Synthesis and Immobilization of Catalysts on Polymer Supports and its Application in Chemo- and Enantioselective Oxidation Reactions

Dissertation

des Doktorgrades der Naturwissenschaften (Dr. rer. nat.)

der Naturwissenschaftlichen Fakultät IV - Chemie und Pharmazie

der Universität Regensburg

vorgelegt von

Tamilselvi Chinnusamy

Aus
Suriampalayam (Indien)

Regensburg - 2010

Diese Arbeit wurde angeleitet von Prof. Dr. O. Reiser

Promotionsgesuch eingereicht am: 20th May, 2010

Tag der mündlichen Prüfung: 18th June, 2010

Prüfungsausschluß: Prof. Dr. A. Buschauer (Vorsitzender)
Prof. Dr. O. Reiser (1. Gutachter)
Prof. Dr. B. König (2. Gutachter)
Prof. Dr. A. Pfitzner (3. Prüfer)

Die vorliegende Arbeit wurde unter der Leitung von Herrn Prof. Dr. O. Reiser in der Zeit von November 2006 bis December 2009 am Institut für Organische Chemie der Universität Regensburg angefertigt.

Herrn Prof. Dr. O. Reiser möchte ich für die Überlassung des äußerst interessanten Themas, die anregenden Diskussionen und stete Unterstützung während der Durchführung dieser Arbeit danken.

In memory of my beloved father

"தொட்டனைத் தூறும் மணற்கேணி மாந்தர்க்குக்
கற்றனைத் தூறும் அறிவு"
-திருக்குறள் (396)
திருவள்ளுவர் (~ கி. மு. முதலாம் நூற்றாண்டு)

"As deep you dig the sand spring flows
As deep you learn the knowledge grows"
-ThirukkuRaL (396)
Thiruvalluvar (~ BC 1st Century)

1 Introduction to oxidation chemistry

2 Synthesis of polymer supported catalysts *via* click chemistry

3 Asymmetric sulfoxidation using polymer supported Schiff base vanadium complexes

4 Kinetic resolution of α-hydroxy carbonyl compounds and pyridyl alcohols by fluorous tag clicked Schiff base vanadium complexes

5 Cyanosilylation of aldehydes using Fluorous tag immobilized Schiff base V(IV) complexes

6 Combination of perfluoroalkyl and triazoles; A new recovery strategy for TEMPO

7 A recyclable TEMPO catalyst for aerobic oxidation of sulfides to sulfoxides

8 Summary

9 Experimental part

10 Appendix

Abbreviations

Abs	absolute
Bn	benzyl
Bu	*n*-butyl
cat	catalytic
dr	diastereomeric ratio
DCM	dichloromethane
DIPEA	di(isopropyl)ethylamine
DMF	dimethyl formamide
ee	enantiomeric excess
eq	equivalents
EI	electronic ionization
Et	ethyl
EtOAc	ethyl acetate
h	hour
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry
^{i}Pr	*iso*-propyl
IR	infrared
L	ligand
M	metal
*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
min	minute
M.p	melting point
MS	molecular sieves
NMR	nuclear magnetic resonance
p-	para
Ph	phenyl
PPh_3	tri-phenyl phosphine
quant	quantitative
rac	racemic
rt	room temperature
sat.	saturated
t/(*tert*)	tertiary
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
Tf	trifluormethanesulfonate
^{t}Bu	*tert*-butyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number

1. Introduction to Oxidation Chemistry

1.1 Biological Oxidation

Oxidation reactions are of fundamental importance in nature, and are key transformations in organic synthesis.[1] The selective oxidation of organic molecules is vital to biological systems. All aerobic organisms utilize molecular oxygen to perform cellular respiration. These redox processes with oxygen are mediated by metalloenzymes, which can be divided into two classes (Figure 1), i.e. oxygenases and oxidases. Oxygenases catalyze by direct incorporation of oxygen into the substrate *via* an intermediate metal-oxo species **1** resulting subsequently in a reduced metal species **2**. In contrast, oxidases (metal oxidant **3**) catalyze by the removal of hydrogen from a substrate with the involvement of oxygen as a hydrogen acceptor. In both the cases, water or hydrogen peroxide is the byproduct.[3]

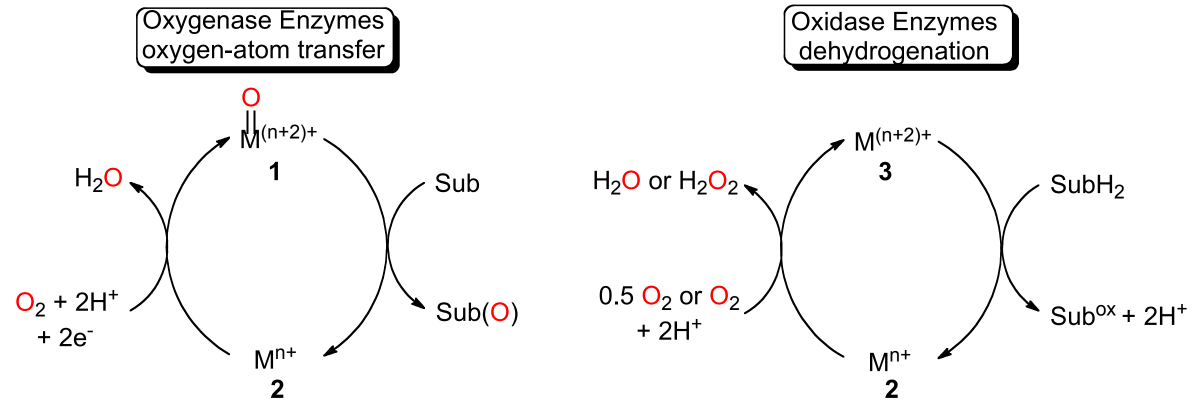
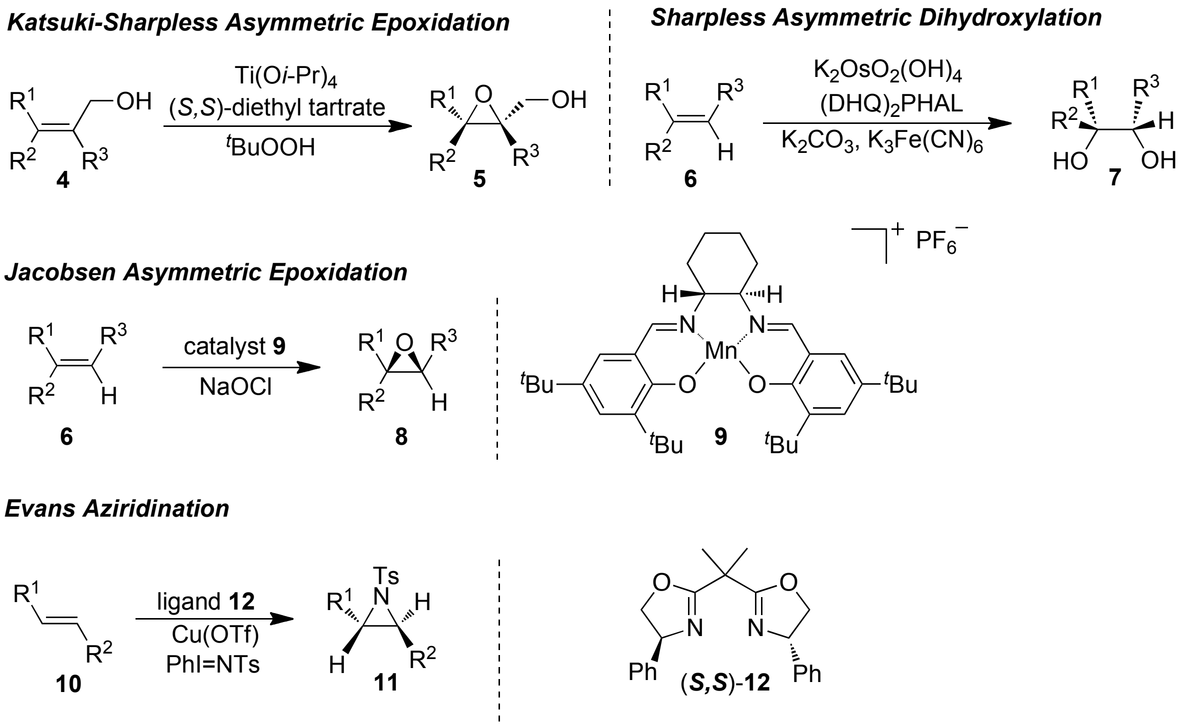


Figure 1. Oxygenase and oxidase enzymes.[2]

1.2 Catalytic Asymmetric Oxidations

1.2.1 Heteroatom transfer asymmetric oxidations

Asymmetric catalytic oxidation chemistry has greatly impacted organic synthesis.[4] Some reactions of particular consequences are shown in Scheme 1 that include the Katsuki-Sharpless asymmetric epoxidation (**4**→**5**) (KSAE),[4a, b, 5] the Sharpless dihydroxylation (**6**→**7**),[6] the Katsuki-Jacobsen epoxidations (**6**→**8**),[4b, 7] and the Evans aziridinations (**10**→**11**).[8] There is no doubt that the KSAE reaction not only covered the way for future directions in enantioselective oxidation chemistry, but also opened the door to a wide range of other catalytic asymmetric reactions. Moreover, the introduction of these reactions led to innumerable advances in the construction of complex molecules by *de novo* asymmetric synthesis. All of these reactions shown in Scheme 1 are examples of oxidations by virtue of heteroatom transfer (oxygenase-type reaction).[9]



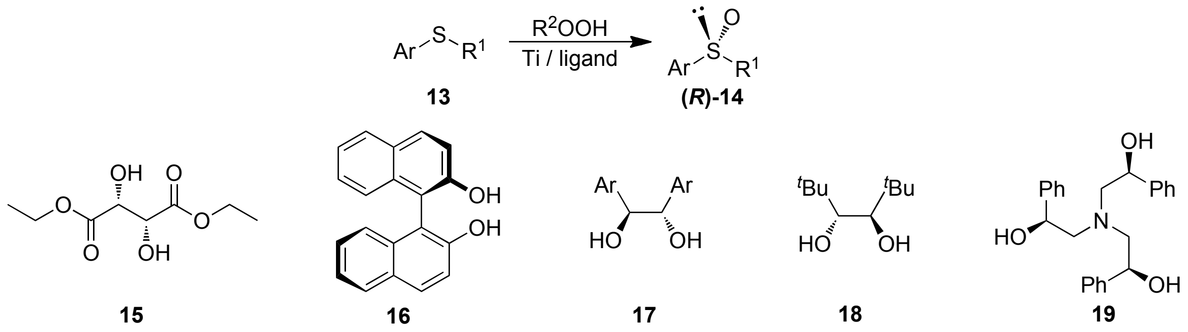
Scheme 1: Heteroatom transfer asymmetric oxidations.

1.2.1.1 Asymmetric sulfoxidation

Catalytic asymmetric sulfoxidation also fall into the category of heteroatom transfer reaction such as an oxygenase-type reaction. Enantiomerically pure sulfoxides are very important chiral auxiliaries in asymmetric synthesis, bioactive ingredients in the pharmaceutical industry and more recently as chiral ligands in asymmetric catalysts.[10]

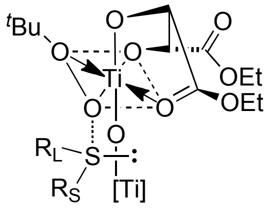
1.2.1.2 Previous catalytic asymmetric sulfoxidation

In 1984, Kagan[11] and Modena[12] simultaneously reported nearly identical system for the oxidation of prochiral sulfides **13** using the modified procedure of the sharpless titanium catalyzed asymmetric epoxidation. Kagan and co-workers discovered that addition of stoichiometric amounts of water to the catalyst was crucial to achieve enantioselectivity in the oxidation of sulfides. Yields and enantioselectivites were high for aryl-alkyl sulfoxides **14** and moderate for dialkyl sulfoxides by using a 1:2:1 ratio of $Ti(O\textit{i}\text{-}Pr)_4$, (*R*,*R*)-diethyl tartrate **15** and water with *tert*-butyl hydroperoxide (TBHP) as stoichiometric oxidant.[11a, 13] While the replacement of TBHP by cumylhydroperoxide led to significant improvement in enantiomeric excess of the sulfoxide.[11b, 14] Further optimizations of ligand **15** have allowed for a decrease in catalyst loading and further improvement in enantioselectivity.[13, 15]



Scheme 2: Chiral diols and triols mediated catalytic asymmetric sulfoxidation.

Modena and co-workers modified the Sharpless protocol for the asymmetric oxidation of allylic alcohols for sulfide oxidation by additing excess of diethyl tartrate **15**.[12] Yields and selectivities were nearly identical to those reported by Kagan and co-workers. The mechanisms of the Kagan or Modena systems are very similar and NMR studies have demonstrated a great complexity for the species in equilibrium in solution and the existence of a peroxotitanium species **20** has been postulated (Figure 2).[16]

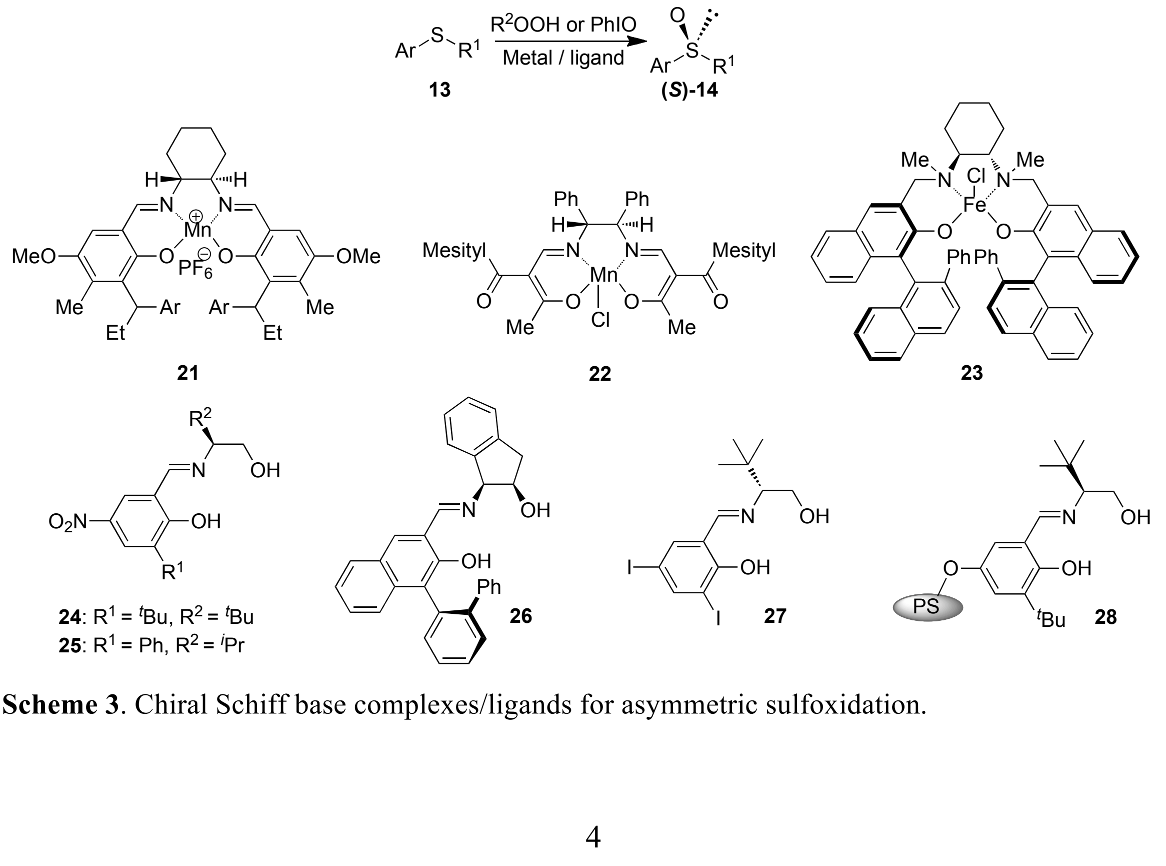


20

Figure 2: Postulated mechanism for asymmetric oxidation of sulfides.[16]

