrees
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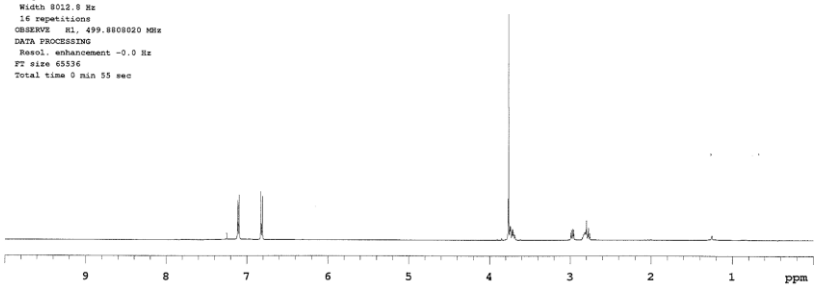


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Archive directory:

Sample directory:

FidFile: OAD-2-155-pure_2_155_01

Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Feb 27 2011

Temp. 25.0 C / 298.1 K
Sample #34, Operator: depaolis
VNMRS-500  "rmr17.bc.edu"

Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
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OBSERVE   C13, 100.5213103 MHz
DECOUPLE  H1, 399.7682756 MHz
Power 40 dB
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Total time 3 hr, 8 min
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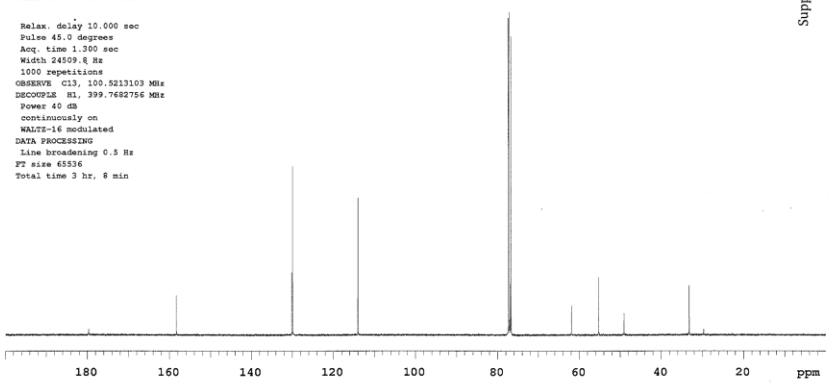
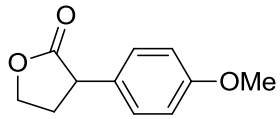
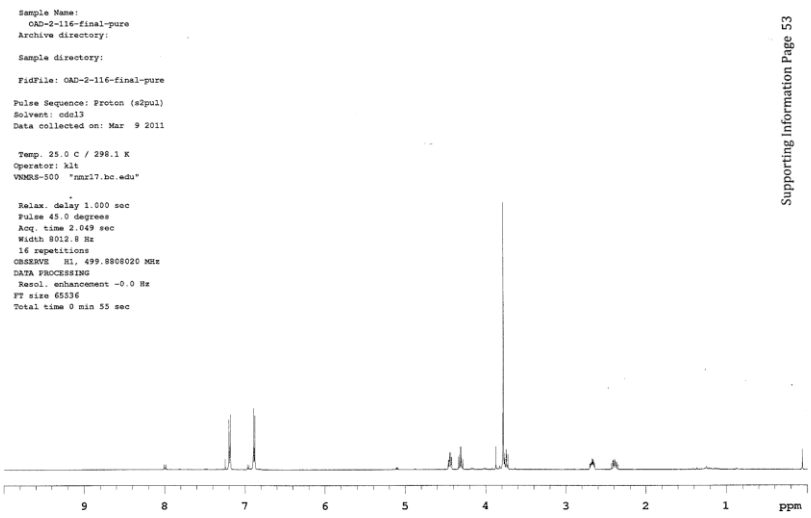
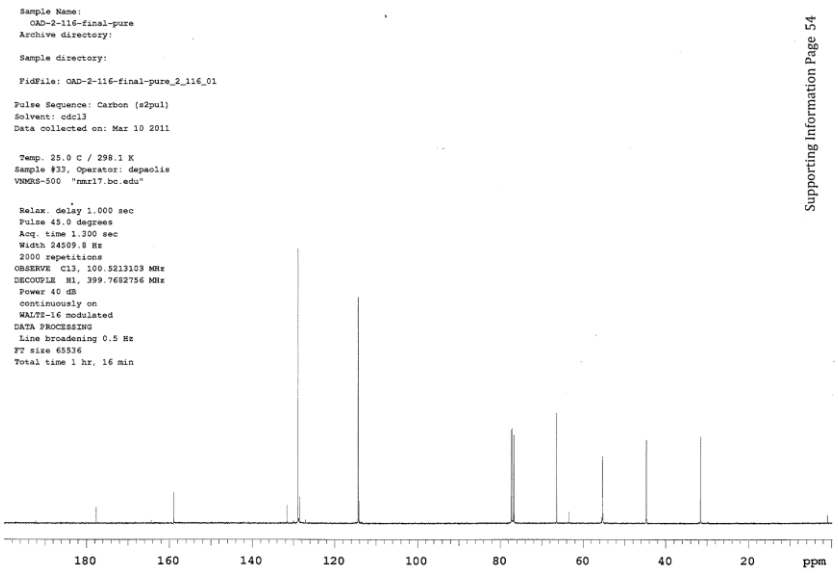
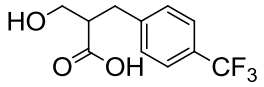




3-(4-Methoxyphenyl)dihydrofuran-2(3*H*)-one. Hydroformylation of (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol was performed following General Procedure E and oxidation following General Procedure F and afforded the title compound in sufficient quantity for analysis. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19 (d, 2H, *J*= 8.5), 6.88 (d, 2H, *J*= 8.5), 4.44 (dt, 1H, *J*= 9.0, 4.0), 4.31 (dt, 1H, *J*= 9.5, 6.5), 3.78 (s, 3H), 3.74 (app t, 1H, *J*= 9.0), 2.70-2.64 (m, 1H), 2.43-2.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.7, 159.0, 131.6, 128.9, 114.3, 66.4, 55.3, 44.7, 31.6; IR: 2917, 1764, 1513, 1242, 1149, 1025 cm^{-1}; HRMS Calcd. for $C_{11}H_{13}O_3$ $[M+H]^+$: 193.0865, Found: 193.0869.

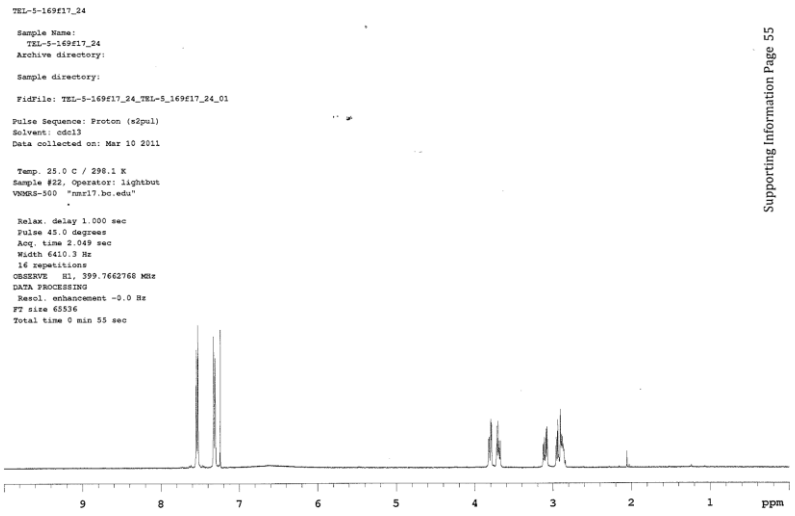


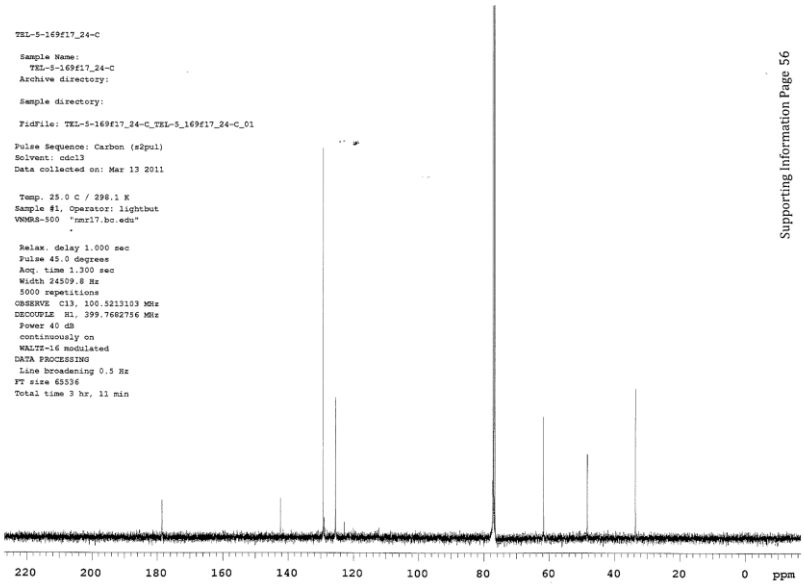


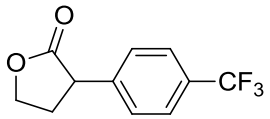


3-Hydroxy-2-(4-(trifluoromethyl)benzyl)propanoic acid (1.21). Hydroformylation of (*E*)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol was performed following General Procedure B [except pressure (50 psi) and acid loading (0.012 mol % *p*-TsOH)] and oxidation following General Procedure G. Analysis of the crude oxidation showed a regioselectivity of >95:5. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a clear oil (30.7 mg, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, 2H, *J*= 8.0), 7.32 (d, 2H, *J*= 8.0), 3.81 (dd, 1H, *J*= 11.2, 3.4), 3.70 (dd, 1H, *J*= 11.2, 6.4), 3.10 (dd, 1H, *J*= 13.4, 6.4), 2.98-2.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.5, 142.3, 129.2, 128.9 (q, J= 32.5), 125.5 (q, *J*= 3.7),

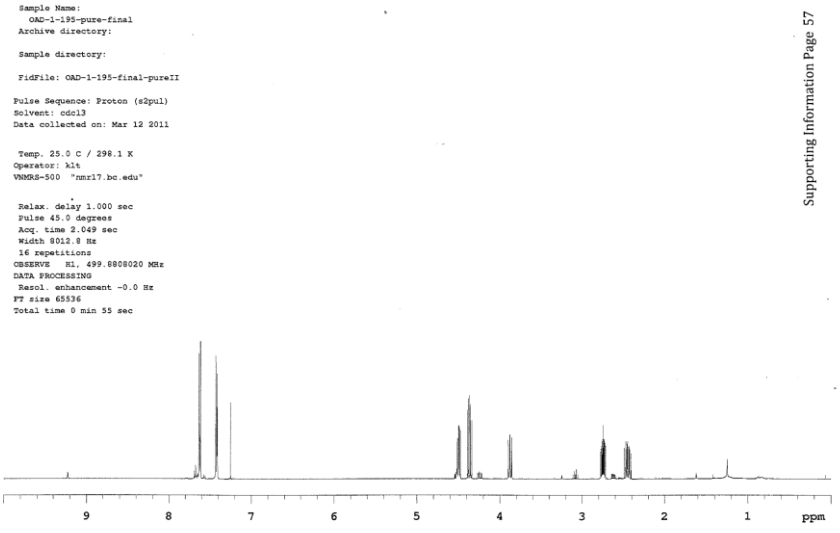
124.1 (q, J= 270), 61.7, 48.4, 33.6; IR: 2942, 1710, 1323, 1161, 1111, 1067, 1019 cm^{-1}; HRMS Calcd. for $C_{11}H_{12}F_3O_3$ $[M+H]^+$: 249.0738, Found: 249.0737.

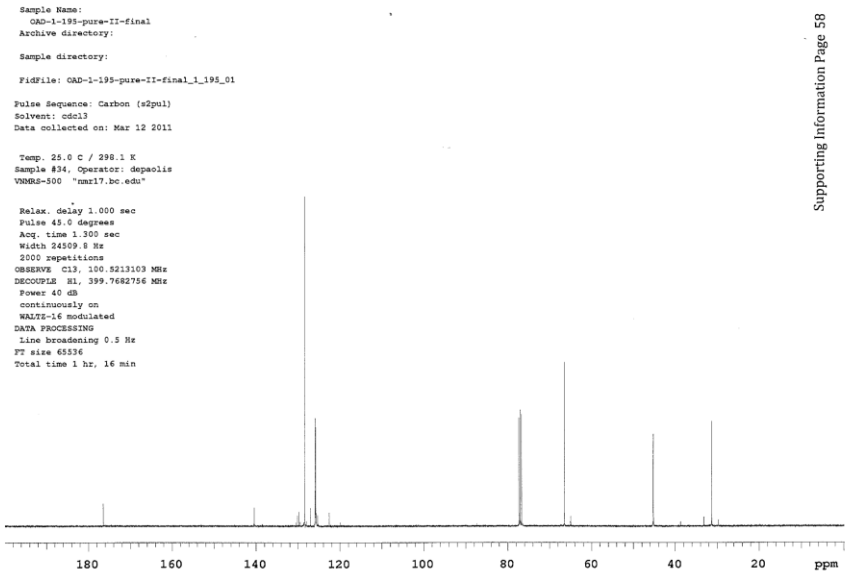


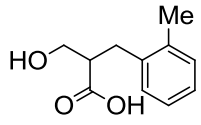




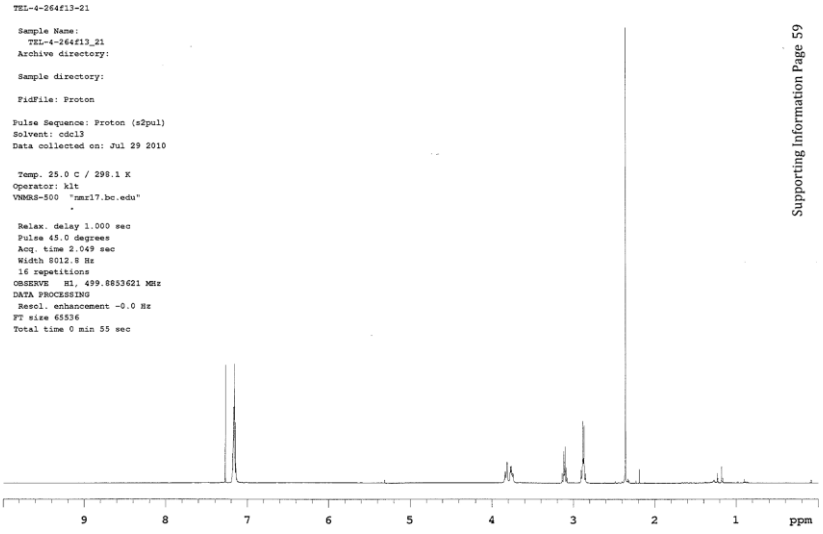
3-(4-(Trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one. Hydroformylation of (*E*)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol was performed following General Procedure E and oxidation following General Procedure F and afforded the title compound in sufficient quantity for analysis. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (d, 2H, *J*= 8.5), 7.42 (d, 2H, *J*= 8.5), 4.49 (dt, 1H, *J*= 8.5, 2.5), 4.36 (dt, 1H, *J*= 9.5, 6.5), 3.87 (app t, 1H, *J*= 9.0), 2.78-2.71 (m, 1H), 2.49-2.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.5, 140.5, 130.0 (q, *J*= 32.5), 128.3, 125.8 (q, *J*= 3.7), 123.9 (q, *J*= 271), 66.5, 45.2, 31.3; IR: 2916, 1768, 1324, 1159, 1114, 1067 cm^{-1}; HRMS Calcd. for $C_{11}H_{10}F_3O_2$ $[M+H]^+$: 231.0633, Found: 231.0642.







3-Hydroxy-2-(2-methylbenzyl)propanoic acid (1.23). Hydroformylation of (*E*)-3-(*o*-tolyl)prop-2-en-1-ol was performed following General Procedure A [except pressure (50 psi) and acid loading (0.012 mol % *p*-TsOH)] and oxidation following General Procedure F. Analysis of the crude oxidation showed a regioselectivity of 94:6. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a clear oil (108 mg, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19-7.13 (m, 4H), 3.86-3.72 (m, 2H), 3.15-3.07 (m, 1H), 2.92-2.84 (m, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.6, 136.5, 136.3, 130.5, 129.6, 126.8, 126.0, 62.0, 47.7, 31.3, 19.3; IR: 3018, 2948, 1704, 1459, 1408, 1382, 1242, 1185, 1026, 740 cm^{-1}; HRMS Calcd. for $C_{11}H_{15}O_3$ $[M+H]^+$: 195.1021, Found: 195.1027.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Solvent: cdcl3
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Pulse 45.0 degrees
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Width 8012.8 Hz
16 repetitions
OBSERVE H1, 499.8853621 MHz
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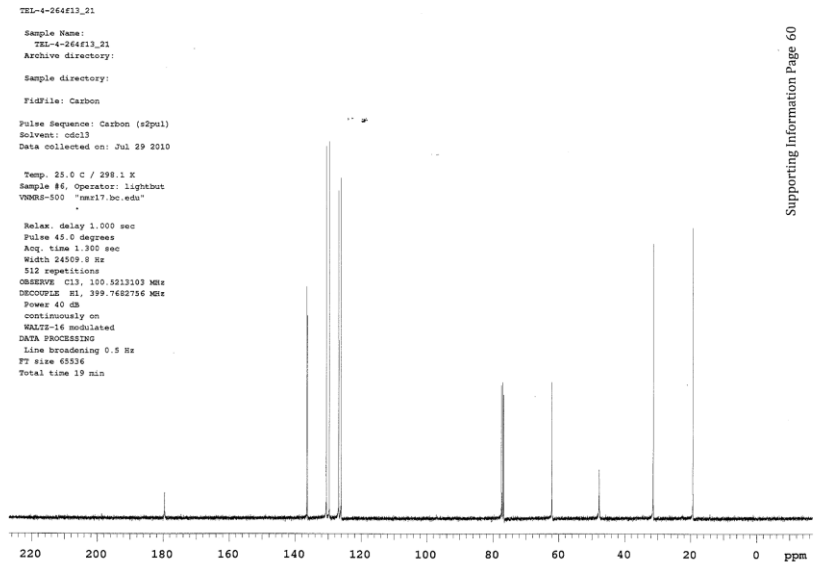
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DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min
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200
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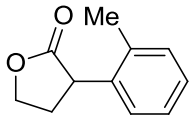
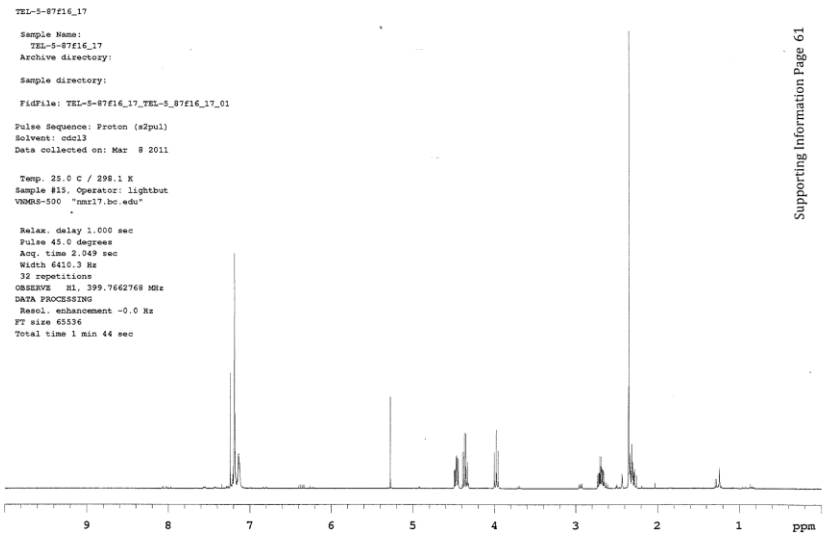
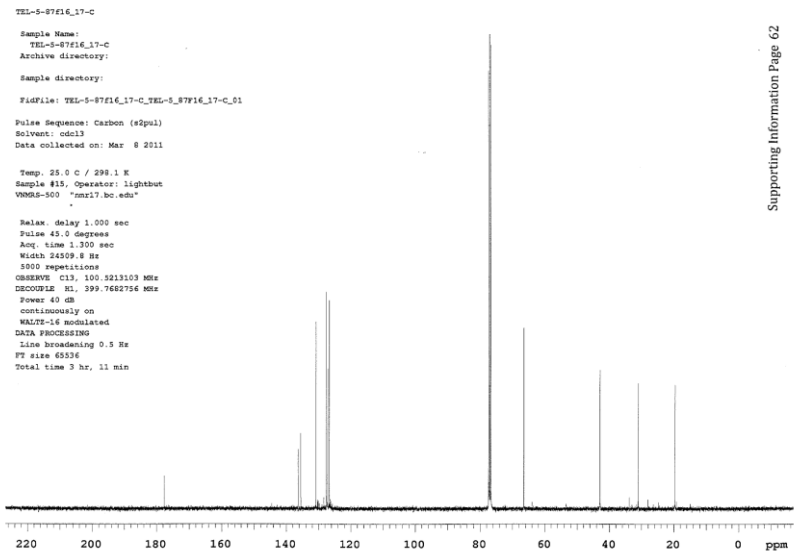
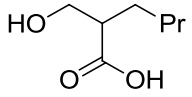
140
120
100
80
60
40
20
0
ppm



3-(*o*-Tolyl)dihydrofuran-2(3*H*)-one. Hydroformylation of (*E*)-3-(*o*-tolyl)prop-2-en-1-ol was performed following General Procedure E and oxidation following General Procedure F and afforded the title compound in sufficient quantity for analysis. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20-7.17 (m, 3H), 7.15-7.11 (m, 1H), 4.47 (app dt, 1H, *J*= 9.2, 4.0), 4.36 (app dt, 1H, *J*=9.2, 7.0), 3.98 (app t, 1H, *J*= 9.2), 2.74-2.64 (m, 1H), 2.36-2.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.7, 136.3, 135.5, 130.8, 127.6, 127.2, 126.6, 66.5, 42.9, 31.1, 19.7; IR: 2980, 2913, 1766, 1494, 1461, 1372, 1152, 1025, 754 cm^{-1}; HRMS Calcd. for $C_{11}H_{13}O_2$ $[M+H]^+$: 177.0916, Found: 177.0919.



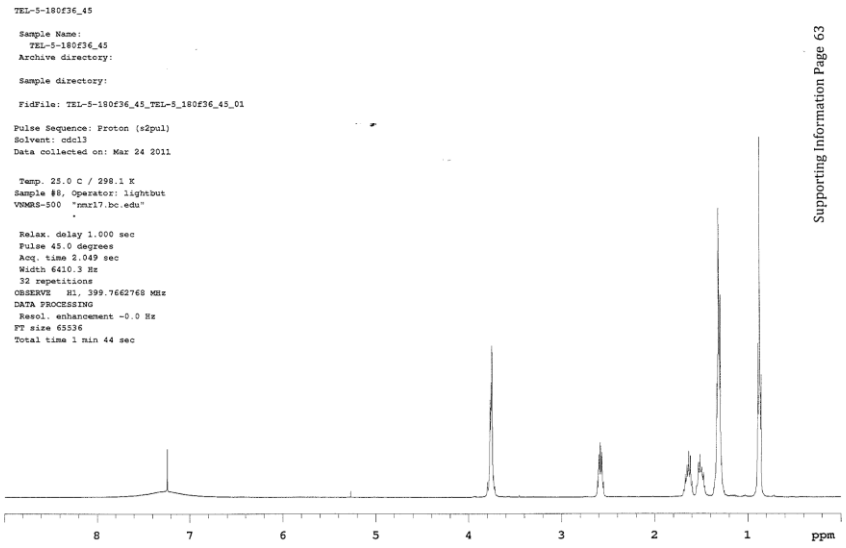


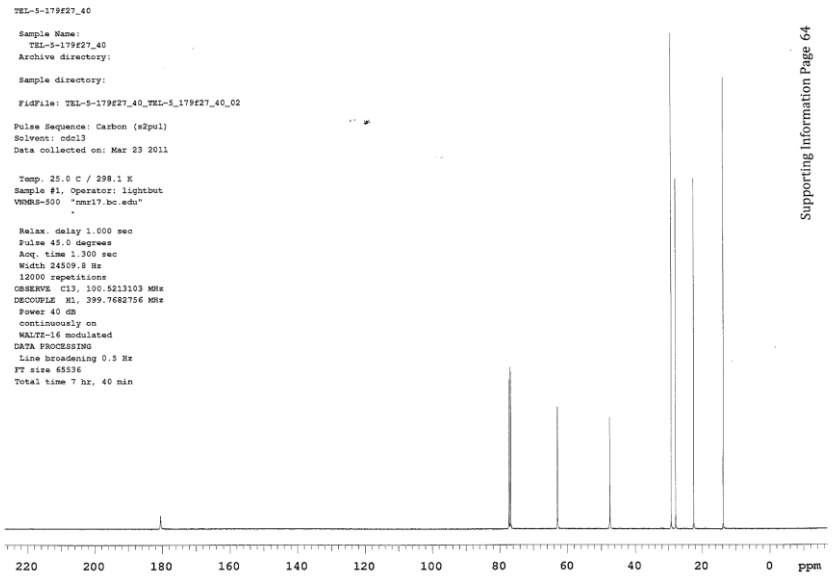


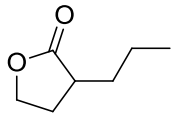
2-(Hydroxymethyl)hexanoic acid (1.25). Hydroformylation of *trans*-2-hexen-1-ol was performed following General Procedure C [except pressure (50 psi) and acid loading (0.10 mol % *p*-TsOH)] and oxidation following General Procedure F. Analysis of the crude oxidation showed a regioselectivity of >95:5. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound (71 mg, 81%).

Hydroformylation of *cis*-2-hexen-1-ol was performed following General Procedure C [except pressure (50 psi) and acid loading (0.10 mol % *p*-TsOH)] and oxidation following General Procedure G. Analysis of the crude oxidation showed a regioselectivity of >95:5. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound (81 mg, 92%).

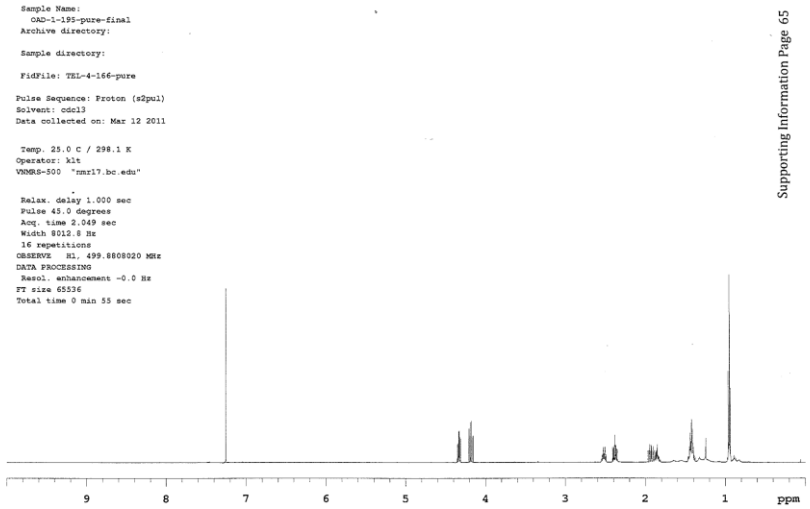
^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79-3.73 (m, 2H), 2.61-2.56 (m, 1H), 1.67-1.62 (m, 2H), 1.54-1.49 (m, 2H), 1.34-1.29 (m, 2H), 0.88 (t, 3H, *J*= 7.0); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.3, 62.9, 47.4, 29.3, 27.9, 22.5, 13.8; IR: 3309 (br), 2956, 2931, 2862, 1704, 1189, 1028, 625, 540 cm^{-1}; HRMS Calcd. for $C_7H_{15}O_3$ $[M+H]^+$: 147.1021, Found: 147.1025.







3-Propyldihydrofuran-2(3*H*)-one. Hydroformylation of *trans*-2-hexen-1-ol was performed following General Procedure E and oxidation following General Procedure F and afforded the title compound in sufficient quantity for analysis. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.33 (app dt, 1H, *J*= 9.0, 3.0), 4.18 (app dt, 1H, *J*= 9.0, 7.0), 2.55-2.48 (m, 1H), 2.41-2.35 (m, 1H), 1.97-1.90 (m, 1H), 1.88-1.82 (m, 1H), 1.47-1.38 (m, 3H), 0.95 (t, 3H, *J*= 7.5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.6, 66.4, 38.9, 32.4, 28.6, 20.5, 13.7; IR: 2958, 1764, 1214, 1078, 865 cm^{-1}; HRMS Calcd. for $C_7H_{13}O_2$ $[M+H]^+$: 129.0916, Found: 129.0910.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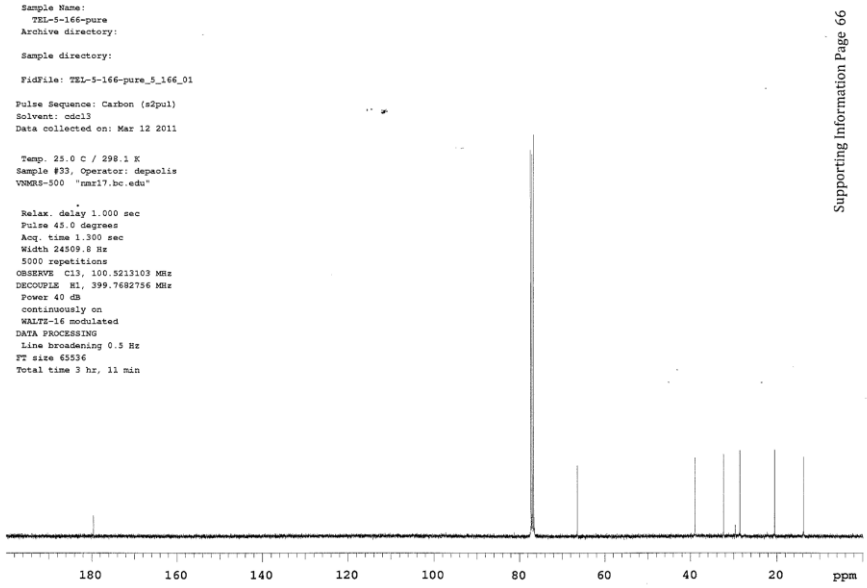
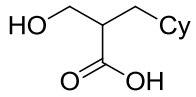
OAD-1-195-pure-final
Archive directory:
Sample directory:
FidFile: TEL-4-166-pure
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 12 2011
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr17.bc.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
16 repetitions
OBSERVE H1, 499.8808020 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min 55 sec
9
8
7
6
5
4
3
2
1
ppm


Sample Name:
TEL-5-166-pure
Archive directory:
Sample directory:
FidFile: TEL-5-166-pure_5_166_01
Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Mar 12 2011
Temp. 25.0 C / 298.1 K
Sample #33, Operator: depaolis
VNMRS-500 "nmr17.bc.edu"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 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 65536
Total time 3 hr, 11 min
180
160
140
120
100
80
60
40
20
ppm



3-Cyclohexyl-2-(hydroxymethyl)propanoic acid (1.28). Hydroformylation of (*E*)-3-cyclohexylprop-2-en-1-ol was performed following General Procedure A [except temperature (35 °C), pressure (50 psi) and acid loading (0.025 mol % *p*-TsOH)] and oxidation following General Procedure F. Analysis of the crude oxidation showed a regioselectivity of >95:5. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a clear oil (80.5 mg, 72%).

Hydroformylation of (*Z*)-3-cyclohexylprop-2-en-1-ol was performed following General Procedure A [except pressure (50 psi) and acid loading (0.025 mol % *p*-TsOH)] and oxidation following General Procedure F. Analysis of the crude oxidation showed a regioselectivity of >95:5. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a clear oil (91.6 mg, 82%)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.78-3.70 (m, 2H), 2.76-2.66 (m, 1H), 1.80-1.52 (m, 6H), 1.38-1.06 (m, 5H), 0.95-0.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.0, 63.3, 44.8, 35.7, 35.2, 33.2, 33.1, 26.4, 26.10, 26.08; IR: 2921, 2851, 1706, 1448, 1191, 1023, 906, 732 cm^{-1}; HRMS Calcd. for $C_{10}H_{19}O_3$ $[M+H]^+$: 187.1334, Found: 187.1333.

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```
 Sample Name:
   TEL-4-105f9_12
 Archive directory:

 Sample directory:

 FidFile: Proton

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Jan 21 2010

 Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500  "nmr17.bc.edu"

 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
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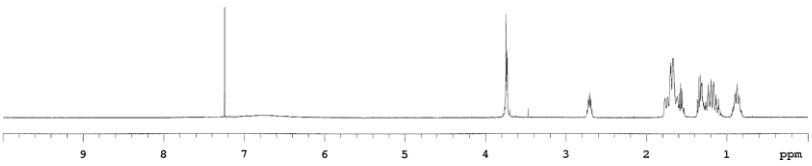

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```
TEL-5-69B

 Sample Name:
   TEL-5-69B
 Archive directory:

 Sample directory:

 FidFile: TEL-5-69B_TEL-5_69B_02

Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Dec  3 2010

 Temp. 25.0 C / 298.1 K
Sample #3, Operator: lightbut
VNMRS-500  "nmr17.bc.edu"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
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 5000 repetitions
OBSERVE   C13, 100.5213103 MHz
DECOUPLE  H1, 399.7682756 MHz
 Power 40 dB
 continuously on
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DATA PROCESSING
 Line broadening 0.5 Hz
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Total time 3 hr, 11 min
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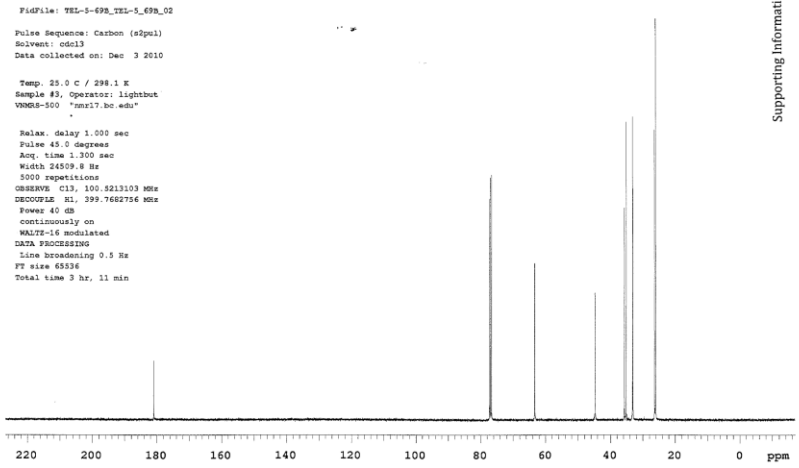
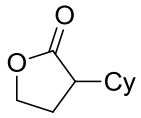
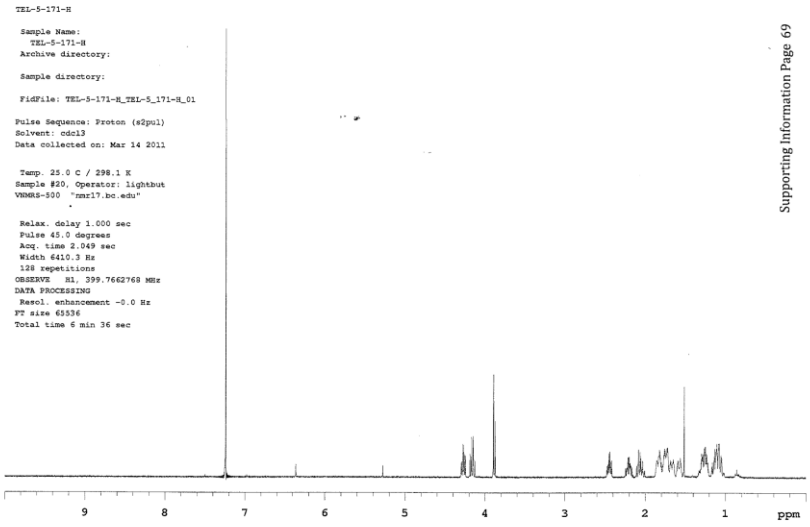
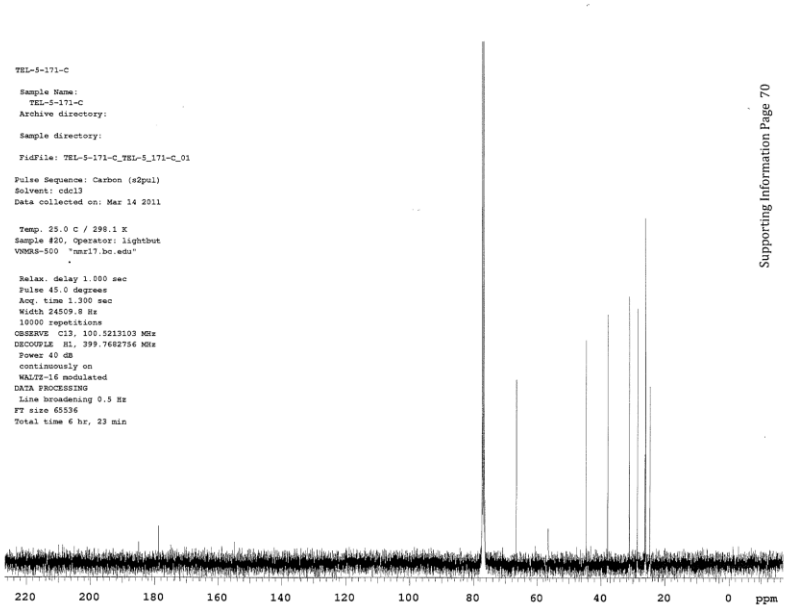
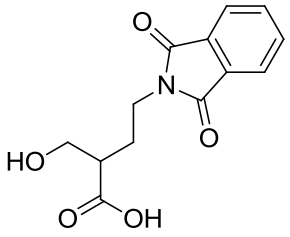




3-Cyclohexyldihydrofuran-2(3*H*)-one. Hydroformylation of (*E*)-3-cyclohexylprop-2-en-1-ol was performed following General Procedure E and oxidation following General Procedure F and afforded the title compound in sufficient quantity for analysis. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (app dt, 1H, *J*= 8.8, 4.0), 4.20-4.12 (m, 1H), 2.49-2.41 (m, 1H), 2.25-2.15 (m, 1H), 2.11-2.00 (m, 1H), 1.88-1.54 (m, 6H), 1.34-1.21 (m, 2H), 1.18-1.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.8, 66.6, 56.5, 44.6, 37.9, 31.1, 28.6, 26.2, 26.1, 24.7; IR: 2924, 2852, 1768, 1581, 1450, 1371, 1185, 1027 cm^{-1}; HRMS Calcd. for $C_{10}H_{17}O_2$ $[M+H]^+$: 169.1228, Found: 169.1222.

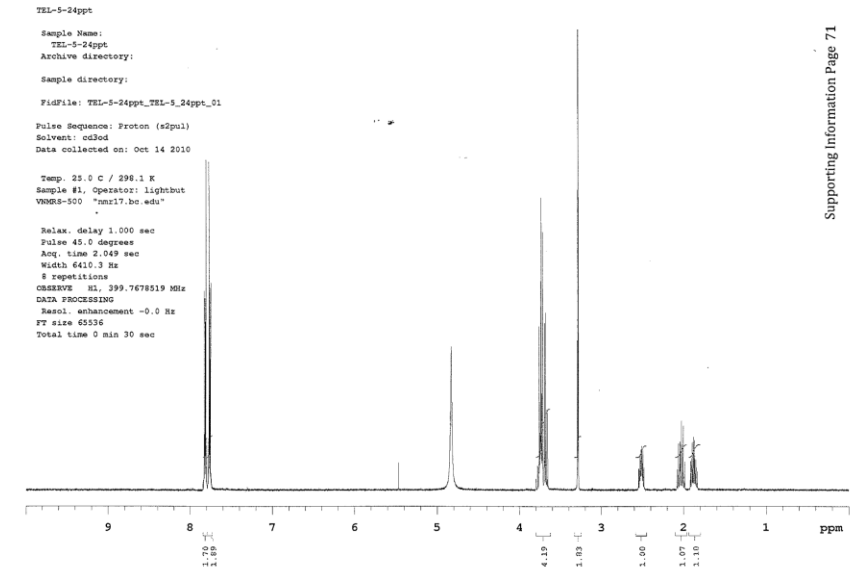


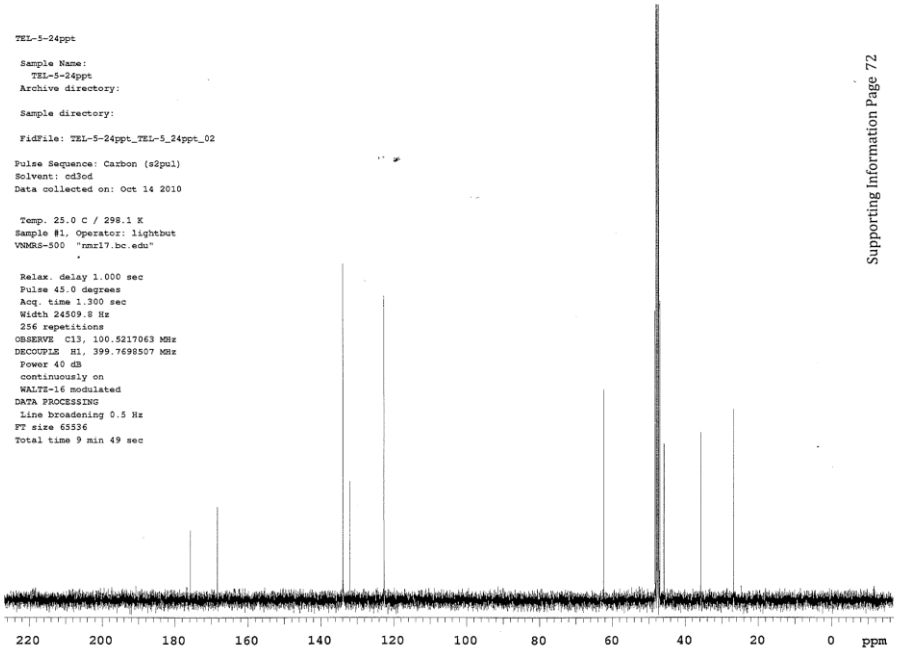


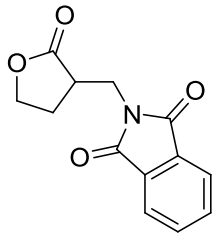


4-(1,3-Dioxoisoindolin-2-yl)-2-(hydroxymethyl)butanoic acid (1.31). Hydroformylation of (*Z*)-2-(4-hydroxybut-2-en-1-yl)isoindoline-1,3-dione was performed following General Procedure A [except acid loading (0.025 mol % *p*-TsOH)] and oxidation following General Procedure F. Analysis of the crude oxidation showed a regioselectivity of 88:12. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a white solid (75.2 mg, 71%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.84-7.80 (m, 2H), 7.79-7.74 (m, 2H), 3.80-3.65 (m, 4H), 2.56-2.48 (m, 1H), 2.09-1.98 (m, 1H), 1.93-1.83 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 175.8, 168.4, 133.9, 132.0, 122.6, 62.4, 45.8, 35.7, 26.8; IR: 3463, 3062, 1699, 1397,

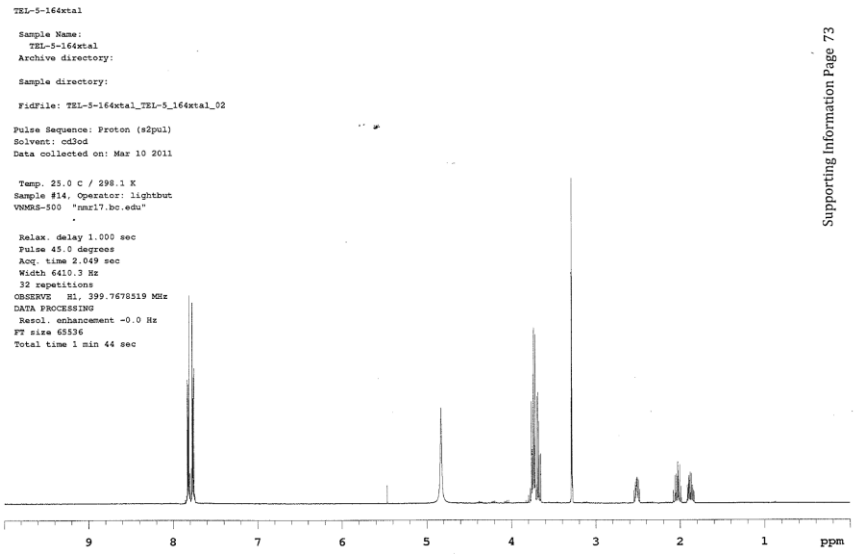
1371, 1187, 908, 717, 529 cm^{-1}; HRMS Calcd. for $C_{13}H_{14}N_1O_5$ $[M+H]^+$: 264.0872, Found: 264.0878.







2-((2-Oxotetrahydrofuran-3-yl)methyl)isoindoline-1,3-dione. Hydroformylation of (*Z*)-2-(4-hydroxybut-2-en-1-yl)isoindoline-1,3-dione was performed following General Procedure E and oxidation following General Procedure F and afforded the title compound in sufficient quantity for analysis. (Note: Chromatography was not required; the title compound spontaneously crystallized out of methylene chloride solution and was filtered and rinsed with pentane yielding pure material.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84-7.80 (m, 2H), 7.79-7.74 (m, 2H), 3.78-3.65 (m, 4H), 2.55-2.48 (m, 1H), 2.08-1.98 (m, 1H), 1.92-1.83 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 175.8, 168.4, 133.8, 132.0, 122.6, 62.4, 45.8, 32.7, 26.8; IR: 3459 (br), 2946, 1699, 1398, 1188, 1039, 720 cm^{-1}; HRMS Calcd. for $C_{13}H_{12}NO_4$ $[M+H]^+$: 246.0766, Found: 246.0765.



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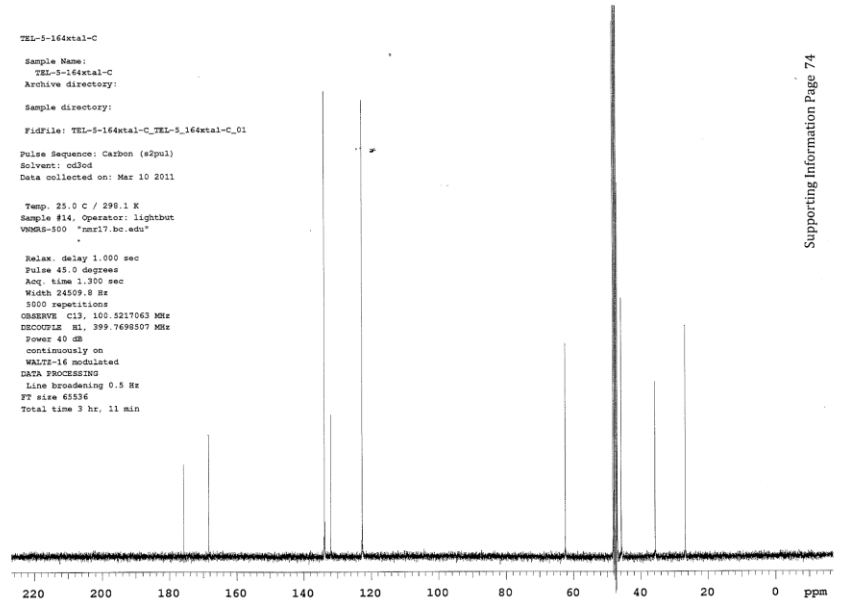

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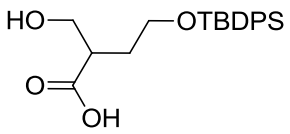
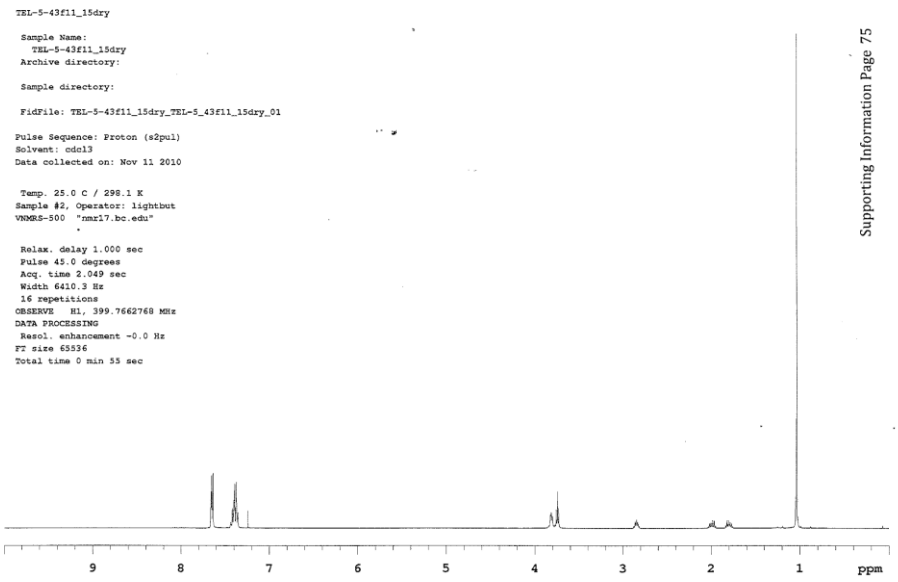
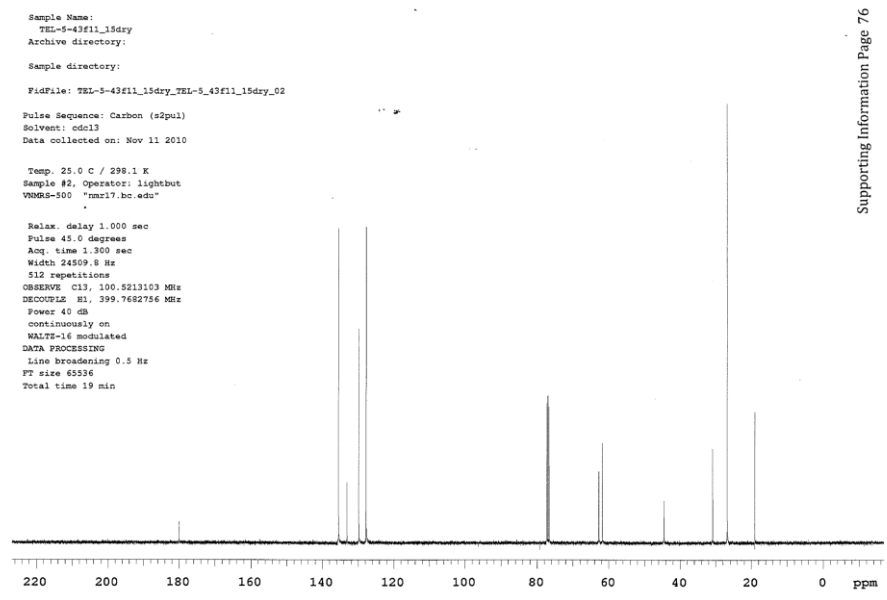


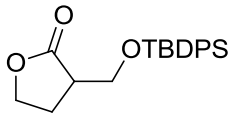
4-((*tert*-Butyldiphenylsilyl)oxy)-2-(hydroxymethyl)butanoic acid (1.33). Hydroformylation of (*Z*)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-en-1-ol was performed following General Procedure A [except acid loading (0.20 mol % *p*-TsOH)] and oxidation following General Procedure F. Analysis of the crude oxidation showed a regioselectivity of 85:15. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a clear oil (187.9 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.63 (m, 4H), 7.45-7.34 (m, 6H), 3.58-3.54 (m, 4H), 2.58-2.56 (m, 1H), 2.04-1.94 (m, 1H), 1.85-1.75 (m, 1H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.0, 135.5, 133.1, 129.8, 127.8, 62.8, 61.8, 44.5, 30.9, 26.8, 19.1; IR: 3071, 2956, 2857, 1708, 1427, 1107, 822, 737, 701, 613, 504 cm^{-1}; HRMS Calcd. for $C_{21}H_{29}O_4Si$ $[M+H]^+$: 373.1835, Found: 373.1845.



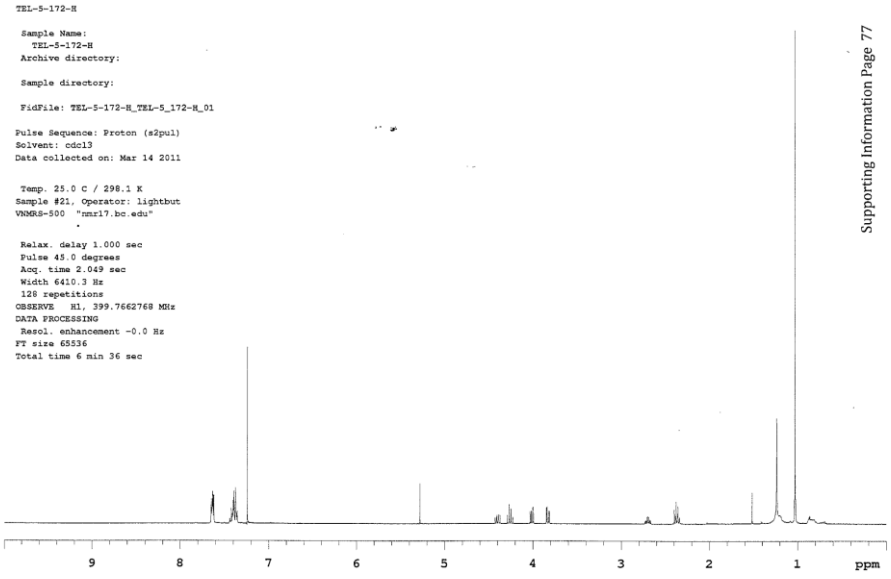
Supporting Information Page 75

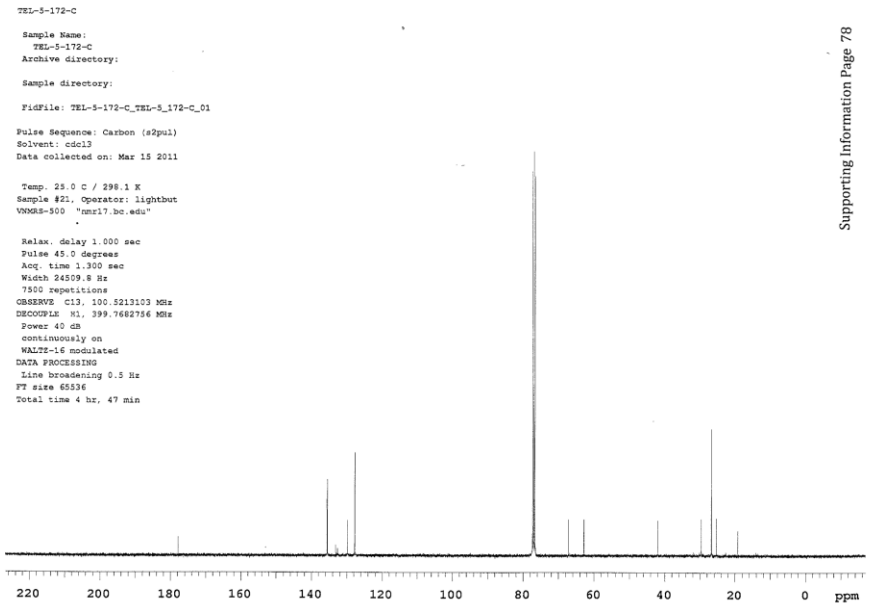


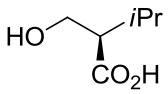
Supporting Information Page 76



3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)dihydrofuran-2(3*H*)-one. Hydroformylation of (*Z*)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-en-1-ol was performed following General Procedure E and oxidation following General Procedure F and afforded the title compound in sufficient quantity for analysis. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67-7.76 (m, 4H), 7.46-7.33 (m, 6H), 4.43-4.35 (m, 1H), 4.30-4.22 (m, 1H), 4.01 (dd, 1H, *J*= 10.0, 4.6), 3.83 (dd, 1H, *J*= 10.0, 3.2), 2.74-2.66 (m, 1H), 2.41-2.31 (m, 2H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9, 135.7, 135.5, 129.8, 127.8, 67.1, 62.8, 42.0, 29.7, 26.7, 25.3; IR: 2931, 2857, 1773, 1428, 1111, 1024, 702, 504 cm^{-1}; HRMS Calcd. for $C_{21}H_{30}NO_3Si$ $[M+NH_4]^+$: 372.1995, Found: 372.1988.

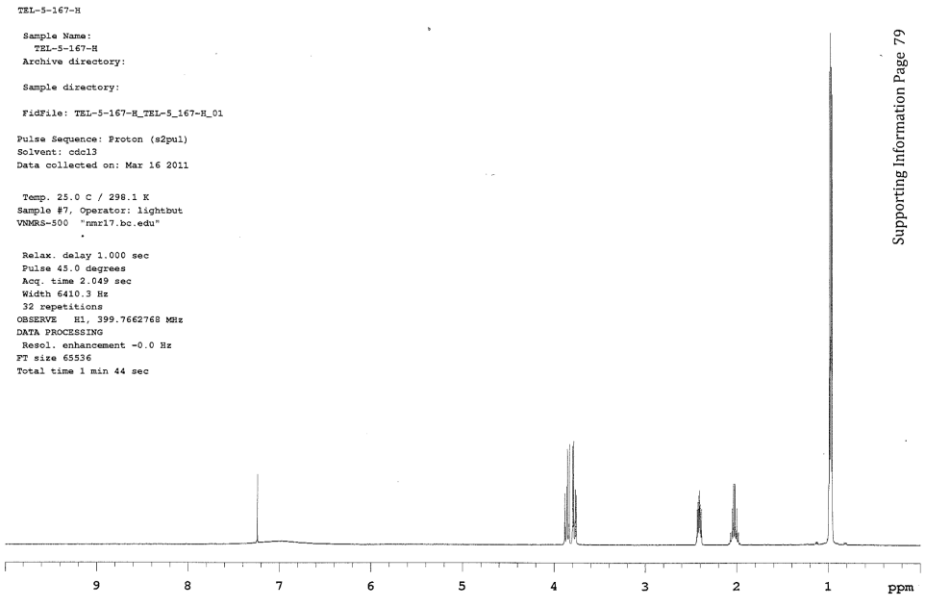


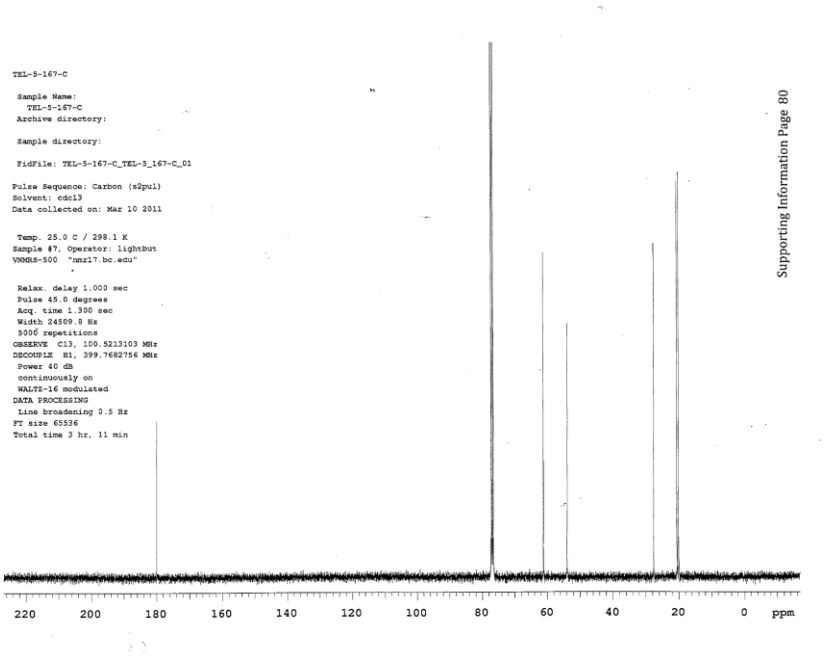


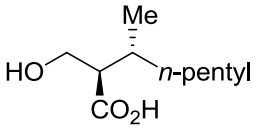


2-(Hydroxymethyl)-3-methylbutanoic acid (1.35). Hydroformylation of 3-methyl-2-buten-1-ol was performed following General Procedure C (except the substrate was included in the solution during preparation in a dry box) and oxidation following General Procedure G. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a clear oil (68 mg, 85%). Note: Due to the water solubility of this compound, the oxidation reaction was quenched and acidified as noted in General Procedure G, and then concentrated to a slurry which was dissolved in methanol and dry loaded on silica gel prior to chromatography. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.86 (dd, 1H, *J*= 11.2, 8.8), 3.61 (dd, 1H, *J*= 11.2, 4.2), 2.41 (ddd, 1H, *J*= 8.8, 7.2, 4.2), 2.08-1.95 (m, 1H), 0.98 (d, 3H, *J*= 6.8), 0.97 (d, 3H, *J*= 6.8); ^{13}C NMR ($CDCl_3$,

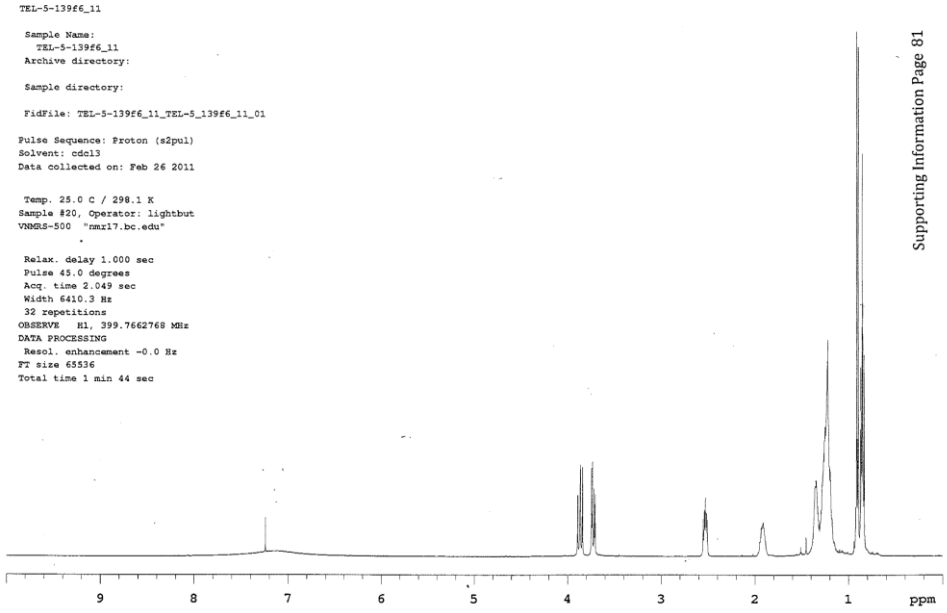
100 MHz) δ 180.0, 61.3, 54.0, 27.6, 20.5, 20.0; IR: 2963, 1705, 1467, 1392, 1269, 1195, 1064, 1013, 830, 659 cm^{-1}; HRMS Calcd. for $C_6H_{13}O_3$ $[M+H]^+$: 133.0865, Found: 133.0860.



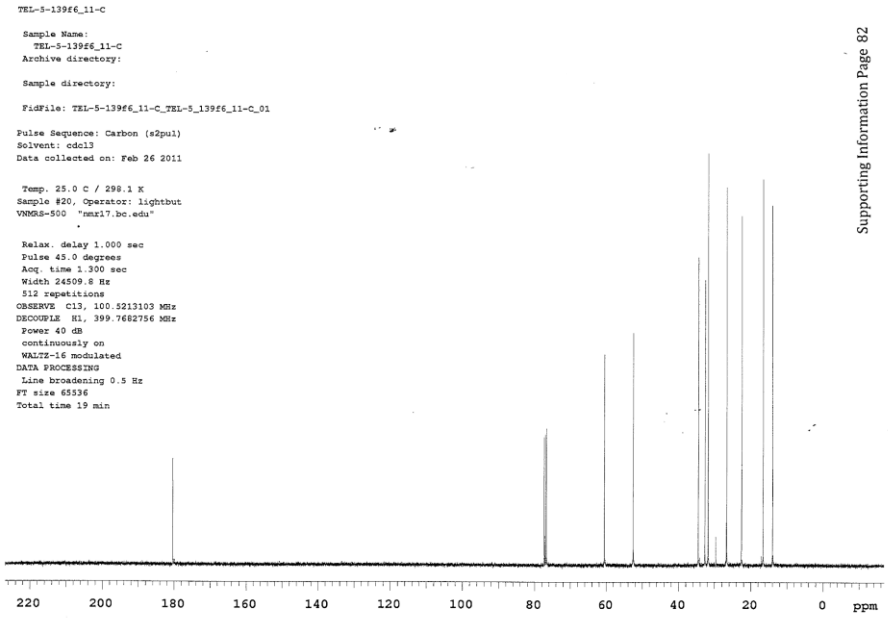




***anti*-2-(Hydroxymethyl)-3-methyloctanoic acid (1.37)**. Hydroformylation of (*E*)-3-methyloct-2-en-1-ol was performed following General Procedure C and oxidation following General Procedure G. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a clear oil (83.3 mg, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.87 (dd, 1H, *J*= 11.2, 9.0), 3.73 (dd, 1H, *J*= 11.2, 3.8), 2.58-2.50 (m, 1H), 1.98-1.86 (m, 1H), 1.42-1.14 (m, 9H), 0.91 (d, 3H, *J*= 6.8), 0.85 (t, 3H, *J*= 6.8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.4, 60.5, 52.5, 34.5, 32.7, 31.8, 26.7, 22.6, 16.6, 14.0; IR: 2957, 2927, 2857, 1707, 1461, 1381, 1188, 1035 cm^{-1}; HRMS Calcd. for $C_{10}H_{21}O_3$ $[M+H]^+$: 189.1491, Found: 189.1500.



Supporting Information Page 81



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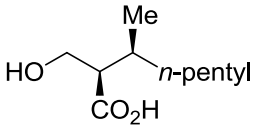
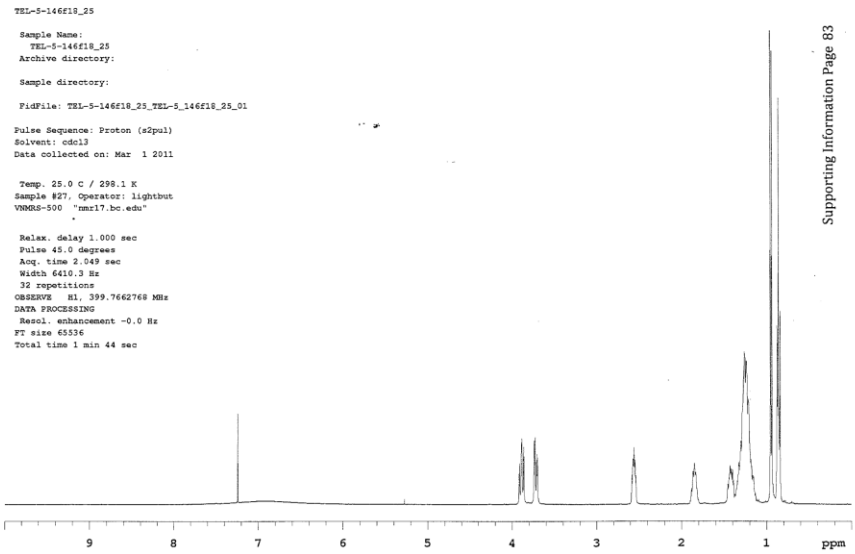


***syn*-2-(Hydroxymethyl)-3-methyloctanoic acid (1.39)**. Hydroformylation of (*Z*)-3-methyloct-2-en-1-ol was performed following General Procedure D and oxidation following General Procedure G. Purification on silica gel eluting with 1-5% methanol in methylene chloride afforded the title compound as a clear oil (32.7 mg, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (dd, 1H, *J*= 11.0, 9.0), 3.72 (dd, 1H, *J*= 11.0, 3.9), 2.61-2.52 (m, 1H), 1.91-1.79 (m, 1H), 1.48-1.10 (m, 9H), 0.94 (d, 3H, *J*= 6.8), 0.86 (t, 3H, *J*= 6.9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.1, 61.5, 52.6, 34.1, 32.6, 31.8, 26.6, 22.6, 17.1, 14.0; IR: 2957, 2927, 2858, 1704, 1461, 1383, 1189, 1015 cm^{-1}; HRMS Calcd. for $C_{10}H_{21}O_3$ $[M+H]^+$: 189.1491, Found: 189.1496.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TEL-5-146f18_25
Archive directory:
Sample directory:
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Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 1 2011
Temp. 25.0 C / 298.1 K
Sample #27, Operator: lightbut
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Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
32 repetitions
OBSERVE H1, 399.7662768 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
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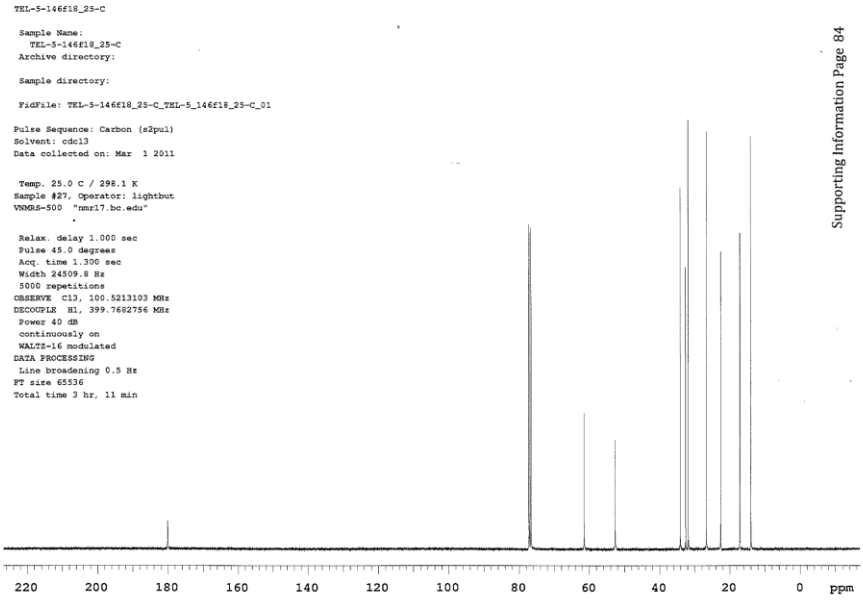
Total time 1 min 44 sec
9
8
7
6
5
4
3
2
1
ppm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Sample Name:
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Sample directory:
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Solvent: cdcl3
Data collected on: Mar 1 2011
Temp. 25.0 C / 298.1 K
Sample #27, Operator: lightbut
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Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5213103 MHz
DECOUPLE H1, 399.7682756 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
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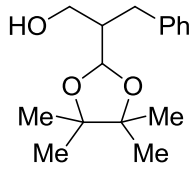
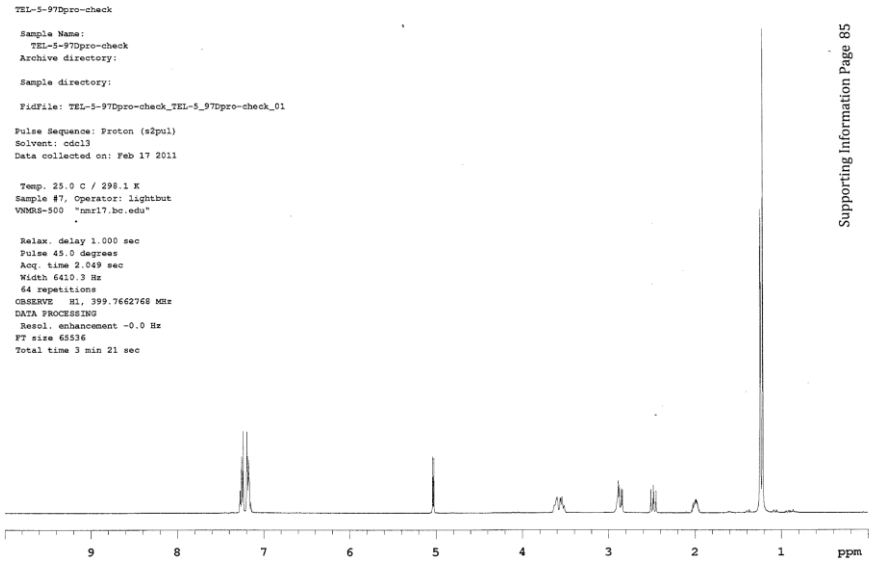
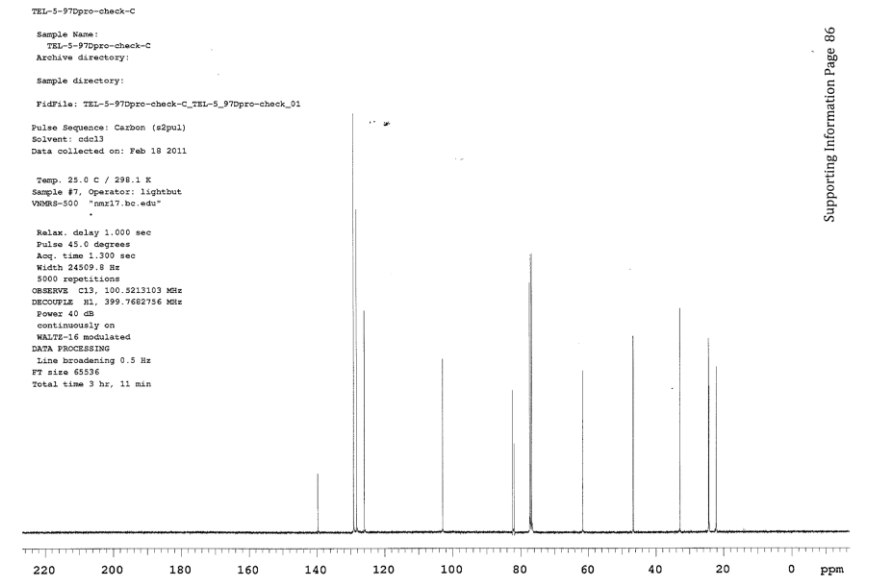


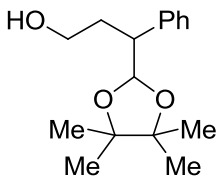
3-Phenyl-2-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)propan-1-ol (1.40). Hydroformylation of cinnamyl alcohol was performed following General Procedure A and pinacol protection following General Procedure H. Analysis of the crude protection reaction showed a regioselectivity of 94:6. Purification on silica gel eluting with 5-20% ethyl acetate afforded the title compound as a clear oil (137 mg, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.23 (m, 2H), 7.21-7.14 (m, 3H), 5.03 (d, 1H, *J*= 5.6), 3.66-3.50 (m, 2H), 2.94-2.82 (m, 2H), 2.53-2.44 (m, 1H), 2.04-1.94 (m, 1H), 1.25 (s, 3H), 1.24 (s, 3H), 1.22 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.6, 129.2, 128.3, 126.0, 102.9, 82.4, 81.8, 61.6, 46.7, 32.8, 24.4, 24.3, 22.22, 22.17; IR: 3464, 2977, 2928, 1454, 1368, 1153, 1134, 1082, 1030 cm^{-1}; HRMS Calcd. for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1804, Found: 265.1804.



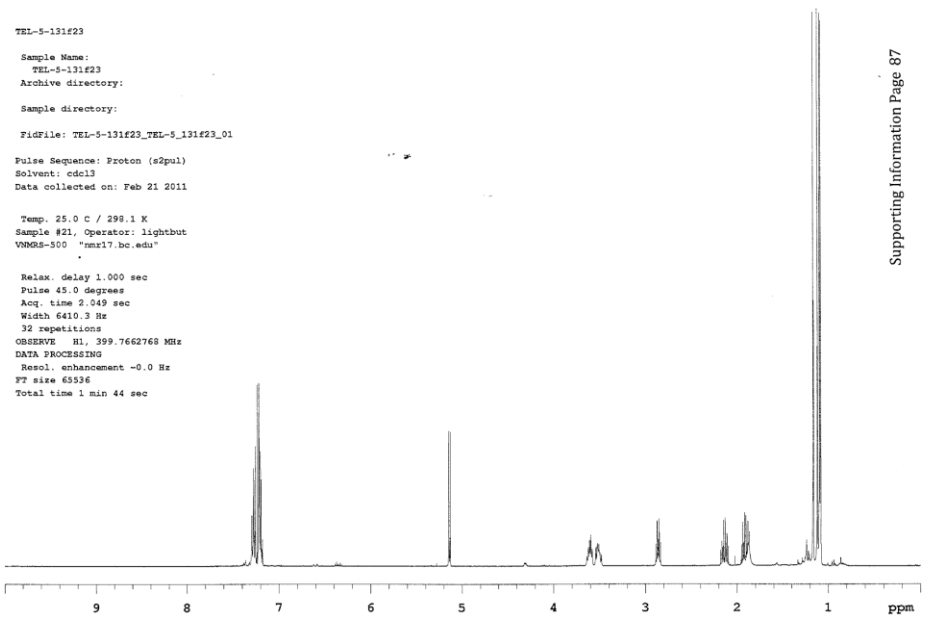
Supporting Information Page 85



Supporting Information Page 86



3-Phenyl-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)propan-1-ol. Hydroformylation of cinnamyl alcohol following General Procedure E and pinacol protection following General Procedure H afforded the title compound in sufficient quantity for analysis. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.25 (m, 2H), 7.23-7.17 (m, 3H), 5.14 (d, 1H, *J*= 5.6), 3.66-3.57 (m, 1H), 3.56-3.46 (m, 1H), 2.90-2.83 (m, 1H), 2.19-2.08 (m, 1H), 1.96-1.83 (m, 2H), 1.17 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.6, 128.9, 128.2, 126.6, 103.0, 82.1, 81.8, 61.3, 48.8, 34.2, 24.1, 24.0, 22.3, 22.1; IR: 3412, 2976, 2930, 2871, 1389, 1156, 1134, 1073, 700 cm^{-1}; HRMS Calcd. for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1804, Found: 265.1810.