Most importantly, the protocol developed by Kagan and co-workers has been used on large scales to prepare enantiomerically pure sulfoxides of industrial importance.[17] Uemura reported a significant advances in the titanium-catalyzed oxidation of sulfides.[18] Substituting binaphthol **16** for tartrate, Uemura and co-workers achieved, improved enantioselectivities with reduced catalyst loading for the synthesis of aryl-alkyl sulfoxides. In contrast to the reactions reported by Kagan, a large positive nonlinear effect was observed, implying a considerable difference in the structures of the respective active catalyst species. Additionally, it was observed that over time the concentration of sulfone in the reaction mixture, the product of a second oxidation, increased and the enantiomeric purity of the remaining sulfoxide also increased. This led Uemura to conclude that an initial moderately enantioselective oxidation process was benefiting from a secondary kinetic resolution in which the minor enantiomer was preferentially oxidized to the corresponding sulfone. Hutton *et al.* applied the reaction conditions to the ustiloxin family of cyclic peptides obtaining excellent selectivity up to >98% ee with moderate yield,[19] while other systems failed to give good results in terms of selectivity. On this series, Rossini *et al*,[20] Imamoto *et al*,[21] and Reetz *et al.*[22] employed Uemura's reaction conditions by modifying different C_2-symmetric 1,2-diols as ligand (**17** and **18**), which afforded the sulfoxide in up to 99% ee. Licini and Nugent screened the use of C_3-symmetric amine **19** as a ligand in combination with titanium for sulfoxidation, obtaining the *ee* values were up to 85%.[23]

A second major class of catalysts used in enantioselective oxidations of sulfides consists of metallo-Schiff base complexes (Scheme 3). Early efforts by Fujita[24] and Jacobsen[25] provided only low levels of enantioselectivity. Following those leads, Katsuki[26] could obtain the sulfoxides in up to 94% ee using manganese salen complex **21** with iodosobenzene as an oxidant. Mukaiyama *et al.*[27] have also studied the family of *β*-oxo aldiminato Mn(III) complex **22** using the combination of pivalaldehyde/molecular oxygen as an oxidant, but the enantioselectivity of the sulfoxides did not exceed 70%. A switch to iron as the metal source with tridentate Schiff base **26** and the use of lithium benzoates as additives allowed further optimization of this method and expanded the substrate scope.[28] Katsuki and co-workers have further advanced the metallo-Schiff base methodology in recent reports.[29] Using a very bulky and fully reduced salan ligand (a better donor than salen) complexed to iron **23**, Katsuki has developed a reaction using aqueous hydrogen peroxide to oxidize a range of sulfides. Notably, this catalyst is capable of oxidizing dialkyl sulfides in addition to aryl alkyl sulfides in high enantioselectivities up to >99%.



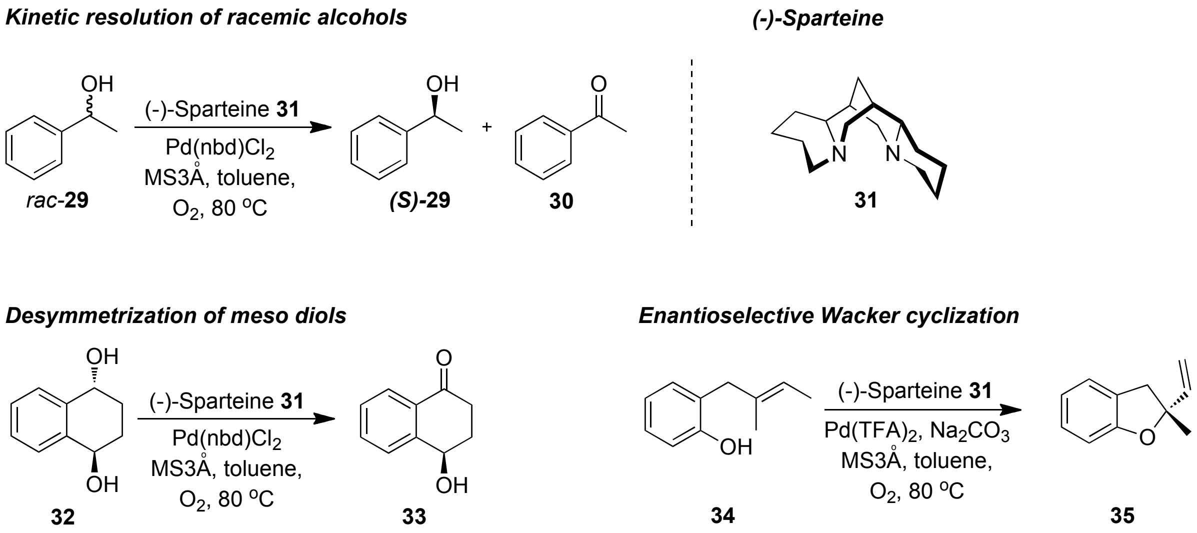
Scheme 3. Chiral Schiff base complexes/ligands for asymmetric sulfoxidation.

In 1995, Bolm *et al*. reported a catalyst formed by VO(acac)$_2$ and *N*-salicylidene aminoalcohol ligand **24**, which could achieve good yields and moderate enantioselectivities of aryl-alkyl sulfoxides under simple operational conditions using hydrogen peroxide as a terminal oxidant.[30] Later, several modifications of tridentate Schiff base ligands **25**, **26** had been reported by Skarzewski[31] and Katsuki.[32] However, the enantioselectivity did not exceed 80%. Ultimately, Jackson *et al.* obtained up to >99% ee using iodo substituted Schiff base ligand **27** utilizing the protocol originally developed by Bolm protocol.[33]

Recently, Barbarini *et al*. have reported the polymer supported chiral Schiff base-complex **28** that catalyzed asymmetric sulfoxidation reactions and the catalyst **28** could be recycled by simple filtration up to four times.[34] However, those immobilized vanadium complexes gave only moderate enantioselectivities (56-51% ee). Therefore, it is desirable to conduct further studies with the goal of making new solid supported catalysts and achieving information on their efficiency on the enantioselective sulfoxidation.

1.2.2 Non-heteroatom transfer asymmetric oxidations

Asymmetric oxidation chemistry that does not involve heteroatom transfer (oxidase type reactions, e.g dehydrogenations) have been relatively less explored. Until recently, few methods existed for catalytic asymmetric dehydrogenations (Scheme 4) such as enantioselective Wacker cyclizations (**34**→**35**),[35] desymmetrization of diols (**32**→**33**),[36] C-C bond forming cyclizations[37] and kinetic resolutions of racemic alcohols (*rac*-**29**→**30**+(*S*)-**29**).[36, 38] In general, dehydrogenation is a complex process, which often results in the formation of unsaturated bonds through the *destruction* of asymmetric centers.[9]

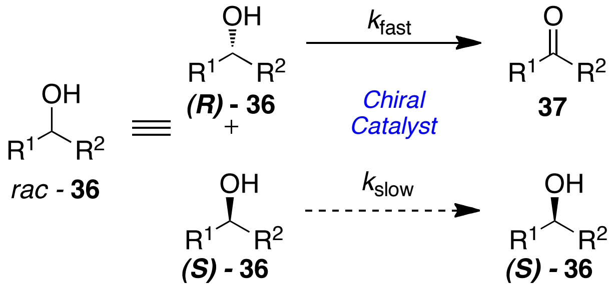


Scheme 4. Non-heteroatom transfer catalytic asymmetric oxidation reactions.

1.2.2.1 Kinetic Resolution

Secondary alcohols of defined absolute stereochemical configuration are key components for enantioselective synthesis. Kinetic resolutions[39] of racemic secondary alcohols represent an attractive catalytic route to these optically pure building blocks, especially in cases where other methods fail to give good enantioselectivity.

A kinetic resolution separates the two enantiomers of a racemic mixture by exploiting their unequal rates in a reaction with an enantiopure reagent or catalyst (Scheme 5). One enantiomer reacts faster with the enantiopure catalyst, with rate k_{fast}, to provide the product. The other enantiomer reacts much slowly (k_{slow}). Ideally, the reaction is terminated when all or most of the faster-reacting enantiomer has been converted to the product. The remaining enantioenriched starting material and product can be separated from the product by standard techniques. The selectivity factor '*s*' of a resolution is determined by measuring the relative rates of reaction of the two enantiomers ($k_{\text{rel}} = k_{\text{fast}} / k_{\text{slow}}$). In practice, the selectivity factor is usually determined by measuring the total conversion of starting material to product and enantiomeric excess of the recovered starting material.

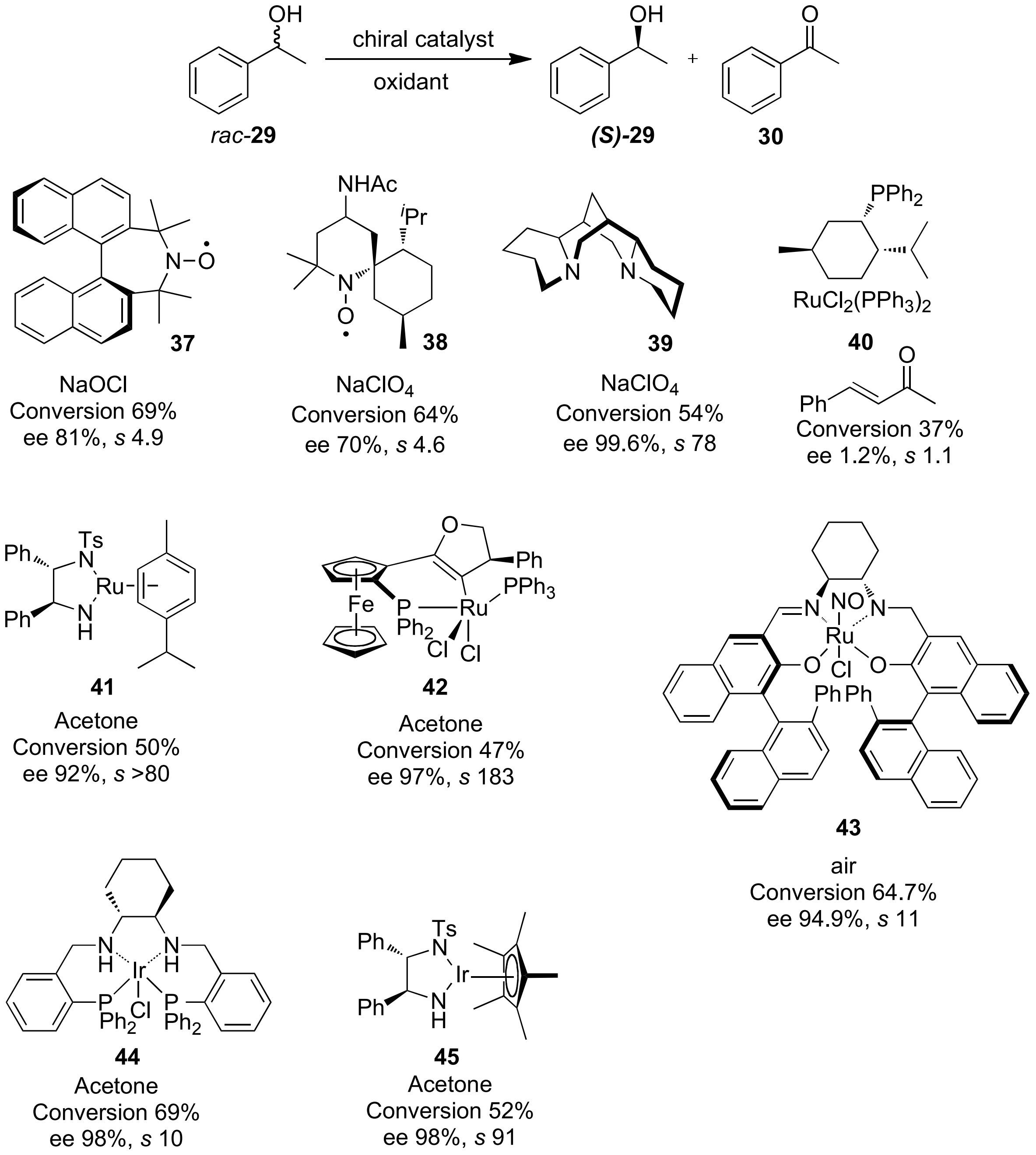


$$\boxed{\text{selectivity factor } s = \frac{k_{\text{fast}}}{k_{\text{slow}}} = \frac{\ln[(1\text{-conv})(1\text{-ee})]}{\ln[(1\text{-conv})(1\text{+ee})]}}$$

Scheme 5. Kinetic resolution overview.

1.2.2.2 Previous catalytic asymmetric alcohol oxidation

The pioneering work by Rychnovsky *et al.* using chiral binaphthyl nitrosyl radical **37** catalyses the oxidation of *sec*-alcohols to corresponding ketone with bleach as terminal oxidant, affording enantioenriched alcohols with moderate selectivity ($s \leq 7.1$).[40] Further studies with different nitrosyl radical did not improve the selectivity.[41] Bobbitt *et al.* described the enantioselective electrocatalytic oxidation of racemic *sec*-alcohols using chiral 1-azaspiro (5,5)-undecane-*N*-oxyl radical **38** with $NaClO_4$ as terminal oxidant.[42] The selectivity was also moderate (*s* 4.1-4.6). Later, improved selectivities was observed for this system using chiral binaphthyl radical **37** under the same reaction condition as reported by Tanaka *et al.*[43] Bobbitt *et al.* have also described an enantioselective electrocatalytic oxidation of racemic alcohols on a TEMPO-modified graphite felt electrode, using a chiral base such as (-)-spartenine **31** with excellent selectivities (*s* 56-184).[44]



Scheme 6. Asymmetric oxidation of 1-phenylethanol using chiral catalyst.

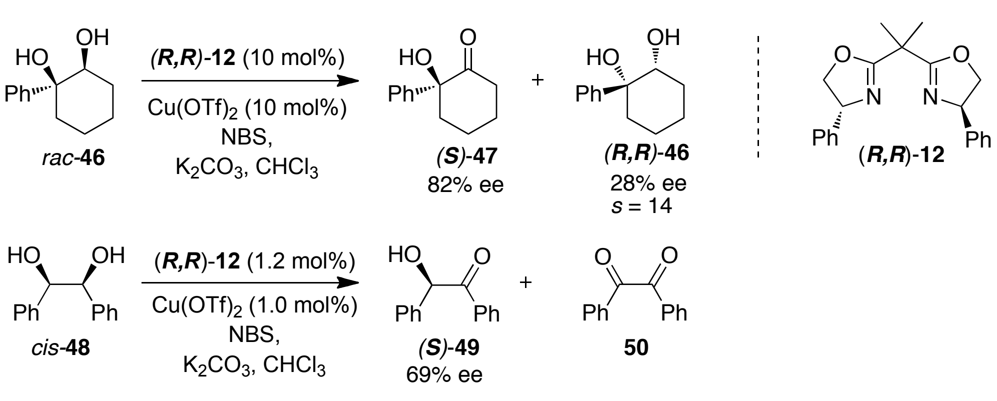
In 1976, the first catalytic enantioselection by chiral transition-metal complexes was reported by Okada *et al.* who was employing a combination of $RuCl_2(PPh_3)_2$ with (+)-

neomenthyldiphosphine **40** at 180 °C,[45] however, this system gave poor selectivity. Furthermore, Yoshikawa *et al.* reported desymmetrization of *meso*-diol by transfer hydrogenation using RhH((-)-DIOP)$_2$ with moderate selectivity.[46]

One of the most significant recent contributions to this area was made in 1997 when Noyori *et al.* reported the use of ruthenium arene complex **41** under transfer hydrogenation conditions with acetone as the terminal oxidant, excellent selectivities (*s* >100) were observed for most of the aryl alcohols.[47] Uemura *et al.* used almost similar system reported by Noyori with ferrocenylphosphine ruthenium catalyst **42**.[48] This system provided excellent selectivities even at low catalyst loading and TON approached 40000 and TOF >800000 h^{-1}. Katsuki *et al.* found optically active nitroso(salen)ruthenium(II)chloride **43** to be an efficient catalyst for an aerobic oxidation of racemic *sec*-alcohol under irradiation with a halogen or fluorescent lamp, which proceeded with good selectivity (*s* 11-20).[49] More recently, improvements in selectivity were observed using additives.[50]

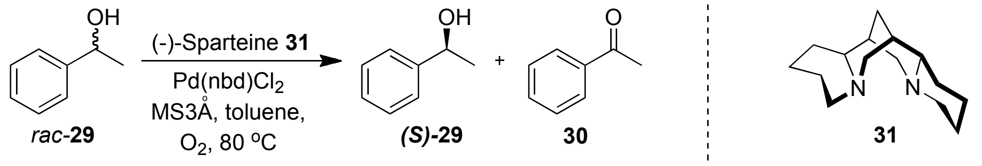
Gao *et al.* employed chiral diaminodiphosphine−Ir(I) complex **44** to efficiently catalyze enantioselective oxidation of racemic secondary alcohols in acetone. In the presence of base, oxidative kinetic resolution of the alcohols proceeded smoothly with excellent enantioselectivity under mild conditions.[51] Furthermore, Ikariya reported the aerobic oxidative kinetic resolution of racemic secondary alcohols with a chiral bifunctional Iridium catalyst **45** which proceeded smoothly under mild conditions to provide the corresponding chiral alcohols in up to 99% *ee* by using air as the terminal oxidant.[52]

Asymmetric oxidation of 1,2-diols using *N*-bromosuccinimide (NBS) in the presence of copper(II) triflate and (*R*,*R*)-Ph-BOX **12** has been exploited by Onomura et al (Scheme 7).[53] This oxidation was applicable to asymmetric desymmetrization of *meso*-hydrobenzoin **48** and racemic-cycloalkane-*cis*-1,2-diols **46** to afford optically active α-ketoalcohols with good to high enantiomeric excess.



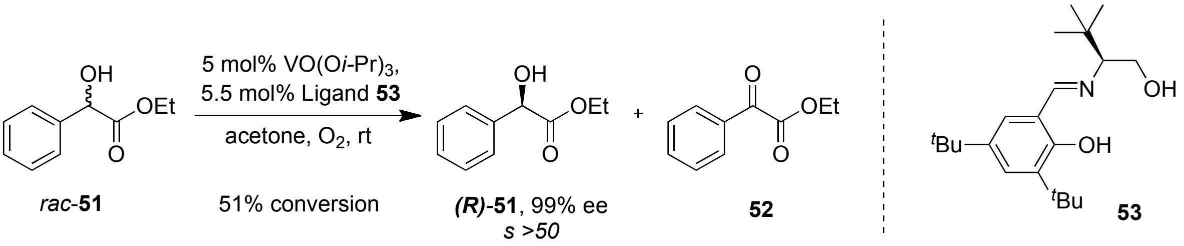
Scheme 7. Onomura copper catalyzed enantioselective oxidation.

Kinetic resolution of alcohols is especially attractive from a green point of view, if oxygen (i.e from air) as the direct and primary oxidant for the reaction can be used. There are many reports on the use of aerobic oxidation for the conversion of alcohols to ketones, however very few of these are enantioselective. One of the significant discoveries in this area was Pd(II)/(-)-sparteine system developed by Stoltz and Sigman which has helped to fuel interest in the field of such asymmetric oxidations (Scheme 8).[36, 38, 54] This system was capable of catalyzing the aerobic oxidative kinetic resolution of alcohols and particularly aryl alcohols to give products of remarkably high *ee*.



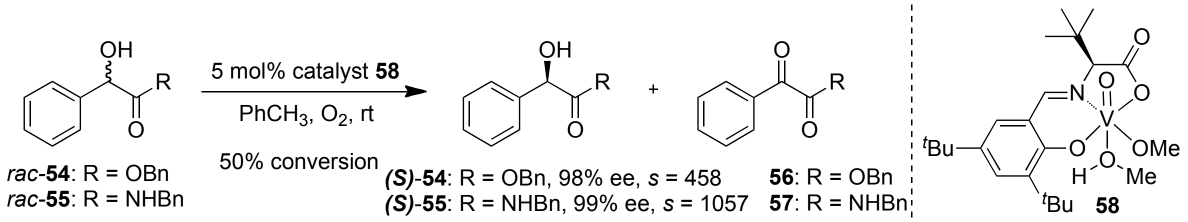
Scheme 8. Stoltz's Pd catalyzed oxidative kinetic resolution of alcohol.

Toste and co-workers have shown that chiral vanadium complexes catalyze the oxidative kinetic resolution (OKR) of alpha-hydroxy esters (Scheme 9).[55] In this report, a tridentate ligand **53** with an O,N,O-binding motif proved most effective. A number of α-hydroxy esters were efficiently resolved with selectivity factors ranging from 12 to >50. Recently, Toste applied this methodology to the enantioselective total synthesis of (–)-octalactin A.[56]



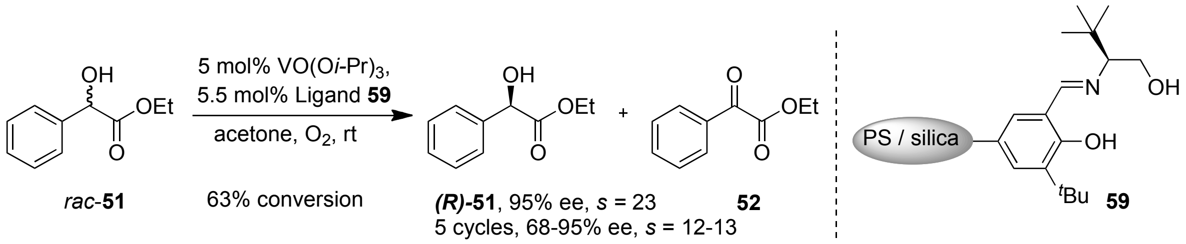
Scheme 9. Toste's vanadium catalyzed oxidative kinetic resolution of α-hydroxy alcohols.

Subsequently, Chen and co-workers have published OKR of both α-hydroxy esters and amides using a similar O,N,O- chelating tridentate ligand (scheme 10).[57] The procedure utilized 3–5 mol% of catalyst **58** in toluene at room temperature under oxygen atmosphere. This catalyst system was most efficient for the OKR of aryl α-hydroxy esters **54** and amides **55** with *s*-values ranging from 5 to 1057 with slightly higher s-values than Toste's method. Overall, the procedure generally resulted in higher *s*-values for the oxidation of benzyl amides relative to the benzyl esters. Vanadium clusters were found to be active catalysts for the aerobic oxidative kinetic resolution of α-hydroxythioesters.[58]



Scheme 10. Chen's vanadium catalyzed oxidative kinetic resolution of α-hydroxy alcohols and amides.

Recently, Shiels *et al*. demonstrated the use of polymeric and solid supported catalysts for asymmetric oxidation in order to get easier purification and catalyst recycling (Scheme 11).[59] Only few α–hydroxy esters were resolved with moderate to good selectivity (*s* 12-23) under the reaction condition reported by Toste *et al*. However, after recycling of supported catalyst was achieved by simple filtration for the oxidation of ethyl mandelate **51** with very low selectivity (*s* 12-13).



Scheme 11. Shiel's recyclable catalyst for OKR of ethyl mandelate.

1.3 Conclusion & aim of the thesis

Due to great interest in the present topic, inspired by biological systems, chemists have developed a number of enantioselective oxidation reactions based on small molecule catalysis. However, one important goal to be achieved to make such process attractive for industrial application is recovery and reuse of precious catalyst without diminishing the enantioselectivity of product and TON of the reaction. Despite efforts by a couple of research groups, a simple and efficient protocol to graft polymers on catalysts for enantioselective oxidation of sulfides and oxidative kinetic resolution of secondary alcohols has remained elusive. So, the efficient immobilizations of the catalyst and its applications on chemo- and enantioselective oxidations are the main theme of this thesis.[30]

1.4 Notes and References

1. (a) *Modern Oxidation Methods*. VCH-Wiley: Weinheim, 2004; (b) Hudlicky, M., *Oxidations in organic chemistry*. ACS: Washington, 1990.
2. Ebner, D. C. Development and application of the palladium-catalysed enantioselective oxidation of secondary alcohols. California Institue of Technology, Pasadena, California, 2009.
3. Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002,** *35*, 774-781.
4. (a) Johnson, R. A.; Sharpless, K. B., Catalytic Asymmetric Epoxidation of Allylic Alcohols In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed. Wiley & Sons: New York, 2000; pp 231-280; (b) Katsuki, T., Asymmetric Epoxidation of Unfunctionalized Olefins and Related Reactions. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed. Wiley & Sons: New York, 2000; pp 287-325; (c) Katsuki, T., *Asymmetric Oxidation Reactions*. Oxford Press: New York, 2001.
5. Katsuki, T., Epoxidation of Allylic Alcohols. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Springer-Verlag: Berlin, 1999; Vol. 2, pp 621-648.
6. (a) Johnson, R. A.; Sharpless, K. B., Catalytic Asymmetric Dihydroxylation-Discovery and Development. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed. Wiley & Sons: New York, 2000; pp 357-398; (b) Markó, I. E.; Svendsen, J. S., Dihydroxylation of Carbon-Carbon Double Bonds. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Springer-Verlag: Berlin, 1999; Vol. 2, pp 713-787.
7. Jacobsen, E. N.; Wu, M. H., Epoxidation of Alkenes Other than Allylic Alcohols. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Springer-Verlag: Berlin, 1999; Vol. 2, pp 649-677.
8. Jacobsen, E. N., Aziridination. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Springer-Verlag: Berlin, 1999; Vol. 2, pp 607-618.
9. Stoltz, B. M. *Chem. Lett.* **2004,** *33*, 362-367.
10. (a) *Organosulfur Chemistry in Asymmetric Synthesis*. Wiley-VCH: Weinheim, 2008; (b) Legros, J.; Dehli, Juan R.; Bolm, C. *Adv. Synth. Catal.* **2005,** *347*, 19-31; (c) Fernandez, I.; Khiar, N. *Chem. Rev.* **2003,** *103*, 3651-3706; (d) Kagan, H. B., Asymmetric Oxidation of Sulfides. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed. Wiley & Sons: New York, 2000; pp 327-356; (e) Carsten, B.; Muñiz, K.; Hildebrand, J. P., Oxidation of Sulfides. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Springer-Verlag: Berlin, 1999; pp 697-710.

11. (a) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984,** *106*, 8188-8193; (b) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984,** *25*, 1049-1052.
12. Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325-326.
13. Zhao, S. H.; Samuel, O.; Kagan, H. B. *Org. Synth.* **1989,** *68*, 49-56.
14. Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987,** *43*, 5135-5144.
15. (a) Diter, P.; Samuel, O.; Taudien, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **1994,** *5*, 549-552; (b) Brunel, J.-M.; Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995,** *60*, 8086-8088; (c) Brunel, J. M.; Kagan, H. B. *Synlett* **1996,** 404-406.
16. (a) Boche, G.; Mobus, K.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1996,** *118*, 2770-2771; (b) Potvin, P. G.; Fieldhouse, B. G. *Tetrahedron: Asymmetry* **1999,** *10*, 1661-1672.
17. (a) Pitchen, P.; France, C. J.; McFarlane, I. M.; Newton, C. G.; Thompson, D. M. *Tetrahedron Lett.* **1994,** *35*, 485-488; (b) Cotton, H.; Elebring, T.; Larsson, M.; Li, L.; Sörensen, H.; von Unge, S. *Tetrahedron: Asymmetry* **2000,** *11*, 3819-3825; (c) Seenivasaperumal, M.; Federsel, H.-J.; Ertan, A.; Szabo, K. J. *Chem. Commun.* **2007**, 2187-2189; (d) Hogan, P. J.; Hopes, P. A.; Moss, W. O.; Robinson, G. E.; Patel, I. *Org. Process Res. Dev.* **2002,** *6*, 225-229; (e) Bowden, S. A.; Burke, J. N.; Gray, F.; McKown, S.; Moseley, J. D.; Moss, W. O.; Murray, P. M.; Welham, M. J.; Young, M. J. *Org. Process Res. Dev.* **2004,** *8*, 33-44; (f) Song, Z. J.; King, A. O.; Waters, M. S.; Lang, F.; Zewge, D.; Bio, M.; Leazer, J. L.; Javadi, G.; Kassim, A.; Tschaen, D. M.; Reamer, R. A.; Rosner, T.; Chilenski, J. R.; Mathre, D. J.; Volante, R. P.; Tillyer, R. *Proc. Natl. Acad. Sci. U. S. A.* **2004,** *101*, 5776-5781.
18. (a) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993,** *58*, 4529-4533; (b) Komatsu, N.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *Tetrahedron Lett.* **1992,** *33*, 5391-5394; (c) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993,** *58*, 7624-7626.
19. (a) Capozzi, M. A. M.; Cardellicchio, C.; Fracchiolla, G.; Naso, F.; Tortorella, P. *J. Am. Chem. Soc.* **1999,** *121*, 4708-4709; (b) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2000,** *65*, 2843-2846.
20. (a) Superchi, S.; Rosini, C. *Tetrahedron: Asymmetry* **1997,** *8*, 349-352; (b) Donnoli, M. I.; Superchi, S.; Rosini, C. *J. Org. Chem.* **1998,** *63*, 9392-9395; (c) Superchi, S.; Donnoli, M. I.; Rosini, C. *Tetrahedron Lett.* **1998,** *39*, 8541-8544.
21. Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1997,** *62*, 8560-8564.
22. Reetz, M. T.; Merk, C.; Naberfeld, G.; Rudolph, J.; Griebenow, N.; Goddard, R. *Tetrahedron Lett.* **1997,** *38*, 5273-5276.
23. Bonchio, M.; Licini, G.; Modena, G.; Bortolini, O.; Moro, S.; Nugent, W. A. *J. Am. Chem. Soc.* **1999,** *121*, 6258-6268.