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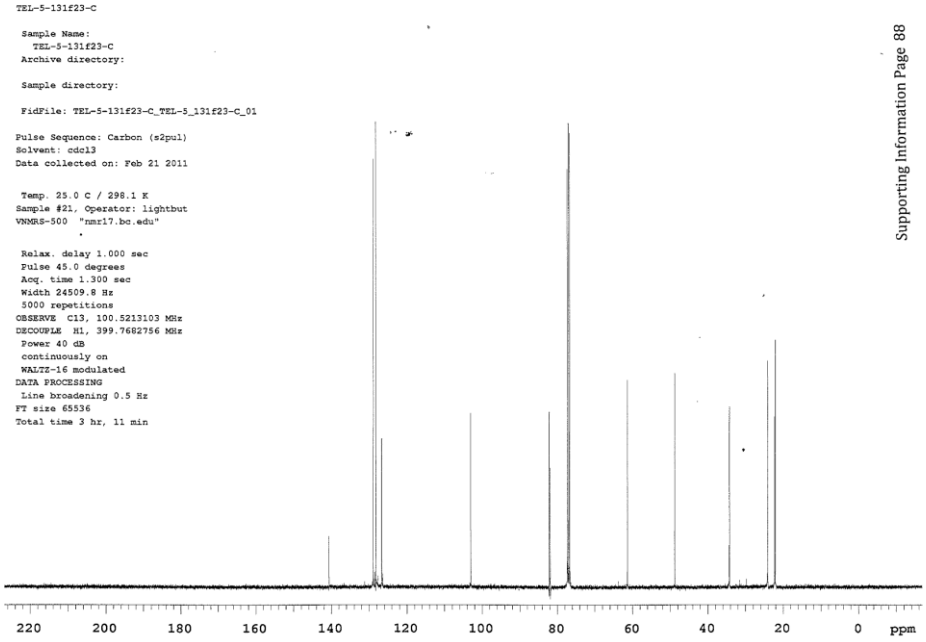

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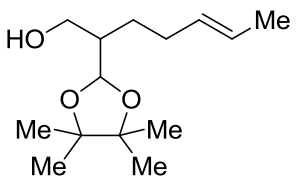
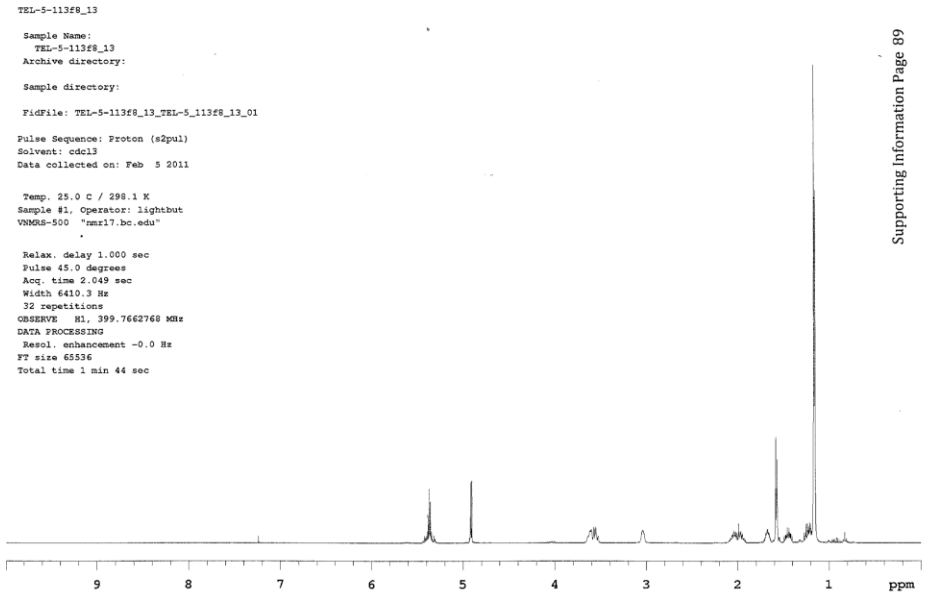


(*E*)-2-(4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl)hept-5-en-1-ol (1.42). Hydroformylation of (2*E*,5*E*)-hepta-2,5-dien-1-ol was performed following General Procedure B and pinacol protection following General Procedure H. Purification on silica gel eluting with 5-20% ethyl acetate afforded the title compound as a clear oil (122.2 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.44-5.29 (m, 2H), 4.91 (d, 1H, *J*= 6.0), 3.68-3.51 (m, 2H), 3.04 (br s, 1H), 2.12-1.91 (m, 2H), 1.72-1.63 (m, 1H), 1.58 (d, 3H, *J*= 4.8), 1.51-1.10 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.9, 125.2, 103.8, 82.1, 81.6, 62.4, 44.4, 30.0, 26.5, 24.3, 24.1, 22.1, 22.0, 17.8; IR: 3454 (br), 2976, 2930, 1450, 1368, 1154, 964 cm^{-1}; HRMS Calcd. for $C_{14}H_{27}O_3$ $[M+H]^+$: 243.1960, Found: 243.1963.



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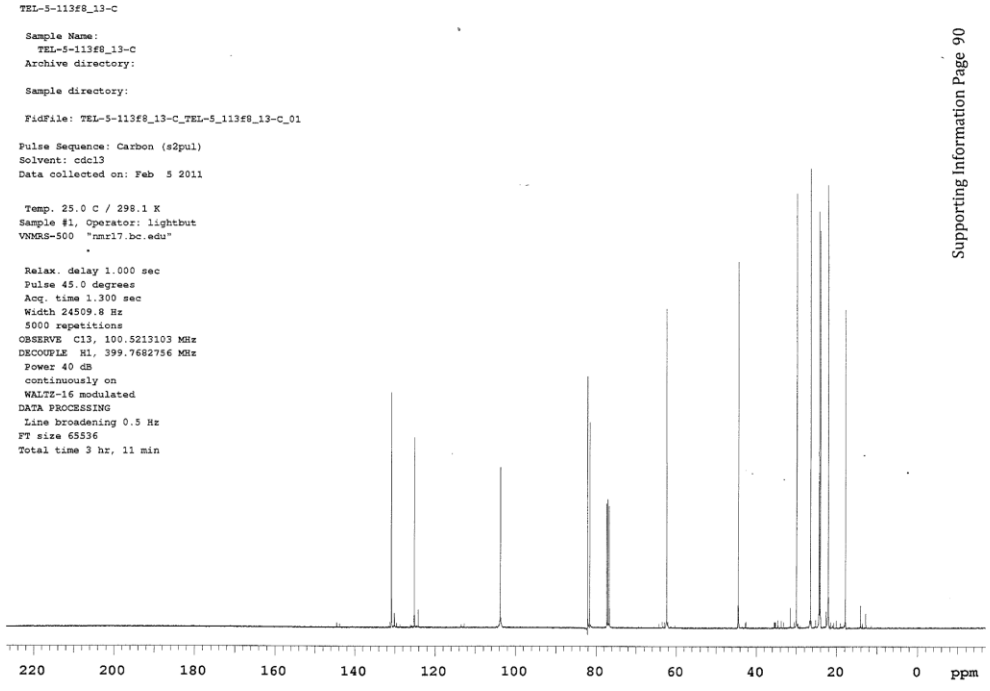

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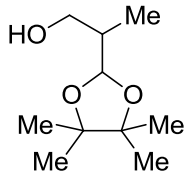
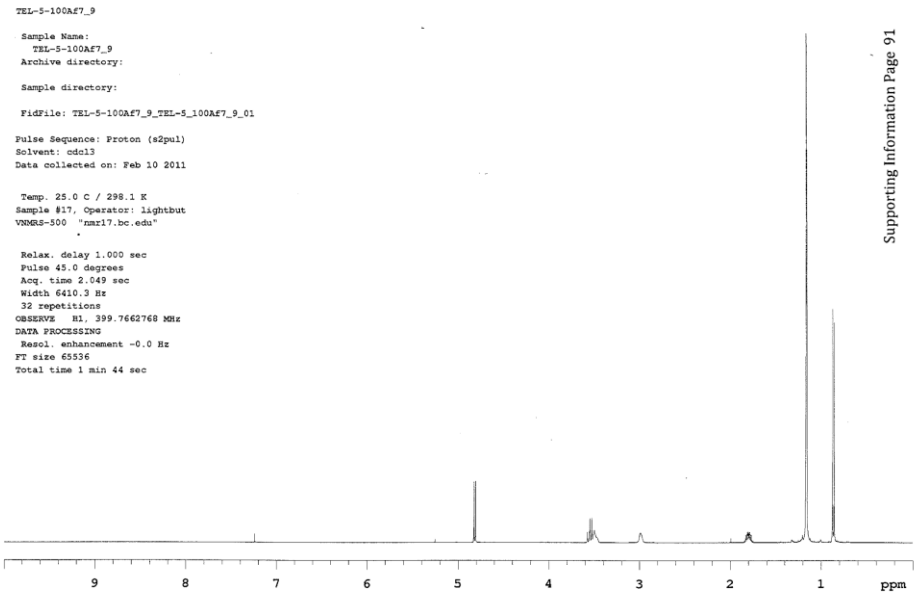


2-(4,4,5,5-Tetramethyl-1,3-dioxolan-2-yl)propan-1-ol (1.44). Hydroformylation of allyl alcohol was performed following General Procedure B [except temperature (30 °C) and acid loading (0.10 mol % *p*-TsOH) and the substrate was included in the solution during preparation in a dry box)] and pinacol protection following General Procedure H [except pinacol (100 mg)]. Analysis of the crude protection reaction showed a regioselectivity of 87:13 as compared to the reported spectra of 3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)propan-1-ol.[11] Purification on silica gel eluting with 5-20% ethyl acetate afforded the title compound as a clear oil (30 mg, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82 (d, 1H, *J*= 6.4), 3.59-3.44 (m, 2H), 2.99 (br s, 1H), 1.86-1.74 (m, 1H), 1,17 (s, 12H), 0.87 (d, 3H, *J*= 7.2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 104.4, 82.2, 81.5, 65.0, 40.6, 24.3, 23.9, 22.1, 21.9, 12.1; IR: 3462 (br), 2976, 2929, 2876, 1458, 1368, 1155, 1104, 1038, 994, 978, 866 cm^{-1}; HRMS Calcd. for $C_{10}H_{21}O_3$ $[M+H]^+$: 189.1491, Found: 189.1497.



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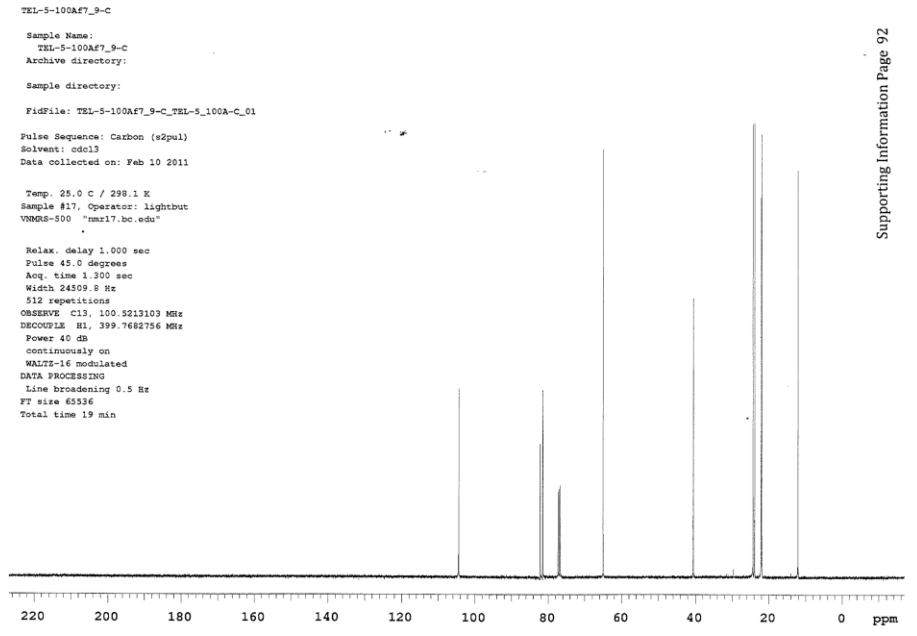

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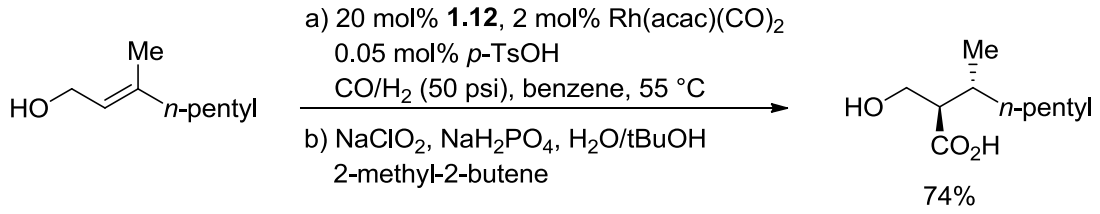
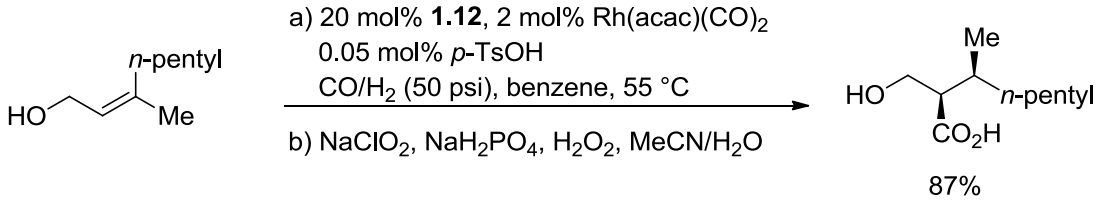
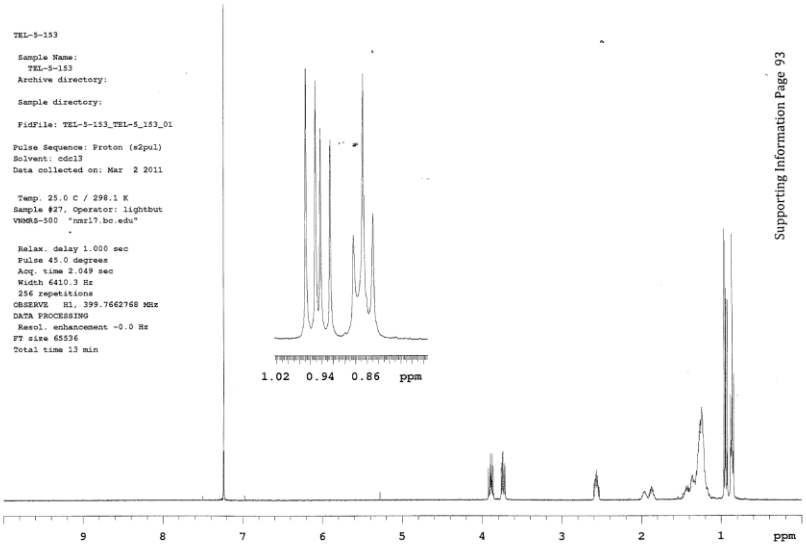
Diastereoselectivity in the Hydroformylation of Trisubstituted Olefins



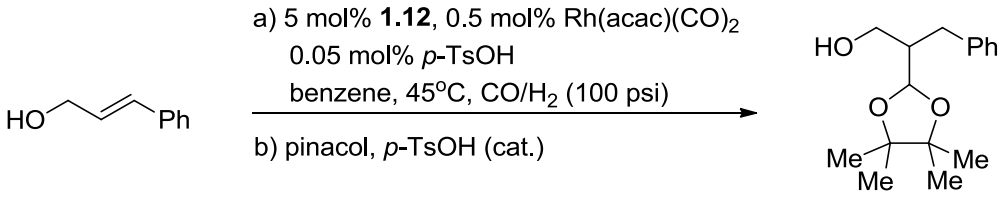


Hydroformylation, being a syn selective addition of hydrogen and carbon monoxide, is expected to give rise to *anti*-2-(hydroxymethyl)-3-methyloctanoic acid from (*E*)-3-methylocta-1,3-diene and to *syn*-2-(hydroxymethyl)-3-methyloctanoic acid from (*Z*)-3-methylocta-1,3-diene after oxidation of the aldehydes to the carboxylic acids. The ^{1}H and ^{13}C NMR NMR spectra of the products gave rise to different signals, and a sample of a mixture of the two products (vide infra) confirms the presence of two distinct diastereomers as evidenced by the appearance of two separate doublets for the 3-methyl substituent in the 500 MHz ^{1}H NMR spectrum.



500 MHz ^{1}H NMR spectrum of a <u>mixture</u> of *syn*- and *anti*-2-(hydroxymethyl)-3-methyloctanoic acid showing two doublets for the 3-methyl substituent, each arising from a separate diastereomer.

<u>Hydroformylation of 10 mmol of Cinnamyl Alcohol Using 5 mol % ligand **1.12** at 0.5 M</u>



10 mmol
0.5 M

83%

Cinnamyl alcohol (1.34 g, 10.0 mmol) was equally divided between four oven-dried reaction vials and was loaded into the Endeavor. The Endeavor was sealed and purged with nitrogen (4 x 100 psi). In a dry box dicarbonyl acetylacetonato rhodium (I) (0.5 mol

%, 12.9 mg, 0.05 mmol), ligand **1** (5.0 mol %, 142.7 mg, 0.5 mmol), and *p*-toluene sulfonic acid (0.003 mol %, 527 mL, 5.69 x 10^{-4} M in benzene) were diluted to a total volume of 4 mL in benzene. 1 mL of this solution was added to each of the four reaction vials via syringe and an additional 4 mL of benzene was added to each reaction vial via syringe. The Endeavor was purged with nitrogen (1 x 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 200 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at 45 °C and 200 psi H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The combined reaction solutions were transferred to a dry 250 mL flask and diluted with benzene (20 mL). Pinacol (5.00 g, 42.3 mmol) and *p*-toluene sulfonic acid monohydrate (5.0 mol %, 95.0 mg, 0.50 mmol) were added. The reaction was heated to 80 °C in an oil bath and stirred for 90 minutes. The reaction was concentrated by rotary evaporation and a crude NMR indicated a 95:5 regioselectivity. Purification on silica gel eluting with a gradient of 5-10% ethyl acetate in hexanes afforded 2.162 g (83%) of the desired compound as a pale yellow oil.

VI. References

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Chapter 2: Scaffolding Catalysis as an Alternate and More Practical Solution to the Site-Selective Functionalization of 1,2-Diols.

I. Background

The power and potential of catalytic directing groups has been recently demonstrated in the metal-catalyzed hydroformylation of olefins[1] and other transformations such as the *ortho* arylation of phenols[2] and hydroacylation of aldehydes.[3] Their use can be further extended to address unsolved problems in organic synthesis, such as the selective functionalization of polyfunctional molecules in a site- and stereocontrolled manner.

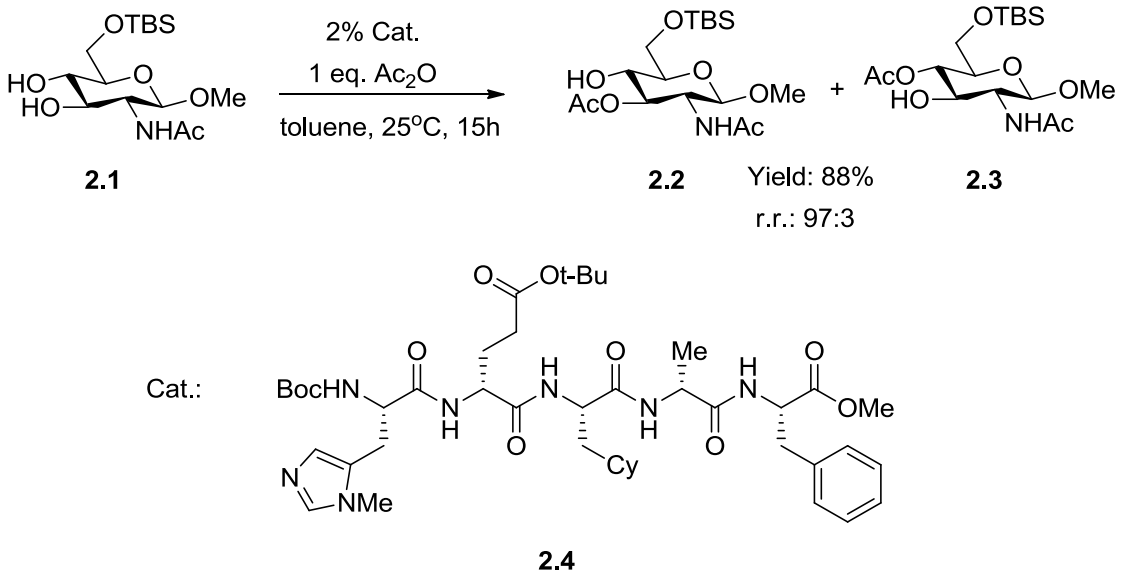
In the past twenty years, a great deal of progress has been made in the design of organocatalysts to mediate various bond-forming processes with effective conveyance of stereochemical information.[4] However, reports of organocatalysts capable of derivatizing a particular functional group in the presence of similar functional groups is not as common.[5] By looking at the features and merits of enzymatic catalysis when compared to small molecule organocatalysts, it becomes clear that enzymes are still superior species in site-selective catalysis. In fact, the site-selective functionalization of polyols in a nonenzymatic fashion is still an ongoing challenge in the synthesis of complex natural

[1] Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.
[2] Bedford, R. B.; Cole, L. J.; Hurthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *115*, 116.
[3] Lee, D.-Y.; Hong, B.-S.; Cho, E.-G.; Lee, H.; Jun, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 6372.
[4] Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601.
[5] Sculimbrene, B. R.; Morgan, A. J.; Miller S. J. *Chem. Comm.* **2003**, *15*, 1781.

products and their subsequent derivatization for the development of new pharmaceutical agents.[6]

In the recent literature, however, there have been several examples that address the issue of site-selective functionalization of a highly oxygenated compound by using a small molecule catalyst that can in part mimic the behavior of an enzyme. Scott Miller[7] has shown that a protected carbohydrate monomer (glucosamine derivative **2.1**) is preferentially acylated with great success at the hydroxyl group in the 4-position (**2.2)** rather than the 5-position (**2.3)** (Scheme 2.1).

Scheme 2.1: Peptide-Based Regioselective Functionalization of a Glucosamine Derivative.



2.4

The transformation was carried out by using the peptide-based catalyst **2.4**, wherein the acetamide group of **2.1** can undergo hydrogen bonding with the catalyst; it is thought that

[6] Lewis, C. A.; Miller, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5616.
[7] Griswold, K. S.; Miller, S. J. *Tetrahedron* **2003**, *59*, 8869.

both selectivity and reactivity are in part due to these noncovalent interactions that help preorganize the activated complex.

The above example shows a catalyst that is able to differentiate between hydroxyl sites of very similar reactivity; however, it is much more challenging to discriminate between sites of vast difference in reactivity as in the case of a primary versus a secondary alcohol.[8]

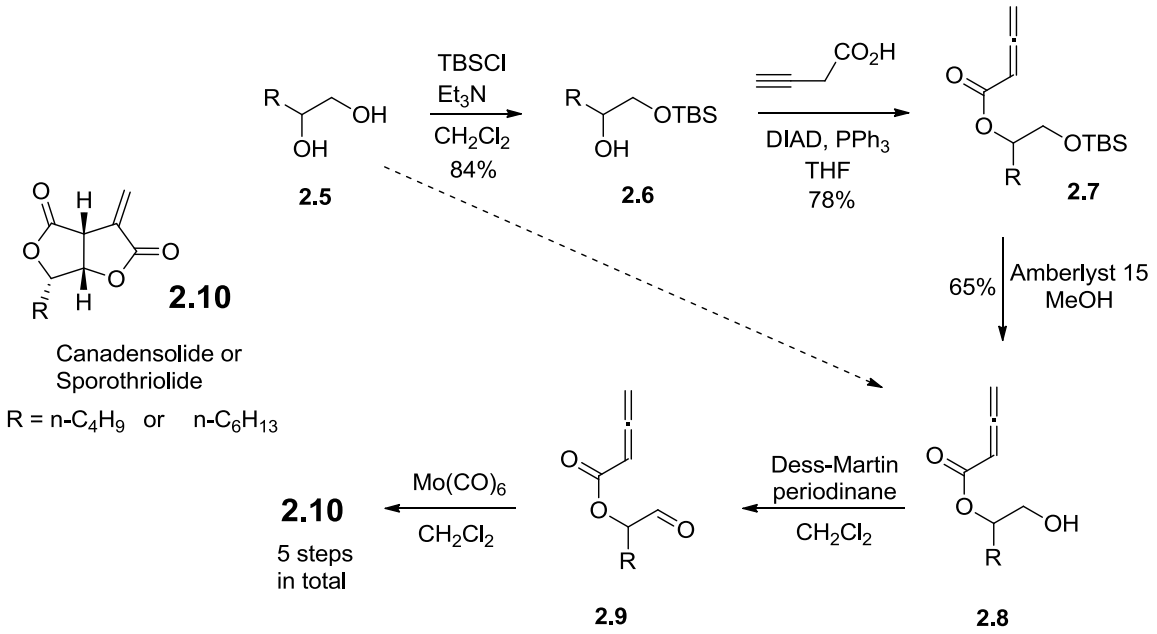
II. Issues of Site-Selectivity in Natural Product Synthesis

The importance of site differentiation can be further appreciated in natural product synthesis where protection of a secondary alcohol in the presence of a primary is not trivial. In a recent report,[9] Yu and coworkers prepared naturally occurring *bis*-lactones, canadensolide and sporothriolide, which have fungicidal activities. During the synthesis, a butynoic acid is coupled with a monoprotected diol **2.6** to obtain allenoester intermediate **2.7**, which is then deprotected to **2.8** for further elaboration to the target compound **2.10** (Scheme 2.2). The protection and deprotection required to mask the reactivity of a primary alcohol renders the sequence inefficient: it generates waste and increases costs in terms of resources and time. To avoid an unnecessary multistep manipulation, the development of a method for the site-selective delivery of an *O*-functionalizing reagent would be valuable. The synthesis outlined above contains a total of five steps to **2.10**, with two of those steps representing protecting group manipulations;

[8] Reginato, G.; Ricci, A.; Roelens, S.; Scapecchi, S. *J. Org. Chem.* **1990**, *55*, 5132.
[9] Kwon, J.; Gong, S.; Woo, S.-H.; Yu, C.-M. *Bull. Korean Chem. Soc.* **2009**, *30*, 773.

in principle the synthetic steps can be reduced by 40% if **2.8** can be directly obtained from **2.5**.

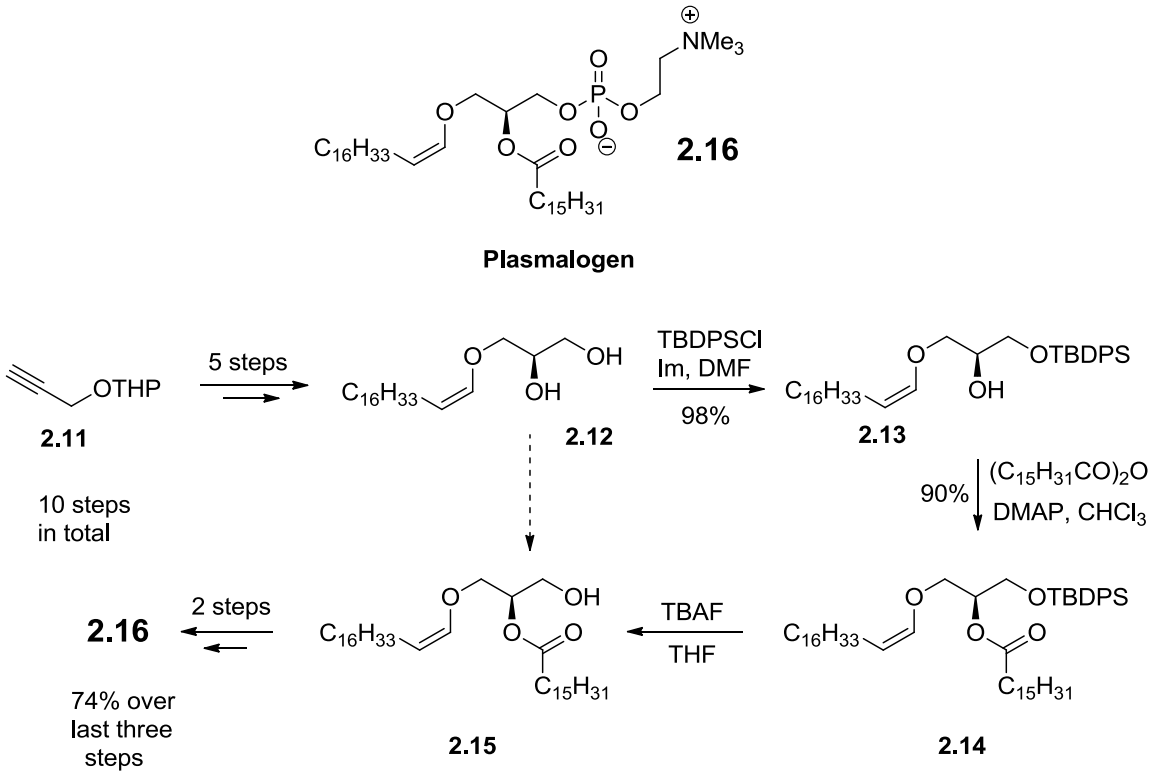
Scheme 2.2: Short Synthesis of Canadensolide and Sporothriolide.



A more recent example from the Hoveyda[10] group, where they report a catalytic, *Z*-selective olefin cross-metathesis of terminal enol ethers, again illustrates the need for a proper site-selective functionalization of diols. The utility of this newly developed method was applied to the synthesis of a natural product: specifically, the assembly of a plasmalogen phospholipid **2.16** that acts as an antioxidant to protect endothelial cells. The synthesis is short, efficient and it is an improvement upon the only other synthesis available in the literature by Qin[11] and coworkers. The route starts from the commercially available, THP-protected propargyl alcohol **2.11**, which is elaborated in a few steps, one

[10] Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461.
[11] Qin, D.; Byun, H.-S.; Bittman, R. *J. Am. Chem. Soc.* **1999**, *121*, 662.

Scheme 2.3: Synthesis of a Plasmalogen Phospholipid.



of which being the *Z*-selective olefin cross metathesis, to enantiopure diol **2.12**. The latter is then manipulated in three steps to **2.15** so that the secondary alcohol is functionalized and the primary alcohol remains free. A total of ten steps are required to arrive at the natural product, two of which are protecting group manipulations; the synthesis can be shortened further by 20% if the secondary alcohol could be acylated directly.

III. Scaffolding Catalysis as a Solution to Site-Selectivity

Based on the aforementioned notions and challenges, the development of a new class of catalysts to achieve site-selective modifications with electrophile transfer reactions is of great importance. Such catalysts would allow an increase in efficiency

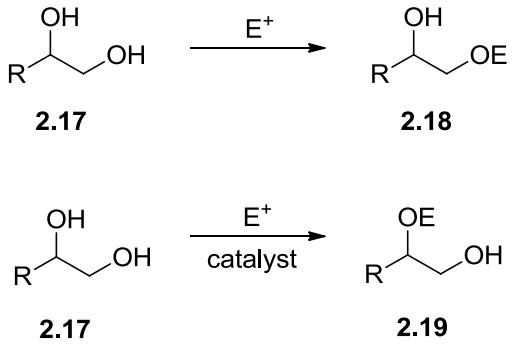
during the process of functionalization in natural product synthesis and derivatization, which usually requires unnecessary protection and deprotection sequences to obtain a single product.

To that end, the challenge synthetic chemists face when functionalizing a secondary alcohol over a vicinal primary is one of reactivity. Within the same compound, a primary alcohol is about two orders of magnitude more reactive than a secondary one. In order to reverse this natural trend and functionalize a secondary alcohol in a single step with high levels of selectivities (i.e. 90:10), it is necessary to have a catalyst that is able to meet an energetic demand of 4 kcal/mol. To put this energetic difference in context for enantioselective reactions, a 4 kcal/mol energy difference yields products in 99.8% ee. Since there are few catalysts that can meet this demand, synthetic routes that provide secondary alcohol functionalization rely on multistep processes. For example, a typical method for the secondary protection of a 1,2-diol relies on *bis*-protection followed by monodeprotection.[12] In designing a catalyst that can meet these energetic demands and provide monoprotected diol **2.19** preferentially (Scheme 2.4), the question becomes: what are the qualities that a successful catalyst should have to fulfill this objective?

A potential solution to the above problem is based on selective binding of the substrate before the functionalization step. We have designed **2.20** (Figure 2.1) as a catalyst that could bind alcohols through a reversible covalent bond; the application of

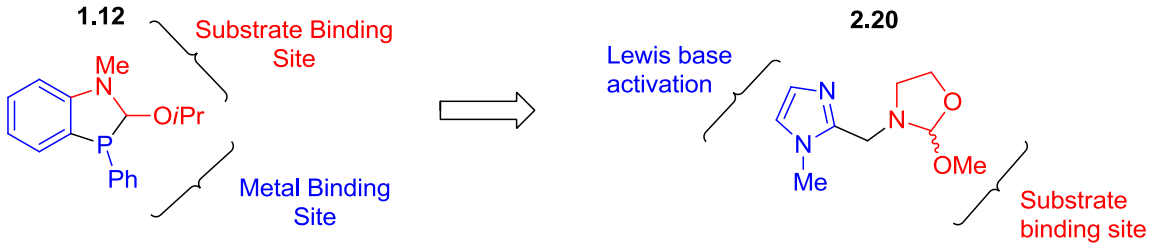
[12] Kobayashi, S.; Alizadeh, B. H.; Sasaki, S.-Y; Oguri, H.; Hirama, M. *Org. Lett.* **2004**, *6*, 751.

Scheme 2.4: Selective Protection of a 1,2-Diol.



this concept proved to be successful during the development of a bifunctional azaphosphole ligand (**1.12**), which simultaneously binds a molecule of substrate and the metal center during the hydroformylation of olefins. Furthermore, **2.20** incorporates an imidazole group that can serve to activate electrophiles and deliver them in an intramolecular fashion to the substrate. An advantage of this strategy is that the catalyst more favorably binds to the more accessible alcohol.

Figure 2.1: Catalyst Design.



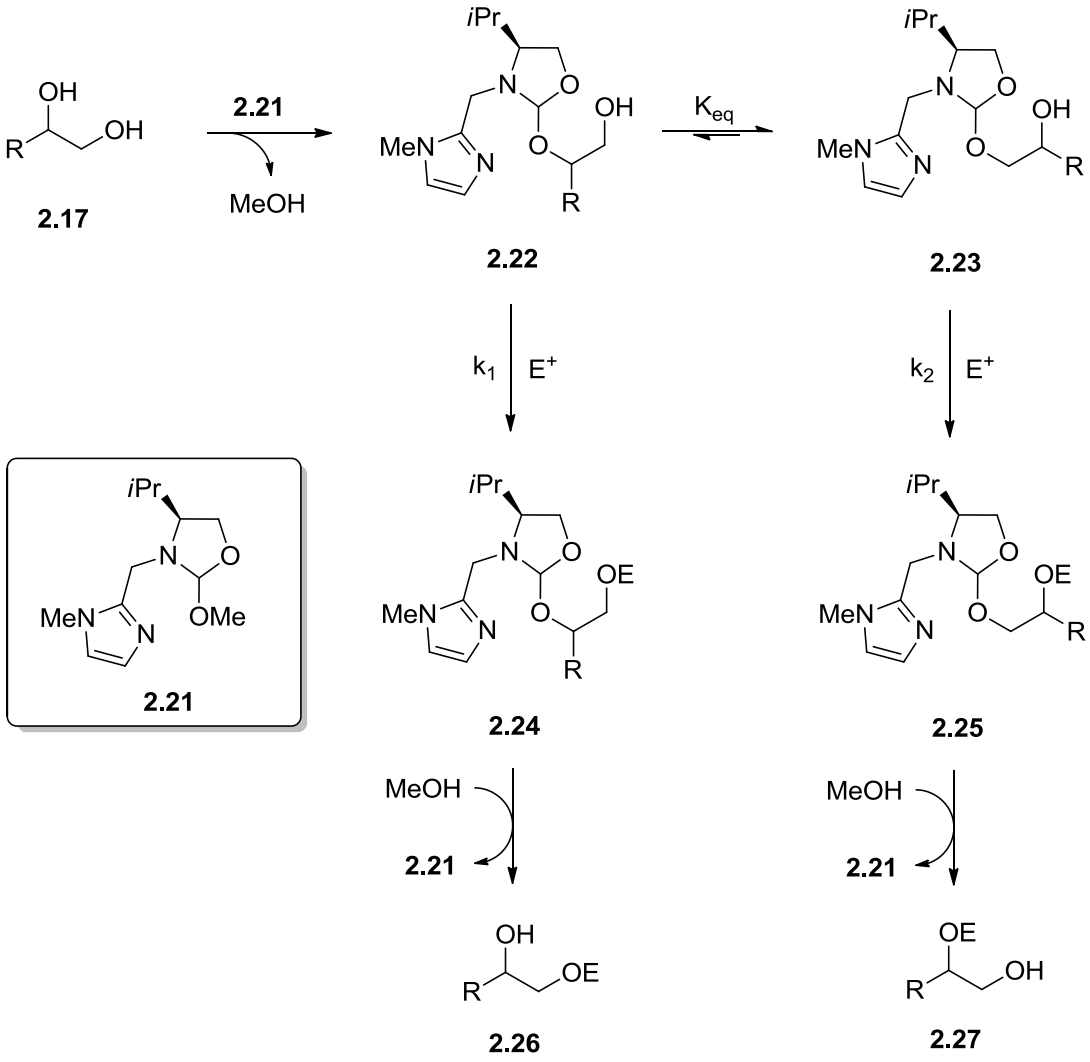
The extent to which preferential binding occurs, as well as the rate of functionalization, will dictate the overall selectivity of the transformation. Given a generic catalyst **2.21**, under conditions where binding of the primary and secondary alcohol to **2.21** is in equilibrium (Curtin-Hammett conditions) (Scheme 2.5), the overall selectivity will be a composite of K_{eq} and the rate of functionalization (k_1 and k_2). In this

case, binding favors the primary alcohol, which leads to the functionalized secondary alcohol. However, it is likely that $k_1 > k_2$ since complex **2.22** contains a more reactive primary hydroxyl.

To suppress the catalyzed pathway originating from complex **2.22**, binding selectivity can be combined with stereoselectivity in order to better control the outcome of the transformation. Stereoselectivity as a control element can be derived from the conformational restrictions imposed by the structure of the catalyst and by the rigid nature of the covalent bond between the substrate and catalyst. These parameters can then lead to a mismatched case when the secondary hydroxyl binds the catalyst, an effect that would decelerate the rate of functionalization to the undesired compound (i.e. slow k_1). Alternatively, when the primary hydroxyl binds, a matched case places the free hydroxyl in the right position for functionalization, thus increasing the value of k_2. At the end of the desired transformation, the bound product in complex **2.25** can be displaced by either methanol or another molecule of substrate to complete the catalytic cycle.

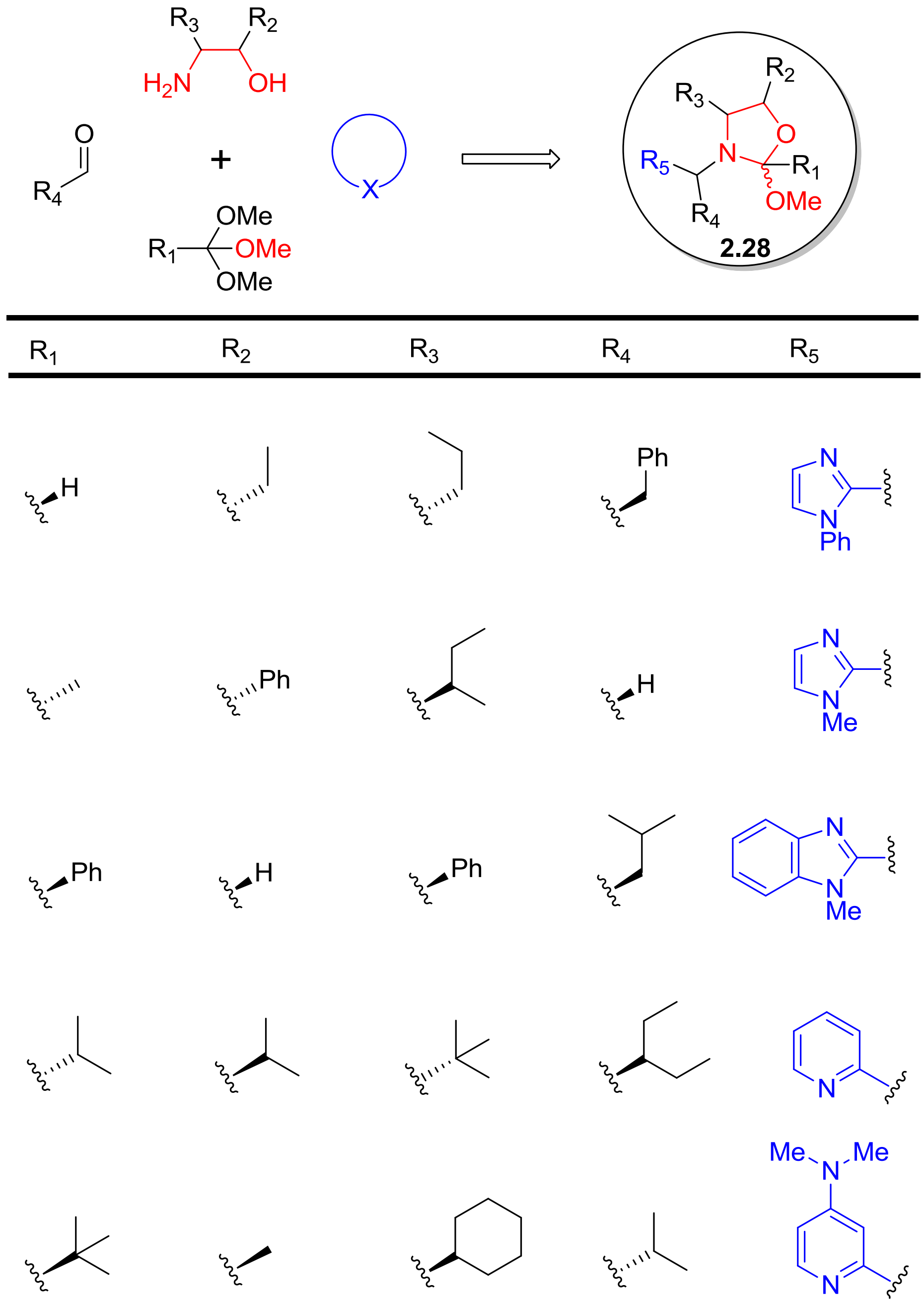
A significant advantage gained from the basic design of **2.20** is the modular nature of its structure. The catalyst (**2.28**) is composed of 4 basic inputs: an aldehyde, a heterocycle, an aminoalcohol and an orthoformate/acetate. This modularity can help address and enhance binding selectivity and stereoselectivity as the control factors that affect overall site-selectivity before and during the functionalization process. To that end, the catalyst can be modified in order to change its activity, stability and selectivity. For example, different Lewis basic moieties can potentially be incorporated, such as pyridine. Different groups can be placed at the exchange site to make the substrate binding more

Scheme 2.5: Mechanism for Site-selectivity.



selective. Alterations can be applied on the backbone that can make the catalyst more stable and rigidified to enforce a desired conformation. With these potential modifications, a large library of catalysts can be created from simple components.