24. Nakajima, K.; Sasaki, C.; Kojima, M.; Aoyama, T.; Ohba, S.; Saito, Y.; Fujita, J. *Chem. Lett.* **1987**, 2189-2192.

25. Palucki, M.; Hanson, P.; Jacobsen, E. N. *Tetrahedron Lett.* **1992,** *33*, 7111-7114.

26. Saito, B.; Katsuki, T. *Tetrahedron Lett.* **2001,** *42*, 3873-3876.

27. Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1995,** *68*, 3241-3246.

28. (a) Legros, J.; Carsten, B. *Angew. Chem., Int. Ed.* **2003,** *42*, 5487-5489; (b) Legros, J.; Carsten, B. *Chem. Eur. J.* **2005,** *11*, 1086-1092.

29. Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007,** *129*, 8940-8941.

30. Bolm, C.; Frank, B. *Angew. Chem., Int. Ed. Engl.* **1995,** *34*, 2640-2642.

31. Skarzewski, J.; Wojaczynska, E.; Turowska-Tyrk, I. *Tetrahedron: Asymmetry* **2002,** *13*, 369-375.

32. Ohta, C.; Shimizu, H.; Kondo, A.; Katsuki, T. *Synlett* **2002,** 0161-0163.

33. (a) Drago, C.; Lorenzo, C.; Richard, F. W. J. *Angew. Chem., Int. Ed.* **2005,** *44*, 7221-7223; (b) Pelotier, B.; Anson, M. S.; Campbell, I. B.; Macdonald, S. J. F.; Priem, G.; Jackson, R. F. W. *Synlett* **2002,** 1055-1060.

34. Barbarini, A.; Maggi, R.; Muratori, M.; Sartori, G.; Sartorio, R. *Tetrahedron: Asymmetry* **2004,** *15*, 2467-2473.

35. Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003,** *42*, 2892-2895.

36. Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001,** *123*, 7725-7726.

37. Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003,** *125*, 9578-9579.

38. Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001,** *123*, 7475-7476.

39. (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988,** *18*, 249-330; (b) Keith, J. M.; Larrow, Jay F.; Jacobsen, Eric N. *Adv. Synth. Catal.* **2001,** *343*, 5-26.

40. Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996,** *61*, 1194-1195.

41. Graetz, B.; Rychnovsky, S.; Leu, W.-H.; Farmer, P.; Lin, R. *Tetrahedron: Asymmetry* **2005,** *16*, 3584-3598.

42. Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J.-i.; Osa, T.; Bobbitt, J. M. *Tetrahedron Lett.* **1999,** *40*, 6469-6472.

43. Kuroboshi, M.; Yoshihisa, H.; Cortona, M. N.; Kawakami, Y.; Gao, Z.; Tanaka, H. *Tetrahedron Lett.* **2000,** *41*, 8131-8135.

44. Kashiwagi, Y.; Yanagisawa, Y.; Kurashima, F.; Anzai, J.-i.; Osa, T.; Bobbitt, J. M. *Chem. Commun.* **1996**, 2745-2746.

45. Ohkubo, K.; Hirata, K.; Yoshinaga, K.; Okada, M. *Chem. Lett.* **1976**, 183-184.

46. Ishii, Y.; Suzuki, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986,** *51*, 2822-2824.

47. Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997,** *36*, 288-290.
48. Nishibayashi, Y.; Yamauchi, A.; Onodera, G.; Uemura, S. *J. Org. Chem.* **2003,** *68*, 5875-5880.
49. Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000,** *41*, 5119-5123.
50. Nakamura, Y.; Egami, H.; Matsumoto, K.; Uchida, T.; Katsuki, T. *Tetrahedron* **2007,** *63*, 6383-6387.
51. Li, Y.-Y.; Zhang, X.-Q.; Dong, Z.-R.; Shen, W.-Y.; Chen, G.; Gao, J.-X. *Org. Lett.* **2006,** *8*, 5565-5567.
52. Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Angew. Chem., Int. Ed.* **2008,** *47*, 2447-2449.
53. Onomura, O.; Arimoto, H.; Matsumura, Y.; Demizu, Y. *Tetrahedron Lett.* **2007,** *48*, 8668-8672.
54. Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006,** *39*, 221-229.
55. Radosevich, A. T.; Musich, C.; Toste, F. D. *J. Am. Chem. Soc.* **2005,** *127*, 1090-1091.
56. Radosevich, A. T.; Chan, Vincent S.; Shih, H.-W.; Toste, F. D. *Angew. Chem., Int. Ed.* **2008,** *47*, 3755-3758.
57. Weng, S.-S.; Shen, M.-W.; Kao, J.-Q.; Munot, Y. S.; Chen, C.-T. *Proc. Natl. Acad. Sci. U. S. A.* **2006,** *103*, 3522-3527.
58. Chen, C.-T.; Bettigeri, S.; Weng, S.-S.; Pawar, V. D.; Lin, Y.-H.; Liu, C.-Y.; Lee, W.-Z. *J. Org. Chem.* **2007,** *72*, 8175-8185.
59. Shiels, R. A.; Venkatasubbaiah, K.; Jones, Christopher W. *Adv. Synth. Catal.* **2008,** *350*, 2823-2834.

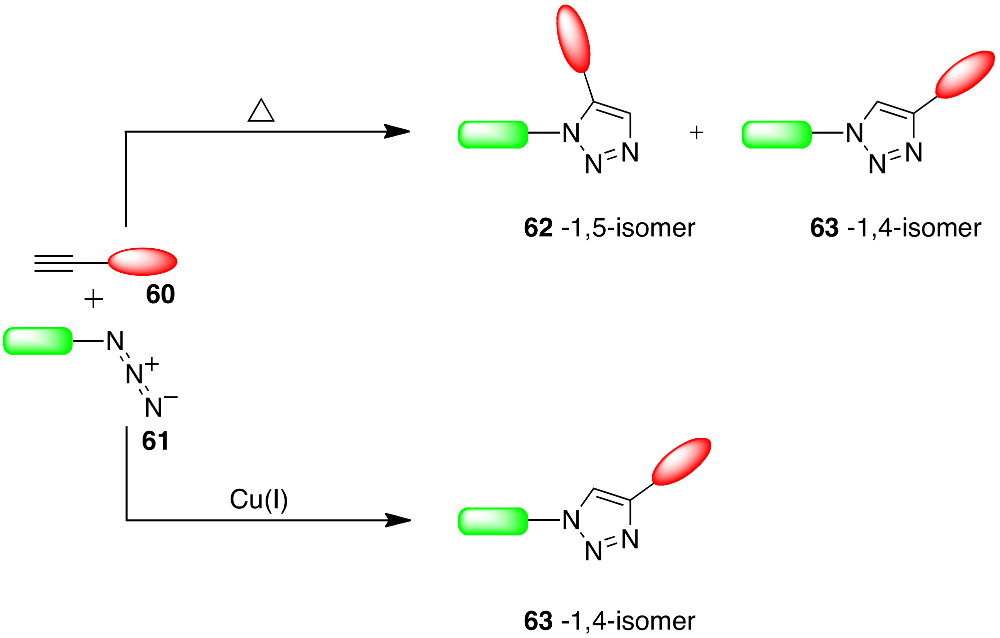
2. Synthesis of polymer supported ligand/catalysts *via* click chemistry

The growth of both polymer supported chemistry and asymmetric catalysis has been tremendous in the past decade. This is not surprising, considering the industrial need for diverse libraries of enantiomerically pure compounds for lead identification in the drug discovery process.[1] Polymer supported catalysts can easily be recovered from the reaction mixture, do not contaminate the product, can be recycled and might even enhance selectivity. The methods which are hitherto known for immobilization of metal complexes on to polymer supports either involve the synthesis of polymer bound ligands followed by complexation[2] or the direct ligation of the preformed metal complex with a functionalized polymer.[3] However, these methods suffer from certain drawbacks such as the need for excess metal complexes and reagents, slow reactions of metal complexes with polymer supports, low catalyst loading and often harsh reaction conditions. To circumvent the limitation associated with the known methods, we focused our attention towards a new ligation strategy, which providing excellent catalyst loading under extremely simplified reaction condition.

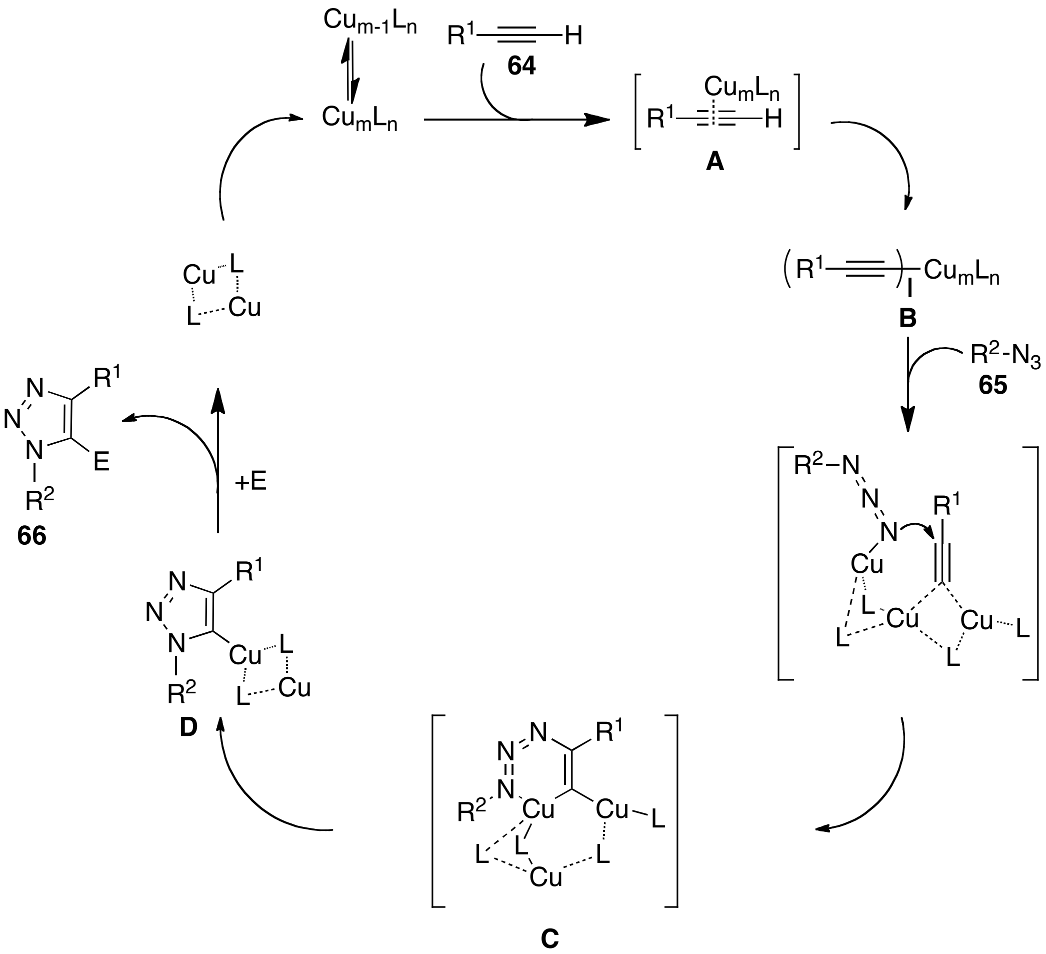
2.1 Click Reaction - A Glimpse into the past

In 1967, Huisgen reported that the 1,3-dipolar cycloaddition between an alkyne and an azide under thermal condition yields a mixture of 1,4 and 1,5-disubstitued regioisomers of triazoles (Scheme 12).[4] Recently, it was found that the copper(I) catalyzed azide alkyne cycloaddition (CuAAC) gives exclusively 1,4-regioisomer of triazole, which was discovered independently by the groups of Meldal[5] and Sharpless[6] in 2002. This powerful bond forming process has proven extremely versatile, and has driven the concept of "click chemistry" (CC) from an ideal to reality.

The mechanism of the CuAAC reaction has been extensively reviewed (Scheme 13).[7] Copper(I) coordinates first with the acetylene π electrons **A**, there-by lowering the pKa of the acetylene proton followed by exothermal formation of copper-acetylide cluster **B**. The Cu^+ acetylide cluster **B** coordinates to the azide followed by rearrangement of the complex in a stepwise manner *via* a six membered metallocycle **C** and further to the copper-metallated triazole **D**. Finally, the copper-triazole complex eventually releases the regioselective formation of the 1,4-triazole and $L_nCu(I)$ by protonation or reaction with electrophiles.



Scheme 12. 1,3-Dipolar cycloaddition between alkyne and azide.



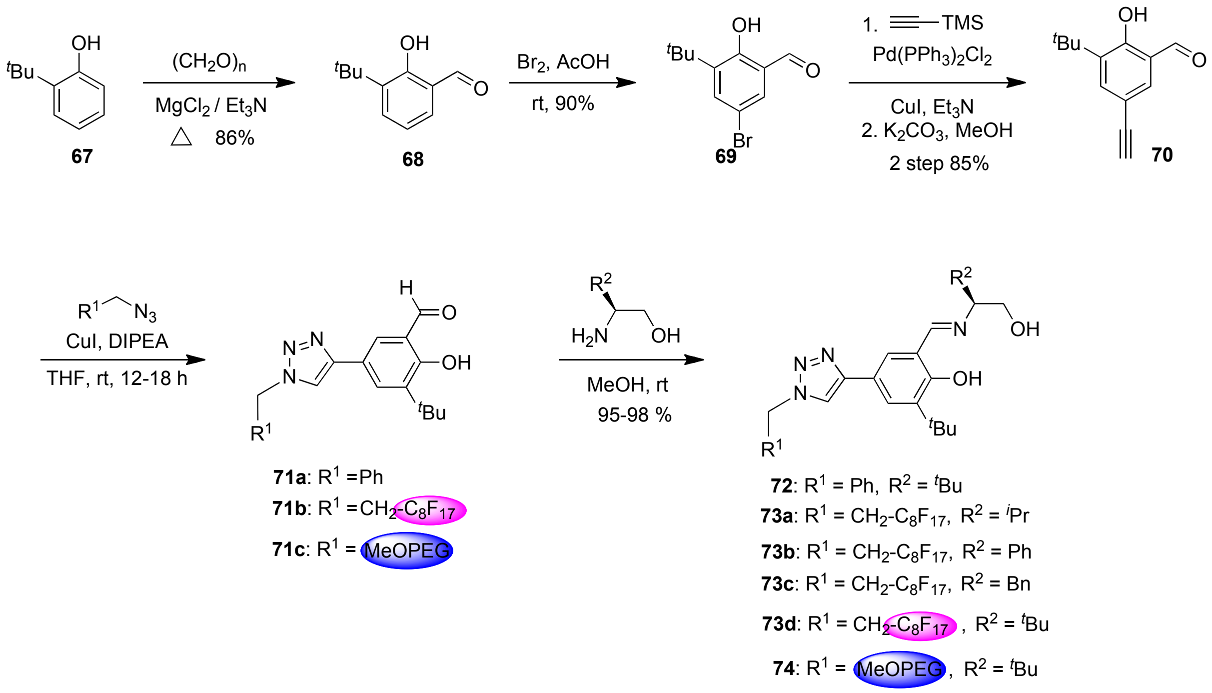
Scheme 13. Outline of plausible mechanism for the CuAAC involving the formation of Cu(I)-clusters.[7]

There are several well-known reactions that comply with the “click chemistry” concept, including hetero-Diels-Alder reactions,[8] the thiol-ene couplings,[9] the Staudinger ligation,[10] native chemical ligation,[11] the amidation reaction between thio acids and sulfonyl azides (sulfo-click)[12] and ruthenium(II)-catalyzed alkyne-azide cycloaddition.[13] The great impact ligation reactions have made in recent years for medicinal chemistry and materials, allowing the reliable connection between two functional groups irrespective of other functionalities present, has also been recognized for attaching catalysts to supports. Especially, the CuAAC has become popular for this purpose among the above mentioned click reactions, having been first utilized with the immobilization of aza(bisoxazoline) ligands to $MeOPEG_{5000}$ in 2005 by Reiser *et al.*[14] Subsequently, this strategy has been applied for grafting azabis(oxazolines) on different polymers or on fluorous tag.[15]

2.2 Synthesis of polymer supported ligands/complexes for asymmetric reactions

2.2.1 Synthesis of homogeneous Schiff base ligands

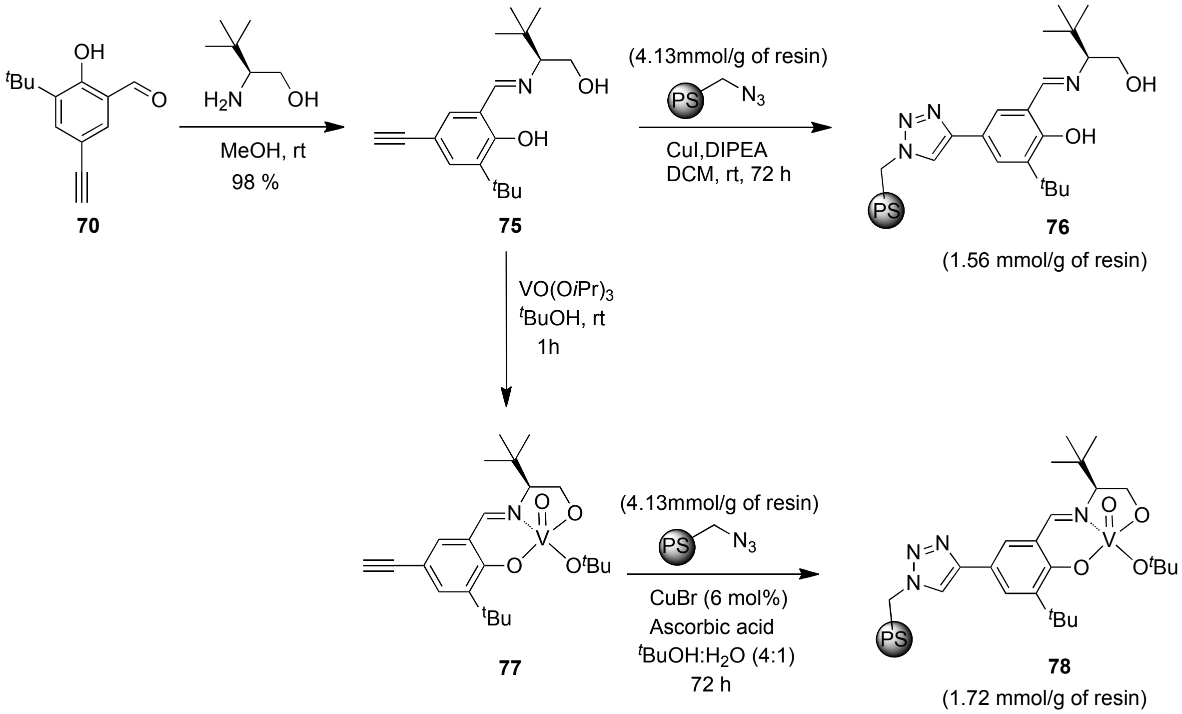
The preparation of MeOPEG and fluorous tag immobilized chiral Schiff bases is depicted in Scheme 14. 2-*tert*-Butyl phenol **67** was ortho formylated according to the literature procedure described by Skattebøl *et al.*[16] The resulting aldehyde **68** was treated with bromine in CH_3CO_2H to afford 5-brominated salicylaldehyde derivative **69** in 90% yield. Compound **69** was treated with trimethylsilylacetylene in a Sonogashira coupling according to a known procedure.[17] The cleavage of the trimethylsilyl group under mild basic conditions using K_2CO_3 led to the free alkyne **70**, which was subsequently subjected to the CuAAC with BnN_3, 1-azido perfluorodecane,[18] and MeOPEG-N_3, respectively to obtain compound **71a**, **71b** and **71c** in high yields. Chiral tridentate Schiff bases **72-74** were prepared by condensation of salicylaldehyde derivatives **71a**, **71b** and **71c** with aminoalcohols in quantitative yield, the progress of reaction was conveniently monitored by TLC. Moreover, the MeOPEG supported ligand **74** could be isolated by precipitation using diethylether, and the loading was almost quantitative as judged by ^{1}H-NMR.



Scheme 14. Immobilization of chiral Schiff base ligands on fluorous tag and MeOPEG supports.

2.2.2 Synthesis of heterogeneous Schiff base vanadium complexes

The preparation of polystyrene immobilized Schiff bases is outlined in Scheme 15. The polystyrene immobilized tridentate Schiff base ligand **76** could be prepared in an easy two-step sequence starting from propargylated salicyaldehyde derivative **70** and merrifield azide (Scheme 16). Propargylated salicyaldehyde **70** underwent condensation with *tert*-leucinol leading to intermediate **75**, which set the stage for the subsequent copper(I)-catalyzed cycloaddition: following a protocol developed by Gmeiner and co-workers,[19] 6 mol% Cu(I)iodide was found to be optimal to achieve the smooth formation of **75** to **76**. The progress of the cycloaddition reaction could be easily monitored by the vanishing of the azide peak by IR spectroscopy ($\tilde{\nu}$ = 2090 cm^{-1}) at different time intervals. The estimated catalyst (**76**) loading based on elemental analysis was 1.56 mmol/g of resin. The azide/alkyne cycloaddition reaction represents a tagging method that proceeds under mild conditions and with tremendous tolerance towards different functionalities, thus it provides the possiblity to click preformed complexes directly onto support. Hence, in an alternative approach preformed vanadium complex was subjected to the CuAAC with Merrifield azide. We synthesized the vanadium Schiff base complex **77** by treating propargylated Schiff base derivative **75** with VO(O*i*Pr)$_3$ in 1:1 molar ratio, which was then grafted onto merrifield resin using 6 mol% of copper(I) bromide in *tert*-butanol/water (4:1) solvent mixture containing 0.2 equivalents of ascorbic acid to afford the desired complex **78** in quantitative yield. The estimated catalyst (**78**) loading based on elemental analysis was 1.72 mmol/g of resin. The principle evidence for the formation of immobilized vanadium complex onto the polystyrene support was found in the disapperance of the typical IR frequency at 2090 cm^{-1} for the azide group. Furthermore, apperance of new peak at 970 cm^{-1} in IR spectroscopy indicates the presence of a V=O bond in the complex. Moreover, a strong hypochromic schift was observed for C=N stretch in the complex from 1630 cm^{-1} to 1620 cm^{-1}, being in accordance with reported literature values.[20]

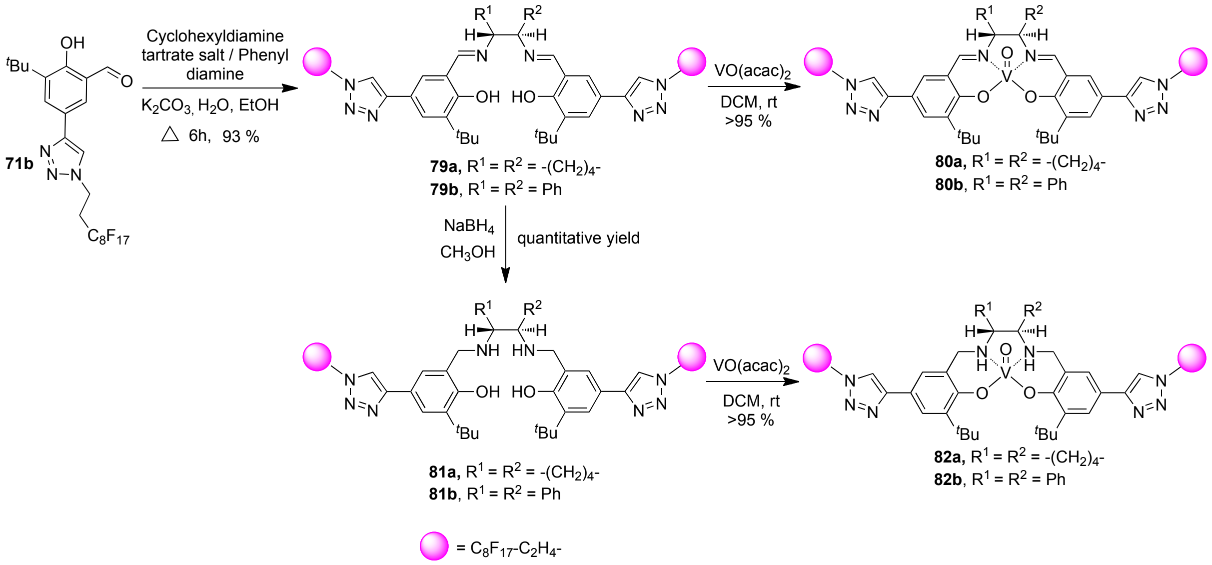


Scheme 15. Synthesis of Merrifield resin supported vanadium complex.

2.2.3 Synthesis of homogeneous salen & salan vanadium complex

The synthetic approach to fluorous tagged chiral Schiff base complexes is outlined in scheme 16. Compound **71b** was treated with (*R,R*)–cyclohexyl diamine tartrate salt/ phenyldiamine and potassium carbonate under reflux condition in ethanol to afford **79a, b** in quantitative yield. Synthesis of V(IV) salen complexes **80a, b** was achieved by treatment of **79a, b** with vanadium oxyacetonylacetonate at ambient temperature in quantitative yield (Scheme 16).

Nitrogen containing ligands belong to the most common types of chiral ligands that are applied for catalytic asymmetric synthesis.[21] It has been reported that chiral ligands containing a secondary amino group (sp^3-hybridized nitrogen atom) are superior in terms of reactivity and enantioselectivity to imino analogues (sp^2-hybridized nitrogen atom).[22] Therefore, we attempted to synthesize the reduced version of salen ligands **81a, b** by reduction of ligand **79a, b** using $NaBH_4$ in methanol followed by vanadium insertion which led to the desired products **82a, b** in more than 95% yield.

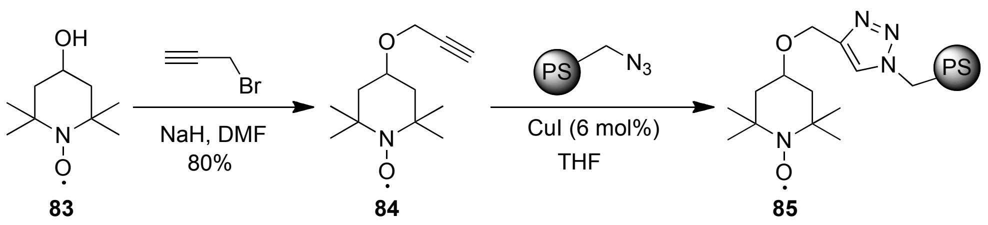


Scheme 16. Fluorous tag clicked salen and salan vanadium complexes.

2.3 Synthesis of polymer supported catalysts for chemoselective oxidation reactions

2.3.1 Synthesis of polystyrene-supported TEMPO

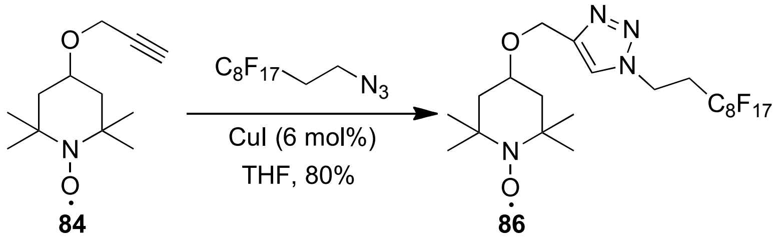
Catalyst **85** could be prepared in an easy two-step sequence starting from commercially available 4-hydroxy-TEMPO **83** and polystyrene-supported azide (Scheme 17).[23] Propargylated **84** was subjected to copper(I)-catalyzed cycloaddition: following a protocol developed by Gmeiner and co-workers[19] 6 mol% Cu(I) iodide which was found to be optimal to achieve the smooth formation of **85** as judged by the complete vanishing of the peak in IR absorption of the azide group (2100 cm^{-1}).



Scheme 17. Synthesis of PS-CLICK-TEMPO **85**.

2.3.2 Synthesis of fluorous tag clicked TEMPO

F_{17}-CLICK-TEMPO **86** was obtained in 80% yield upon reacting 4-propargylated TEMPO **84** with 1-azido-perfluorodecane[18] in the presence of 6 mol% of CuI, proving again the high efficiency of this ligation method (Scheme 18).