Figure 2.2: Catalyst Library.



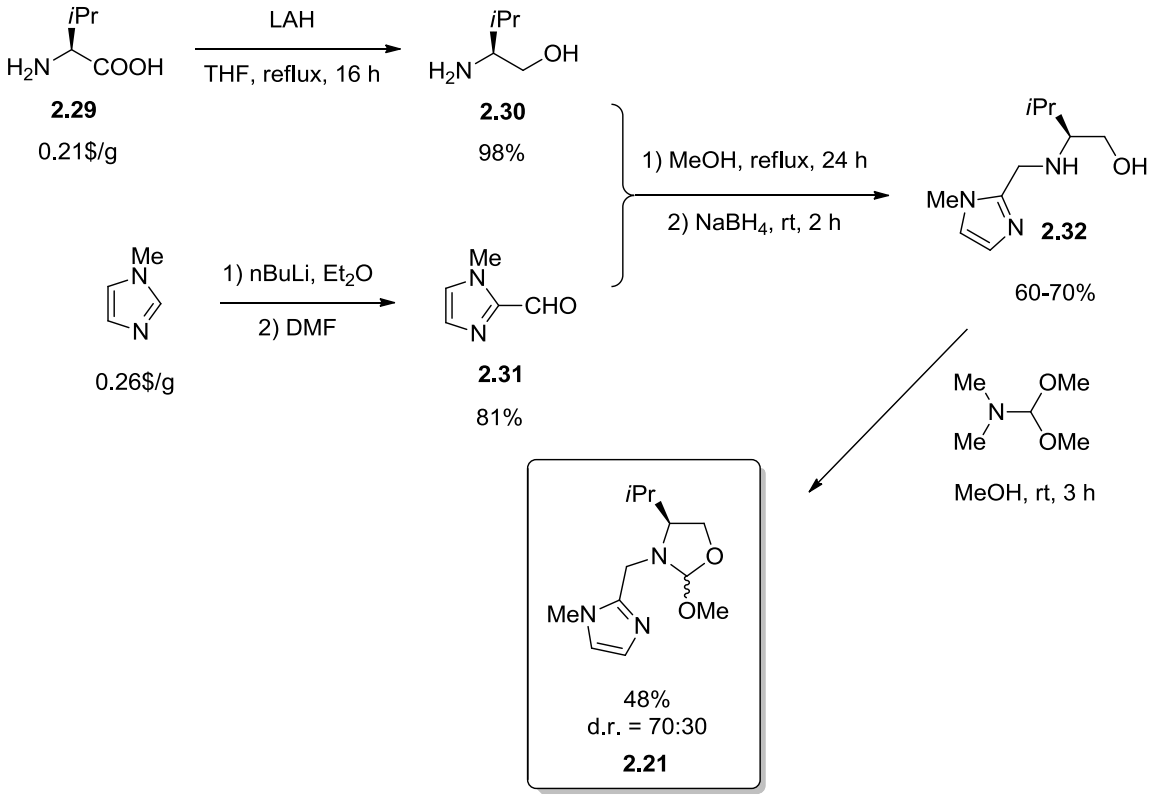
IV. Catalyst Synthesis

Catalyst **2.21** is simple and inexpensive to make and it can be prepared in four steps with good overall yield (Scheme 2.6). The synthetic route starts with *L*-valine (**2.29**). Reduction of *L*-valine with lithiumaluminum hydride (LAH) under reflux conditions overnight affords *L*-valinol (**2.30**) in high yields and purity (98%). Compound **2.31**, *L*-valinol coupling partner, is made in 81% yield by deprotonation of *N*-methylimidazole (NMI) with *n*-butyllithium and then trapping with dimethylformamide (DMF). Reductive amination between **2.30** and **2.31** forms aminoalcohol **2.32** in 60-70% yield. The last step of the catalyst synthesis is ring closure of aminoalcohol **2.32** with *N*,*N*-dimethylformamide dimethylacetal in methanol to obtain the the *L*-valine-based catalyst (**2.21**) in 48% yield after distillation.

V. Exchange Studies with the Scaffolding Catalyst

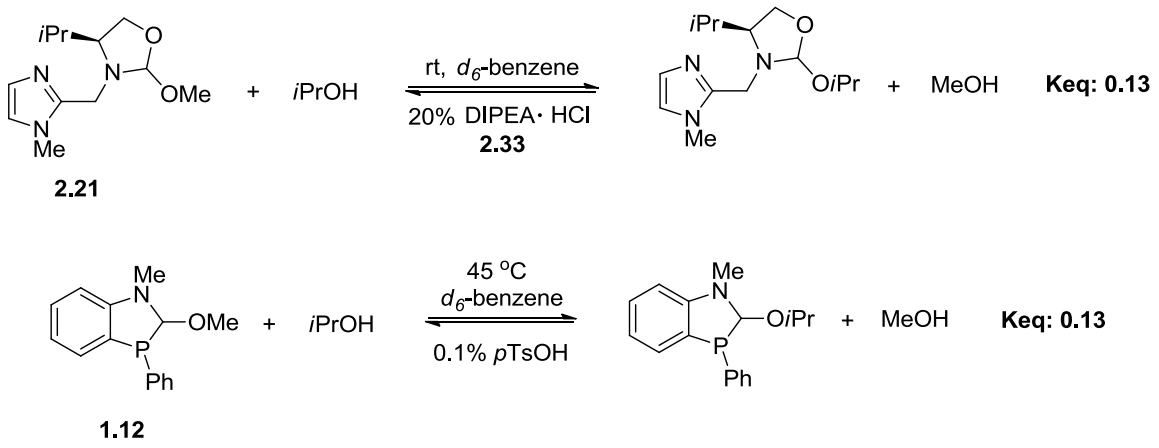
In order to develop a viable catalytic system, the exchange ability of the newly synthesized catalyst had to be determined. Initial studies commenced by investigating exchange between **2.21** and *i*PrOH. Under equilibrating conditions, the scaffolding catalyst exchanges with *i*PrOH with a K_{eq} of 0.13, which indicates a binding affinity to methanol that is eight times higher when compared to a secondary alcohol. This result is similar to the one observed with phosphine **1.12** (Scheme 2.7). In contrast to phosphine **1.12**, which requires more than two hours to reach equilibrium at 45 ^{o}C, catalyst **2.21** equilibrates in ten minutes at room temperature. This is likely due to the more electron-donating aliphatic nitrogen atom as compared to the aniline nitrogen in the phosphine

Scheme 2.6: Catalyst Synthesis.



ligand. Exchange occurs in the presence of the hydrochloride salt of diisopropylethyl amine (**2.33**) as the acid source; in the absence of an acid source equilibration is significantly slower (>72 hours). The difference in binding affinity between **2.21** and alcohols of different steric size, as it was observed above, would be crucial for the differentiation of hydroxyl sites in 1,2-diol substrates. Additionally the speed of exchange has to be high enough to outcompete any undirected pathway.

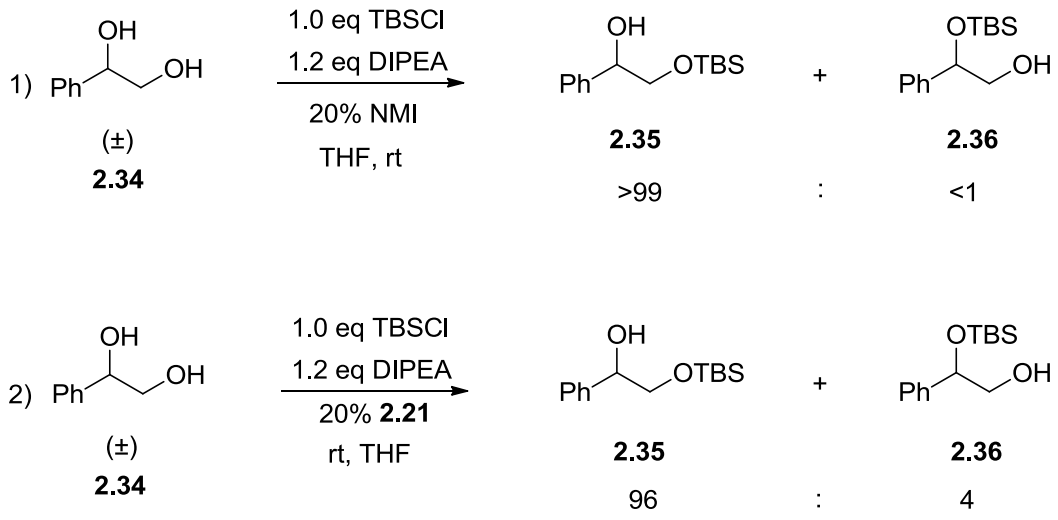
Scheme 2.7: Equilibration Abilities of 2.21 and Phosphine Ligand.



VI. Preliminary Studies in the Development of an Effective Site-Selective Functionalization of 1,2-Diols.

In initial studies using these scaffolding catalysts, 1-phenyl-1,2-ethanediol (**2.34)** was used as the nucleophile, in addition to a silyl reagent as the electrophile. Using *tert*-butyldimethylsilyl chloride (TBSCl) as the electrophile and *N*-methylimidazole as the control catalyst, it is clear that there is a preference for the TBS group to be placed on a primary alcohol (>99%) rather than a more hindered secondary one (Scheme 2.8, eq. 1); the secondary-protected diol **2.36** is not detected by GC. Under similar reaction conditions, but using **2.21** in place of *N*-methylimidazole, the selectivity for the desired product was found to be 4% (Scheme 2.8, eq. 2). A possible rationale for the low levels of selectivity is that it is energetically difficult to overturn inherent preferences when using TBSCl as the electrophile.

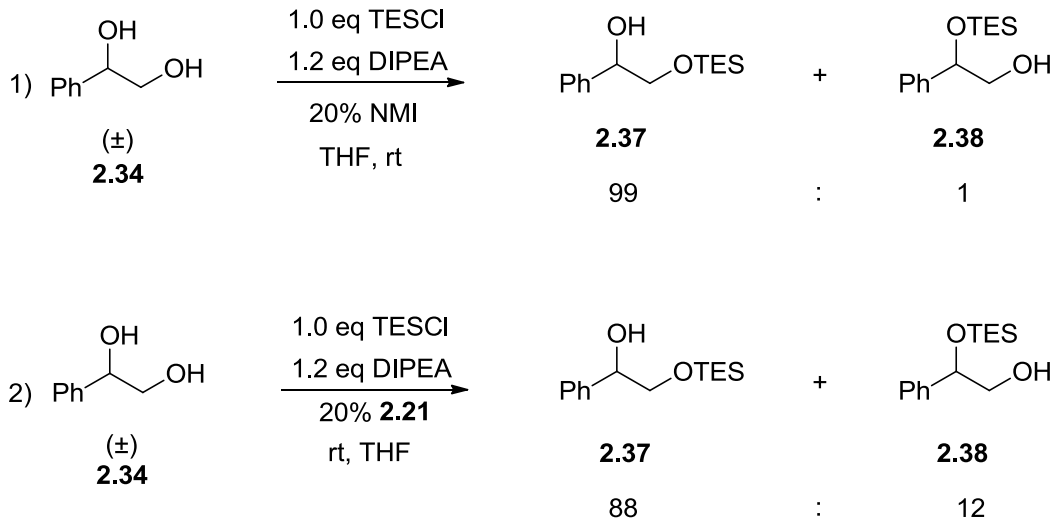
Scheme 2.8: Silylation of 2.34 with TBSCl.



With this data in hand, a smaller and less selective electrophile was screened, triethylsilyl chloride (TESCl). Carrying out a control experiment with NMI gave a 99:1 selectivity in favor of the primary-protected diol **2.37** (Scheme 2.9, eq. 1). Though still highly favorable for primary protection under control conditions, this time the secondary-protected product **2.38** was observed on GC. With **2.21**, an 88:12 ratio was obtained (Scheme 2.9, eq. 2), which represents a ten-fold increase when compared to the undirected reaction.

Based on the encouraging results outlined above, ways to diminish competing intermolecular background reactions promoted by the Lewis base functionality on the scaffolding catalyst were investigated. A way to address this problem is dilution of the reaction mixture. The original concentration of 0.2M (Table 2.1, entry 1) was decreased to 0.07M, which results in a two-fold increase in selectivity (Table 2.1, entry 2); any further dilution, however, does not lead to higher levels of selectivity (Table 2.1, entry 3).

Scheme 2.9: Silylation of 2.34 with TESCl.

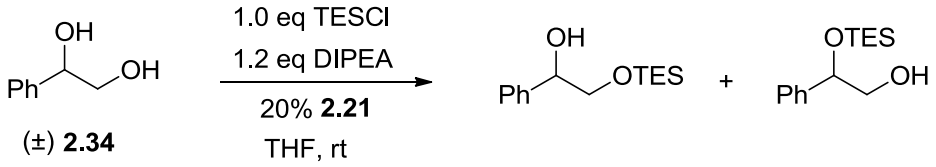


An additional solution to the problem is based on another important factor, which is the speed of binding between substrate and catalyst. It is crucial that the substrate exchanges onto the catalyst at a rate faster than the intermolecular transfer of the electrophile. Addition of a small amount of acid at the very beginning of the transformation increases the initial rate of exchange (Table 2.1, entry 4); in the absence of acid the exchange can be slow enough to be detrimental to the transformation. The combination of dilution and addition of acid leads to 33% selectivity for the secondary-protected product (Table 2.1, entry 5). An additional concern to be addressed was the possibility of *bis*-silylation of the desired product at the end of the directed transformation; some *bis*-silylation was indeed observed but it was only in very small quantities (<5%) in all cases.

Using a chiral catalyst and substrate in the reaction could lead to a matched-mismatched case, where the individual enantiomers of the substrate in the racemic form would behave differently. To test this, the individual enantiomers were synthesized from

enantiopure styrene oxide, obtained by hydrolytic kinetic resolution;[13] once in hand, they were tested separately under the optimal conditions, giving rise to significant difference

Table 2.1: Effects of Dilution and Acid Addition.

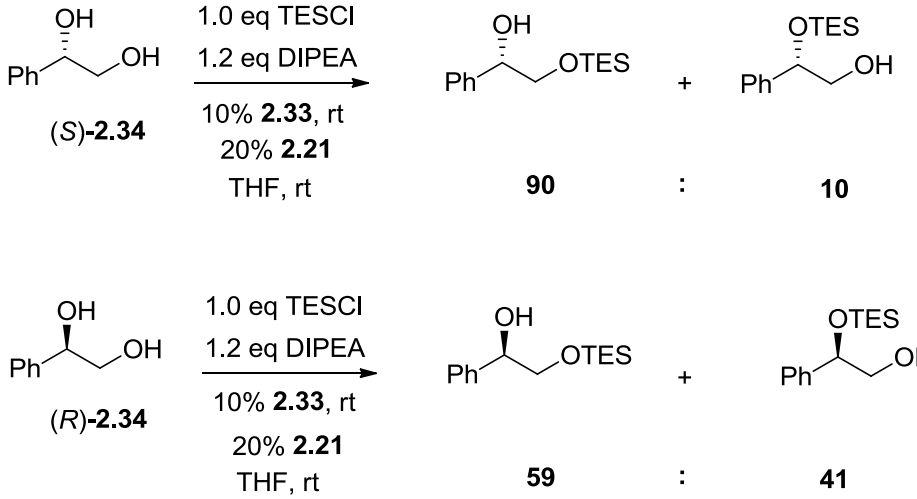


Entry	Concentration	mol% 2.33	2.37		2.38
1	0.2M	0%	88	:	12
2	0.07M	0%	80	:	20
3	0.035M	0%	79	:	21
4	0.2M	0.2%	75	:	25
5	0.07M	0.2%	67	:	33

in selectivities (Scheme 2.10): 10% of the desired compound was obtained with (*S*)-**2.34** and 41% was obtained with the (*R*)-**2.34**. An explanation for this outcome is that the binding selectivity, in the matched case, orients the substrate in such a way that allows for the free hydroxyl group to be in close proximity to the catalytic residue for effective intramolecular transfer during the functionalization step. Since the (*R*)-diol was the matched case, we used it as the substrate for most of the screening process.

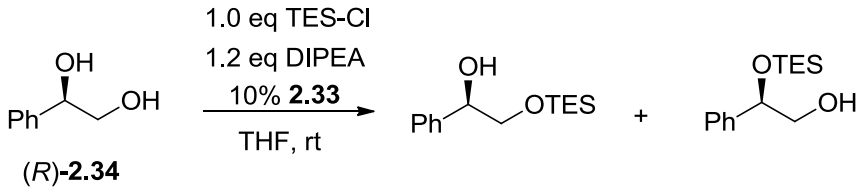
[13] Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, N. E. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

Scheme 2.10: Selectivity of the Individual Enantiomers of 2.34.



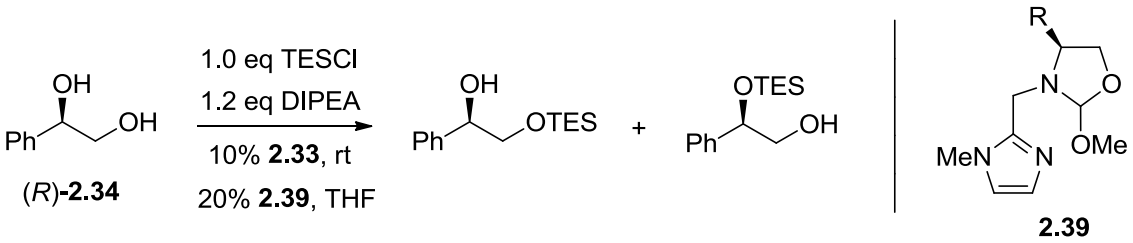
Among the variables to be considered in the screening process, the effects of catalyst **2.21** loading were tested. Changing the amount of catalyst does not have any impact on the selectivity of the reaction (Table 2.2). As low as 10% loading and as high as 50% loading does not lead to larger amounts of the desired product. It is highly likely that all background processes have been suppressed, and that the selectivity for this particular catalyst has reached a plateau under these conditions.

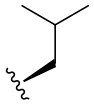
Table 2.2: Effects of Catalyst Loading.



catalyst 2.21 loading:	**2.37**		**2.38**	**Conversion** (%)
10%	58	:	42	98
20%	58	:	42	99
50%	58	:	42	98

Table 2.3: Variation of the Aminoacid Backbone.

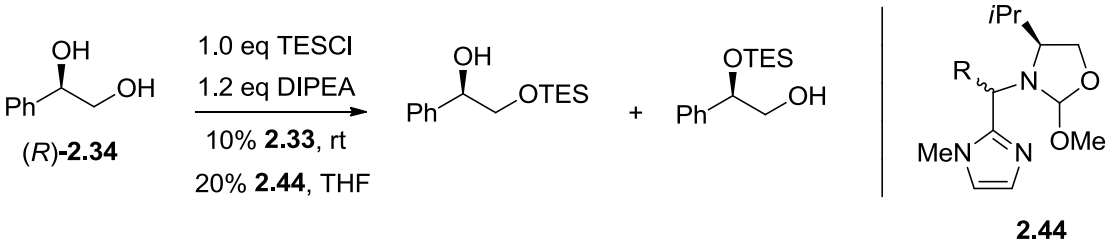


	d.r.:	2.37		2.38	Conversion (%)
2.40 R = 	(85:15)	55	:	45	96
2.21 R = 	(70:30)	58	:	42	98
2.41 R = 	(75:25)	78	:	22	97
2.42 R = 	(66:34)	69	:	31	95
2.20 R = H		83	:	17	95
2.43 R = 	(60:40)	89	:	11	97

Considering the fact that the *L*-valine-based catalyst might not be able to provide better selectivities than what was observed so far, other aminoacid-based derivatives were explored in the form of structure **2.39** (Table 2.3). The results did not display any definitive trends. The *L*-tertleucine-based catalyst (**2.40**) gave results similar to catalyst

2.21, with derivatives from *L*-alanine (**2.42**), *L*-leucine (**2.41**) and *L*-phenyl glycine (**2.43**) providing lower selectivities. The lower selectivity observed in the case of the *L*-phenyl glycine-based catalyst may arise from lowering of the basicity of the oxazolidine nitrogen which might not be as effective in promoting exchange. The unsubstituted version of the catalyst (**2.20**), which is the simplest catalyst derivative, was screened to no avail.

Table 2.4: Structural Variation at the Position α to the Imidazole Ring.



		d.r.:		2.37		2.38	Conversion (%)
2.45	R = 	(56:44)	(*R*)-**2.34**	97	:	3	90
			(*S*)-**2.34**	95	:	5	81
2.46	R = 	(90:10)	(*R*)-**2.34**	96	:	4	95
			(*S*)-**2.34**	94	:	6	96
2.47	R = 	(99:1)	(*R*)-**2.34**	91	:	9	99
			(*S*)-**2.34**	93	:	7	78
2.48	R = 	(99:1)	(*R*)-**2.34**	97	:	3	99
			(*S*)-**2.34**	53	:	47	82

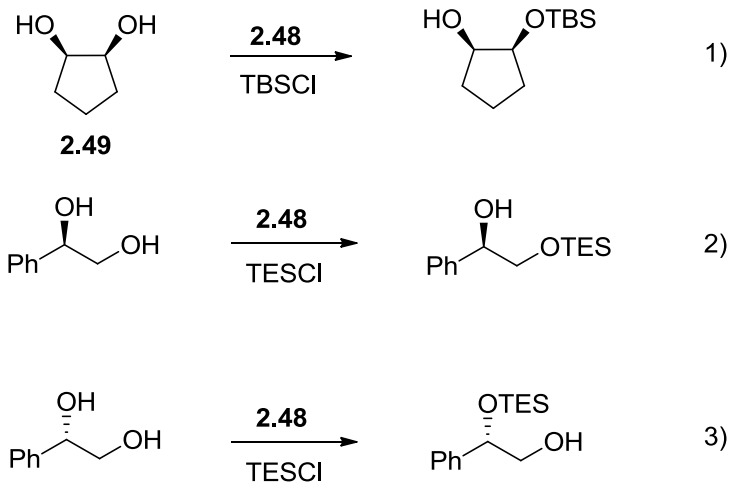
Another important factor to consider is the fact that the catalysts form a mixture of diastereomers. It is possible that in these cases a particular diastereomer of the catalyst is more active and selective than the other, which could affect reactivity and selectivity.

The work to fine-tune the structure of the catalyst moved on to the position α to the imidazole ring. Variation of the substitution pattern at that position could in principle allow the elevation of the matched-mismatched case observed earlier. The introduction of a new stereogenic center would provide a structure in the form of **2.44** (Table 2.4). Surprisingly, catalyst **2.48**, prepared as a single diastereomer, provided high selectivity for the secondary protected product arising from (*S*)-**2.34**, whereas catalyst **2.21** was matched for (*R*)-**2.34**. These results are consistent with what was observed in the enantioselective desymmetrization of *meso* diols.[14] In that case it was hypothesized that when the *R* alcohol of diol **2.49** binds to **2.48**, the free hydroxyl is oriented toward the imidazole group, thus promoting functionalization (Scheme 2.11, eq. 1). Conversely, the *S* alcohol has the free hydroxyl placed away from the catalytic site, thereby preventing intramolecular processes. In the case of site-selectivity, the *S* alcohol of (*S*)-**2.34** is well positioned for functionalization after binding of the primary hydroxyl (Scheme 2.11, eq. 3), whereas the *R* alcohol of (*R*)-**2.34** does not meet that requirement and instead allows intramolecular transfer onto the primary hydroxyl to become dominant (Scheme 2.11, eq. 2). Other catalysts within this class were also prepared with high levels of diastereoselectivities (**2.46** and **2.47**), but their activity and selectivities were much lower

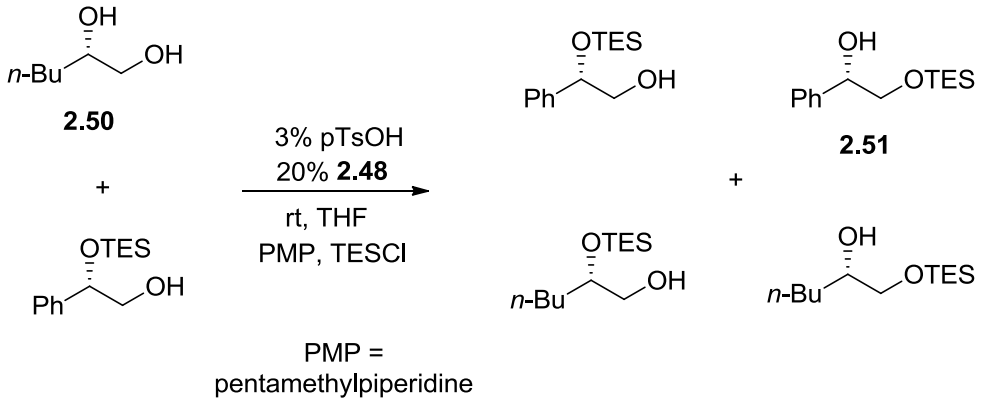
[14] Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8167.

than expected. Future experimental efforts will focus on studying the exchange abilities of these catalysts and further screening of structural variations.

Scheme 2.11: Matched-Mismatched Cases in Diol Functionalization



Scheme 2.12: Control Reaction for Potential Intramolecular Silyl Transfer.



Another concern to be considered was the possibility of silyl transfer from the secondary hydroxyl to the primary hydroxyl once the catalyzed reaction took place, thus leading to artificially lower selectivities. To confront that possibility, we carried out a control reaction (Scheme 2.12) in which we subjected the authentic product under similar reaction conditions in the presence of another 1,2-diol substrate (**2.50**) and catalyst **2.48**;

to our delight, formation of compound **2.51** was not observed, ruling out silyl transfer as a cause for the observed background selectivity.

VII. Desymmetrization of Glycerol through Scaffolding Catalysis.

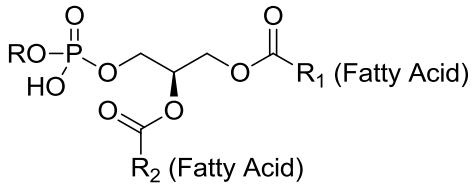
Glycerol represents an important building block found in a number of natural products (Figure 2.3), particularly as the backbone in lipids known as triglycerides. Compounds derived from glycerol are also found in specialty chemicals widely employed in the food, pharmaceutical and cosmetic industries.[15] Among the derivatives of glycerol, many are prepared when the two enantiotopic primary hydroxyl groups are differentially functionalized. In their enantiomerically pure forms, such compounds are important synthetic intermediates to the extent that their preparation has become the focus of much attention in the past two decades.

Figure 2.3: Representative Glycerol Derivatives.

R = H
(Diacyl glycerol phosphates)

R = Inositol Phosphate(s)
(Phosphatidylinositol phosphates)

R = Oligosaccharide(s)
(GPI-associated antigens)

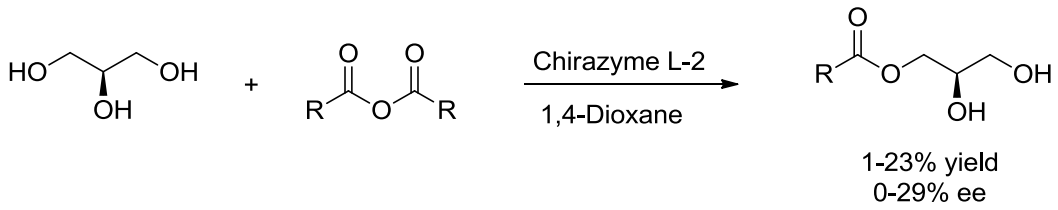


In terms of catalysis, among several demonstrations for the desymmetrization of glycerol are based on enzymes such as lipases. Asano[15a] and coworkers reported the esterification of glycerol in the presence of Chirazyme using both aromatic and aliphatic

[15] a) Batovska, D. I.; Tsubota, S.; Kato, Y.; Asano, Y.; Ubukata, M. *Tetrahedron:Asymmetry* **2004**, *15*, 3551. b) Takano, S. *Pure Appl. Chem.* **1987**, *59*, 353.

anhydrides as the acyl donors (Scheme 2.13); unfortunately, poor yields and enantioselectivities were obtained from most of the substrates.

Scheme 2.13: Enzymatic Desymmetrization of Glycerol



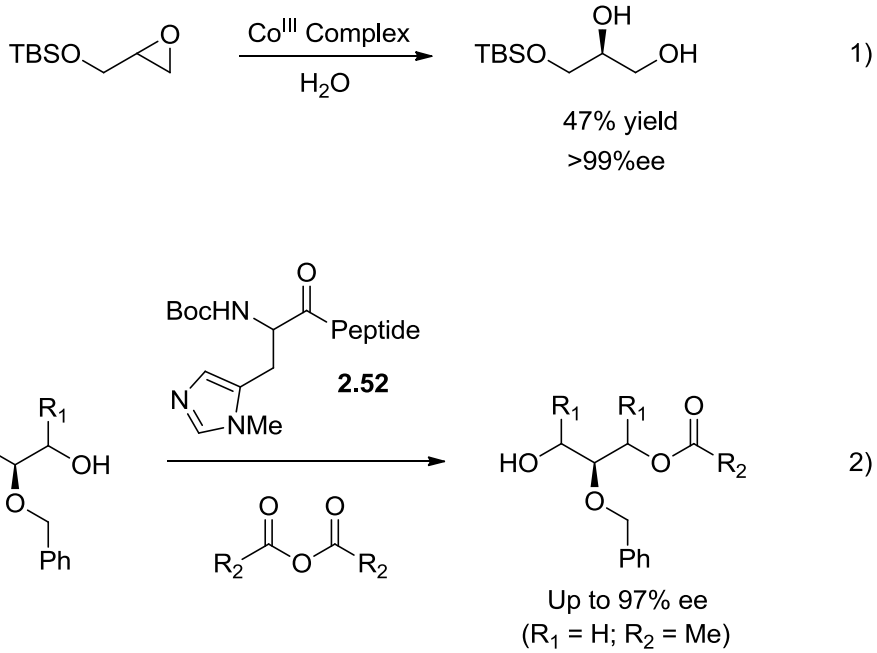
Over the years a few nonenzymatic approaches to the enantioselective desymmetrization of glycerol have been reported in the literature. For example, a simple method to the enantioselective functionalization of glycerol is through a hydrolytic kinetic resolution of a racemic terminal epoxide bearing an ether functionality.[13] The resolution is carried out by using a low loading (0.5 mol %) of a chiral (salen) Co^{III} complex to provide a 47% yield and >99% ee of the desired compound (Scheme 2.14, eq. 1). In a recent example, Miller and coworkers[16] reported desymmetrization reactions of glycerol derivatives through asymmetric acylation (Scheme 2.14, eq. 2). The pentapeptide catalyst **2.52** was employed for the transformation and provided high levels of enantioselectivities (up to 97%) and moderate yields (up to 52%). The products obtained represent useful chiral building blocks that can be further elaborated to more complex structures of interest.

Given the successful application of scaffolding catalysis to the enantioselective desymmetrization of *meso* diols carried out by our group,[14] we thought possible that the application of the same approach could be useful in the enantioselective

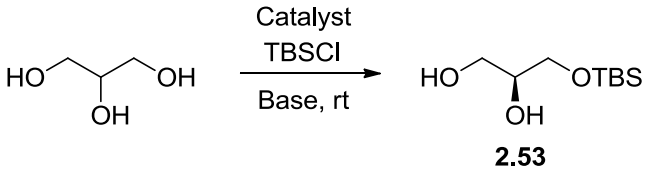
[16] Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3021.

desymmetrization of *meso* polyols such as glycerol. The transformation can be carried out in the presence of a catalyst, with TBSCl as the electrophile of choice, for the asymmetric monoprotection of unsubstituted glycerol (**2.53**) in a single step (Scheme 2.15). As previously observed in the site-selective functionalization of 1,2-diols, TBSCl is reluctant to be placed on a secondary hydroxyl group. Also, combined with the binding properties of a catalyst such as **2.20**, we thought possible that TBSCl could be directed onto the primary hydroxyl in an asymmetric fashion.

Scheme 2.14: Enantioselective Functionalization of Glycerol

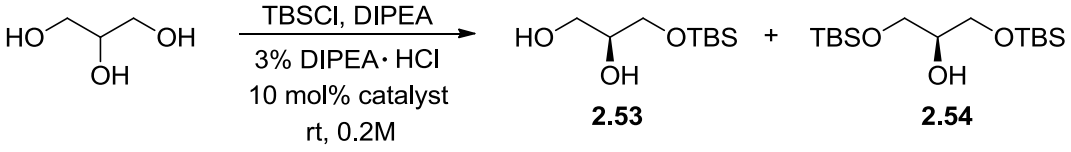


Scheme 2.15: Enantioselective Desymmetrization of Glycerol with TBSCl.



Preliminary studies for the above reaction relied on catalysts **2.21** and **2.48** to furnish the desired transformation. Under conditions very similar to the ones used in the enantioselective desymmetrization of *meso* diols, glycerol was initially treated with 10 mol % of **2.21**, in the presence of a catalytic amount of acid to facilitate exchange, followed by addition of TBSCl in acetonitrile; under these conditions, the product was formed as a racemic mixture (Table 2.5, entry 1). The same results were obtained when 10 mol % of **2.48** was employed (Table 2.5, entry 2). By changing the solvent to THF, better enantioselectivities were observed; catalyst **2.21** afforded 22% ee (Table 2.5, entry 3), while catalyst **2.48** afforded 34% ee (Table 2.5, entry 4). A significant amount of *bis*-protected product is also obtained during functionalization, which accounts for about 30% of converted starting material; it is possible that its formation is promoted through an undesirable background pathway.

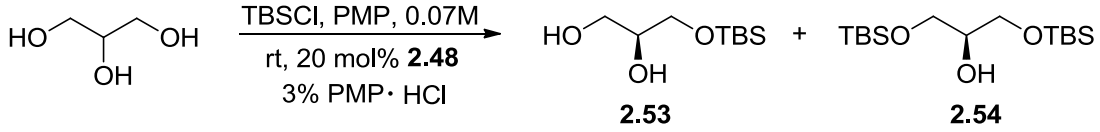
Table 2.5: Preliminary Catalyst Screening in the Enantioselective Desymmetrization of Glycerol.



Entry	Catalyst	Solvent	Yield of 2.53	Yield of 2.54	ee
1	**2.21**	CH_3CN	N/A	N/A	0%
2	**2.48**	CH_3CN	N/A	N/A	0%
3	**2.21**	THF	52%	25%	22%
4	**2.48**	THF	52%	31%	34%

Initial screening efforts focused on testing a variety of solvents, while using **2.48** as the preferred catalyst, in order to suppress background reactions while improving yields and enantioselectivities of the desired product. To that end, reactions were run under more dilute conditions by changing the concentration from 0.2M to 0.07M; the amount of *bis*-protected product being formed was thus diminished to below 20% in all cases (Table 2.6). Among the solvents that were screened, *tert*-butanol furnished good yields and moderate enantioselectivity (Table 2.6, entry 4), while diethyl ether and methylene chloride appeared to be ineffective. Diethyl ether led to very poor yields

Table 2.6: Effects of Solvent in the Enantioselective Desymmetrization of Glycerol



Entry	Solvent	Yield of 2.53	Yield of 2.54	ee
1	CH_2Cl_2	62%	17%	6%
2	THF	68%	18%	81%
3	Et_2O	19%	16%	N/A
4	*t*-BuOH	61%	16%	44%
5	EtOAc	60%	18%	80%

(Table 2.6, entry 3), while methylene chloride led to very poor enantioselectivities (Table 2.6, entry 1). Good yields and significantly improved enantioselectivities were observed when the reaction was carried out in EtOAc (Table 2.6, entry 5). The best yield and enantioselectivity were obtained when employing THF as the solvent (Table 2.6, entry 2), in the presence of 20 mol % of catalyst. Given these promising preliminary results, the

use of different catalyst structures and a more extensive fine-tuning of the reaction conditions in future screening efforts can lead to higher levels of yields and enantioselectivities.

VIII. Conclusion

The concepts of reversible covalent binding and intramolecular activation can be a powerful way of controlling regio- and enantioselectivities and allow for challenging transformations to be carried out under mild conditions.

In terms of site-selectivity, to be able to overturn selectivity from 99:1 to almost 1:1 (56:44) is a gain in energy of 2.7 kcal/mol, an impressive feat in itself. Rapid exchange and conformational restrictions are crucial aspects of a viable catalytic system; having that in mind, it is important to suppress the inherent background silylation caused by the catalyst itself through fine-tuning of the structure in order to meet those requirements. The reactivity of most catalysts that have been prepared so far is remarkable and a more extensive catalyst synthesis and design can be the solution to the problem. Further exploration of different classes of catalysts with a variety of electronic and steric perturbations can provide us with the necessary energy to completely overturn the natural selectivity. Also, besides silylating agents, different electrophiles such acyl chlorides or anhydrides and different diol substrates can be screened to expand the reaction scope.

In terms of enantioselective desymmetrization, the selective monoprotection of glycerol in a nonenzymatic manner has been the subject of study for several years. There

are a few methods available for that purpose, but none of them can do so in a single step. Scaffolding catalysis has the potential to carry out such desymmetrization in a single operation, with preliminary studies showing levels of enantioselectivities as high as 80% ee and yields in the 60% range. Once the proper conditions to reach higher levels of enantioselectivity have been found, the desymmetrization process can be coupled with the selective functionalization of the secondary alcohol to provide an efficient method for the derivatization of glycerol to a variety of natural products.

IX. Experimental

General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lithium reagents were titrated against 2-pentanol using 1,10-phenanthroline as the indicator. 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 syringe and cannula techniques, 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 NMR were performed on either a Varian Gemini 400 MHz, Varian Gemini 500 MHz or a Varian Unity Inova 500 MHz spectrometer. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. C_6D_6 was degassed by three successive freeze-pump-thaw cycles and stored over 3Å molecular

sieves in a dry box under a nitrogen atmosphere. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C NMR. Coupling constants are reported in Hz. 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}. All GC analyses were performed on an Agilent Technologies 7890A GC System. HRMS data were generated in Boston College facilities with DART-TOF as the ionization technique. Analytical chiral high-performance liquid chromatography (HPLC) was performed on a Shimadzu-LC-2010A HT.

Site-Selectivity General Procedure

Site-Selectivity General Procedure A. To an oven-dried glass reaction vial, a solution of **2.34** (27.6 mg, 0.20 mmol), catalyst (0.040 mmol, 20 mol %), and **2.33** (3.3 mg, 0.02 mmol, 10 mol %) in anhydrous THF (1.0 mL) was added. The reaction was stirred at room temperature for 10 minutes. Diisopropylethylamine (42 μL, 0.24 mmol) was added, followed by addition of triethylchlorosilane (33 μL, 0.20 mmol). After stirring at room temperature for 12 hours, the reaction was quenched by addition of diisopropylethylamine (30 μL) and methanol (5 μL). The mixture was stirred at room temperature for 10 minutes and filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (10 mL). GC analysis determined the selectivitiy of the desired product.

Site-Selectivity General Procedure B. Identical to General Procedure A, with compound **2.33** being excluded.

Site-Selectivity General Procedure C. Identical to General Procedure A, with compound **2.33** being excluded and with the concentration being decreased to either 0.070 M or 0.035 M.

Site-Selectivity General Procedure D. Identical to General Procedure A, with the concentration changed to 0.07M.

Site-Selectivity General Procedure E. To an oven-dried glass reaction vial, a solution of **2.34** (27.6 mg, 0.20 mmol) and catalyst (20.0 mg, 0.040 mmol), in anhydrous THF (0.5 mL) was added. The reaction was stirred at room temperature for 10 minutes. Diisopropylethylamine (42 μL, 0.24 mmol) was added, followed by addition of a solution of *tert*-butylchlorodimethylsilane (30.0 mg, 0.20 mmol) in anhydrous THF (0.5 mL). After stirring at room temperature for 12 hours, the reaction was quenched by addition of diisopropylethylamine (30 μL) and methanol (5 μL). The mixture was stirred at room temperature for 10 minutes and filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (10 mL). GC analysis afforded the selectivitiy of the desired product.

Glycerol Desymmetrization General Procedure

Desymmetrization General Procedure A. In an oven-dried glass reaction vial, glycerol (18.4 mg, 0.20 mmol), catalyst (0.02 mmol, 10 mol %) and **2.33** (1.2 mg, 3 mol %) were combined together. The mixture was then dissolved in anhydrous solvent (0.5 mL) and the reaction was stirred at room temperature for 10 minutes. Diisopropylethylamine (42 μL, 0.24 mmol) was added, followed by addition of a solution of *tert*-

butylchlorodimethylsilane (30.0 mg, 0.20 mmol) in anhydrous solvent (0.5 mL). After stirring at room temperature for 12 hours, the reaction was quenched by addition of diisopropylethylamine (30 μL) and methanol (5 μL). The mixture was stirred at room temperature for 10 minutes and filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (10 mL). The yield of the product was determined by NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene (50 μL of 0.40M in EtOAc, 0.020 mmol) as the internal standard. The ee of the product was determined by chiral HPLC analysis of the 1-naphthylcarboxylate ester (obtained by acylation with 1-naphthoyl chloride in CH_2Cl_2 in the presence of diisopropylethylamine).

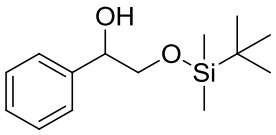
Desymmetrization General Procedure B. Identical to Desymmetrization General Procedure A, with the application of the following changes: compound **2.33** was replaced by 1,2,2,6,6-pentamethylpiperidine hydrochloride, diisopropylethylamine was replaced by 1,2,2,6,6-pentamethylpiperidine, catalyst loading was increased to 20 mol % and the concentration was decreased to 0.07M.

GC and HPLC Analysis Methods

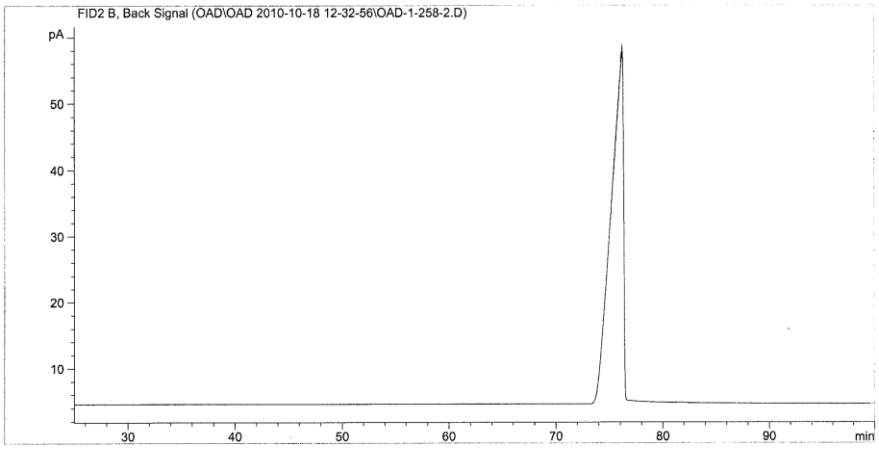
GC Method. An Agilent Technologies 7890A GC System equipped with a 7683B Series Injector was used to introduce samples into a J&W Scientific column (HP-5, 30 m, 0.320 mm ID, 0.25 μm film). The GC was run at 100 ^{o}C for 80 minutes, and then the temperature was ramped 8 ^{o}C/min. to a final temperature of 180 ^{o}C. Compounds were detected by FID and data was analyzed with Agilent Technologies GC Chemstation software. Retention times are reported in minutes.

HPLC Method. A Shimadzu-LC-2010A HT HPLC System was used to introduce samples into a Chiralcel OD column (hexanes/*i*PrOH = 97/3, 1.0 mL/min, 230 nm).[3] Retention times are reported in minutes.

Product Syntheses and Characterizations



2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethanol (2.35). A 100 mL flask was charged with *tert*-butyldimethylsilyl chloride (545 mg, 3.62 mmol) in THF (18 mL). Diisopropylethylamine (0.630 mL, 3.62mmol), *N*-methylimidazole (58uL, 0.72 mmol) and 1-phenyl-1,2-ethanediol (500 mg, 3.62 mmol) in THF was slowly added as a mixture. The reaction was allowed to stir for 48 hours before quenching with MeOH. The resulting mixture was evaporated in vacuo and the crude product was purified on silica gel with 5% EtOAc in hexanes to yield 630 mg (69%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.28 (m, 5H), 4.77-4.74 (m, 1H), 3.78 (dd, 1H, *J*= 4.0, 10.0), 3.56 (dd, 1H, *J*= 8.5, 10.0), 3.00 (d, 1H, *J*= 2.0), 0.93 (s, 9H), 0.083 (s, 3H), 0.077 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.3, 128.3, 127.7, 126.2, 74.4, 68.9, 25.9, 18.3, -5.3, -5.4; IR: 3443, 3063, 2953, 2856, 1253, 1103, 833, 698 cm^{-1}; HRMS Calcd. for $C_{14}H_{25}O_2Si$ $[M-H]^+$: 253.1623, Found: 253.1617. GC Method: 76.2 min.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40
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20
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30
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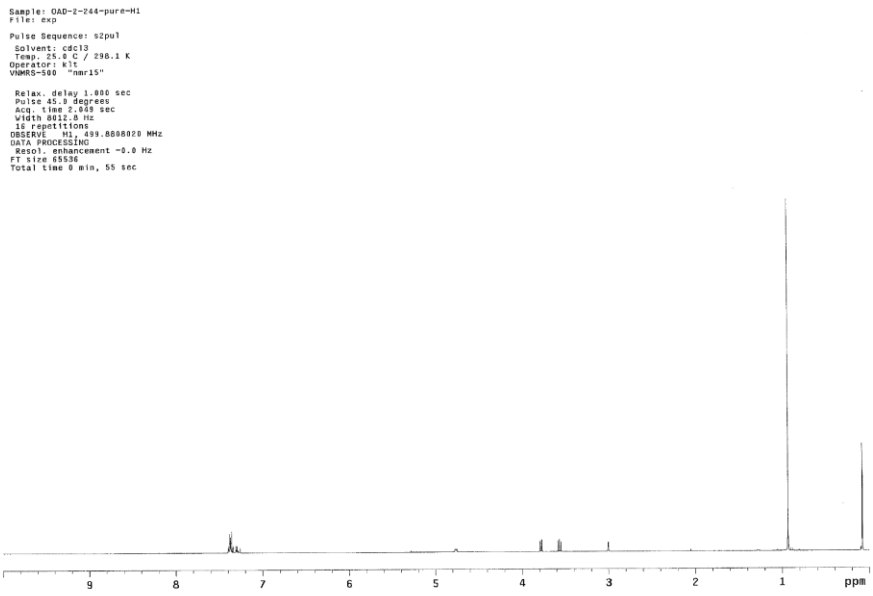
50
60
70
80
90
min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File: exp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
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Relax. delay 1.000 sec
Pulse 45.0 degrees
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Width 8012.8 Hz
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OBSERVE H1, 499.8808020 MHz
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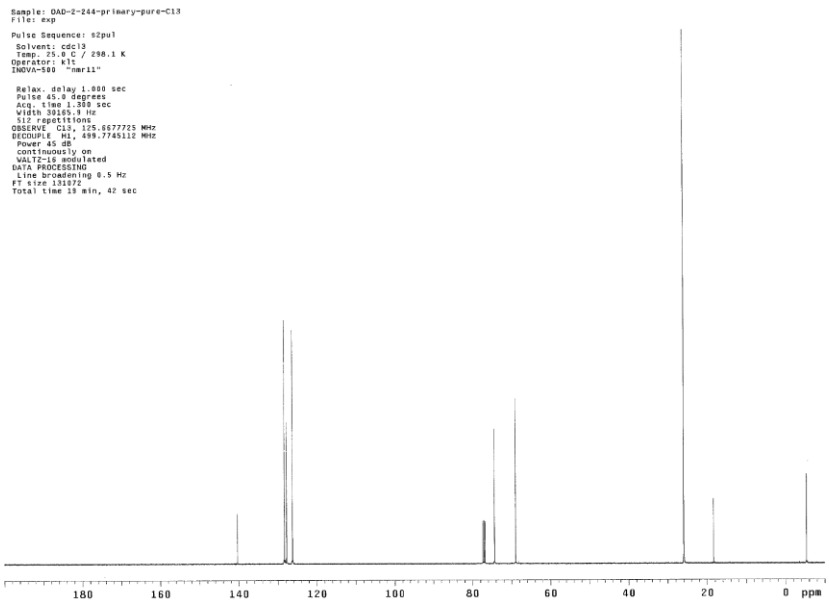
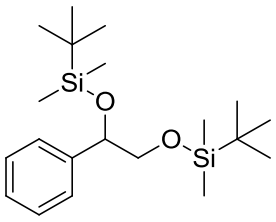
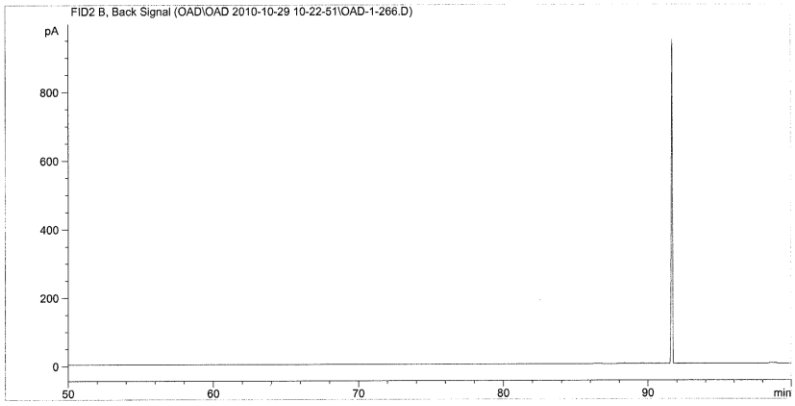
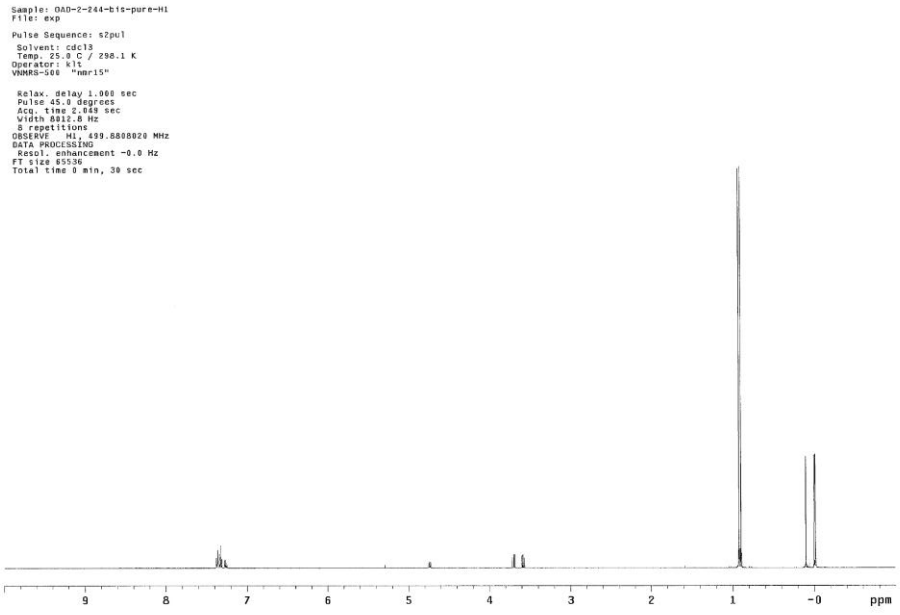


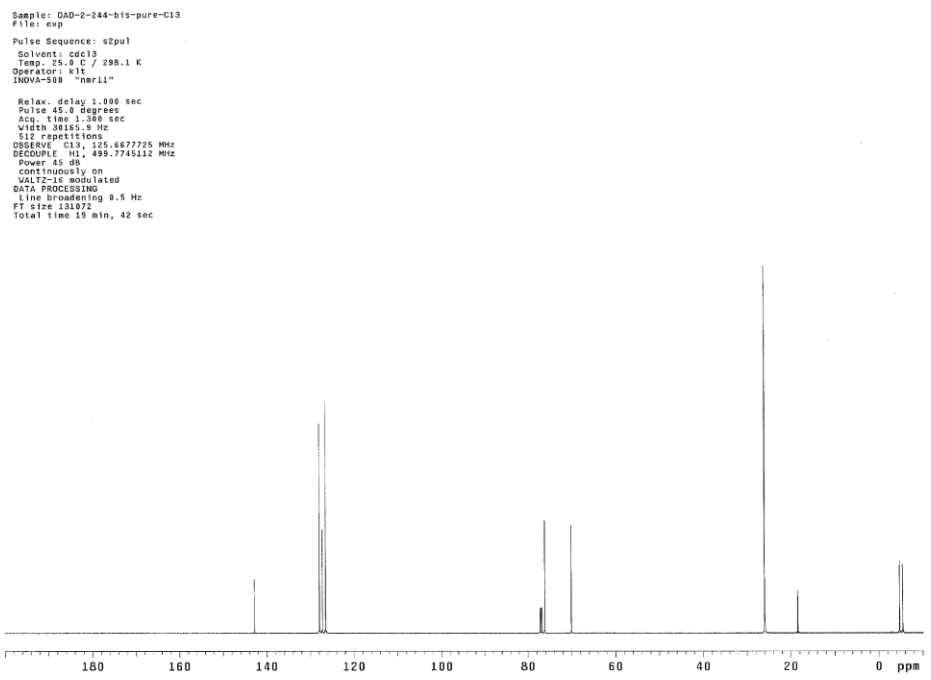


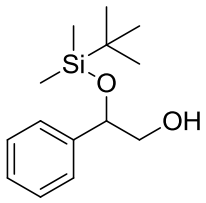
2,2,3,3,8,8,9,9-Octamethyl-5-phenyl-4,7-dioxa-3,8-disiladecane. A 100 mL flask was charged with *tert*-butyldimethylsilyl chloride (2.4 g, 15.9 mmol) in THF (18 mL). *N*-methylimidazole (1.3 mL, 15.9 mmol) and 1-phenyl-1,2-ethanediol (1.0 g, 7.24 mmol) in THF was slowly added as a mixture. The reaction was allowed to stir for 48 hours before quenching with MeOH. The resulting mixture was evaporated in vacuo and the crude product was purified on silica gel with 2% EtOAc in hexanes to yield 1.3 g (49%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.26 (m, 5H), 4.73 (dd, 1H, *J*= 5.5, 7.5), 3.70 (dd, 1H, *J*= 7.0, 10.5), 3.58 (dd, 1H, *J*= 5.0, 10.0), 0.92 (s, 9H),

0.89 (s, 9H), 0.10 (s, 3H), 0.001 (s, 3H), -0.012 (s, 3H), -0.016 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.8, 127.9, 127.2, 126.5, 76.1, 70.1, 26.0, 25.9, 18.4, 18.3, -4.64, -4.75, -5.38, -5.48; IR: 2954, 2928, 2856, 1471, 1253, 1095, 830, 774 cm^{-1}; HRMS Calcd. for $C_{20}H_{42}NO_2Si_2$ $[M+NH_4]^+$: 384.2763, Found: 384.2754. GC Method: 91.7 min.



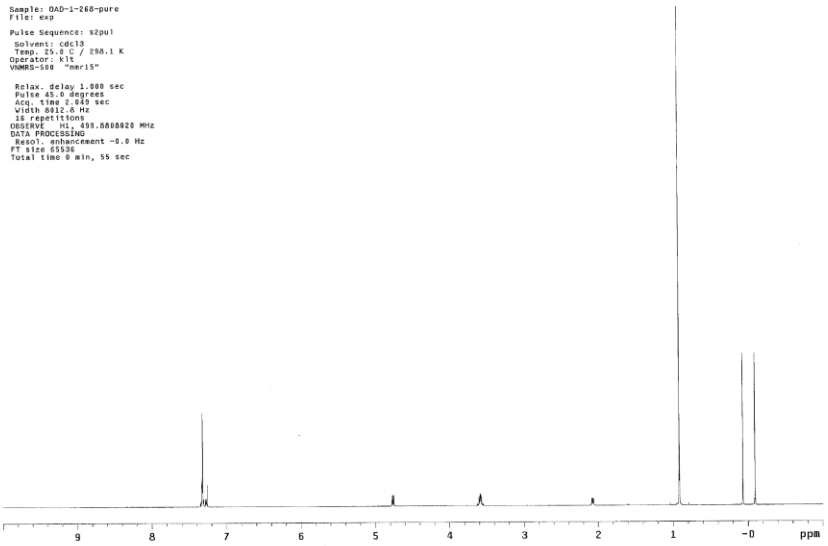


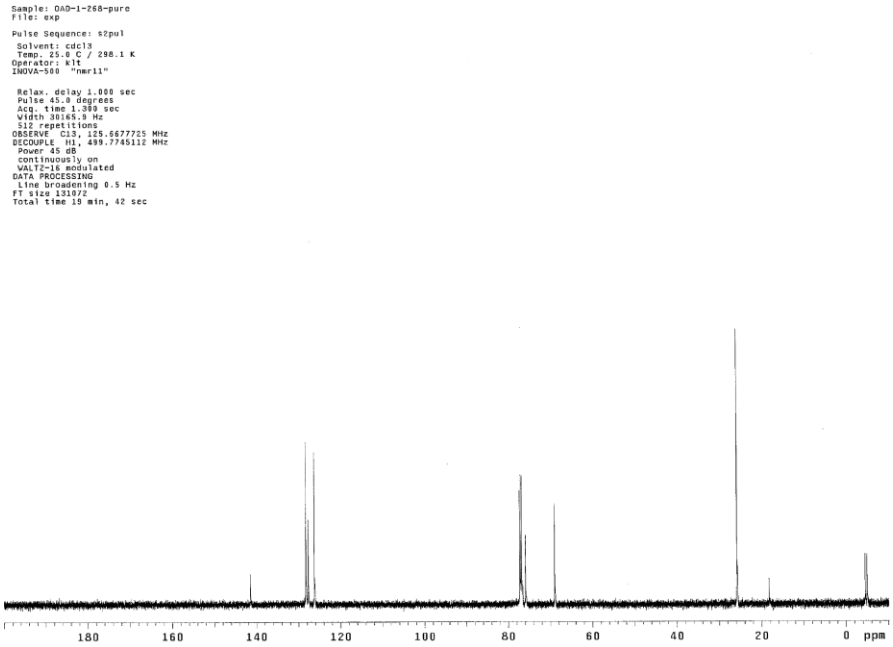


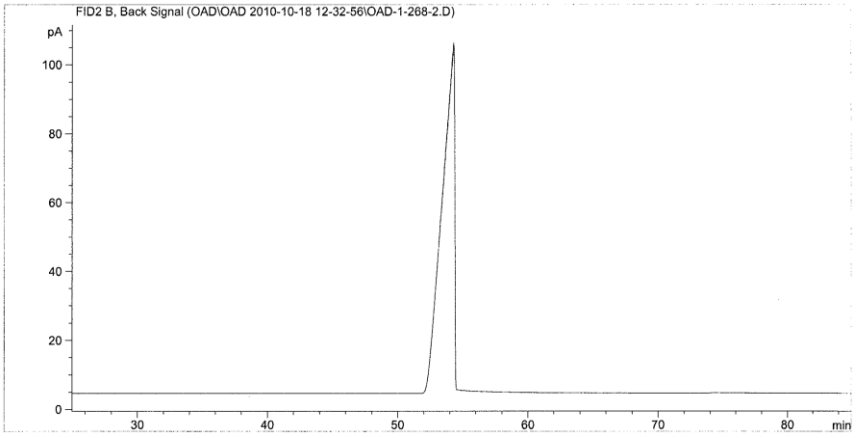


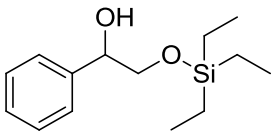
2-((*tert*-Butyldimethylsilyl)oxy)-2-phenylethanol (2.36). A 100 mL flask was charged with 2,2,3,3,8,8,9,9-octamethyl-5-phenyl-4,7-dioxa-3,8-disiladecane (1.3 g, 3.55 mmol) in ethanol (7 mL), followed by addition of PPTS (0.892g, 3.55 mmol). The reaction was allowed to stir for 13 hours before quenching with triethylamine. The crude mixture was evaporated in vacuo and the crude product was purified on silica gel eluting with 5% EtOAc in hexanes to yield 647 mg (72%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.26 (m, 5H), 4.76 (dd, 1H, *J*= 4.5, 7.5), 3.60-3.57 (m, 2H), 2.07 (dd, 1H, *J*= 5.0, 8.5), 0.91 (s, 9H), 0.068 (s, 3H), -0.094 (s, 3H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 141.4, 128.3, 127.7, 126.3, 75.9, 68.9, 25.8, 25.6, 18.2, -4.53, -4.96; IR: 3433, 2953, 2856, 1252, 1098, 912, 776, 698 cm^{-1}; HRMS Calcd. for $C_{14}H_{25}O_2Si$ $[M+H]^+$: 253.1623, Found: 253.1620. GC Method: 61.3 min.



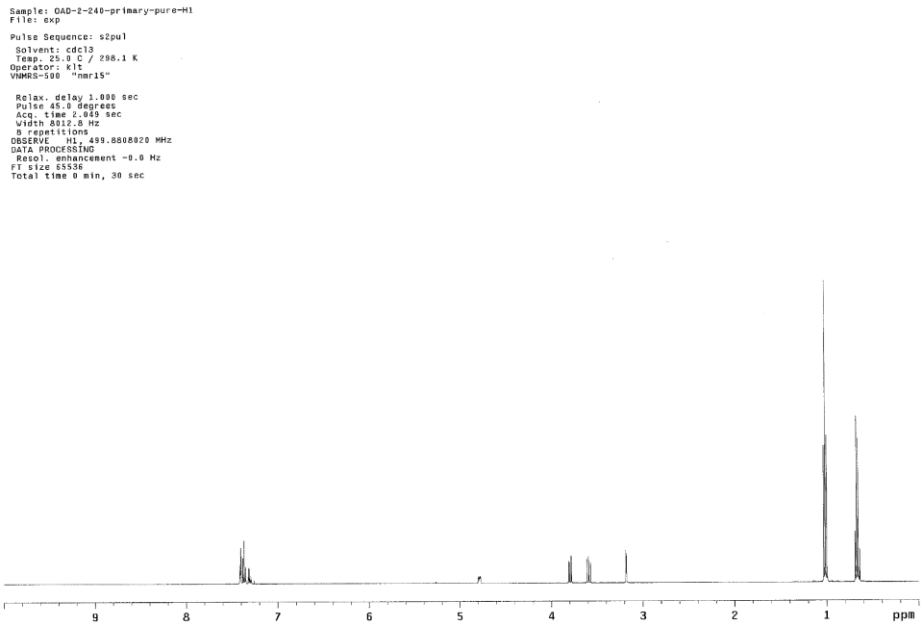


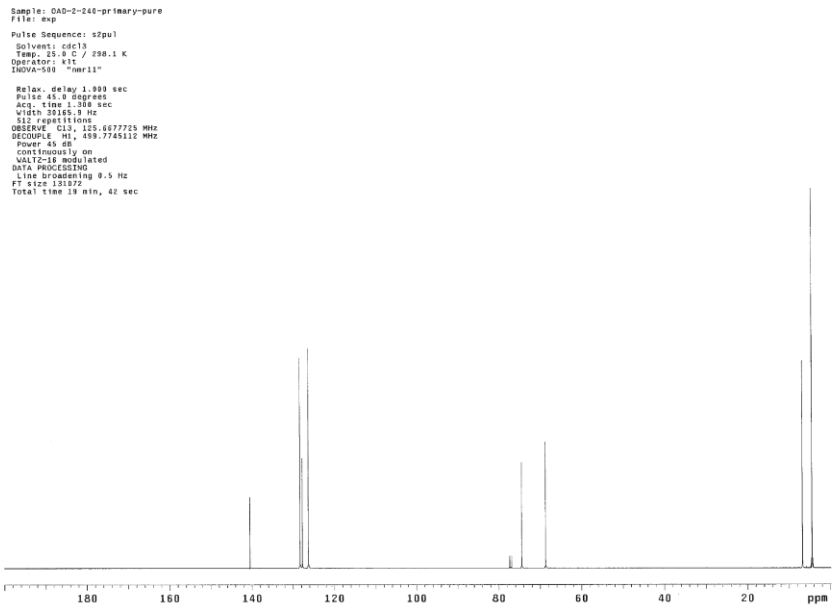


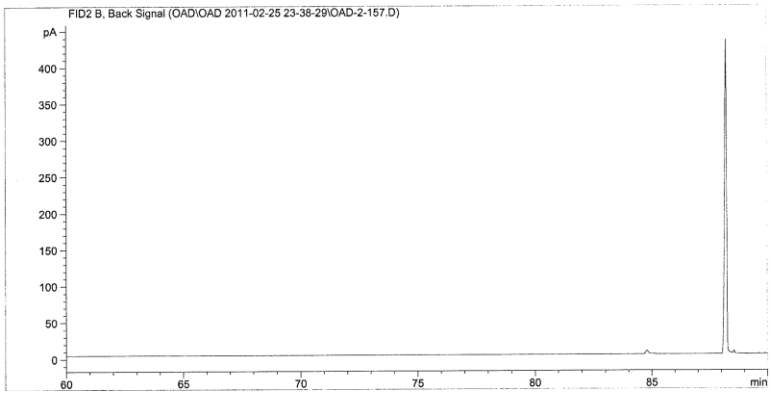


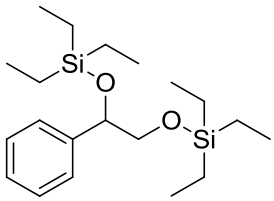
1-phenyl-2-((triethylsilyl)oxy)ethanol (2.37). A 100 mL flask was charged with triethylchlorosilane (1.09 g, 7.24 mmol) in THF (18 mL). *N*-methylimidazole (578uL, 7.24

mmol) and 1-phenyl-1,2-ethanediol (1.0 g, 7.24 mmol) in THF (18 mL) was slowly added as a mixture. The reaction was allowed to stir for 48 hours before quenching with MeOH. The resulting mixture was evaporated in vacuo and the crude product was purified on silica gel with 2% EtOAc in hexanes to yield 898 mg (49%) of the title compound as a clear oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.42-7.29 (m, 5H), 4.79-4.77 (m, 1H), 3.79 (dd, 1H, *J*= 3.5, 10.0), 3.59 (dd, 1H, *J*= 9.0, 10.5), 3.17 (d, 1H, *J*= 2.0), 1.01 (t, 9H, *J*= 8.0), 0.66 (q, 6H, *J*= 8.0); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 140.5, 128.3, 127.7, 126.2, 74.5, 68.7, 6.73, 4.42; **IR**: 3456, 2954, 2876, 1454, 1104, 1005, 743, 699 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{14}H_{25}O_2Si$ $[M+H]^+$: 253.1623, found: 253.1624. **GC Method:** 88.2 min.



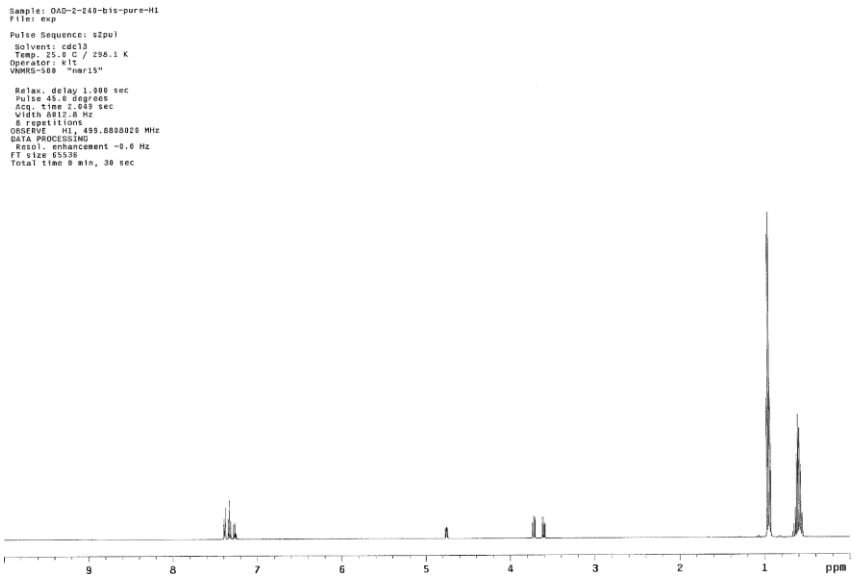


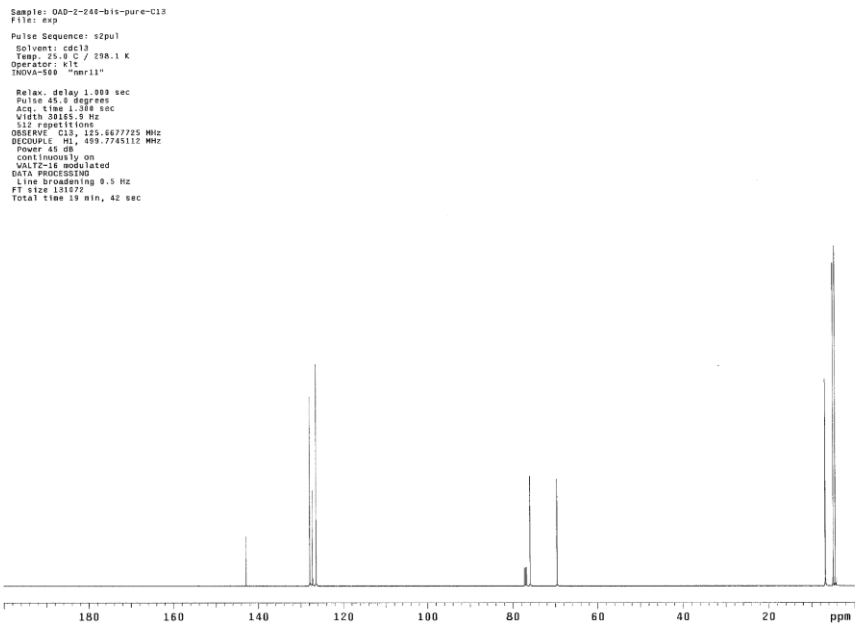


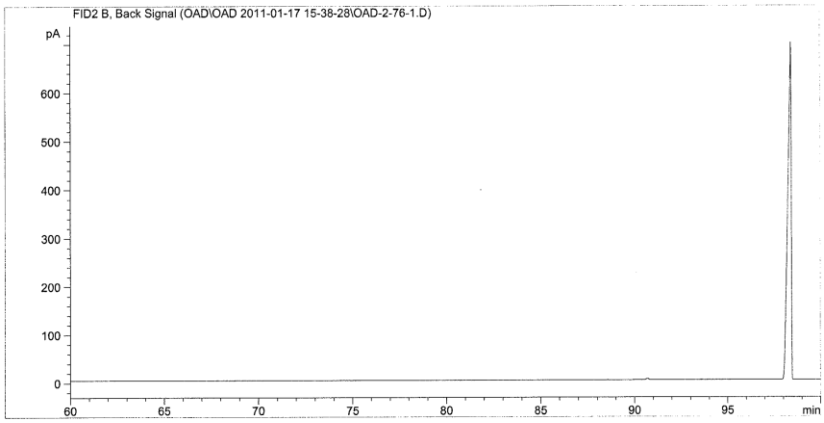


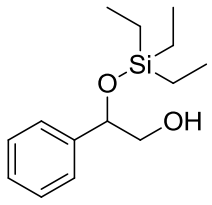
3,3,8,8-Tetraethyl-5-phenyl-4,7-dioxa-3,8-disiladecane. A 100 mL flask was charged with triethylchlorosilane (2.4 g, 15.93 mmol) in THF (9 mL). *N*-methylimidazole (1.3 g,

15.93 mmol) and 1-phenyl-1,2-ethanediol (1.0 g, 7.24 mmol) in THF (9 mL) was slowly added as a mixture. The reaction was allowed to stir for 96 hours before quenching with MeOH. The resulting mixture was evaporated in vacuo and the crude product was purified on silica gel with 2% EtOAc in hexanes to yield 824 mg (31%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.26 (m, 5H), 4.75 (dd, 1H, *J*= 5.0, 7.0), 3.72 (dd, 1H, *J*= 7.0, 10.0), 3.60 (dd, 1H, 5.0, 10.0), 0.97-0.92 (m, 18H), 0.65-0.55 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.9, 127.9, 127.2, 126.4, 75.9, 69.6, 6.77, 6.72, 4.89, 4.40; IR: 2953, 2876, 1124, 1095, 1004, 723, 697 cm^{-1}; HRMS Calcd. for $C_{20}H_{39}O_2Si_2$ $[M+H]^+$: 367.2488, Found: 367.2495. GC Method: 98.4 min.



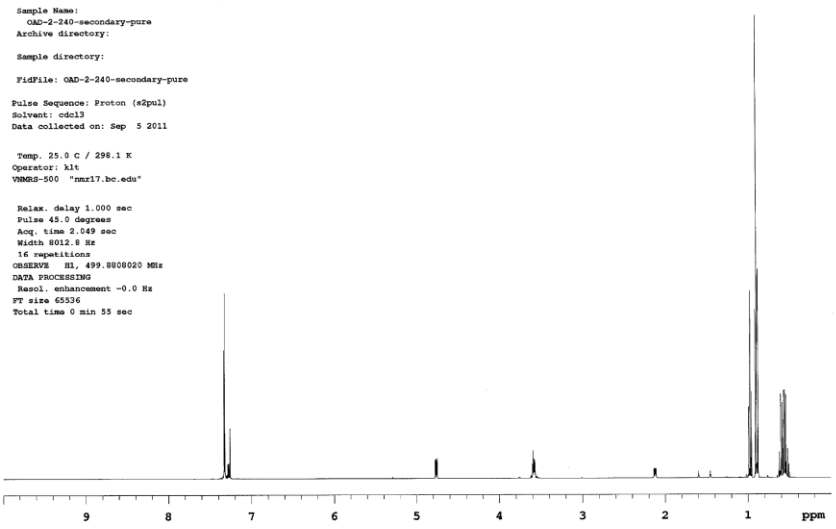


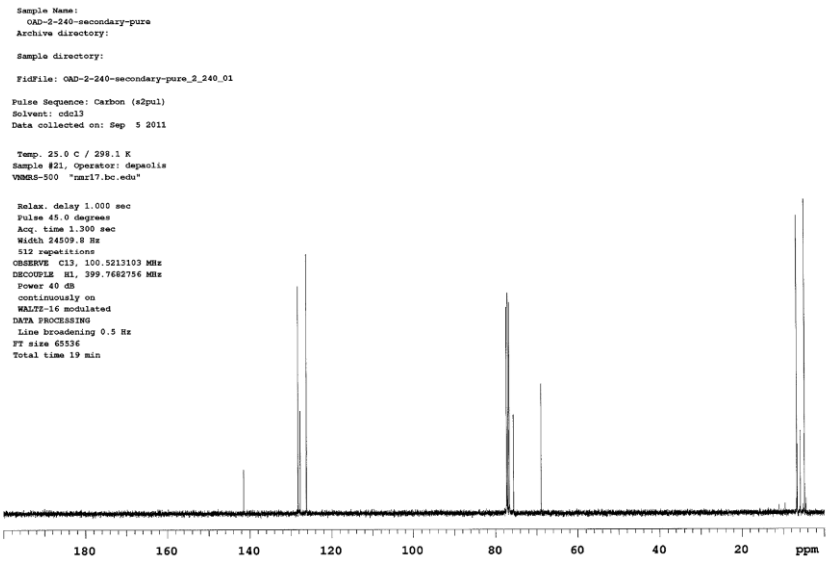


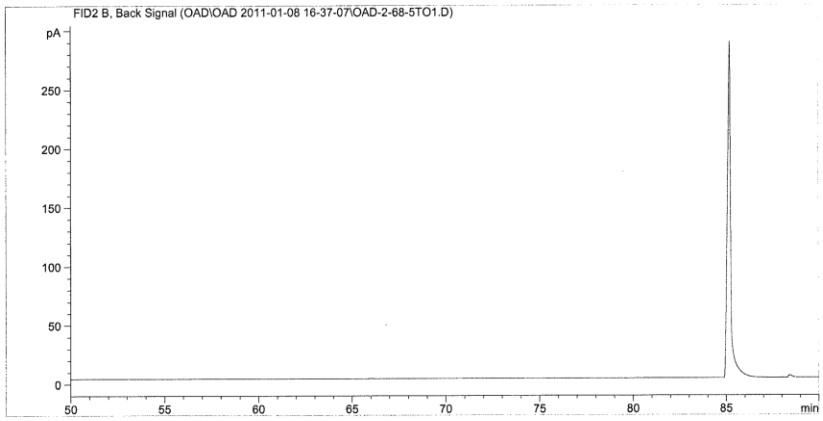


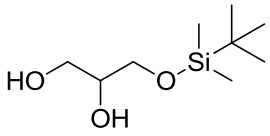
2-Phenyl-2-((triethylsilyl)oxy)ethanol (2.38). A 50 mL flask was charged with 3,3,8,8-tetraethyl-5-phenyl-4,7-dioxa-3,8-disiladecane (0.83 g, 2.26 mmol) in ethanol (5 mL),

followed by addition of PPTS (0.57g, 2.26 mmol). The reaction was allowed to stir for 14 hours before quenching with triethylamine. The crude mixture was evaporated in vacuo and the crude product was purified on silica gel eluting with 2% EtOAc in hexanes to yield 280 mg (49%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33-7.26 (m, 5H), 4.76 (dd, 1H, *J*= 4.5, 7.5), 3.60-3.57 (m, 2H), 2.12 (dd, 1H, *J*= 5.0, 8.5), 0.89 (t, 9H, *J*= 8.5), 0.59 (q, 6H, *J*= 8.5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.5, 128.2, 127.7, 126.2, 75.6, 68.9, 6.66, 4.77; IR: 3406, 2953, 2875, 1454, 1098, 1004, 725, 698 cm^{-1}; HRMS Calcd. for $C_{14}H_{25}O_2Si$ $[M+H]^+$: 253.1623, Found: 253.1634**.** GC Method: 85.1 min.