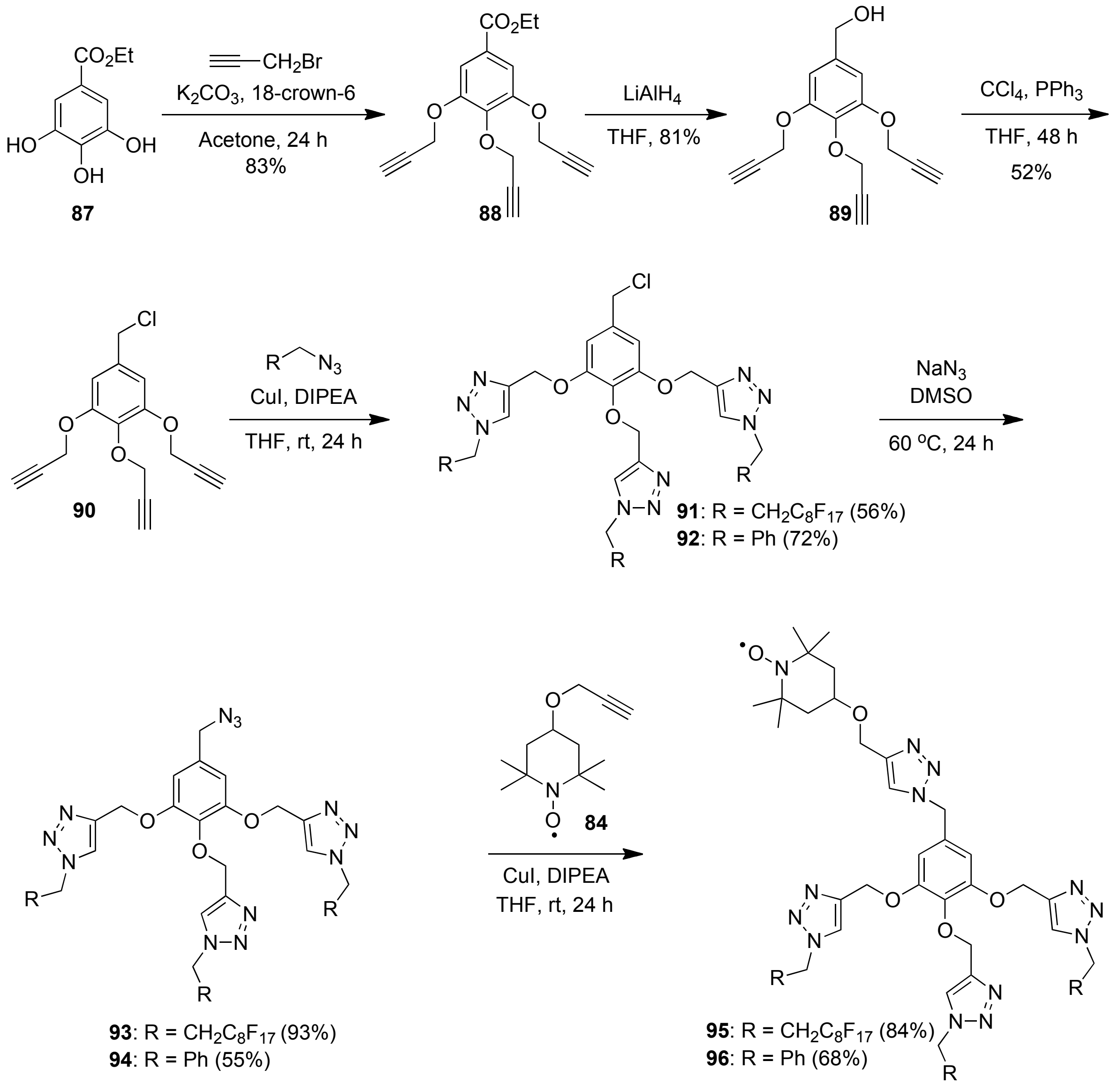


Scheme 18. Synthesis of F_{17}-CLICK-TEMPO **86**.

2.3.3 Synthesis of Novel TEMPO reagents with mutiple triazole and perfluoroalkyl moieties

Sharpless and co-workers reported the preparation of triazole dendrimers from 3,4,5-trihydroxylbenzyl derivatives as primary building blocks *via* a click reaction.[24] Inspired by their work, we prepared the propargyloxybenzyl chloride **90** in a three-steps procedure starting from commercially available polyhydroxybenzoic **87** (Scheme 19). Then, the chlorides were smoothly clicked with 1-azido-perfluorodecane and benzyl azide to give the corresponding clicked-chlorides **91** and **92** in moderate to good yields. The next step was the introduction of the azide functionality; the azides **93** and **94** were obtained in high yields by a nucleophilic substitution using sodium azide in warm DMSO.

The perfluorinated azide **93** were only slightly soluble in organic solvents at room temperature. Nevertheless, the azides **93**, **94** smoothly underwent the CuAAC with propargylated TEMPO **84** to give immobilized TEMPO **95** and **96** in good yields. **95** was precipitated from the reaction mixture and could consequently be conveniently isolated by simple filtration and purified from residual copper catalysts by washing with sat. NH_4Cl followed by water. The absence of the typical azide band at around 2100 cm^{-1} in the IR-spectrum further indicated that the product was obtained free from the starting material **95**.



Scheme 19. Synthesis of Novel TEMPO reagents with mutiple triazole and perfluoroalkyl moieties.

2.4 Notes and References

1. (a) Chaiken, I. M., *Molecular Diversity and Combinatorial Chemistry*. American Chemical Society: Washington, DC, 1996; (b) Noyori, R., *Asymmetric Catalysis in Organic Synthesis*. Wiley: NewYork, 1994.
2. (a) Ribeiro, S. M.; Serra, A. C.; Rocha Gonsalves, A. M. D. A. *Tetrahedron* **2007,** *63*, 7885-7891; (b) Takizawa, S.; Patil, M. L.; Marubayashi, K.; Sasai, H. *Tetrahedron* **2007,** *63*, 6512-6528.
3. (a) Gupta, K. C.; Sutar, A. K. *J. Mol. Catal. A: Chem.* **2007,** *272*, 64-74; (b) Tada, M.; Kojima, N.; Izumi, Y.; Taniike, T.; Iwasawa, Y. *The Journal of Physical Chemistry B* **2005,** *109*, 9905-9916.
4. Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1967,** *100*, 2494-2507.

5. Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002,** *67*, 3057-3064.

6. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002,** *41*, 2596-2599.

7. (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005,** *127*, 210-216; (b) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005,** *44*, 2210-2215; (c) Bock, V. D.; Hiemstra, H.; Maarseveen, J. H. v. *Eur. J. Org. Chem.* **2006,** 51-68; (d) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008,** *108*, 2952-3015.

8. Gacal, B.; Durmaz, H.; Tasdelen, M. A.; Hizal, G.; Tunca, U.; Yagci, Y.; Demirel, A. L. *Macromolecules* **2006,** *39*, 5330-5336.

9. Posner, T. *Berichte der deutschen chemischen Gesellschaft* **1905,** *38*, 646-657.

10. (a) Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett.* **2000,** *2*, 2141-2143; (b) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000,** *2*, 1939-1941; (c) Saxon, E.; Bertozzi, C. R. *Science* **2000,** *287*, 2007-2010.

11. (a) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. *Science* **1994,** *266*, 776-779; (b) Ruttekolk, I. R.; Duchardt, F.; Fischer, R.; Wiesmüller, K.-H.; Rademann, J. R.; Brock, R. *Bioconjugate Chem.* **2008,** *19*, 2081-2087.

12. (a) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003,** *125*, 7754-7755; (b) Merkx, R.; Brouwer, A. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005,** *7*, 1125-1128; (c) Kolakowski, R. V.; Shangguan, N.; Sauers, R. R.; Williams, L. J. *J. Am. Chem. Soc.* **2006,** *128*, 5695-5702; (d) Barlett, K. N.; Kolakowski, R. V.; Katukojvala, S.; Williams, L. J. *Org. Lett.* **2006,** *8*, 823-826; (e) Merkx, R.; van Haren, M. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *J. Org. Chem.* **2007,** *72*, 4574-4577.

13. (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005,** *127*, 15998-15999; (b) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008,** *130*, 8923-8930.

14. Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005,** *7*, 2325-2328.

15. (a) Rasappan, R.; Olbrich, T.; Reiser, O. *Adv. Synth. Catal.* **2009,** *351*, 1961-1967; (b) Gissibl, A.; Padie, C.; Hager, M.; Jaroschik, F.; Rasappan, R.; Cuevas-Yanez, E.; Turrin, C.-O.; Caminade, A.-M.; Majoral, J.-P.; Reiser, O. *Org. Lett.* **2007,** *9*, 2895-2898.

16. Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999,** *53*, 258-262.

17. Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995,** *27*, 127-160.

18. Szonyi, F.; Cambon, A. *J. Fluorine Chem.* **1989,** *42*, 59-68.

19. Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2003,** *5*, 1753-1755.

20. Shiels, R. A.; Krishnan, V.; Christopher , W. J. *Adv. Synth. Catal.* **2008,** *350*, 2823-2834.

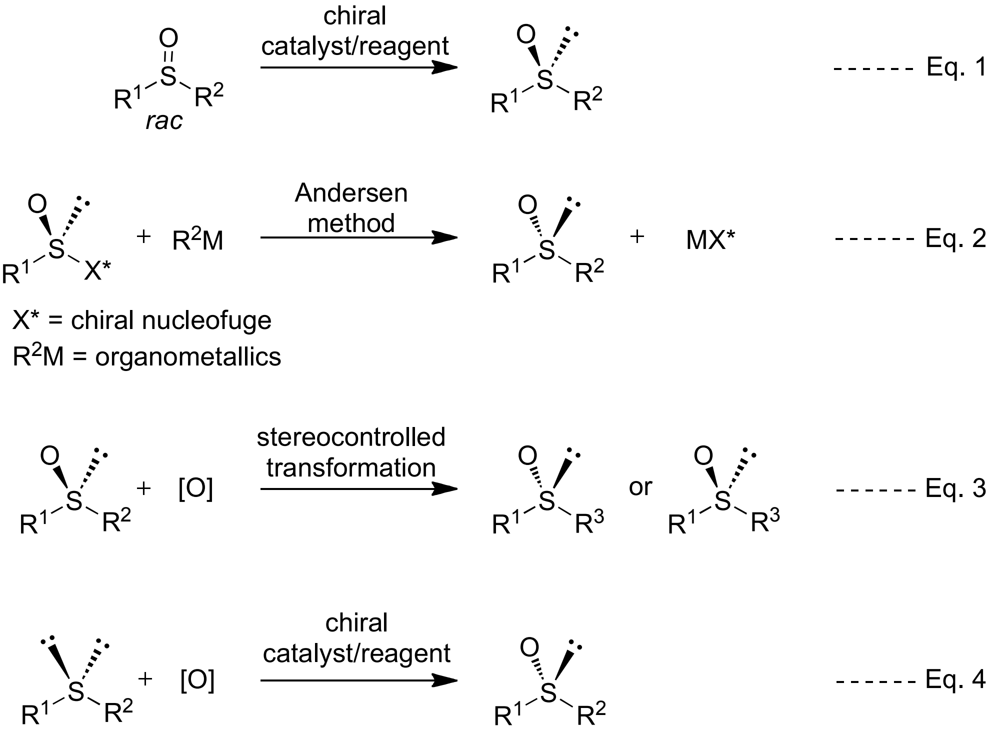
21. Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000,** *100*, 2159-2232.

22. Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. *Chem. Eur. J.* **2007,** *13*, 829-833.
23. Arseniyadis, S.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2002,** *43*, 9717-9719.
24. Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004,** *43*, 3928-3932.

3. Asymmetric sulfoxidation using polymer supported Schiff base vanadium complexes

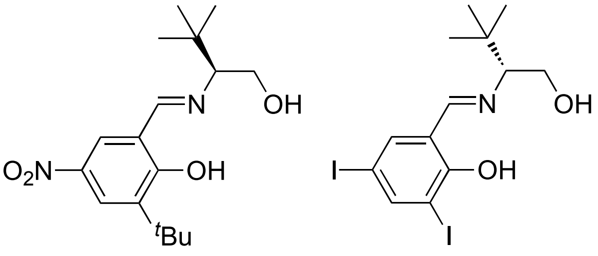
3.1 General routes to enantiopure sulfoxides

Optically pure sulfoxides are very important chiral auxiliaries in asymmetric synthesis and also bioactive ingredients in the pharmaceutical industry.[1] The general four routes to optically pure sulfoxides are depicted in Scheme 20, these are (1) Kinetic resolution of racemic sulfoxides either by using chiral catalyst or an enzymatic reaction (Eq. 1);[2] (2) Conversion of chiral sulfinates, occurring with inversion on sulfur into sulfoxides with various types of organometallic reagents (Eq. 2);[3] (3) Stereocontrolled transformation- in which the chiral sulfoxide structure could be modified without loss of stereochemistry at sulfur atom (Eq. 3);[4] (4) Asymmetric oxidation of prochiral sulfides by enzymatic or non-enzymatic method (Eq. 4).[5]



Scheme 20. General routes to chiral sulfoxides.[1a]

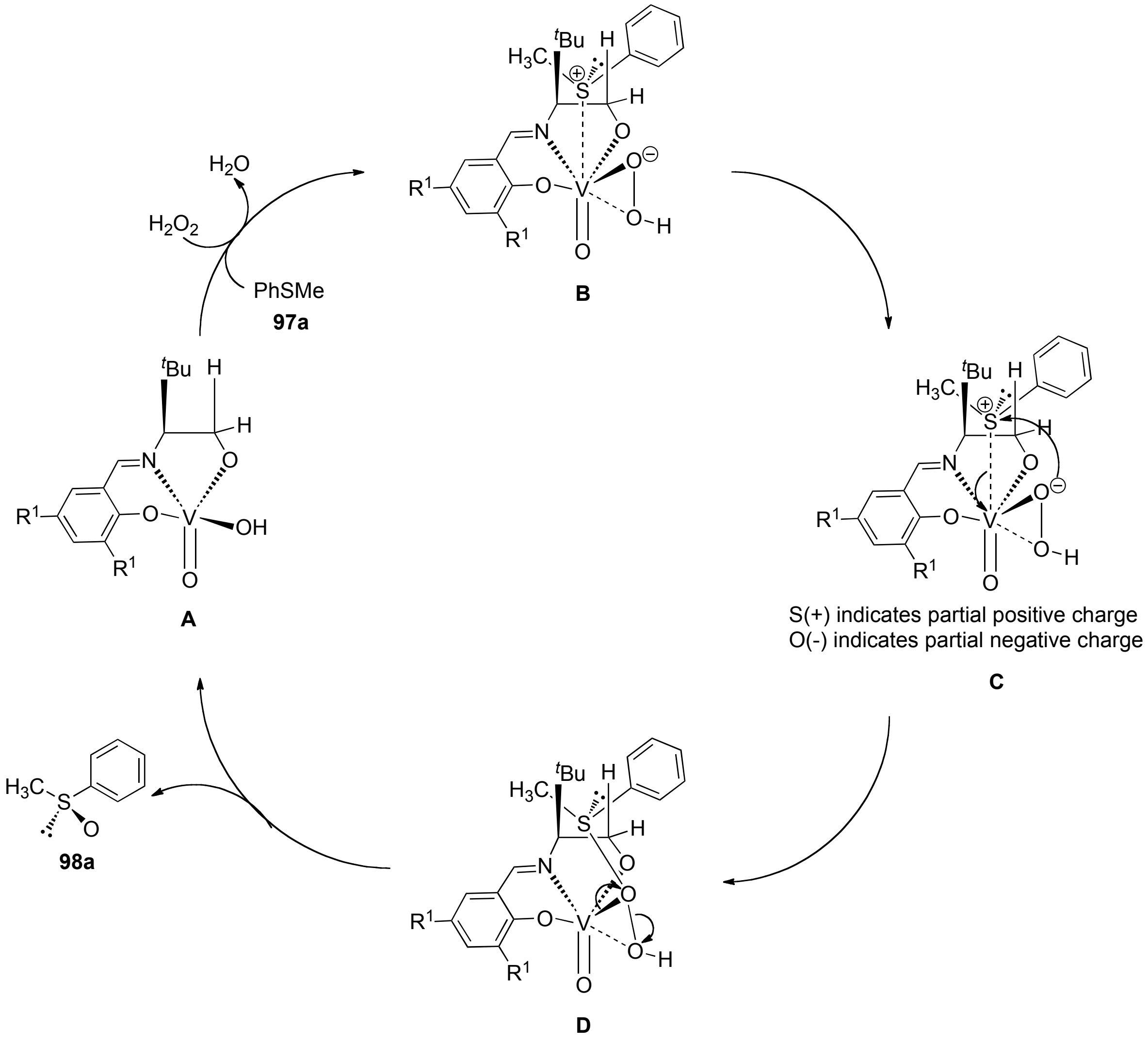
The methods to synthesize enantioenriched sulfoxides using chiral auxiliaries are remarkably efficient and have been widely utilized. However, inherent limitations in the methodology have generally restricted their application to simple sulfoxides. Given the prevalence of sulfoxides in complex organic molecules including many drug targets, the development of asymmetric oxidations of prochiral sulfides has generated considerable interest. Various transition metals have been employed in combination with chiral catalysts, including titanium,[5a, b, 6] vanadium,[5c, 7] iron,[8] manganese,[9] and tungsten.[10] Among those, the most extensively studied vanadium-based system has been developed by Bolm and co-workers, who employed a combination of Schiff bases derived from chiral amino alcohol **24** and VO(acac)$_2$ (1.0 mol%) using aq. H_2O_2 as an oxidant for enantioselective sulfoxidation.[5c] The catalysts employed gave moderate enantioselectivity and good yields for aryl-alkyl sulfides (53-76% ee, 55-94% yield). Improved enantioselectivity (up to >99.5% ee) was achieved by Jackson *et al.* using **27** (Figure 3).[11] Furthermore, the authors strongly suggested that the bulky electron withdrawing substitution on the aromatic ring markedly increases the enantioselectivity of the sulfoxides.