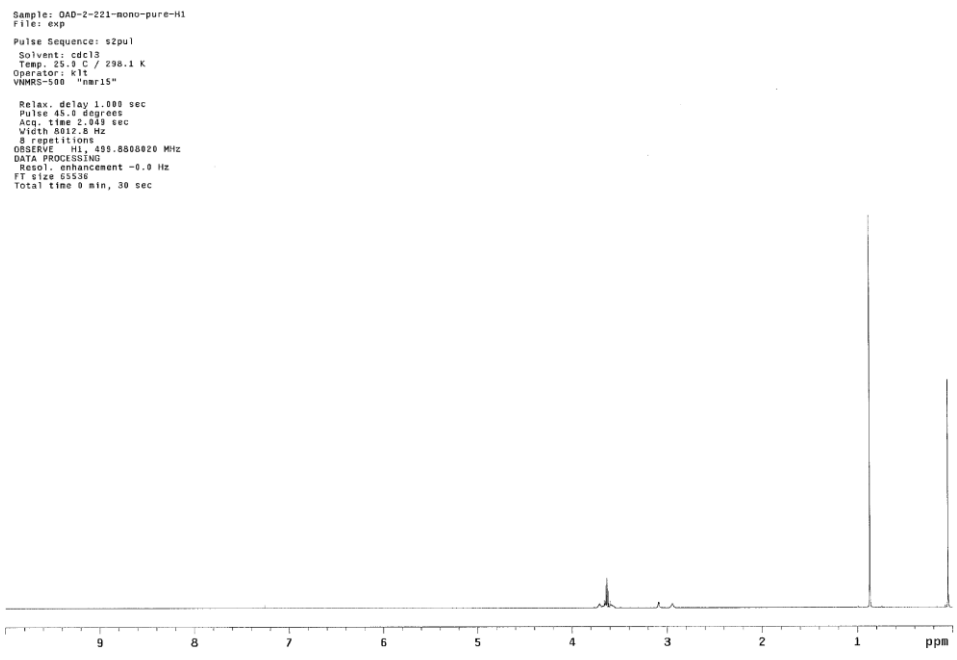


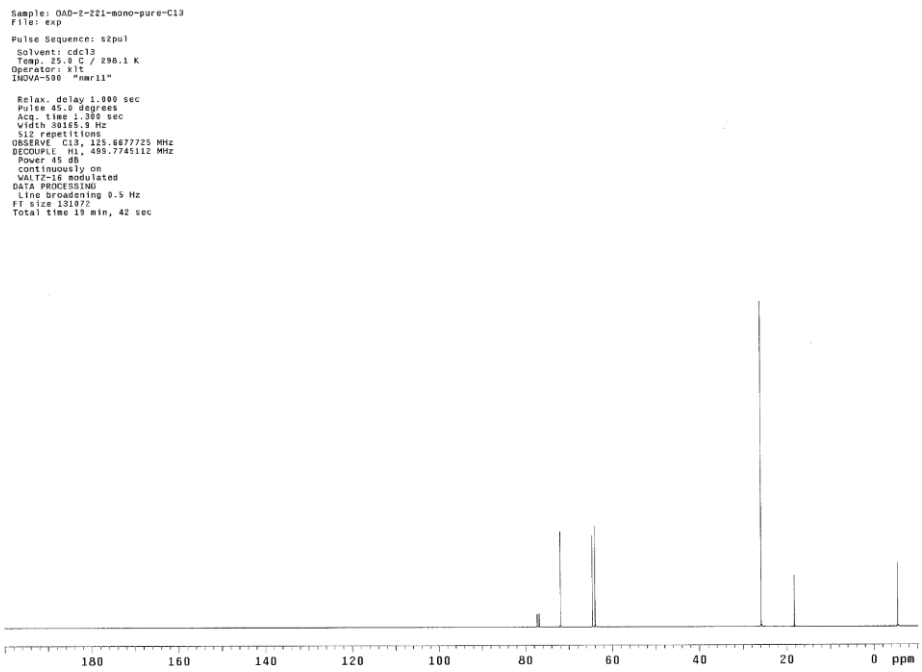


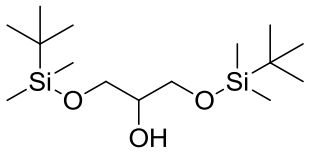


3-((*tert*-Butyldimethylsilyl)oxy)propane-1,2-diol (2.53). A 100 mL flask was charged with glycerol (2.0 g, 21.7 mmol) in CH_3CN (20 mL). Diisopropylethylamine (3.8 mL, 21.7 mmol), *N*-methylimidazole (173 μL, 2.17 mmol) and *tert*-butyldimethylsilyl

chloride (3.3 g, 21.7 mmol) in CH_3CN (20 mL) was slowly added as a mixture. The reaction was allowed to stir for 48 hours before quenching with MeOH. The resulting mixture was evaporated in vacuo and the crude product was purified on silica gel with 20% EtOAc in hexanes to yield 2.2 g (49%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.72-3.55 (m, 5H), 3.08 (d, 1H, *J*= 5.0), 2.94 (appt, 1H, *J*= 5.0), 0.87 (s, 9H), 0.047 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.9, 64.6, 63.9, 25.8, 18.2, -5.46, -5.48; IR: 3384, 2928, 2857, 1253, 832, 774 cm^{-1}; HRMS Calcd. for $C_9H_{23}O_3Si$ $[M+H]^+$: 207.1416, Found: 207.1426.

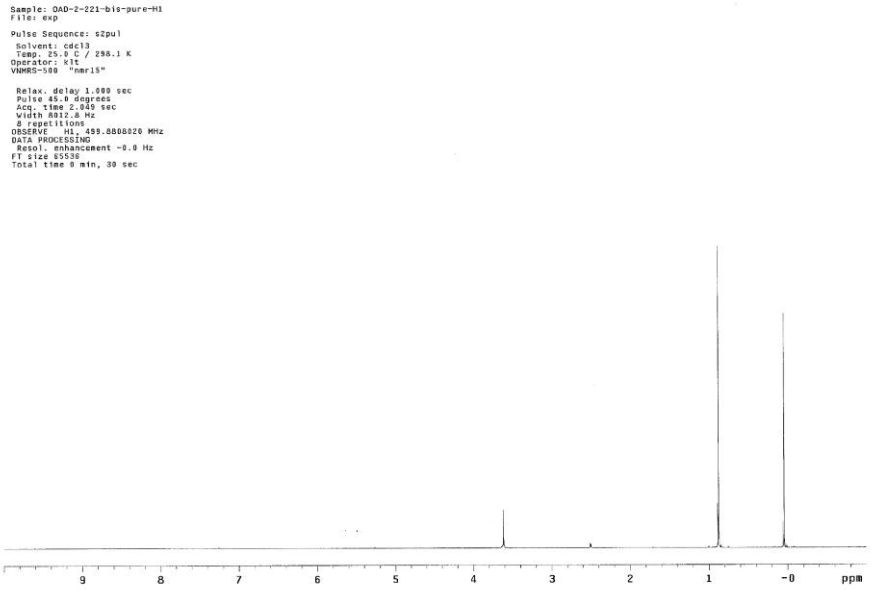


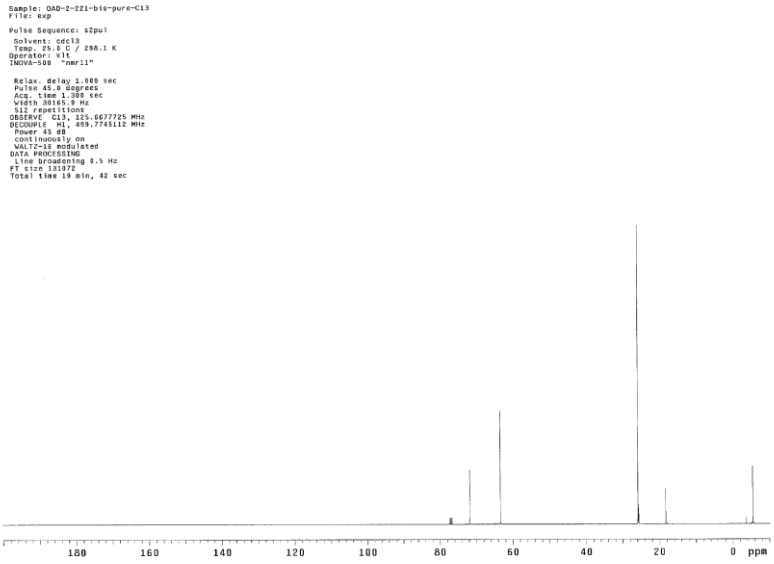


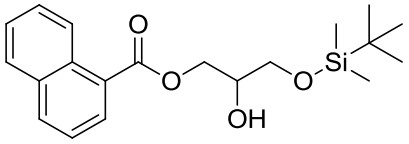


2,2,3,3,9,9,10,10-Octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (2.54). A 100 mL flask was charged with glycerol (2.0 g, 21.7 mmol) in CH_3CN (20 mL). Diisopropylethylamine (3.8 mL, 21.7 mmol), *N*-methylimidazole (173 μL, 2.17 mmol) and *tert*-butyldimethylsilyl chloride (3.3 g, 21.7 mmol) in CH_3CN (20 mL) was slowly added as a mixture. The reaction was allowed to stir for 48 hours before quenching with MeOH. The resulting mixture was evaporated in vacuo and the crude product was purified on silica gel with 20% EtOAc in hexanes to yield 2.2 g (32%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.64-3.60 (m, 5H), 2.50 (d, 1H, *J*= 5.5), 0.87 (s, 18H),

0.044 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.8, 63.4, 25.8, 25.6, 18.2, -5.44, -5.45; IR: 3490, 2953, 2857, 1463, 1252, 1091, 831, 773 cm^{-1}; HRMS Calcd. for $C_{15}H_{37}O_3Si_2$ $[M+H]^+$: 321.2281, Found: 321.2283.





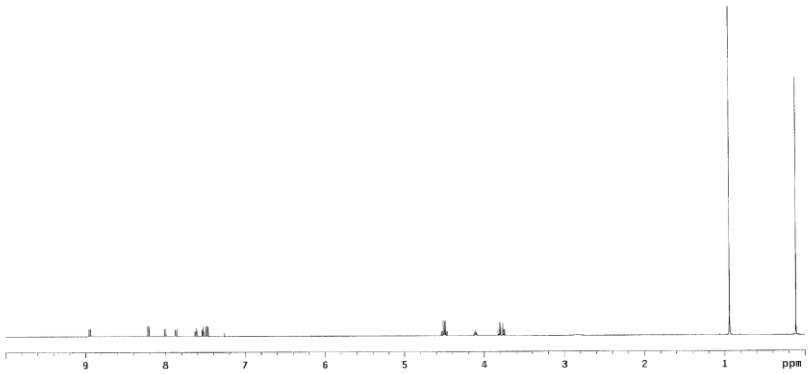


3-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxypropyl 1-naphthoate. A 100 mL flask was charged with 3-((tert-butyldimethylsilyl)oxy)propane-1,2-diol (1.0 g, 4.84 mmol) in DCM (6 mL) and cooled down to 0 ^{o}C. Diisopropylethylamine (0.843 mL, 4.84 mmol) and naphthoyl chloride (0.730 mL, 4.84 mmol) in DCM (6 mL) was slowly added as a mixture. The reaction was allowed to stir at ambient temperature for 18 hours before quenching with MeOH. The resulting mixture was evaporated in vacuo and the crude product was purified on silica gel with 10% EtOAc in hexanes to yield 1.06 g (61%) of the title compound as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.94 (dd, 1H, *J*= 1.0, 9.0), 8.21 (dd, 1H, *J*= 1.5, 7.0), 8.00 (appd, 1H, 8.0), 7.87-7.85 (m, 1H), 7.63-7.59 (m, 1H), 7.54-7.46 (m, 2H), 4.53-4.46 (m, 2H), 4.10 (appq, 1H, J= 4.5), 3.82-3.74 (m, 2H), 2.84 (bs, 1H), 0.93 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 133.9, 133.6, 131.4, 130.4, 128.6, 127.8, 126.9, 126.3, 125.8, 124.5, 70.2, 65.8, 63.9, 25.9, 18.3, -5.36, -5.37; IR: 3467, 2952, 2856, 1715, 1243, 1131, 835, 778 cm^{-1}; HRMS Calcd. for $C_{20}H_{29}O_4Si$ $[M+H]^+$: 361.1835, Found: 361.1839. HPLC Method: t_R = 14.8 min, t_R = 17.9 min.

Sample: OAD-2-222-pure-H1
File: exp

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

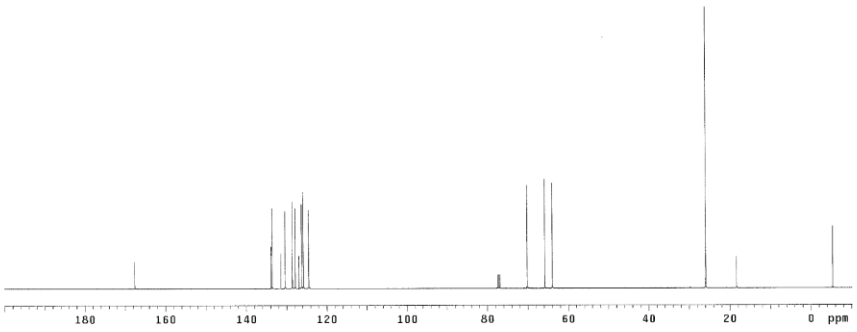
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.849 sec
Width 8812.8 Hz
8 repetitions
OBSERVE H1, 499.8886020 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

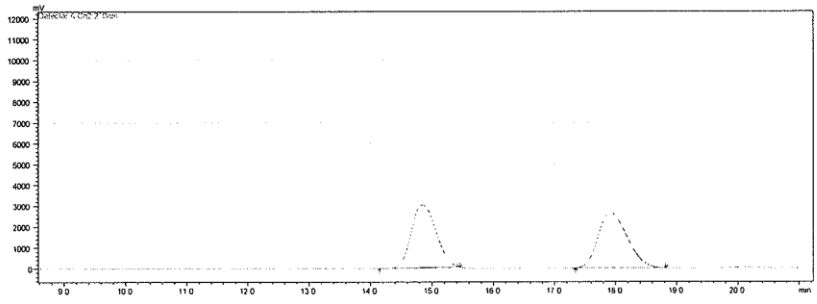


Sample: OAD-2-222-pure-C13
File: exp

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr11"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
512 repetitions
OBSERVE C13, 125.6677725 MHz
DECOUPLE H1, 499.7745112 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 42 sec





PeakTable

Detector A Ch1 230nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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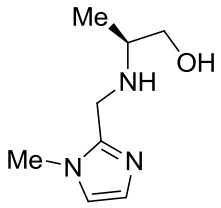
2	17.880	63338452	1820945	49.966	44.519
Total		126762345	4090267	100.000	100.000

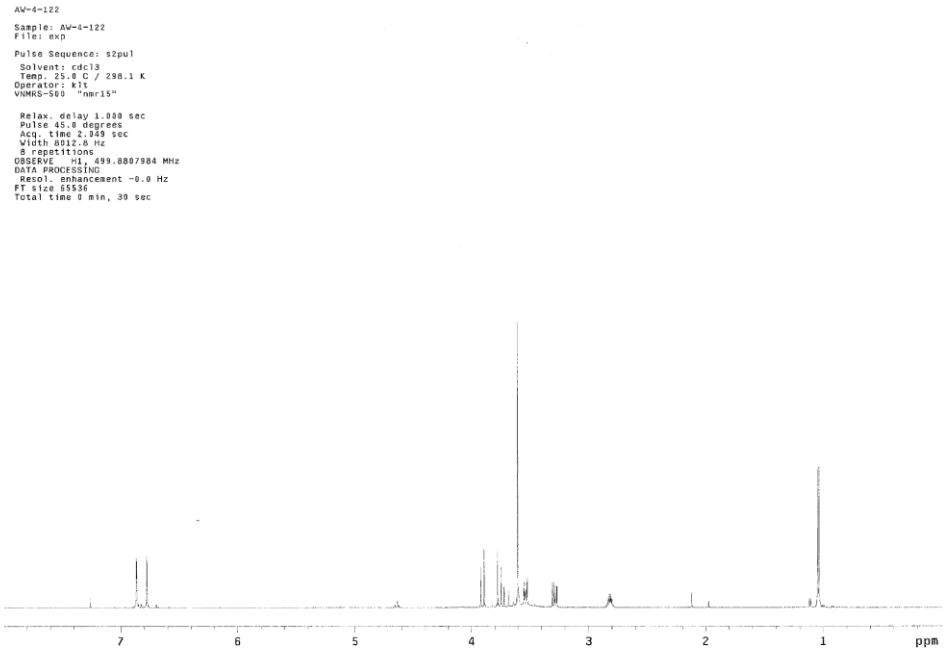
Catalyst Synthesis

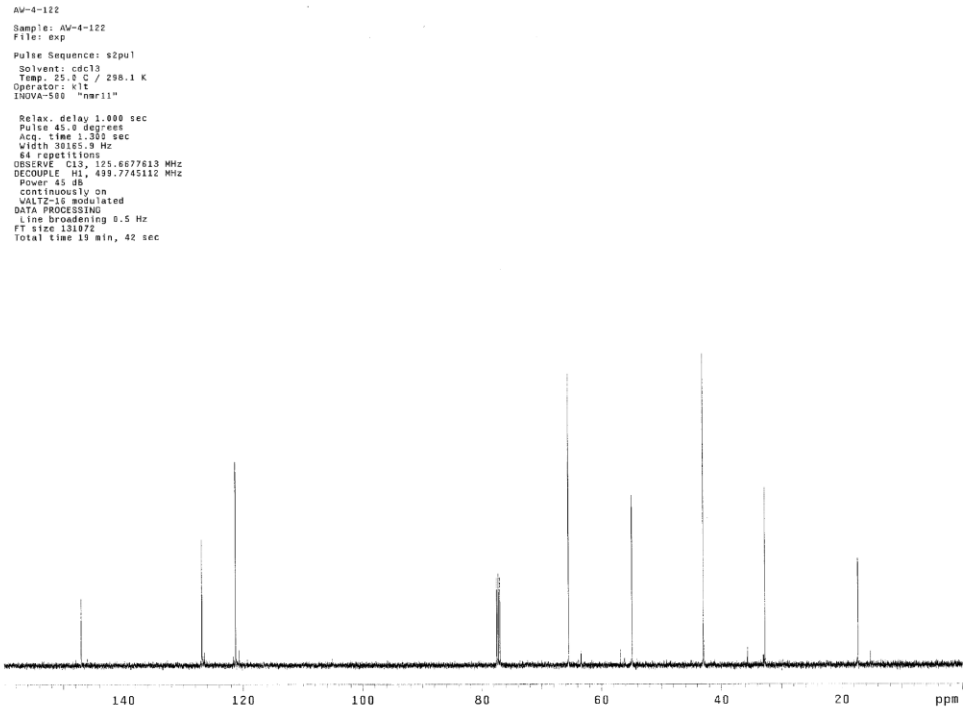
N-methyl-imidazole-2-carboxaldehyde[1] was made following literature procedures and matched reported spectra.

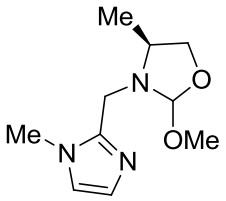


(*S*)-2-((1-Methyl-1H-imidazol-2-yl)methylamino)propan-1-ol.[2] To a solution of *N*-methyl-imidazole-2-carboxaldehyde (650 mg, 8.7 mmol) in methanol (17 mL) was added (*S*)-Alaninol (960 mg, 8.7 mmol) and 4Å molecular sieves (1.7 g). After refluxing for 24 hours, the reaction was cooled to room temperature, and $NaBH_4$ (340 mg, 8.7 mmol) was added. The reaction was stirred at room temperature for 2 hours, followed by quenching with dropwise addition of concentrated HCl (0.44 mL). The resulting mixture was further neutralized with Na_2CO_3 (1.4 g). The precipitated salts were filtered off, and the filtrate

was concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 10:1) afforded pure product as a colorless oil (1.0 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.865 (d, 1H, *J* = 1.2), 6.777 (d, 1H, *J* = 1.2), 3.91 (d, 1H, *J* = 14.4), 3.76 (d, 1H, *J* = 14.4), 3.60 (s, 3H), 3.53 (dd, 1H, *J* = 11.0, 3.9), 3.26-3.30 (m, 1H), 2.82 (qt, 1H, *J* = 10.3, 3.9), 1.04 (d, 3H, *J* = 6.4); ^{13}C NMR (C_6D_6, 126 MHz) δ 147.0, 126.9, 121.2, 65.5, 54.9, 42.9, 32.7, 17.3; IR: 3201, 2872, 1636, 1499, 1452, 1283, 1048, 736, 662 cm^{-1}; HRMS Calcd. for $C_8H_{16}N_3O$ $[M+H]^+$: 170.1293, Found: 170.1292.

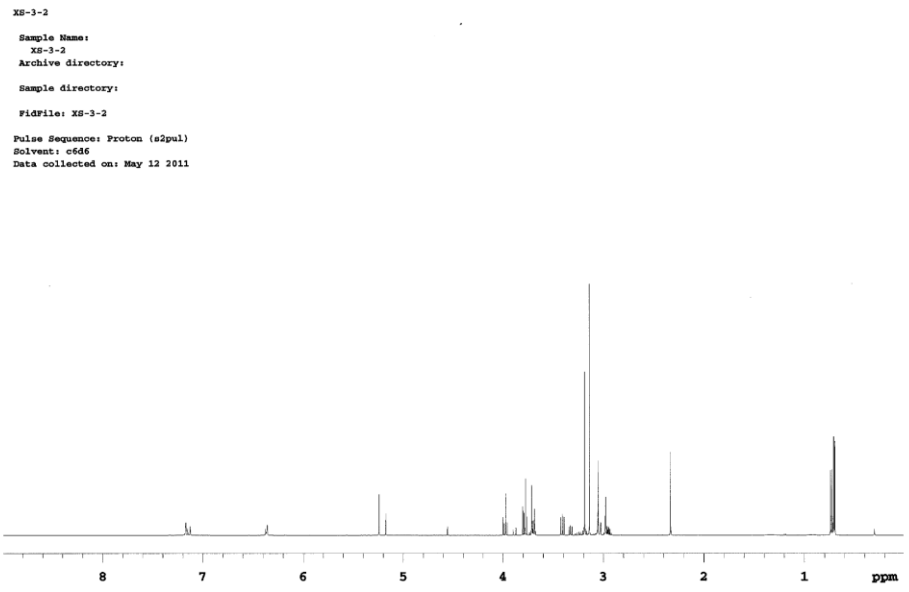


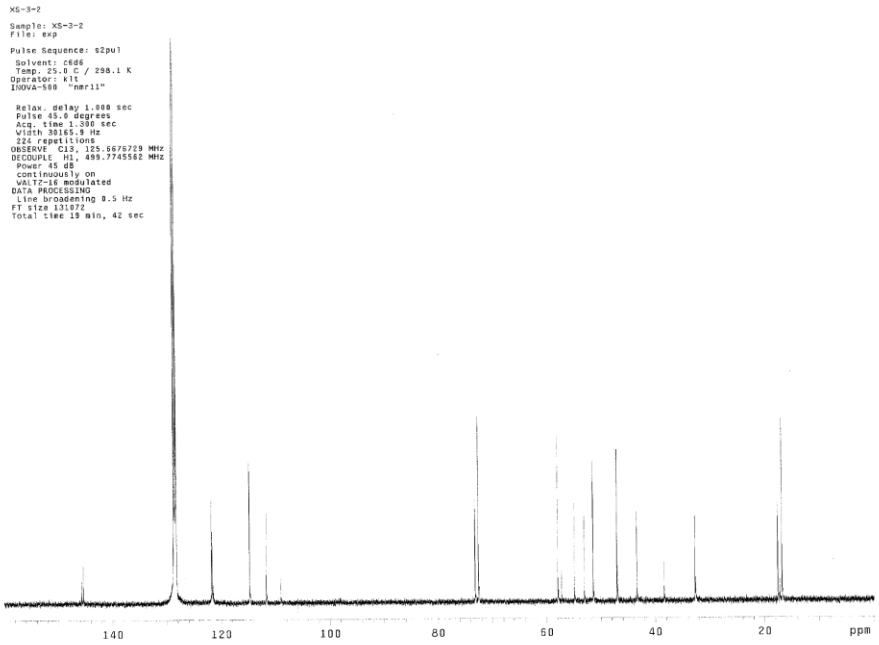


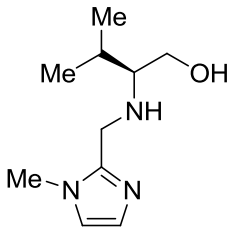


(*4S*)-2-Methoxy-4-methyl-3-((1-methyl-1H-imidazol-2-yl)methyl)oxazolidine (2.42) (66:34 dr). To a solution of (*S*)-2-(((1-methyl-1H-imidazol-2-yl)methyl)amino)propan-1-ol (1.0 g, 6.0 mmol) in anhydrous methanol (24 mL) under argon was added *N*,*N*-dimethylformamide dimethyl acetal (0.80 mL, 6.0 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (24 mL), and the reaction was stirred at room temperature for another 2 hours, at which time ^{1}H NMR analysis showed that all the substrate was consumed and product had formed. The solvent was removed under

vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentane. The pentane was removed under vacuum, and Kugelrohr distillation (170 °C @ 0.05 mm Hg) afforded pure product as a colorless oil (330 mg, 26%). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.15 (s, 0.34H), 7.125 (d, 0.66H, *J* = 0.1), 6.37 (s, 0.34H), 6.36 (s, 0.34H), 5.24 (s, 0.66H), 5.17 (s, 0.34H), 3.98 (t, 0.34H, *J* = 7.3), 3.78 (t, 0.66H, *J* = 6.8), 3.68-3.72 (m, 2H), 3.36-3.43 (m, 0.66H), 3.32-3.34 (m, 0.34H), 3.28 (s, 0.66H), 3.23 (s, 0.66H), 3.14 (s, 0.34H), 3.07 (s, 0.34H), 2.94-2.96 (m, 1H), 0.735 (d, 1H, *J* = 6.1), 0.705 (d, 2H, *J* = 5.9); ^{13}C NMR (C_6D_6, 126 MHz) δ 145.7, 145.4, 121.8, 121.7, 114.7, 111.7, 109.0, 73.1, 72.6, 57.9, 54.9, 53.1, 51.4, 47.1, 43.4, 38.3, 32.7, 17.5, 16.8; IR: 2928, 1501, 1458, 1284, 1162, 1113, 1066, 1017, 975, 742 cm^{-1}; HRMS Calcd. for $C_{19}H_{14}N_3O$ [M-OMe]: 180.1137, Found: 180.1142.

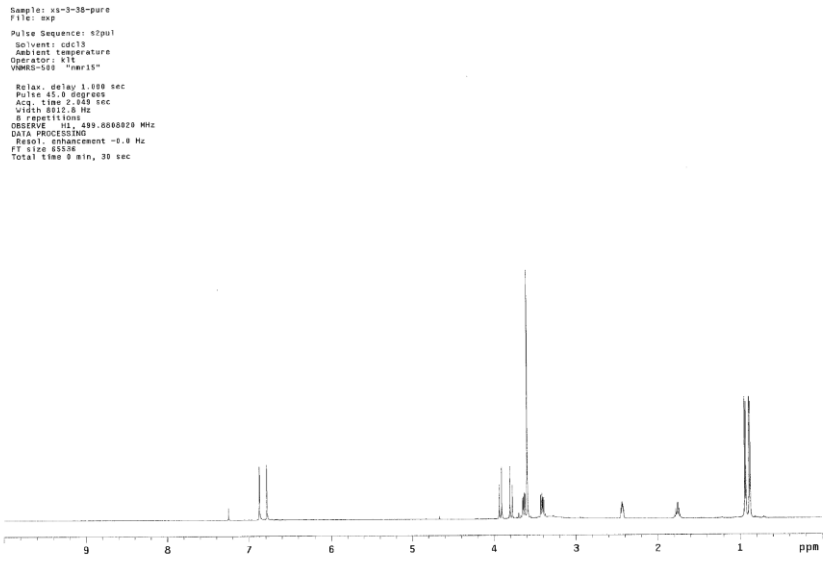


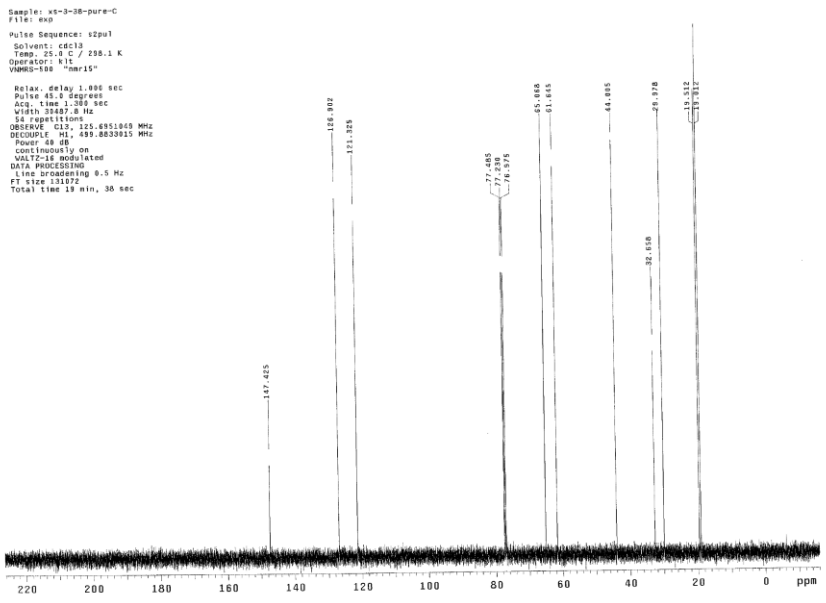


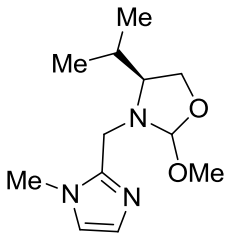


(*S*)-3-Methyl-2-((1-methyl-1H-imidazol-2-yl)methylamino)butan-1-ol (2.32).[2] To a solution of *N*-methyl-imidazole-2-carboxaldehyde (2.1 g, 20 mmol) in methanol (40 mL) was added (*S*)-Valinol (2.2 g, 20 mmol) and 4Å molecular sieves (4.0 g). After refluxing for 24 hours, the reaction was cooled to room temperature, and $NaBH_4$ (760 mg, 20 mmol) was added. The reaction was stirred at room temperature for 2 hours, followed by quenching with dropwise addition of concentrated HCl (1.0 mL). The resulting mixture was further neutralized with Na_2CO_3 (3.3 g). The precipitated salts were filtered off, and the filtrate was concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 10:1)

afforded the pure product as a colorless oil (2.3 g, 58%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.86 (d, 1H, *J* = 1.5), 6.77 (d, 1H, *J* = 1.2), 3.90 (d, 1H, *J* = 14.7), 3.78 (d, 1H, *J* = 14.9), 3.62 (dd, 1H, *J* = 11.2, 3.7), 3.58 (s, 3H), 3.39 (dd, 1H, *J* = 11.0, 7.3), 2.42 (m, 1H), 1.74 (m, 1H), 0.92 (d, 3H, *J* = 6.8), 0.87 (d, 3H, *J* = 6.8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.4, 126.9, 121.3, 65.1, 61.6, 44.0, 32.6, 30.0, 19.5, 19.0; IR: 3199, 2955, 2871, 1500, 1465, 1283, 1043, 734, 705, 661 cm^{-1}; HRMS Calcd. for $C_{10}H_{20}N_3O$ $[M+H]^+$: 198.1606, Found:198.1606.







(*4S*)-4-Isopropyl-2-methoxy-3-((1-methyl-1H-imidazol-2-yl)methyl)oxazolidine (2.21) (70:30 dr). To a solution of (*S*)-3-methyl-2-(((1-methyl-1H-imidazol-2-yl)methyl)amino)butan-1-ol (860 mg, 4.4 mmol) in anhydrous methanol (18 mL) under argon was added *N*,*N*-dimethylformamide dimethyl acetal (580 μL, 4.4 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (18 mL), and the reaction was further stirred at room temperature for 2 more hours until ^{1}H NMR analysis showed that all of the substrate was consumed and product had formed. The solvent was removed

under vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentane. The pentane was removed under vacuum, and Kugelrohr distillation (130 °C @ 0.05 mm Hg) afforded pure product as colorless oil (490 mg, 47%). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.15 (d, 0.3H, *J* = 1.2), 7.12 (d, 0.7H, *J* = 1.0), 6.36 (d, 0.3H, *J* = 1.0), 6.35 (d, 0.7H, *J* = 1.2), 5.34 (s, 0.3H), 5.21 (s, 0.7H), 4.02 (d, 0.3H, *J* = 13.9), 3.895 (t, 0.6H, *J* = 8.1), 3.84 (d, 0.3H, *J* = 13.9), 3.79 (t, 0.7H), 3.74 (d, 0.7H, *J* = 13.4), 3.67-3.70 (m, 0.7H), 3.65 (d, 0.7H, *J* = 13.7), 3.17 (s, 0.9H), 3.09 (s, 2.1H), 3.07 (s, 2.1H), 2.98 (s, 09H), 2.82-2.86 (m, 1H), 1.67 (dt, 0.7H, *J* = 20.5, 6.8), 1.58 (ddd, 0.3H, *J* = 13.9, 6.8, 3.7), 0.715 (d, 0.3H, *J* = 6.8), 0.685 (d, 0.7H, *J* = 6.8), 0.645 (d, 0.7H, *J* = 6.8), 0.58 (d, 0.3H, *J* = 7.1); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 145.9, 145.5, 128.7, 128.2, 121.6, 121.3, 115.1, 111.9, 68.3, 67.1, 65.6, 64.7, 53.0, 51.8, 49.3, 43.9, 32.5, 32.4, 30.7, 28.7, 20.1, 19.9, 17.5, 15.4; IR: 2956, 1500, 1466, 1284, 1158, 1123, 1080, 1062, 986, 741 cm^{-1}; HRMS Calcd. for $C_{11}H_{18}N_3O$ [M-OMe]: 208.1450, Found: 208.1459.

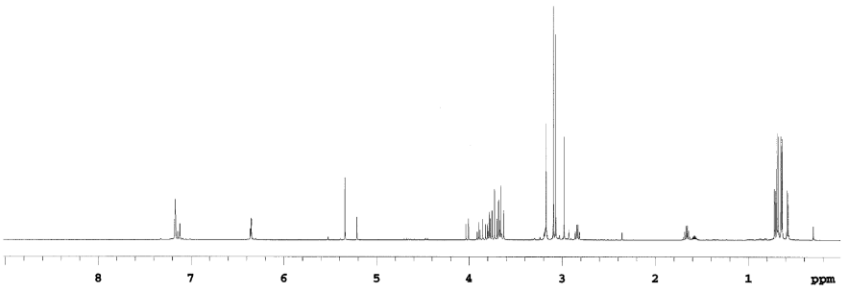
XS-3-40

Sample Name:
XS-3-40
Archive directory:

Sample directory:

FidFile: XS-3-40

Pulse Sequence: Proton (s2pul)
Solvent: c6d6
Data collected on: May 12 2011

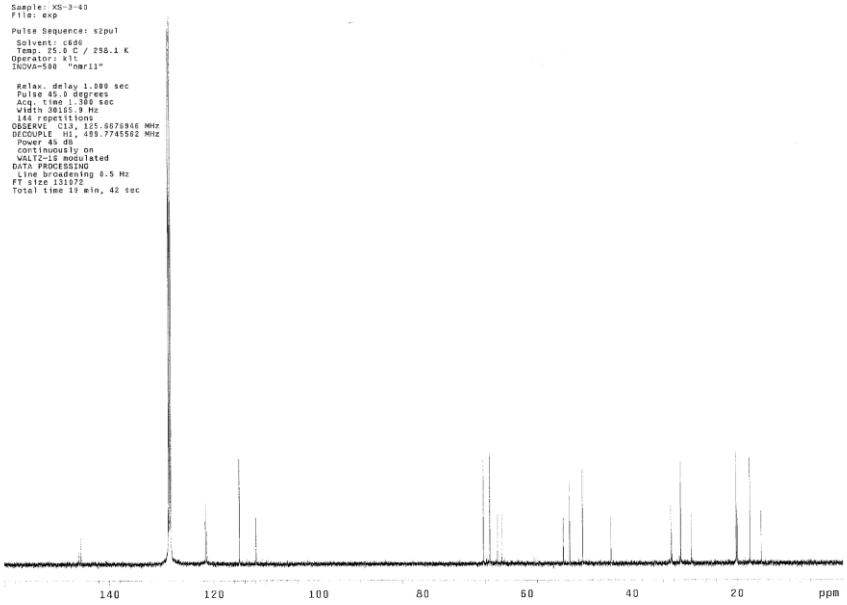


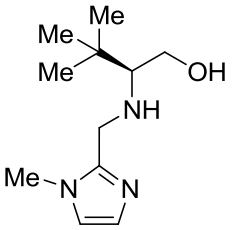
XS-3-40

Sample: XS-3-40
File: exp

Pulse Sequence: s2pul
Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr11"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
144 repetitions
OBSERVE C13, 125.8676946 MHz
DECOUPLE H1, 499.7745562 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 13 min, 42 sec



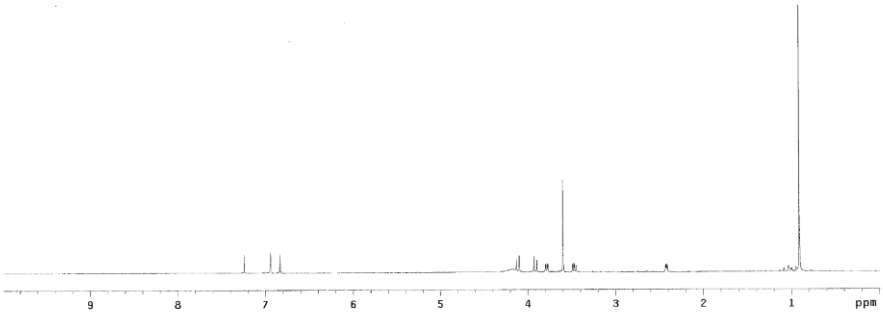


(*S*)-3,3-Dimethyl-2-((1-methyl-1H-imidazol-2-yl)methylamino)butan-1-ol.[2] To a solution of *N*-methyl-imidazole-2-carboxaldehyde (750 mg, 6.8 mmol) in methanol (14 mL) was added (*S*)-*tert*-Leucinol (0.80 g, 6.8 mmol) and 4Å molecular sieves (1.4 g). After refluxing for 24 hours, the reaction was cooled to room temperature, and $NaBH_4$ (260 mg, 6.8 mmol) was added. The reaction was stirred at room temperature for 2 hours, followed by quenching with dropwise addition of concentrated HCl (0.34 mL). The resulting mixture was further neutralized with Na_2CO_3 (1.1 g). The precipitated salts were filtered off, and the filtrate was concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 10:1) afforded the pure product as a colorless oil (720 mg, 50%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.97 (d, 1H, *J* = 1.5), 6.88 (d, 1H, *J* = 1.0), 4.20 (br s, 2H), 4.15 (d, 1H, *J* = 15.9), 3.97 (d, 1H, *J* = 15.6), 3.82 (dd, 1H, *J* = 11.2, 3.7), 3.45 (s, 3H), 3.51 (dd, 1H, *J* = 11.2, 8.1), 2.45 (dd, 1H, *J* = 8.1, 3.7), 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.7, 126.0, 121.6, 68.7, 62.1, 46.0, 35.1, 32.9, 27.2; IR: 3333, 2950, 2868, 1501, 1476, 1283, 1110, 1045, 736 cm^{-1}; HRMS Calcd. for $C_{11}H_{22}N_3O$ $[M+H]^+$: 212.17629, Found: 212.17638.