24 **27**

Figure 3. Bolm's and Jackson's ligands for asymmetric sulfoxidation.

Penta-coordinated oxovanadium Schiff base complex **A** has been postulated as a starting point to explain the catalytic cycle of these oxidations (Scheme 21). The hydroxyl of the oxovanadium complex **A** is exchanged with hydroperoxide to release H_2O. Then an electron pair from thioanisole coordinates with the vanadium complex **B**, marking the rate-determining step. Due to steric repulsion, the other lone pair of electrons on thioanisole will point to the amino alcohol moiety and the bulky phenyl will locate between the ^{t}Bu group and V(O$_2$H), which will determine the absolute configuration of the product sulfoxide. The coordinated thioanisole will show a partial positive, the hydroxyl group shows a partial negative charge, and S-V-O is in a space-favourable triangle **C**. Therefore, the oxygen atom of hydroperoxyl attacks the sulfur atom of sulfide (to produce the *S* form of the sulfoxide) and an electron pair of the S-V bond moves to vanadium. Sequentially, the electrons of the V-O(OH) bond will turn to S-O bond, which triggers the breaking of the O-O bond of hydroperoxyl. Thus, the *S*-sulfoxide is released from the cycle and the penta-coordinated oxovanadium complex **A** is generated.



Scheme 21. Proposed mechanism for asymmetric sulfoxidation catalyzed by vanadium-Schiff base complexes.[12]

Recent studies on catalyst immobilization from our[13] and other groups[14] revealed that the copper-catalyzed azide-alkyne cycloaddition (CuAAC) is a facile method for grafting catalysts onto polymers or nanoparticles. Using an azido-functionalized support like MeOPEG, fluorous tag and polystyrene and an alkyne ligand or metal-ligand complex, high loading of the immobilized derivative close to the maximum capacity of the support has been achieved.

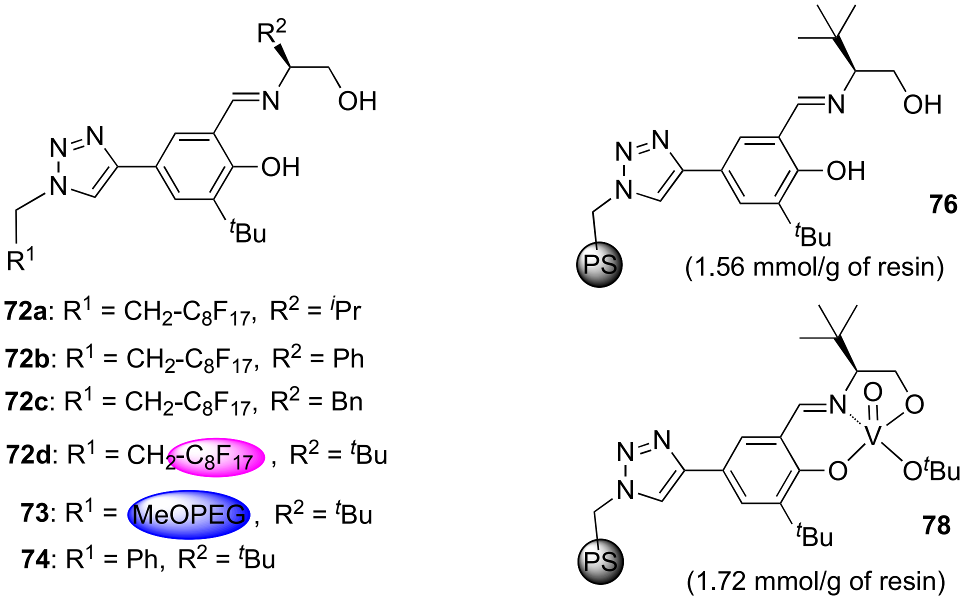


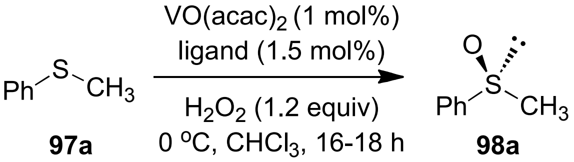
Figure 4. Immobilized ligands/catalyst on various polymers.

3.2 Evaluation of catalysts

To evaluate the catalytic potential of these immobilized ligands **72a-74** and complex **78** for metal catalysis, we chose the asymmetric oxidation of sulfides following a protocol intially developed by Bolm *et al*. Oxidation of thioanisole was first examined with ligand **72a-74, 76**, for which vanadium complexes were generated *in situ* and preformed complex **78** at 0 ^{o}C using 1.2 equivalent of H_2O_2. The results are summarized in table 1. From the first four entries (Table 1), it is quite apparent that the sterically less demanding substituents on the amino alcohol part of the ligand led to a decrease in enantioselectivity, while the sterically bulky ^{t}Bu substituted ligand gave the best result (80% ee, entry 4, Table 1).

In order to find out the influence of the fluorous tail on the enantioselectivity, we also synthesized ligand **74** bearing a benzyl group instead of the $C_{18}F_{17}CH_2CH_2$-moiety. When using compound **74** as a ligand in the asymmetric oxidation of thioanisole we obtained 80% *ee* (entry 6, Table 1), which is similar to the result found with ligand **72d**. Therefore, we concluded that there is no influence by the fluorous tail on the enantioselectivity. The reaction with a *in situ* generated vanadium complex **76** gave lower enantioselectivity 28% (entry 7, Table 1), whereas preformed complex **78** gave 77% yield with 65% *ee* (entry 8, Table 1). The enantioselectivities obtained by using complex **78** was similar to already reported values for solid-supported vanadium catalysts.[15] The lower ee observed with catalyst **76** can be attributed to a competitive process caused by non-complexed $VO(acac)_2$ which might be absorbed in the cavity of the polystyrene support. Nevertheless, the reaction with homogeneous polymer supported ligand **72d** and **73** proceeded smoothly with good yields and high enantioselectivities (entry 4 and 5, Table 1) respectively.

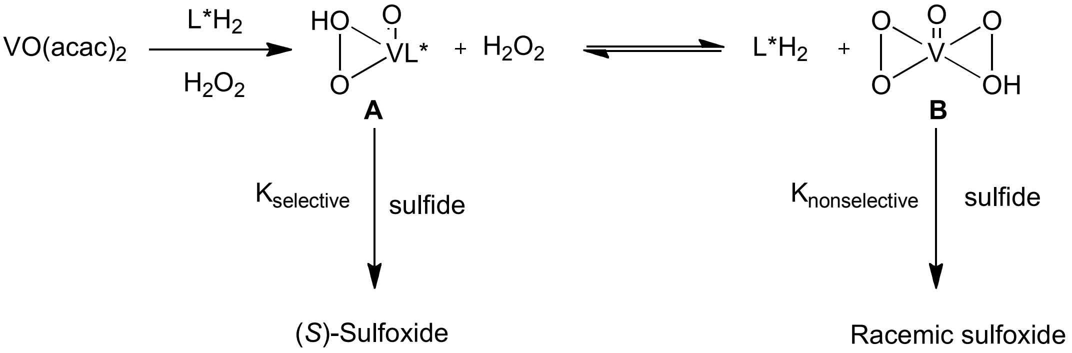
Table 1. Asymmetric oxidation of thioanisole.[a]



entry	catalyst	yield (%)[b]	ee (%)[c]
1	**72a**	81	50
2	**72b**	80	26
3	**72c**	86	34
4	**72d**	75	80
5	**73**	80	78
6	**74**	73	80
7	**76**	71	28
8	**78**	77	65

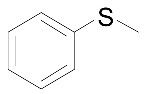
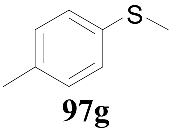
[a] Reaction conditions: the *in situ* catalyst from VO(acac)$_2$ (0.01 mmol) and ligand (0.015 mmol), thioanisole (1 mmol) at 0 °C for 16-18 h. [b] Isolated yield. [c] Determined by chiral HPLC.

To improve the enantioselectivity of the sulfoxide, the reaction was carried out with different amounts of the vanadium complex. We carried out the reaction with ligand **72d** using thioanisole as model substrate. Using 1 mol% of the vanadium complex gave 80% ee (entry 2, Tabe 2), while increasing the concentration of the complex to 4 mol% led to over oxidation of the product: When using 4 mol% of the complex instead of 1 mol%, the ratio of sulfone increased significantly from 20 to 55%. We then focused on the effect of a fluorous solvent on the enantioselectivity of the sulfoxidation reaction. When chloroform was used as a solvent in the oxidation of thioanisole and 4-chlorothioanisole with 1.2 equiv H_2O_2 and in presence of **72d**-vanadium complex, the product was obtained with enantioselectivities of 80% and 96% respectively (entry 2&4, Table 2). Changing the solvent to 1,1,2-trichloro-1,2,2-trifluoroethane ($C_2Cl_3F_3$), the enantioselectivities dropped to 54 and 76% ee respectively (entry 3&6, Table 2). The good solubility of the **72d**–vanadium complex in chloroform at 0 °C makes it a very effective catalyst for the reaction. When the amount of H_2O_2 was increased from 1.2 to 1.5 equiv respectively, a decrease in enantioselectivity was observed (entry 1 and 5, Table 2). It has been proposed that the Schiff base vanadium complex reacts with 1 equivalent of H_2O_2, giving rise to the active species peroxovanadium(V) complex **A**, which reacts with substrate selectively led to the desired sulfoxide. At higher concentration of hydrogen peroxide, complete displacement of Schiff base ligand from the active species **A** occurs, which leads to the formation of achiral oxo-diperoxovanadium complex **B**. This complex can nonselectively oxidize sulfides to give racemic sulfoxide (Scheme 22).[16]



Scheme 22. Model for the observed loss of enantioselectivity at higher concentration of H_2O_2.[16]

Table 2. Screening of solvents in asymmetric sulfoxidations using ligand **72d**.[a]

entry	substrate	solvent	H_2O_2 (aq)	yield (%)[b]	ee (%)[c]
1	 **97a**	$CHCl_3$	1.5	69	70
2		$CHCl_3$	1.2	75	80
3		$C_2Cl_3F_3$	1.2	65	54
4	 **97g**	$CHCl_3$	1.2	72	96
5		$CHCl_3$	1.5	68	88
6		$C_2Cl_3F_3$	1.2	70	76

[a] Reaction conditions: the *in situ* catalyst from $VO(acac)_2$ (0.01 mmol) and ligand (0.015 mmol), sulfide (1 mmol), $CHCl_3$ at 0 °C for 16 h. [b] Isolated yield. [c] Determined by chiral HPLC. The absolute configuration was

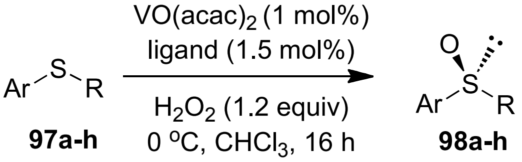
assigned by comparing HPLC elution order and the sign of $[\alpha]_D$ to literature data. All of the major isomers are in the *S* form.

From these above results, it is quite apperant that the ligand **72d, 73** are superior over **77** and **78**. Having the optimized conditon and suitable ligands in hand, we screened the oxidation of other prochiral sulfides with **72d, 73** (Table 3).

3.3 Substrate scope

Oxidations of various alkyl-aryl sulfides bearing electron donating substituent on the phenyl ring proceeded with high enantioselectivities and good yields (entries 5, 6, 15 and 16, Table 3). Notably, substrates with electron withdrawing groups bearing phenyl alkyl sulfide such as 4-chlorothioanisole afforded 84% ee with ligand **73** (entry 4, Table 3) and >99% ee with ligand **72d** (entry 3, Table 3), which is the best result that has been observed with a tridentate Schiff base vanadium system. We also examined the oxidation of benzyl phenyl sulfide with ligand **72d**. Interestingly, the reaction proceeded smoothly with an excellent enantioselectivity >99% ee and yield (entries 7 and 8, Table 3). Recently, Reiser *et al.*[17] disclosed that excess of ligand can have a detrimental effect for the enantioselectivity of the product in some reactions. This is quite in contrast to the usual observation in asymmetric catalysis that an excess of chiral ligand is beneficial in order to avoid background reactions by uncomplexed metal. We turned our attention to this point and carried out asymmetric oxidation of 2-naphthylmethyl sulfide as a substrate model using 1:1 ratio of **72d/73** with $VO(acac)_2$. From entries 9-12, it became apparent that there is not significant influence in enantioselectivity as well as yield.