Sample: xs-2-212-pure
File: exp

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8868079 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec



Sample Name:
xs-2-212-pure-C
Archive directory:

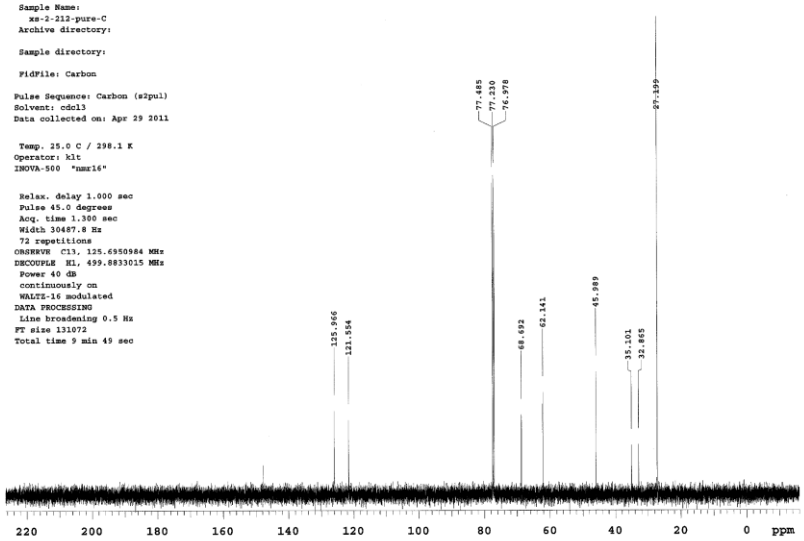
Sample directory:

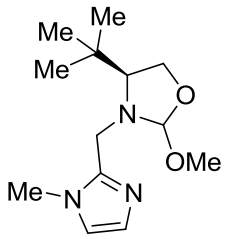
FidFile: Carbon

Pulse Sequence: Carbon (s2pul)
Solvent: cdcl3
Data collected on: Apr 29 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 30487.8 Hz
72 repetitions
OBSERVE C13, 125.6950984 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 9 min 49 sec





(*4S*)-4-*tert*-Butyl-2-methoxy-3-((1-methyl-1H-imidazol-2-yl)methyl)oxazolidine (2.40) (85:15 dr). To a solution of (*S*)-3,3-dimethyl-2-(((1-methyl-1H-imidazol-2-yl)methyl)amino)butan-1-ol (0.70 g, 3.3 mmol) in anhydrous methanol (13 mL) under argon was added *N*,*N*-dimethylformamide dimethyl acetal (0.40 mL, 3.3 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (13 mL), and the reaction was again stirred at room temperature for 2 hours until ^{1}H NMR analysis showed all the substrate was consumed and product had formed. The solvent was removed under vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentane. The pentane was removed under vacuum, and Kugelrohr distillation (180 °C @ 0.05 mm Hg) afforded the pure product as a colorless oil (190 mg, 23%). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.21 (s, 1H), 6.38 (s, 1H), 5.55 (s, 0.85H), 5.28 (s, 0.15H), 3.95 (d, 1H, *J* = 13.4), 3.85-3.89 (m, 1H), 3.78-3.81 (m, 1H), 3.65 (d, 1H, *J* = 13.4), 3.15 (s, 0.5H), 3.13 (s, 2.5H), 3.01 (s, 2.5H), 3.00 (s, 0.5H), 2.65-2.68 (m, 1H), 0.85 (s, 1.4H), 0.83 (s, 7.6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 145.2, 127.3, 121.7, 120.9, 114.9, 111.0, 72.3, 68.8, 66.3, 65.1, 53.2, 52.5, 51.8, 38.1, 34.6, 33.5, 33.3, 26.7, 26.4; IR: 2955, 2905, 1499, 1477, 1285, 1147, 1132, 1082, 1066, 993, 740 cm^{-1}; HRMS Calcd. for $C_{12}H_{20}N_3O$ [M-OMe]: 222.1606, Found: 222.1612.

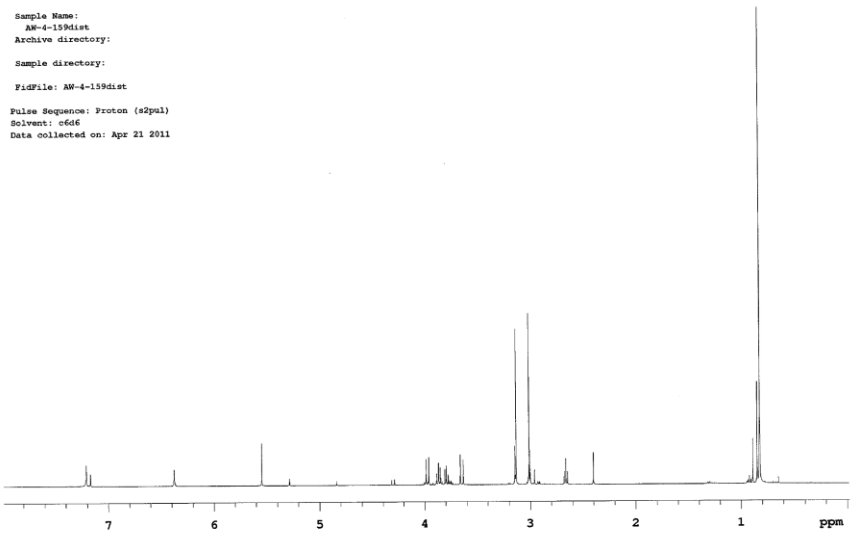
AW-4-159dist

Sample Name:
AW-4-159dist
Archive directory:

Sample directory:

FidFile: AW-4-159dist

Pulse Sequence: Proton (s2pul)
Solvent: c6d6
Data collected on: Apr 21 2011

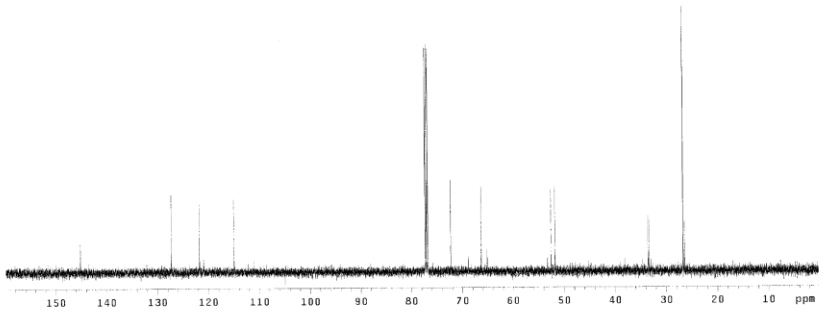


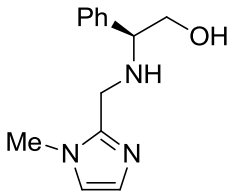
AW-4-159

Sample: AW-4-159
File: exp

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr11"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.389 sec
Width 30165.9 Hz
240 repetitions
OBSERVE C13, 125.6677725 MHz
DECOUPLE H1, 499.7745112 MHz
Power 65 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 10 min, 42 sec





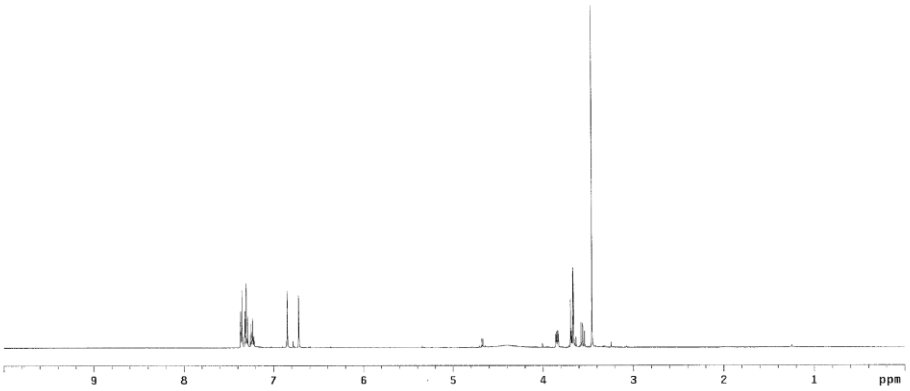
(*S*)-2-(((1-Methyl-1H-imidazol-2-yl)methyl)amino)-2-phenylethanol.[2] To a solution of *N*-methyl-imidazole-2-carboxaldehyde (1.37 g, 10.0 mmol) in benzene (30 mL) was added (*S*)-Glycinol (1.10 g, 10.0 mmol) and 3Å molecular sieves (1.4 g). After refluxing for 24 hours, the reaction was cooled to room temperature and the solvent was removed in vacuo. The resulting residue was redissolved in MeOH (30 mL) and $NaBH_4$ (378 mg, 10.0 mmol) was added. The reaction was stirred at room temperature for 2 hours, followed by quenching with dropwise addition of concentrated HCl (0.51 mL). The resulting mixture was further neutralized with Na_2CO_3 (1.67 g). The precipitated salts were filtered off, and the filtrate was concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 10:1) afforded the pure product as a yellow oil (1.88 g, 81%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.21 (m, 5H), 6.84 (d, 1H, *J*= 1.0), 6.72 (d, 1H, *J*= 1.0), 3.86-3.82 (m, 1H), 3.69-3.66 (m, 3H), 3.55 (dd, 1H, *J*= 9.5, 11.0), 3.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.8, 140.8, 128.5, 127.6, 127.5, 126.8, 121.0, 66.9, 65.3, 55.9, 43.3, 32.6; IR: 3299, 2914, 2842, 1493, 1283, 1050, 758, 702 cm^{-1}; HRMS Calcd. for $C_{13}H_{18}N_3O$ $[M+H]^+$: 232.1449, Found: 232.1454.

Sample: OAD-2-243-pure-H1
File: exp

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.9 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8888028 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

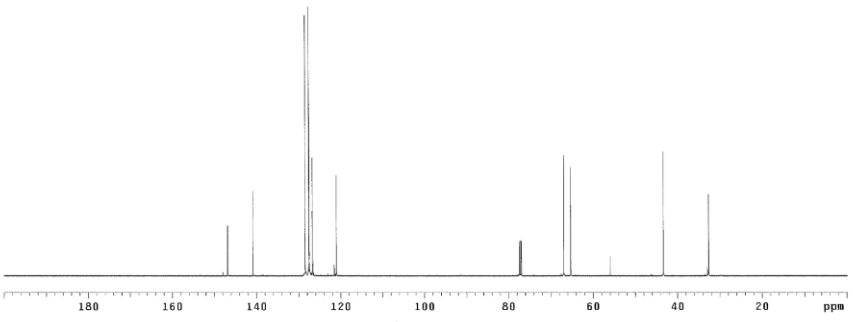


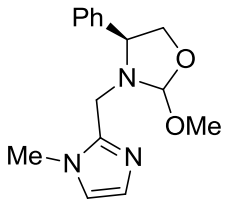
Sample: OAD-2-243-pure-C13
File: exp

Pulse Sequence: s2pul

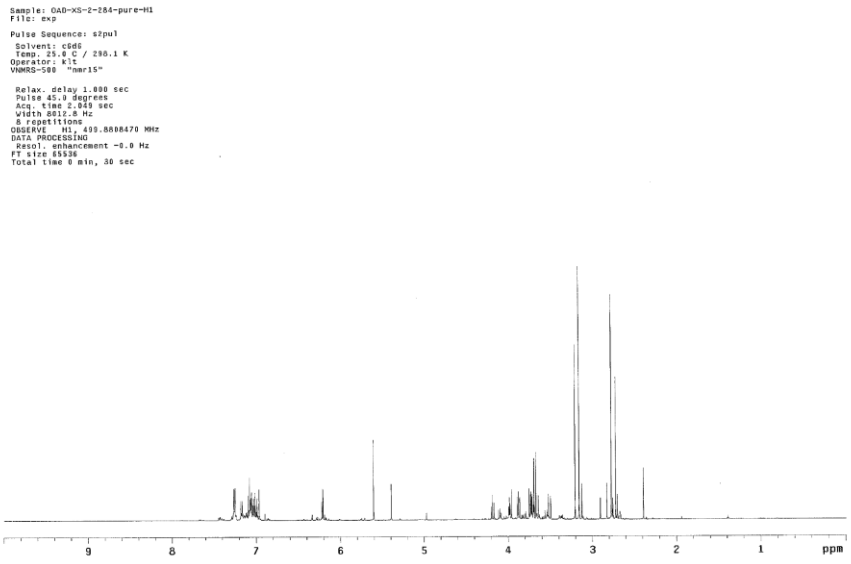
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr11"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30165.9 Hz
512 repetitions
OBSERVE C13, 125.6677725 MHz
DECOUPLE H1, 499.7745112 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 42 sec





(4*S*)-2-Methoxy-3-((1-methyl-1H-imidazol-2-yl)methyl)-4-phenyloxazolidine (2.43) (60:40 dr). To a solution of (*S*)-2-(((1-methyl-1H-imidazol-2-yl)methyl)amino)-2-phenylethanol (1.88 g, 8.1 mmol) in anhydrous methanol (30 mL) under argon was added *N*,*N*-dimethylformamide dimethyl acetal (1.09 mL, 8.1 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (13 mL), and the reaction was again stirred at room temperature for 1 hour until ^{1}H NMR analysis showed all the substrate was consumed and product had formed. The solvent was removed under vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentane to afford the pure product as a pale yellow oil (1.95 g, 88%). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.26-7.24 (m, 1.2H), 7.18-7.15 (m, 0.8H), 7.09-6.99 (m, 3H), 6.98 (d, 0.4H, *J*= 1.0), 6.96 (d, 0.6H, *J*= 1.0), 6.22 (d, 0.4H, *J*= 1.0), 6.20 (d, 0.6H, *J*= 1.0), 5.60 (s, 0.6H), 5.39 (s, 0.4H), 4.18 (t, 0.6H, *J*= 8.0), 4.09 (t, 0.4H, *J*= 8.0), 3.98-3.95 (m, 1H), 3.87 (dd, 0.6H, *J*= 7.0, 8.0), 3.72 (dd, 0.4H, *J*= 8.0, 9.5), 3.70-3.67 (m, 0.8H), 3.70 (d, 0.6H, *J*= 14.0), 3.65 (d, 0.6H, *J*= 14.0), 3.20 (s, 0.4H), 3.15 (s, 0.6H), 2.77 (s, 0.6H), 2.72 (s, 0.4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 144.2, 143.9, 140.6, 138.9, 128.2, 127.1, 120.5, 120.4, 113.1, 110.5, 109.1, 106.5, 73.2, 72.3, 66.0, 63.3, 52.7, 50.9, 44.9, 44.0, 41.8, 37.5, 32.0, 31.6; IR: 2943, 1498, 1453, 1283, 1155, 1042, 731, 700 cm^{-1}; HRMS Calcd. for $C_{14}H_{16}N_3O$ [M-OMe]: 242.1293, Found: 242.1308.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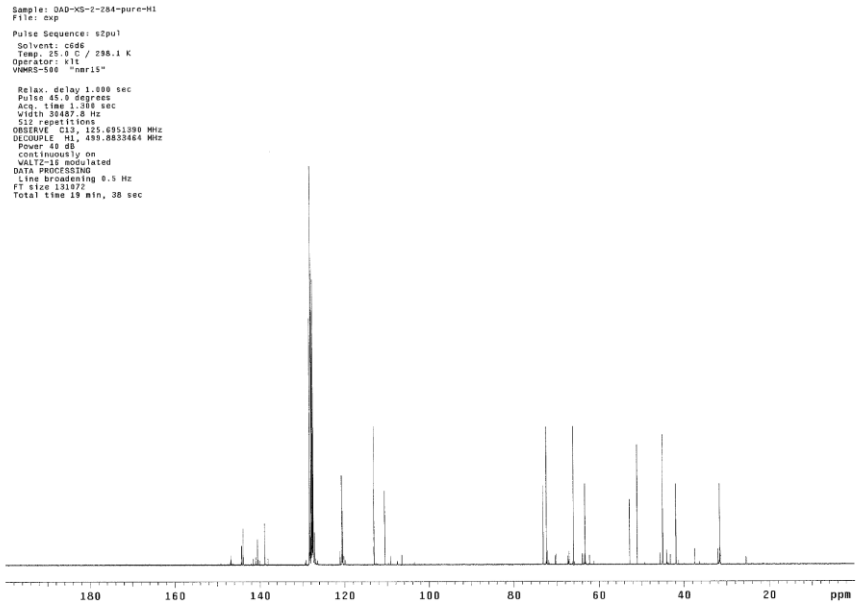
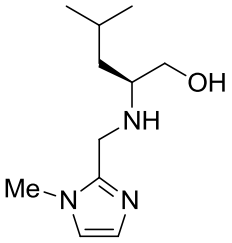
File: exp
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.849 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8808470 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
9
8
7
6
5
4
3
2
1
ppm


Sample: OAD-XS-2-284-pure-H1
File: exp
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.388 sec
Width 30487.8 Hz
512 repetitions
OBSERVE C13, 125.6951390 MHz
DECOUPLE H1, 499.8833464 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 38 sec
180
160
140
120
100
80
60
40
20
ppm



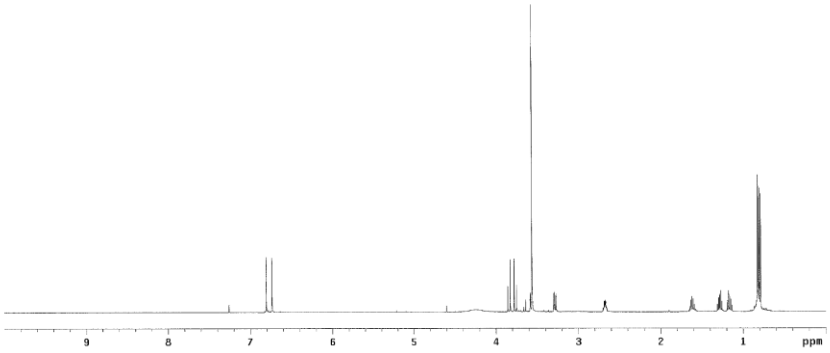
(*S*)-4-Methyl-2-(((1-methyl-1H-imidazol-2-yl)methyl)amino)pentan-1-ol.[2] To a solution of *N*-methyl-imidazole-2-carboxaldehyde (1.65 g, 15.0 mmol) in benzene (30 mL) was added (*S*)-Leucinol (1.17 g, 10.0 mmol) and 3Å molecular sieves (1.4 g). After refluxing for 24 hours, the reaction was cooled to room temperature and the solvent was removed in vacuo. The resulting residue was redissolved in MeOH (30 mL) and $NaBH_4$ (567 mg, 15.0 mmol) was added. The reaction was stirred at room temperature for 2 hours, followed by quenching with dropwise addition of concentrated HCl (0.51 mL). The resulting mixture was further neutralized with Na_2CO_3 (1.67 g). The precipitated salts were filtered off, and the filtrate was concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 10:1) afforded the pure product as a yellow oil (1.58 g, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.80 (d, 1H, *J*= 1.0), 6.73 (d, 1H, *J*= 1.0), 3.84 (d, 1H, *J*= 14.5), 3.76 (d, 1H, *J*= 14.5), 3.56 (s, 3H), 3.30-3.26 (m, 1H), 2.69-2.65 (m, 1H), 1.65-1.58 (m, 1H), 1.31-1.25 (m, 1H), 1.19-1.14 (m, 1H), 0.817 (d, 3H, *J*= 6.5), 0.793 (d, 3H, *J*= 6.5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.9, 126.6, 121.2, 63.1, 57.1, 42.6, 41.1, 32.6, 24.8, 22.8, 22.7; IR: 3281, 2952, 2867, 1500, 1466, 1051, 735 cm^{-1}; HRMS Calcd. for $C_{11}H_{22}N_3O$ $[M+H]^+$: 212.1762, Found: 212.1761.

Sample: OAD-2-247-pure-H1
File: exp

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.949 sec
Width 8812.6 Hz
8 repetitions
OBSERVE H1, 499.8808020 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

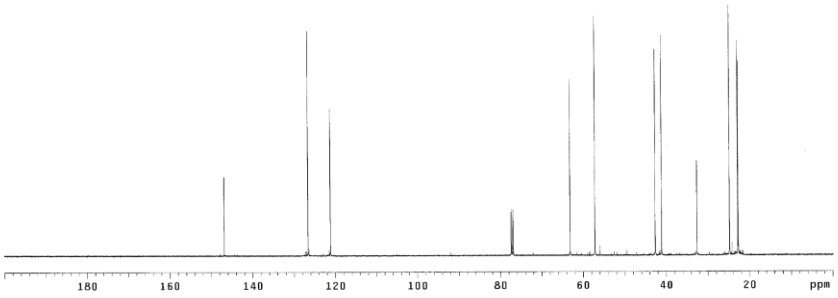


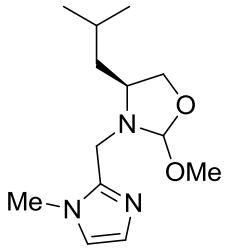
Sample: OAD-2-247-pure-C13
File: exp

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr11"

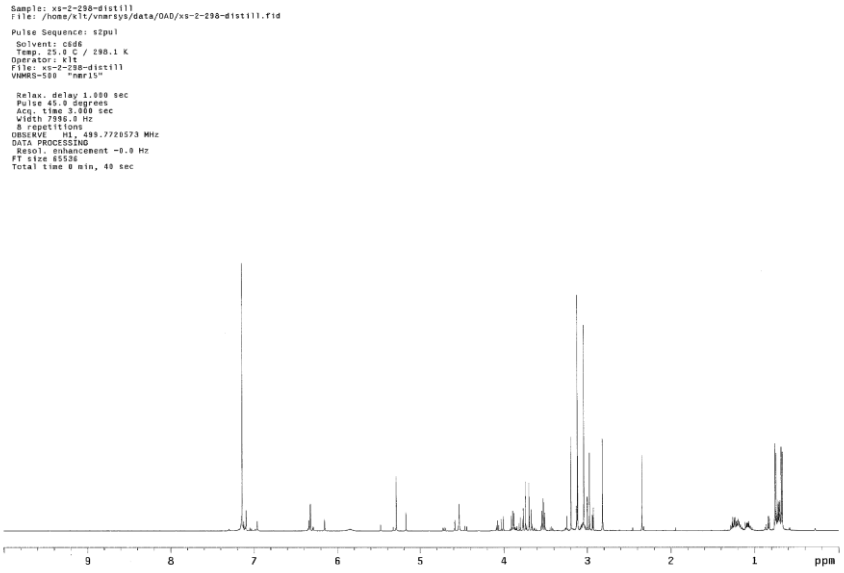
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.308 sec
Width 30165.9 Hz
512 repetitions
OBSERVE C13, 125.6877725 MHz
DECOUPLE H1, 499.7745112 MHz
Power 45 dB
continuously ON
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 42 sec

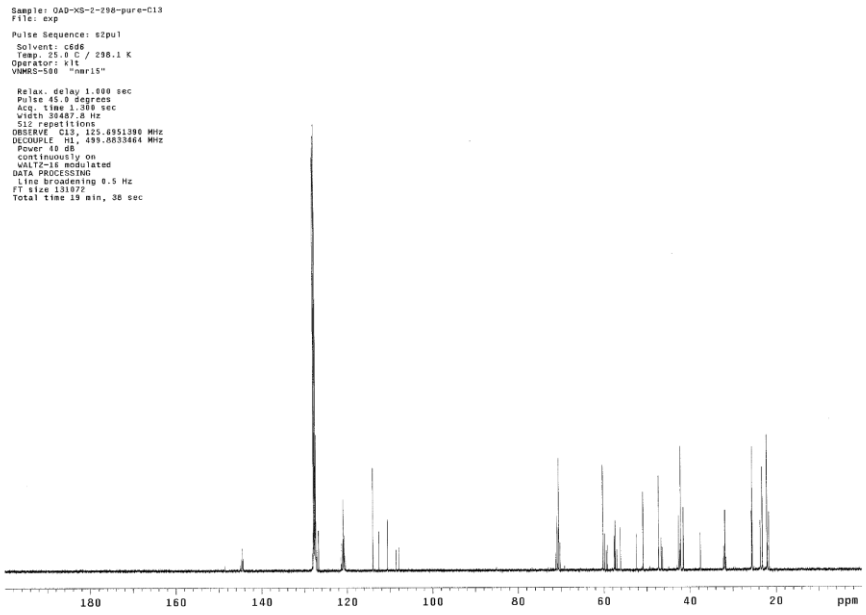


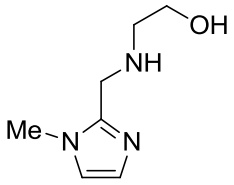


(4*S*)-4-Isobutyl-2-methoxy-3-((1-methyl-1H-imidazol-2-yl)methyl)oxazolidine (2.41) (75:25 dr). To a solution of (*S*)-4-methyl-2-(((1-methyl-1H-imidazol-2-yl)methyl)amino)pentan-1-ol (0.70 g, 3.3 mmol) in anhydrous methanol (13 mL) under argon was added *N*,*N*-dimethylformamide dimethyl acetal (0.40 mL, 3.3 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (13 mL), and the reaction was again stirred at room temperature for 2 hours until ^{1}H NMR analysis showed all the substrate was consumed and product had formed. The solvent was removed under vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentane. The pentane was removed under vacuum, and Kugelrohr distillation (180 °C @ 0.05 mm Hg) afforded the pure product as a pale green oil (190 mg, 23%). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.12 (d, 0.25H, *J*= 1.0), 7.09 (d, 0.75H, *J*= 1.0), 6.34 (d, 0.25H, *J*= 1.0), 6.32 (d, 0.75H, *J*= 1.0), 5.29 (s, 0.75H), 5.17 (s, 0.25H, *J*= 1.0), 3.92-3.87 (m, 0.75H), 3.86-3.84 (m, 0.25H), 3.81-3.76 (m, 0.5H), 3.75 (d, 0.75H, *J*= 13.5), 3.68 (d, 0.75H, *J*= 13.5), 3.55-3.49 (m, 0.75H), 3.44-3.40 (m, 0.25H), 3.19 (s, 0.75H), 3.11 (s, 2.25H), 3.09-3.01 (m, 1H), 3.04 (s, 2.25H), 2.97 (s, 0.75H), 1.28-1.15 (m, 2.25H), 1.11-1.05 (m, 0.75H), 0.748 (d, 0.75H, *J*= 6.5), 0.722 (d, 0.25H, *J*= 6.5), 0.701 (d, 0.75H, *J*= 6.5), 0.674 (d, 0.25H, *J*= 6.5); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 144.6,

126.7, 120.7, 114.0, 112.6, 110.6, 71.1, 70.9, 70.5, 70.1, 57.5, 56.1, 52.3, 50.8, 47.2, 42.6, 42.1, 41.5, 37.5, 31.9, 25.5, 23.6, 23.5, 22.1, 21.7; IR: 2953, 1500, 1284, 1160, 1076, 1036, 736 cm^{-1}; HRMS Calcd. for $C_{12}H_{20}N_3O$ [M-OMe]: 222.1606, Found: 222.1611.

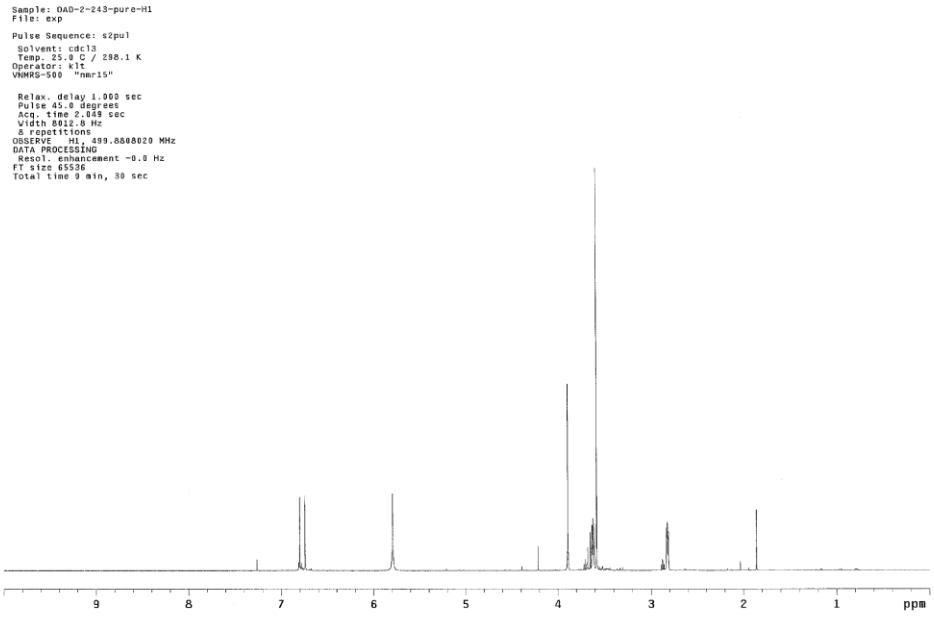


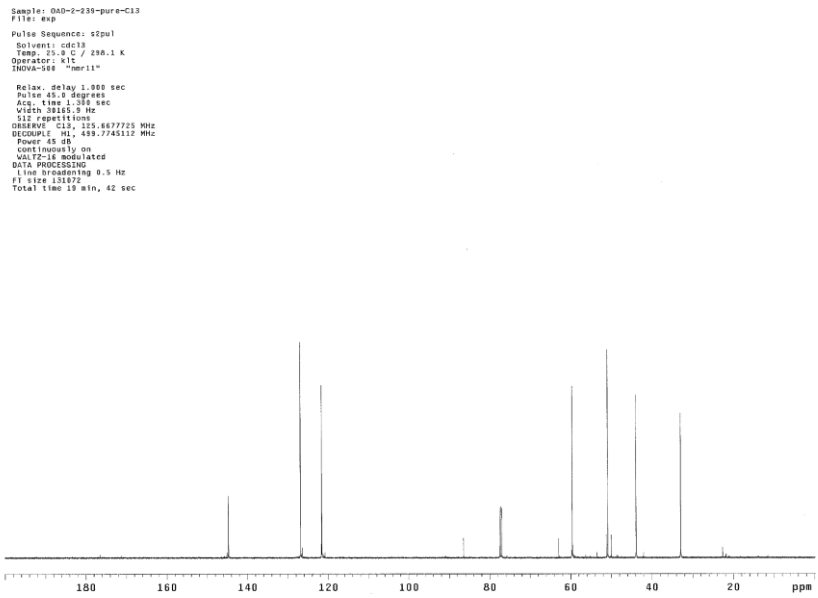


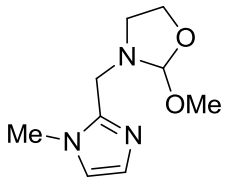


2-(((1-Methyl-1H-imidazol-2-yl)methyl)amino)ethanol.[2] To a solution of *N*-methyl-imidazole-2-carboxaldehyde (2.0 g, 18 mmol) in methanol (40 mL) was added ethanolamine (1.1 mL, 18 mmol) and 3Å molecular sieves (1.4 g). After refluxing for 24 hours, the reaction was cooled to room temperature, and $NaBH_4$ (1.0 g, 27 mmol) was added. The reaction was stirred at room temperature for 2 hours, followed by quenching with dropwise addition of concentrated HCl (0.88 mL). The resulting mixture was further neutralized with Na_2CO_3 (2.9 g). The precipitated salts were filtered off, and the filtrate was concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 9:1) afforded the pure product as a yellow oil (1.9 g, 68%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.81 (d, 1H, *J*=

1.0), 6.74 (d, 1H, *J*= 1.0), 5.79 (s, 2H), 3.89 (s, 2H), 3.62 (t, 2H, *J*= 5.0), 3.58 (s, 3H), 2.82 (t, 2H, *J*= 5.0); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.7, 126.8, 121.6, 59.5, 50.8, 43.8, 32.9; IR: 3280, 2947, 1496, 1282, 1049, 748, 655 cm^{-1}; HRMS Calcd. for $C_7H_{14}N_3O$ $[M+H]^+$: 156.1136, Found: 156.1141.

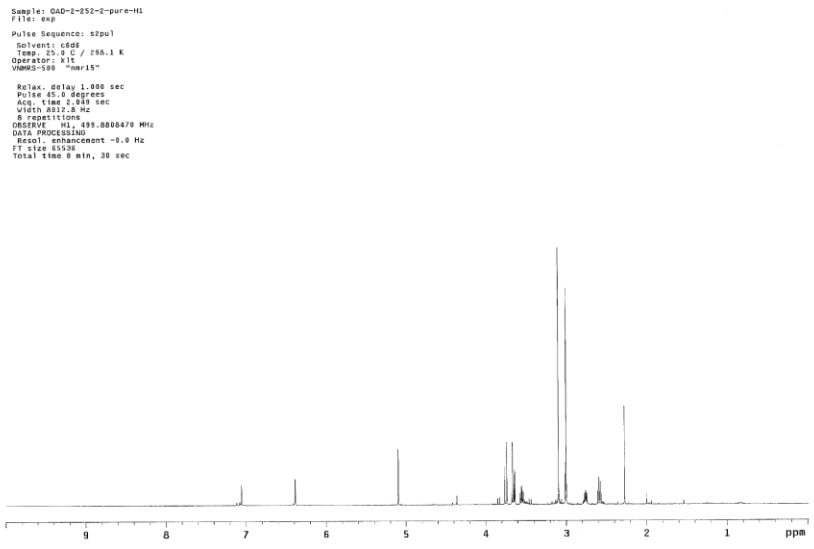


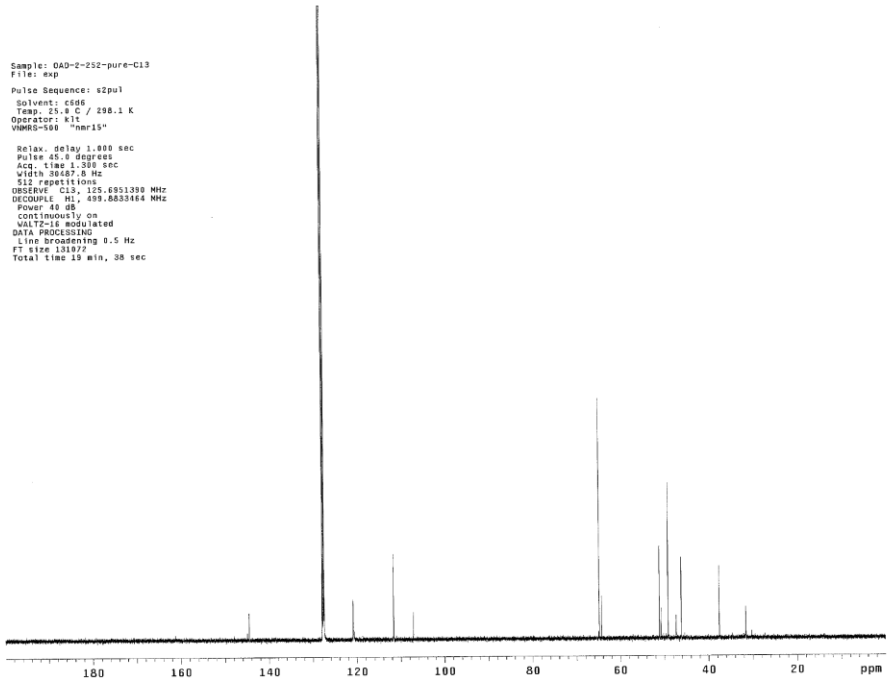


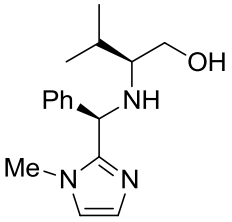


2-Methoxy-3-((1-methyl-1H-imidazol-2-yl)methyl)oxazolidine (2.20). To a solution of 2-(((1-methyl-1H-imidazol-2-yl)methyl)amino)ethanol (0.50 g, 3.2 mmol) in anhydrous methanol (11 mL) under argon was added *N*,*N*-dimethylformamide dimethyl acetal (0.51 mL, 3.8 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (11 mL), and the reaction was again stirred at room temperature for 2 hours until ^{1}H NMR analysis showed all the substrate was consumed and product had formed. The solvent was removed under vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentane to afford the pure

product as a colorless oil (324 mg, 51%). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.05 (d, 1H, *J*= 1.0), 6.38 (d, 1H, *J*= 1.0), 5.09 (s, 1H), 3.74 (d, 1H, *J*= 13.0), 3.65 (d, 1H, *J*= 13.0), 3.67-3.63 (m, 1H), 3.57-3.53 (m, 1H), 3.09 (s, 3H), 2.99 (s, 3H), 2.77-2.73 (m, 1H), 2.60-2.56 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 144.6, 120.9, 111.6, 107.1, 64.8, 51.1, 49.1, 46.1, 37.6; IR: 2948, 2894, 1500, 1284, 1046, 953, 736 cm^{-1}; HRMS Calcd. for $C_8H_{12}N_3O$ [M-OMe]: 166.0980, Found: 166.0980.







(*S*)-3-Methyl-2-(((*R*)-(1-methyl-1H-imidazol-2-yl)(phenyl)methyl)amino)butan-1-ol.[2]

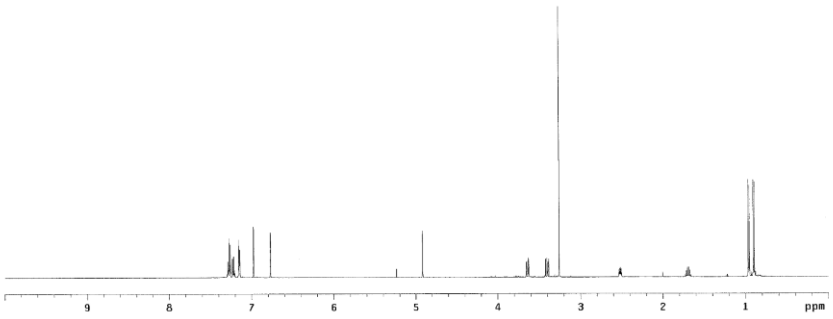
To a solution of benzaldehyde (2.0 mL, 20.0 mmol) in benzene (30 mL) was added (*S*)-Valinol (2.0 g, 20.0 mmol) and 3Å molecular sieves (1.4 g). After refluxing for 24 hours, the reaction was cooled to room temperature and the solvent was removed in vacuo. ^{1}H NMR analysis showed that the imine had formed. The resulting residue was redissolved in diethyl ether (20 mL). In another oven-dried glass reaction flask, to the solution of *N*-methylimidazole (5.6 mL, 70 mmol) in anhydrous diethyl ether (50 mL) under nitrogen atmosphere was added *n*-butyllithium (7.0 mL, 10 M in hexanes, 70 mmol) dropwise at –

78 °C. The solution was stirred at –78 °C for 30 minutes, and then slowly cannula transferred into the solution of pre-formed imine at –78 °C. The resulting mixture was stirred at –78 °C for 2 hours and then at room temperature overnight. Aqueous NH_4Cl was added slowly to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (3:1 Hex/EtOAc to 100% EtOAc) afforded pure product as a yellow oil (3.8 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.14 (m, 5H), 6.97 (d, 1H, *J*= 1.0), 6.77 (d, 1H, *J*= 1.0), 4.91 (s, 1H), 3.63 (dd, 1H, *J*= 3.5, 11.0), 3.40 (dd, 1H, *J*= 8.0, 11.0), 3.26 (s, 3H), 2.53-2.49 (m, 1H), 1.71-1.67 (m, 1H), 0.96 (d, 3H, *J*= 6.5), 0.90 (d, 3H, *J*=6.5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.3, 140.8, 128.9, 127.8, 127.6, 126.5, 121.6, 63.7, 62.9, 59.4, 32.6, 31.7, 19.3; IR: 3339, 2955, 2870, 1492, 1281, 1048, 700 cm^{-1}; HRMS Calcd. for $C_{16}H_{24}N_3O$ $[M+H]^+$: 274.1919, Found: 274.1925.

Sample: OAD-2-248-pure-H1
File: exp

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

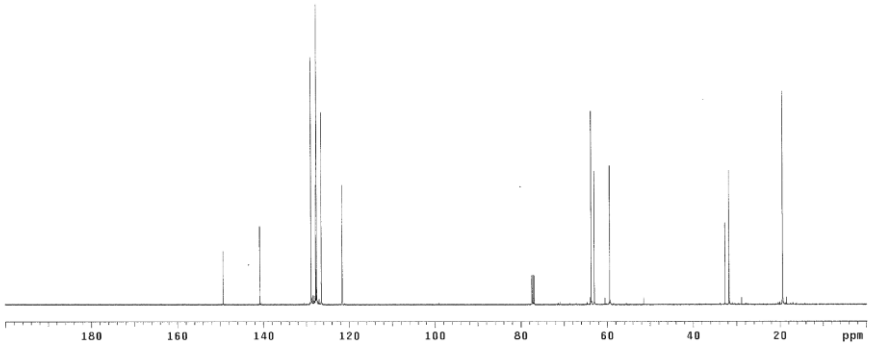
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.649 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8808020 MHz
DATA PROCESSING
Resol. enhancement -0.6 Hz
FT size 65536
Total time 3 min, 30 sec

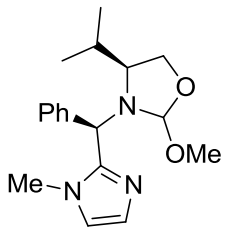


Sample: OAD-2-248-pure-C13
File: exp

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr11"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.309 sec
Width 30165.9 Hz
512 repetitions
OBSERVE C13, 125.6677725 MHz
DECOUPLE H1, 499.7745112 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 42 sec





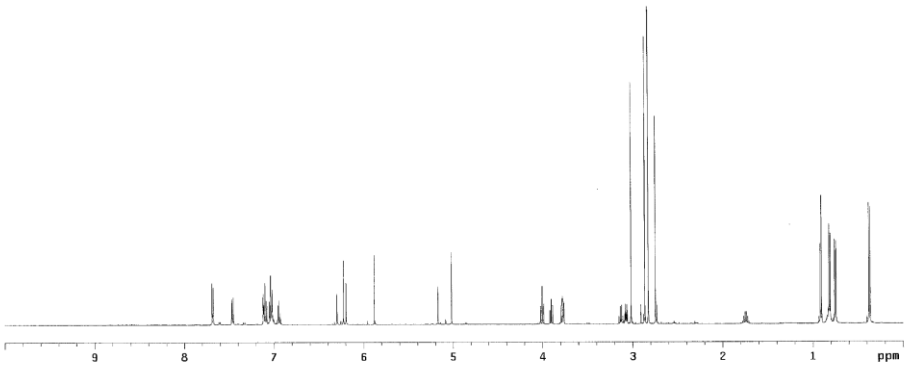
(4*S*)-4-Isopropyl-2-methoxy-3-((*R*)-(1-methyl-1H-imidazol-2-yl)(phenyl)methyl)-oxazolidine (2.45) (56:44 dr). To a solution of (*S*)-3-methyl-2-(((*R*)-(1-methyl-1H-imidazol-2-yl)(phe nyl)methyl)amino)butan-1-ol (1.0 g, 4.0 mmol) in anhydrous methanol (16 mL) under nitrogen atmosphere was added *N*,*N*-dimethylformamide dimethyl acetal (0.53 mL, 4.0 mmol). The reaction was stirred at 50 °C overnight, concentrated, redissolved in MeOH (16 mL), and stirred for 2 hours, at which time ^{1}H NMR analysis showed complete conversion to product. The solvent was removed under vacuum and extraction with degassed pentanes afforded the product as an orange oil (820 mg, 65%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96-7.66 (m, 1.12H), 7.47-7.44 (m, 0.88H), 7.12-6.92 (m, 3H), 6.29 (d, 0.44H, *J*= 1.5), 6.22 (s, 0.56H), 6.19 (d, 0.56H, *J*= 1.5), 5.88 (s, 0.44H), 5.17 (s, 0.44H), 5.01 (s, 0.56H), 4.00 (t, 0.56H, *J*= 8.0), 3.90 (t, 0.44H, *J*= 8.0), 3.15-3.10 (m, 0.44H), 3.08-3.05 (m, 0.56H), 3.01 (s, 1.32H), 2.86 (s, 1.68H), 2.82 (s, 1.68H), 2.74 (s, 1.32H), 1.77-1.70 (m, 1H), 0.91 (d, 1.68H, *J*= 7.0), 0.81 (d, 1.32H, *J*= 6.5), 0.75 (d, 1.32H, *J*= 6.5), 0.37 (d, 1.68H, *J*=7.0); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.9, 146.4, 140.4, 139.2, 129.5, 129.4, 129.3, 120.6, 119.6, 119.5, 112.4, 111.7, 66.7, 65.3, 64.3, 63.9, 59.6, 59.3, 52.3, 51.1, 31.6, 31.5, 30.5, 29.5, 29.4, 29.3, 19.5, 19.2, 19.1, 17.2, 14.3, 14.2; IR: 2953, 1490, 1279, 1157, 1055, 962, 700 cm^{-1}; HRMS Calcd. for $C_{17}H_{22}N_3O$ [M-OMe]: 284.1762, Found: 284.1748.

Sample: OAD-XS-3-46-pure-H1
File: exp

Pulse Sequence: s2pul

Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8808476 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

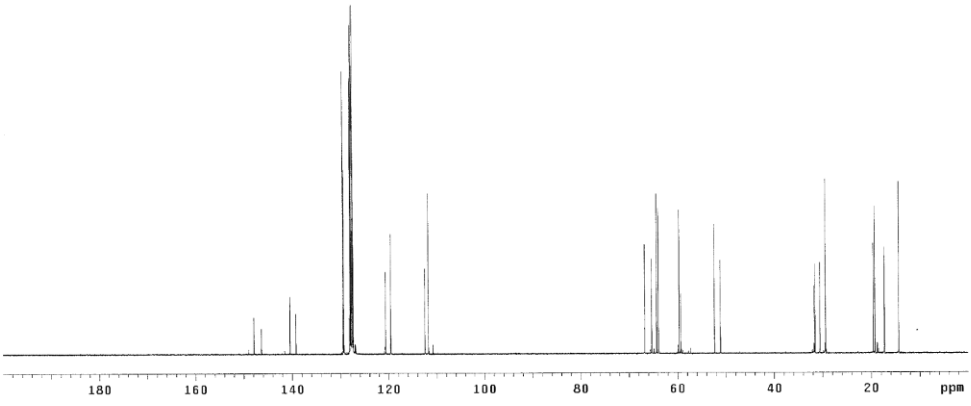


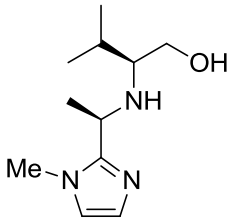
Sample: OAD-XS-3-46-pure-H1
File: exp

Pulse Sequence: s2pul

Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

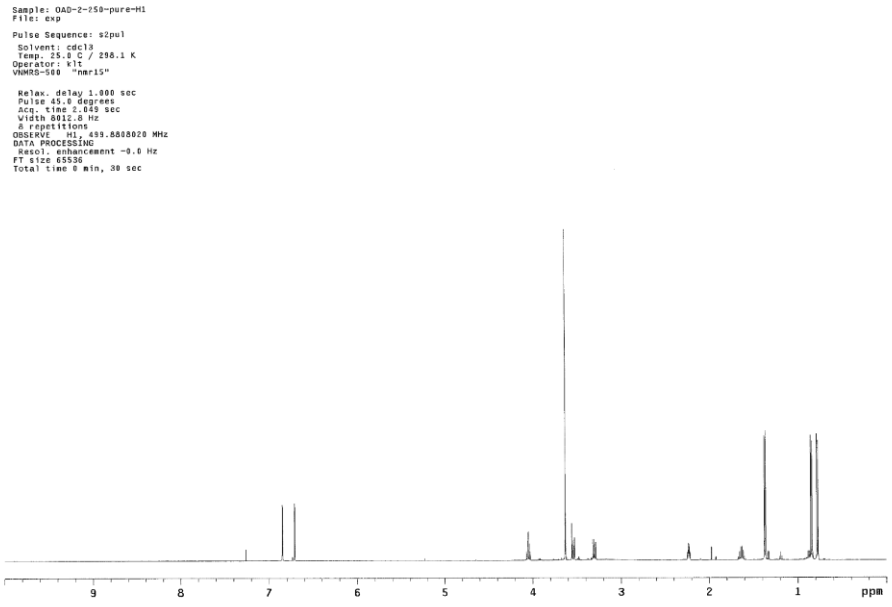
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.360 sec
Width 30487.8 Hz
512 repetitions
OBSERVE C13, 125.6951390 MHz
DECOUPLE H1, 499.8833464 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 38 sec

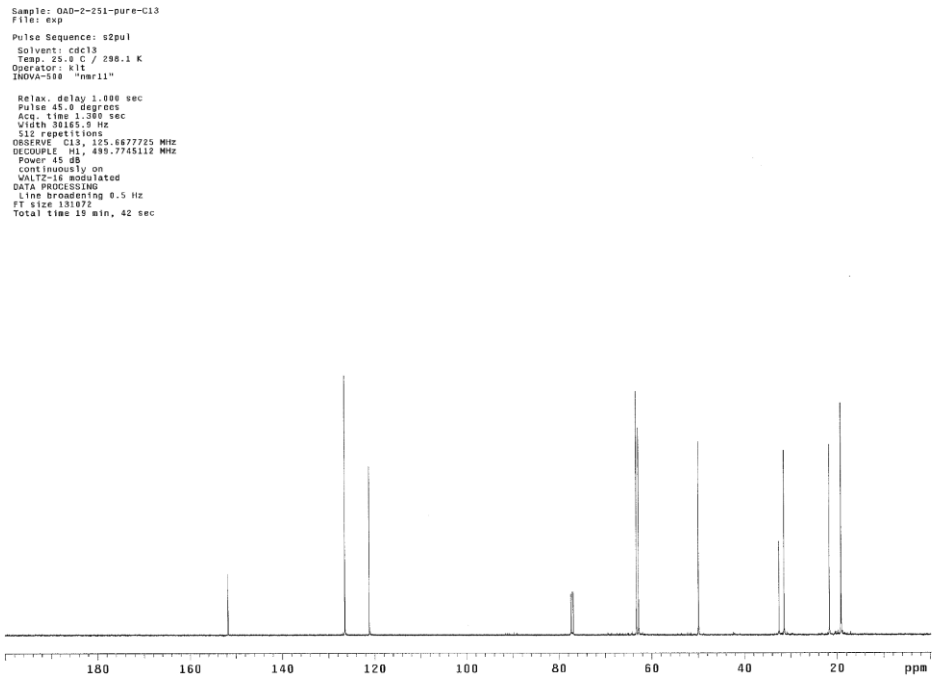


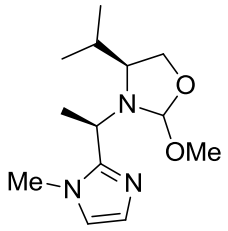


(*S*)-3-Methyl-2-(((*R*)-1-(1-methyl-1H-imidazol-2-yl)ethyl)amino)butan-1-ol.[2] To a stirring solution of (*S*)-Valinol (2.0 g, 20 mmol) in anhydrous diethyl ether (10 mL) under nitrogen atmosphere was added a solution of acetaldehyde (1.1 mL, 20 mmol) in anhydrous diethyl ether (10 mL). $MgSO_4$ (4.0 g) was added, and the solution was stirred at room temperature for 1 hour. ^{1}H NMR analysis showed that the imine had formed. Solvent was pumped off and residue was redissolved in anhydrous diethyl ether (20 mL). In another oven-dried glass reaction flask, to the solution of *N*-methylimidazole (5.6 mL, 70 mmol) in anhydrous diethyl ether (50 mL) under nitrogen atmosphere was added *n*-butyllithium (7.0 mL, 10 M in hexanes, 70 mmol) dropwise at –78 °C. The solution was stirred at –78 °C for 30 minutes, and then slowly cannula transferred into the solution of pre-formed imine at –78 °C. The resulting mixture was stirred at –78 °C for 2 hours and then at room temperature overnight. Aqueous NH_4Cl was added slowly to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (3:1 Hex/EtOAc to 100% EtOAc) afforded pure product as a yellow oil (971 mg, 23%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.84 (d, 1H, *J*= 1.2), 6.72 (d, 1H, *J*= 1.2), 3.9 (q, 1H, *J*= 7.0), 3.55 (s, 3H), 3.47 (dd, 1H, *J*= 3.5, 11.0), 3.30 (dd, 1H, *J*= 8.5, 11.0), 2.29-2.25 (m, 1H), 1.61-1.56 (m, 1H), 1.31 (d, 3H,

J= 7.0), 0.87 (d, 3H, *J*= 6.5), 0.87 (d, 3H, *J*= 6.5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.7, 126.5, 121.2, 63.3, 62.8, 49.9, 32.5, 31.4, 21.6, 19.2, 19.1; IR: 3234, 2957, 1492, 1281, 1121, 1052, 725 cm^{-1}; HRMS Calcd. for $C_{11}H_{22}N_3O$ $[M+H]^+$: 212.1762, Found: 212.1764.

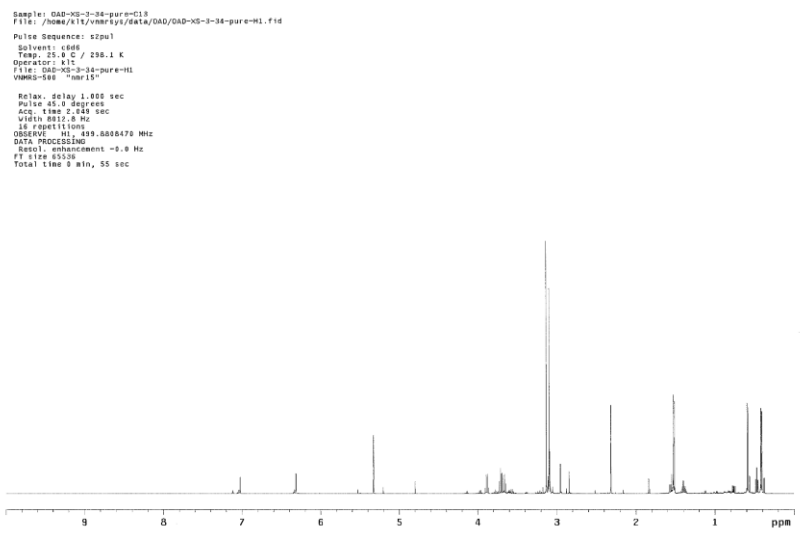


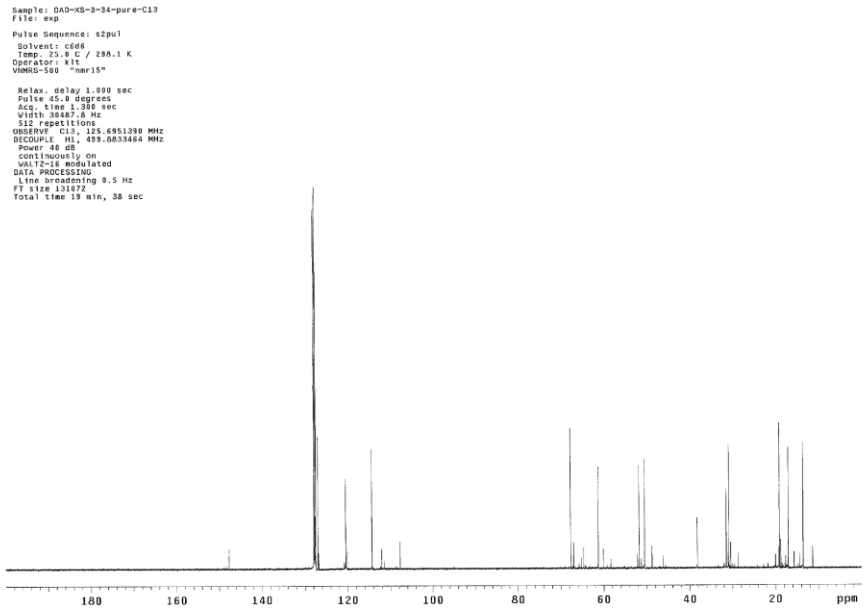


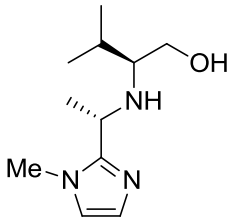


(4*S*)-4-Isopropyl-2-methoxy-3-((*R*)-1-(1-methyl-1H-imidazol-2-yl)ethyl)oxazolidine (2.46) (90:10 dr). To a solution of (*S*)-3-methyl-2-(((*R*)-1-(1-methyl-1H-imidazol-2-yl)ethyl)amino)butan-1-ol (902 mg, 4.3 mmol) in anhydrous methanol (17 mL) under nitrogen atmosphere was added *N*,*N*-dimethylformamide dimethyl acetal (0.57 mL, 4.3 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (17 mL), and another 0.5 equivalence of *N*,*N*-dimethylformamide dimethyl acetal was added to the

mixture. The reaction was again stirred at room temperature for 2 hours until ^{1}H NMR analysis showed all the substrate was consumed and product had formed. The solvent was removed under vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentanes to afford the pure product as a yellow oil (380 mg, 35%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.04 (d, 0.1H, *J*= 1.5), 7.02 (d, 0.9H, *J*= 1.0), 6.33 (d, 0.1H, *J*= 1.5), 6.31 (d, 0.9H, *J*= 1.0), 5.53 (s, 0.1H), 5.33 (s, 0.9H), 3.97 (q, 0.1H, *J*= 6.5), 3.88 (q, 0.9H, *J*= 6.5), 3.72-3.64 (m, 1.8H), 3.62-3.56 (m, 0.2H), 3.13 (s, 2.7H), 3.10-3.08 (m, 1H), 3.09 (s, 2.7H), 2.95 (s, 0.3H), 2.84 (s, 0.3H), 1.83 (d, 0.3H, *J*= 6.5), 1.51 (d, 2.7H, *J*= 6.5), 1.43-1.36 (m, 1H), 0.586 (d, 2.7H, *J*= 7.0), 0.559 (d, 0.3H, *J*= 7.0), 0.412 (d, 2.7H, *J*= 7.0), 0.380 (d, 0.3H, *J*= 7.0); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.7, 126.9, 120.4, 114.3, 112.0, 107.7. 67.6, 67.0, 61.2, 60.1, 52.2, 51.7, 50.4, 48.7, 46.0, 38.2, 31.4, 30.8, 30.4, 28.7, 19.0, 18.7, 17.1, 15.6, 13.5, 11.3; IR: 2954, 1496, 1281, 1153, 1068, 970, 728 cm^{-1}; HRMS Calcd. for $C_{12}H_{20}N_3O$ [M-OMe]: 222.1606, Found: 222.1615.


Sample: DAD-XS-3-34-pure-C13
File: /home/klt/vnmrsys/data/DAD/DAD-XS-3-34-pure-H1.fid
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: klt
File: DAD-XS-3-34-pure-H1
VNMRS-500 "nmr15"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.849 sec
Width 8812.8 Hz
16 repetitions
OBSERVE H1, 499.8808470 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 55 sec
9
8
7
6
5
4
3
2
1
ppm


Sample: DAD-XS-3-34-pure-C13
File: exp
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
512 repetitions
OBSERVE C13, 125.6951390 MHz
DECOUPLE H1, 499.8833464 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 38 sec
180
160
140
120
100
80
60
40
20
ppm

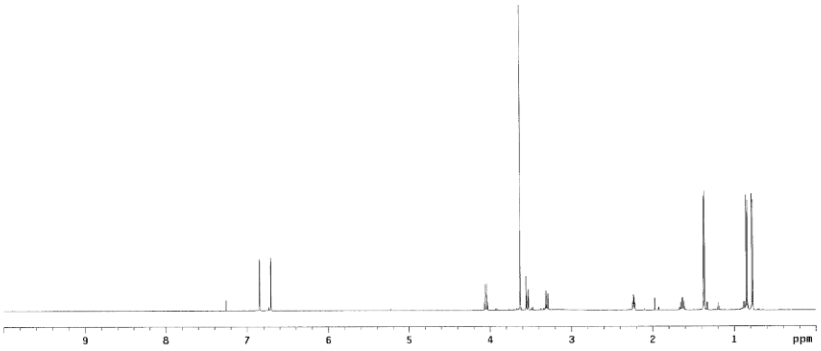


(*S*)-3-Methyl-2-(((*S*)-1-(1-methyl-1H-imidazol-2-yl)ethyl)amino)butan-1-ol.[2] To a solution of *N*-methyl-imidazole-2-carboxaldehyde (3.42 g, 31.0 mmol) in benzene (90 mL) was added (*S*)-Valinol (3.20 g, 10.0 mmol) and 3Å molecular sieves (1.4 g). After refluxing for 24 hours, the reaction was cooled to room temperature and the solvent was removed in vacuo. The resulting residue was redissolved in anhydrous diethyl ether (180 mL). The solution was cooled to -78 ^{o}C and MeLi (31 mL, 3.0M in dimethoxyethane, 93 mmol) was added dropwise. The reaction was allowed to stir for 24 hours before quenching with aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 10:1) afforded pure product as a yellow oil (2.5 g, 38%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.84 (d, 1H, *J*= 1.5), 6.70 (d, 1H, *J*= 1.5), 4.04 (q, 1H, *J*= 6.5), 3.63 (s, 3H), 3.55-3.52 (m, 1H), 3.31 (dd, 1H, *J*= 6.5, 11.0), 2.25-2.22 (m, 1H), 1.65-1.61 (m, 1H), 1.36 (d, 3H, *J*= 6.5), 0.845 (d, 3H, *J*= 7.0), 0.777 (d, 3H, *J*= 7.0); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.8, 126.8, 120.9, 62.2, 60.7, 47.9, 32.7, 29.3, 21.4, 19.4, 18.8; IR: 3311, 2956, 1467, 1280, 1049, 725 cm^{-1}; HRMS Calcd. for $C_{11}H_{22}N_3O$ $[M+H]^+$: 212.1762, Found: 212.1769.

Sample: OAD-2-250-pure-H1
File: exp

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

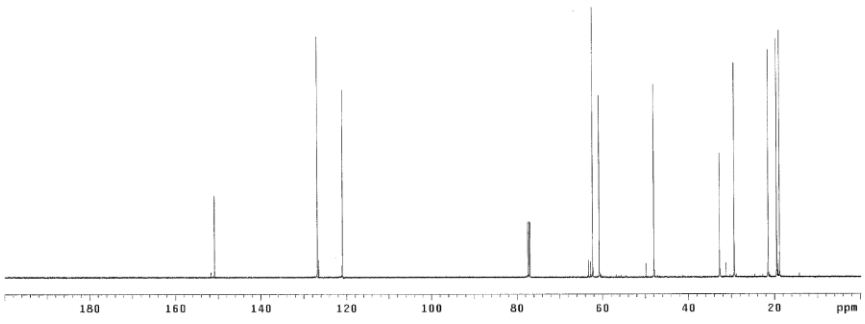
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 8012.8 Hz
 8 repetitions
OBSERVE   H1, 499.8888020 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

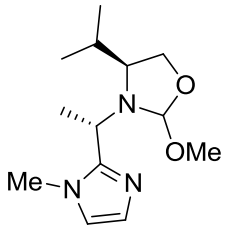


Sample: OAD-2-250-pure-C13
File: exp

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: klt
INOVA-500 "nmr11"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 30165.9 Hz
 512 repetitions
OBSERVE   C13, 125.6677725 MHz
DECOUPLE   H1, 499.7745112 MHz
 Power 45 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 42 sec





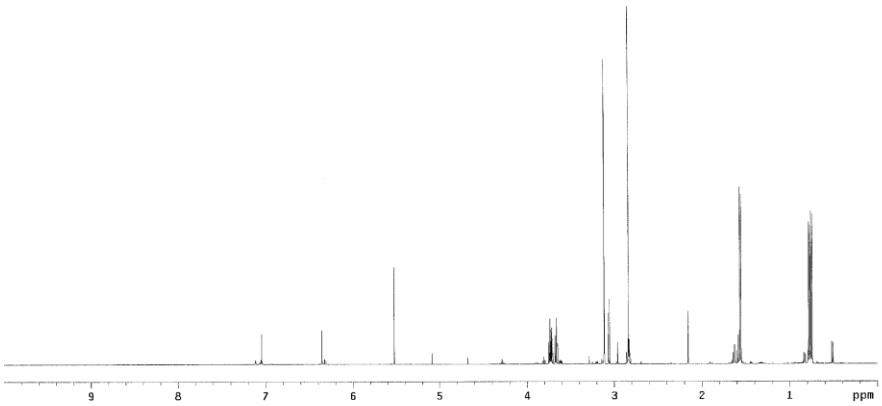
(4*S*)-4-Isopropyl-2-methoxy-3-((*S*)-1-(1-methyl-1H-imidazol-2-yl)ethyl)oxazolidine (2.47) (99:1 dr). To a solution of (*S*)-3-methyl-2-(((*S*)-1-(1-methyl-1H-imidazol-2-yl)ethyl)amino)butan-1-ol (4.3 g, 18 mmol) in anhydrous methanol (36 mL) under nitrogen atmosphere was added *N*,*N*-dimethylformamide dimethyl acetal (12 mL, 90 mmol). The reaction was stirred at 50 °C overnight, concentrated, redissolved in methanol, and stirred for 2 hours, at which time, ^{1}H NMR analysis showed complete conversion to product. The solvent was removed under vacuum, and Kugelrohr distillation (130 °C @ 0.05 mm Hg) afforded the product as a colorless oil (3.7 g, 73%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.04 (d, 1H, *J*= 1.5), 6.35 (d, 1H, *J*= 1.5), 5.52 (s, 1H), 3.75-3.64 (m, 3H), 3.11 (s, 3H), 2.85-2.81 (m, 1H), 2.83 (s, 3H), 1.66-1.59 (m, 1H), 1.55 (d, 3H, *J*= 7.0), 0.77 (d, 3H, *J*= 7.0), 0.75 (d, 3H, *J*= 7.0); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.0, 126.9, 120.8, 111.5, 66.9, 65.1, 51.8, 51.2, 32.0, 30.9, 19.9, 17.6, 13.5; IR: 2954, 1281, 1155, 1056, 971, 728 cm^{-1}; HRMS Calcd. for $C_{12}H_{20}N_3O$ [M-OMe]: 222.1606, Found: 222.1615.

Sample: OAD-XS-3-20-pure-H1
File: exp

Pulse Sequence: s2pul

Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

Relax. delay 1.800 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6012.8 Hz
8 repetitions
OBSERVE H1, 499.8808479 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

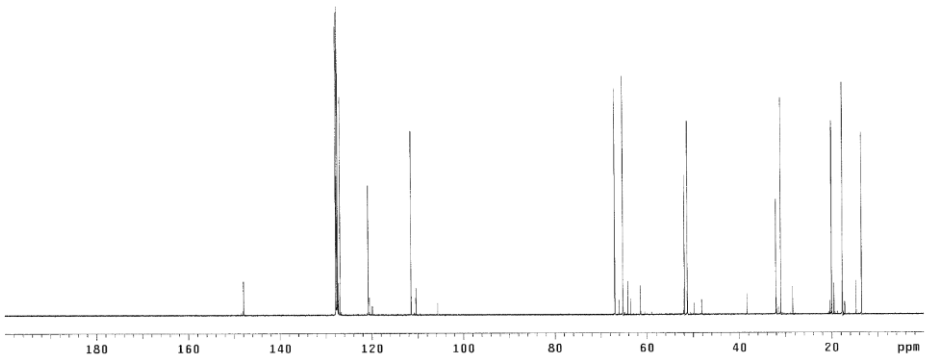


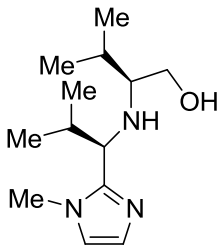
Sample: OAD-XS-3-20-pure-C13
File: exp

Pulse Sequence: s2pul

Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: klt
VNMRS-500 "nmr15"

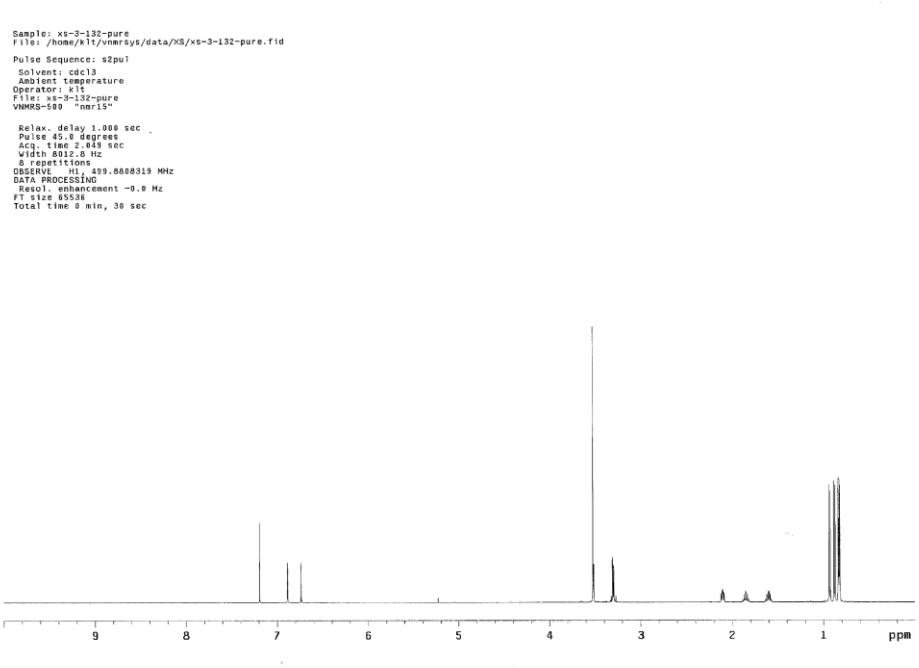
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.360 sec
Width 30487.8 Hz
512 repetitions
OBSERVE C13, 125.6951390 MHz
DECOUPLE H1, 499.8833464 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 38 sec

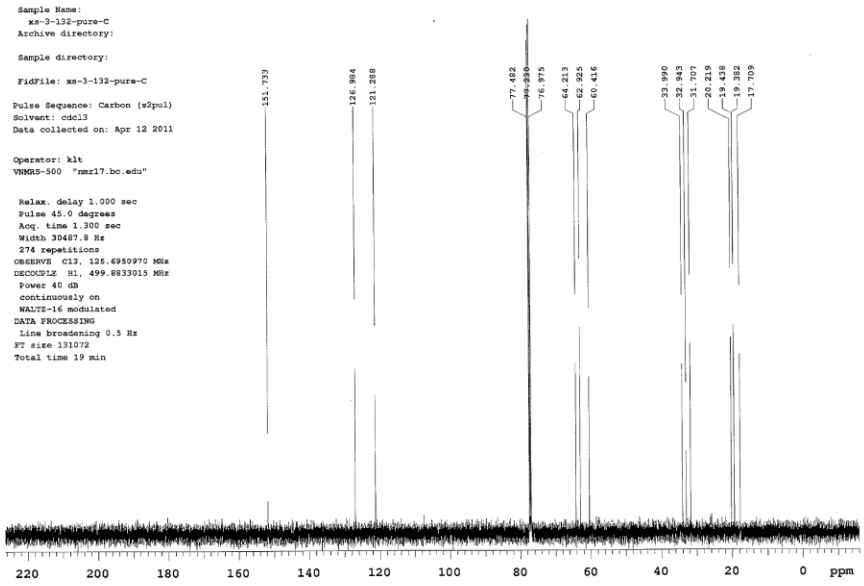


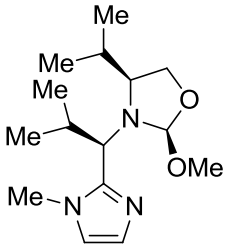


(*S*)-3-Methyl-2-((*R*)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propylamino)butan-1-ol.[2] To a stirring solution of (*S*)-Valinol (6.8 g, 66 mmol) in anhydrous diethyl ether (66 mL) under nitrogen atmosphere was added a solution of isobutyraldehyde (4.8 g, 66 mmol) in anhydrous diethyl ether (66 mL). $MgSO_4$ (13 g) was added, and solution was stirred at room temperature overnight. ^{1}H NMR analysis showed that the imine had formed. In another oven-dried glass reaction flask, to the solution of *N*-methylimidazole (19 g, 230 mmol) in anhydrous THF (160 mL) under nitrogen atmosphere was added *n*-butyllithium (23 mL, 10 M in hexanes, 230 mmol) dropwise at –78 °C. The solution was stirred at –78 °C for 30 minutes, and then slowly cannula transferred into the solution of pre-formed imine at –78 °C. The resulting mixture was stirred at –78 °C for 2 hours and then at room temperature overnight. Aqueous NH_4Cl was added slowly to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (2:1 Hex/EtOAc to 100% EtOAc) afforded pure product as colorless oil (12 g, 76%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (d, 1H, *J* = 1.2), 6.78 (d, 1H, *J* = 1.2), 3.56 (m, 4H), 3.35 (d, 1H, *J* = 1.2), 3.34 (d, 1H, *J* = 3.9), 2.15 (m, 1H), 1.90 (m, 1H), 1.64 (m, 1H), 0.98 (d, 3H, *J* = 6.8), 0.93 (d, 3H, *J* = 6.8), 0.88 (d, 3H, *J* = 2.9), 0.87 (d, 3H, *J* = 2.9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.7,

127.0, 121.3, 64.2, 62.9, 60.4, 34.0, 32.9, 31.7, 20.2, 19.5, 19.4, 17.7; IR: 2956, 2871, 1488, 1468, 1280, 1045, 725 cm^{-1}; HRMS Calcd. for $C_{13}H_{26}N_3O$ $[M+H]^+$: 240.2076, Found: 240.2087.

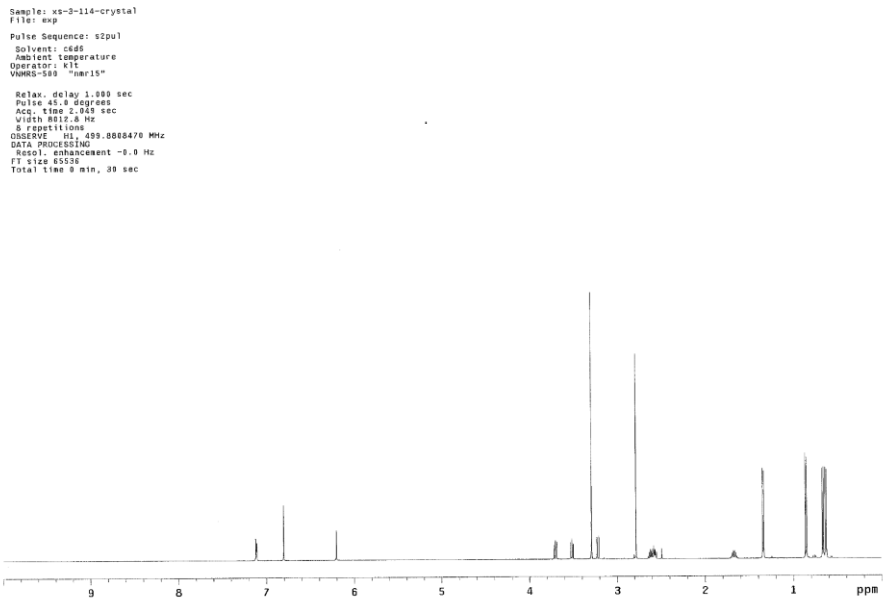


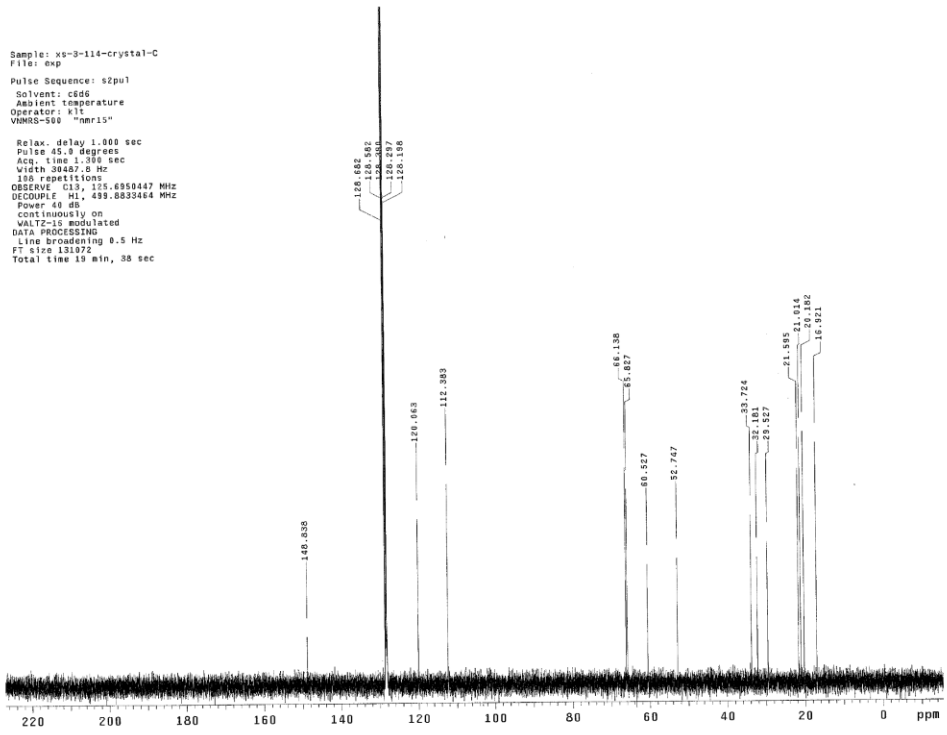




(*4S*)-4-Isopropyl-2-methoxy-3-((*R*)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propyl)-oxazolidine (2.48) (99:1 dr). To a solution of (*S*)-3-methyl-2-(((*R*)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propyl)amino)butan-1-ol (4.3 g, 18 mmol) in anhydrous methanol (36 mL) under nitrogen atmosphere was added *N*,*N*-dimethylformamide dimethyl acetal (12 mL, 90 mmol). The reaction was stirred at 50 °C overnight, concentrated, redissolved in methanol, and stirred for 2 hours, at which time, ^{1}H NMR analysis showed complete conversion to product. The solvent was removed under vacuum, and Kugelrohr distillation (130 °C @ 0.05 mm Hg) afforded the product as a

colorless oil (3.7 g, 73%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12 (d, 1H, *J* = 1.2), 6.80 (s, 1H), 6.20 (d, 1H, *J* = 1.2), 3.70 (dd, 1H, *J* = 9.0, 8.1), 3.52 (dd, 1H, *J* = 7.8, 7.1), 3.29 (s, 3H), 3.22 (d, 1H, *J* = 10.8), 2.78 (s, 3H), 2.60 (m, 2H), 1.68 (m, 1H), 1.34 (d, 3H, *J* = 6.4), 0.85 (d, 3H, *J* = 6.8), 0.66 (d, 3H, *J* = 6.8), 0.63 (d, 3H, *J* = 6.6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.8, 128.7, 120.1, 112.4, 66.1, 65.8, 60.5, 52.7, 33.7, 32.2, 29.5, 21.6, 21.0, 20.2, 16.9; IR: 2956, 1470, 1281, 1052, 964 cm^{-1}; HRMS Calcd. for $C_{14}H_{24}N_3O$ [M-OMe]: 250.1919, Found: 250.1926.





X. References

1) Plater, M. J.; Barnes, P.; McDonald, L. K.; Wallace, S.; Archer, N.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B. *Org. Biomol. Chem.* **2009**, *7*, 1633.

2) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull*. **1983**, *31*, 2895.

3) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould A. E.; Furrow, M. E.; Jacobsen, N. E. *J. Am. Chem. Soc.* **2002**, *124*, 1307.