Table 3. Asymmetric oxidation of alkyl-aryl sulfides with ligand **72d** and **73**.[a]



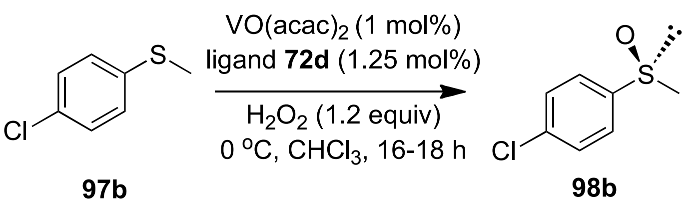
entry	Ar	R	ligand	product	yield (%)[b]	ee (%)[c]
1	C_6H_5	CH_3	**72d**	**98a**	75	80
2	C_6H_5	CH_3	**73**	**98a**	80	78
3	*p*-ClC_6H_4	CH_3	**72d**	**98b**	70	>99
4	*p*-ClC_6H_4	CH_3	**73**	**98b**	70	84
5	*p*-$CH_3OC_6H_4$	CH_3	**72d**	**98c**	78	80
6	*p*-$CH_3OC_6H_4$	CH_3	**73**	**98c**	74	83
7	C_6H_5	$CH_2C_6H_5$	**72d**	**98d**	80	>99
8	C_6H_5	$CH_2C_6H_5$	**73**	**98d**	63	92
9	2-Naphthyl	CH_3	**72d**	**98e**	73	96
10	2-Naphthyl	CH_3	**73**	**98e**	61	>99
11[d]	2-Naphthyl	CH_3	**72d**	**98e**	73	99
12[d]	2-Naphthyl	CH_3	**73**	**98e**	59	98
13	C_6H_5	C_2H_5	**72d**	**98f**	78	88
14	C_6H_5	C_2H_5	**73**	**98f**	68	88
15	*p*-$CH_3C_6H_4$	CH_3	**72d**	**98g**	72	96
16	*p*-$CH_3C_6H_4$	CH_3	**73**	**98g**	67	88
17	C_6H_5	C_3H_7	**72d**	**98h**	69	80

[a] Reaction conditions: the *in situ catalyst* from VO(acac)$_2$ (0.01 mmol) and ligand (0.015 mmol), aq. H_2O_2 (1.2 equiv.), sulfide (1 mmol), $CHCl_3$ at 0 °C for 16 h. [b] Isolated yield. [c] Determined by chiral HPLC. The absolute configuration was assigned by comparing HPLC elution order and the sign of $[\alpha]_D$ to literature data. All of the major isomers are in the *S* form. [d] Reaction conditions: the *in situ catalyst* from VO(acac)$_2$ (0.01 mmol) and ligand (0.01 mmol), aq. H_2O_2 (1.2 equiv.), sulfide (1 mmol), $CHCl_3$ at 0 °C for 16 h.

3.4 Recovery of fluorous catalyst [V(O).72d]

Furthermore, we attempted to recover the fluorous-tagged Schiff base **72d -** vanadium complex using fluorous silica gel.[18] However, we were not able to get good separation of the catalyst from the sulfoxidation products on this stationary phase. The complex **V(O)•72d** behaves quite unusual for one of two reasons. **72d** gave relatively sharp peaks in fluorous HPLC, but retention times were shorter than expected based on similar fluorinated compounds that do not bear a triazole moiety. Consequently, due to the lower affinity of **72d** to fluorous SPE separation from other organic compounds is not efficient. Likewise, the vanadium complex of **72d** was not soluble in fluorous solvents (eg. perfluoromethyl cyclohexane and perfluoro-1,3-dimethylcyclohexane) at room temperature, preventing liquid–liquid phase separation. This behaviour can be attributed to the relatively low fluorine content (F = 41%), but also to the presence of a polar linker in the molecule, namely the triazole ring. However, the triazole moiety present in the vanadium complex of **72d**, beyond its chemical stability, could shift the overall polarity of the molecule and therefore, allow a better separation from the reaction mixture through another method. Ultimately, the new fluorous tagged vanadium complex could be recovered by precipitation from diethylether and hexanes (Figure 5). The precipitated catalyst was recovered by simple filtration and re-used without further activation in four consecutive runs of 4-chloro methyl phenylsulfide as representative substrate by adding fresh reactants after each recycling step. Runs 2-4 proceeded in good yields with excellent enantioselectivities (Table 4). Moreover, the complex was quite stable under air atmosphere.

Table 4. Asymmetric oxidation of 4-chlorothioanisole – recycling experiment.[a]



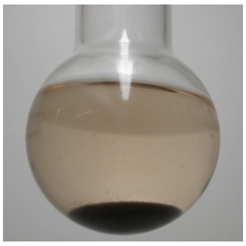


Figure 5. Precipitation of **72d-V(V)**.

entry	run	time (h)	yield (%)[b]	ee (%)[c]
1	1	16	70	>99
2	2	16	73	96
3	3	18	69	90
4	4	18	72	90

[a] Reaction conditions: the *in situ catalyst* from VO(acac)$_2$ (1 mol%) and ligand **72d** (1.25 mol%), aq. H_2O_2 (1.2 equiv), 4-Cl thioanisole (2 mmol) at 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC.

3.5 Conclusion

We have shown that the vanadium catalysts derived from Schiff base **72d** and **73** proved to be highly effective in the asymmetric oxidation of sulfides with aq. H_2O_2. Moreover, the fluorous tagged Schiff base vanadium complex of **72d** can be easily recovered and recycled for four consecutive runs without much loss of catalytic activity.

3.6 Notes and references

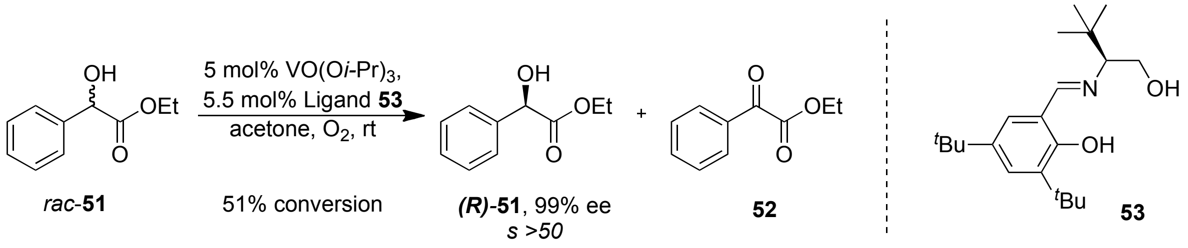
1. (a) *Organosulfur Chemistry in Asymmetric Synthesis*. Wiley-VCH: Weinheim, 2008; (b) Legros, J.; Juan , R. D.; Carsten, B. *Adv. Synth. Catal.* **2005,** *347*, 19-31; (c) Fernandez, I.; Khiar, N. *Chem. Rev.* **2003,** *103*, 3651-3706.
2. (a) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993,** *58*, 7624-7626; (b) Sun, J.; Zhu, C.; Dai, Z.; Yang, M.; Pan, Y.; Hu, H. *J. Org. Chem.* **2004,** *69*, 8500-8503; (c) Drago, C.; Lorenzo, C.; Richard, F. W. J. *Angew. Chem., Int. Ed.* **2005,** *44*, 7221-7223.
3. (a) Andersen, K. K. *Tetrahedron Lett.* **1962,** *3*, 93-95; (b) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964,** *86*, 5637-5646.
4. (a) Wudl, F.; Lee, T. B. K. *J. Chem. Soc., Chem. Commun.* **1972**, 61-62; (b) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973,** *95*, 6349-6358; (c) Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991,** *32*, 5885-5888.
5. (a) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984,** *106*, 8188-8193; (b) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325-326; (c) Bolm, C.; Frank, B. *Angew. Chem., Int. Ed. Engl.* **1995,** *34*, 2640-2642.

6. (a) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993,** *58*, 4529-4533; (b) Saito, B.; Katsuki, T. *Tetrahedron Lett.* **2001,** *42*, 3873-3876; (c) Peng, Y.; Feng, X.; Cui, X.; Jiang, Y.; Chan, A. S. C. *Synth. Commun.* **2001,** *31*, 2287-2287.
7. (a) Vetter, A. H.; Berkessel, A. *Tetrahedron Lett.* **1998,** *39*, 1741-1744; (b) Ohta, C.; Shimizu, H.; Kondo, A.; Katsuki, T. *Synlett* **2002,** 0161-0163; (c) Pelotier, B.; Anson, M. S.; Campbell, I. B.; Macdonald, S. J. F.; Priem, G.; Jackson, R. F. W. *Synlett* **2002,** 1055-1060; (d) Jeong, Y.-C.; Choi, S.; Hwang, Y. D.; Ahn, K.-H. *Tetrahedron Lett.* **2004,** *45*, 9249-9252; (e) Karpyshev, N. N.; Yakovleva, O. D.; Talsi, E. P.; Bryliakov, K. P.; Tolstikova, O. V.; Tolstikov, A. G. *J. Mol. Catal. A: Chem.* **2000,** *157*, 91-95; (f) Bryliakov, K. P.; Karpyshev, N. N.; Fominsky, S. A.; Tolstikov, A. G.; Talsi, E. P. *J. Mol. Catal. A: Chem.* **2001,** *171*, 73-80.
8. (a) Legros, J.; Carsten, B. *Angew. Chem., Int. Ed.* **2003,** *42*, 5487-5489; (b) Legros, J.; Carsten, B. *Angew. Chem., Int. Ed.* **2004,** *43*, 4225-4228; (c) Legros, J.; Carsten, B. *Chem. Eur. J.* **2005,** *11*, 1086-1092.
9. (a) Palucki, M.; Hanson, P.; Jacobsen, E. N. *Tetrahedron Lett.* **1992,** *33*, 7111-7114; (b) Sasaki, H.; Irie, R.; Katsuki, T. *Synlett* **1994,** *1994*, 356-358.
10. Thakur, V. V.; Sudalai, A. *Tetrahedron: Asymmetry* **2003,** *14*, 407-410.
11. Drago, C.; Caggiano, L.; Jackson, R. F. W. *Angew. Chem., Int. Ed.* **2005,** *44*, 7221-7223.
12. Zeng, Q.; Wang, H.; Weng, W.; Lin, W.; Gao, Y.; Huang, X.; Zhao, Y. *New J. Chem.* **2005,** *29*, 1125-1127.
13. (a) Rasappan, R.; Olbrich, T.; Reiser, O. *Adv. Synth. Catal.* **2009,** *351*, 1961-1967; (b) Gheorghe, A.; Chinnusamy, T.; Cuevas-Yañez, E.; Hilgers, P.; Reiser, O. *Org. Lett.* **2008,** *10*, 4171-4174; (c) Schätz, A.; Grass, Robert N.; Stark, Wendelin J.; Reiser, O. *Chem. Eur. J.* **2008,** *14*, 8262-8266; (d) Jain, S.; Reiser, O. *ChemSusChem* **2008,** *1*, 534-541; (e) Gissibl, A.; Padie, C.; Hager, M.; Jaroschik, F.; Rasappan, R.; Cuevas-Yanez, E.; Turrin, C.-O.; Caminade, A.-M.; Majoral, J.-P.; Reiser, O. *Org. Lett.* **2007,** *9*, 2895-2898; (f) Fraile, J. M.; Pérez, I.; Mayoral, José A.; Reiser, O. *Adv. Synth. Catal.* **2006,** *348*, 1680-1688.
14. (a) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006,** *8*, 4653-4655; (b) Meise, M.; Rainer, H. *ChemSusChem* **2008,** *1*, 637-642; (c) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008,** *37*, 1666-1688; (d) Bastero, A.; Font, D.; Pericas, M. A. *J. Org. Chem.* **2007,** *72*, 2460-2468.
15. Barbarini, A.; Maggi, R.; Muratori, M.; Sartori, G.; Sartorio, R. *Tetrahedron: Asymmetry* **2004,** *15*, 2467-2473.
16. Blum, S. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2003,** *68*, 150-155.
17. Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Org. Lett.* **2006,** *8*, 6099-6102.
18. Schwinn, D.; Heiko, G.; Bannwarth, W. *Helv. Chim. Acta* **2003,** *86*, 188-195.

4 Kinetic Resolution of α-hydroxy carbonyl compounds and pyridyl alcohols by fluorous tag clicked Schiff base vanadium complexes

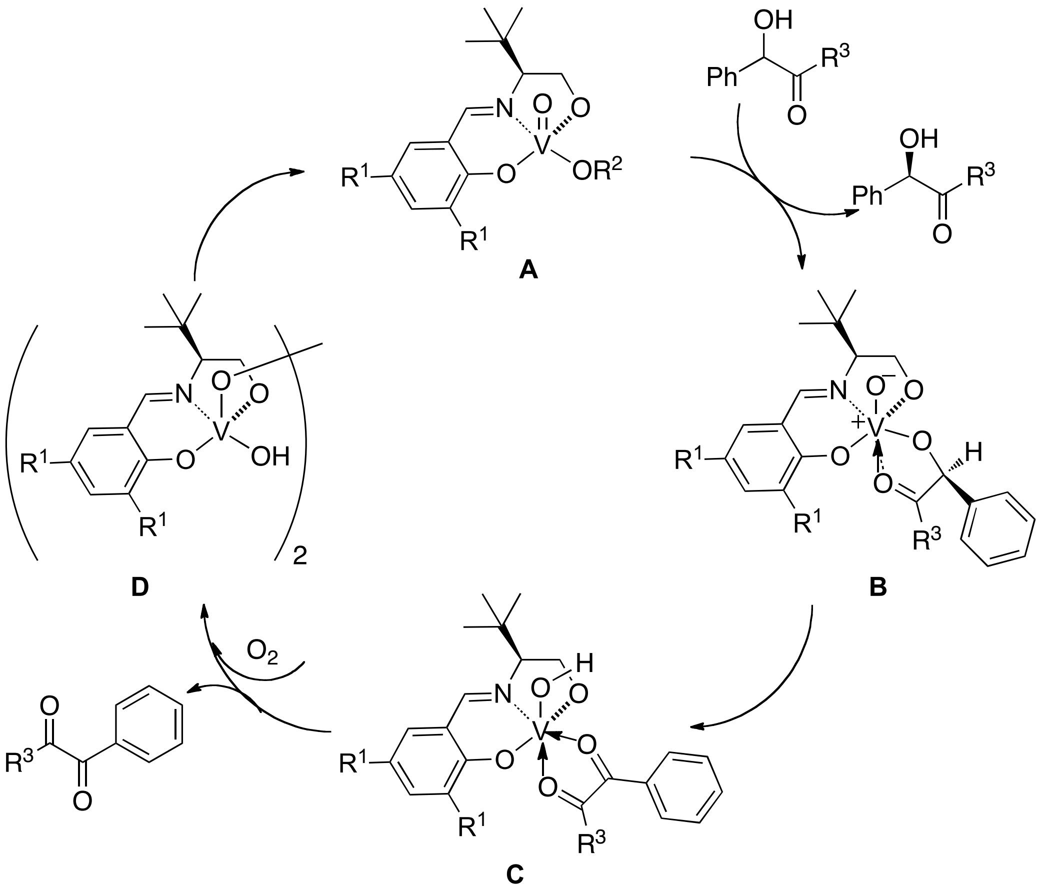
4.1 Introduction

Enantiopure α-hydroxy carbonyl compounds are important key components for the synthesis of a wide range of natural products, chiral ligands and biologically active compounds.[1] A great deal of research has been devoted to discovering catalytic systems that can efficiently generate enantiomerically pure α-hydroxy esters and an important strategy to such compounds exploits the kinetic resolution[2] of racemic substrates through the appropriate selection of catalyst and reaction conditions.[3] One type of catalytic system that effectively carries out kinetic resolutions to yield enantiomerically pure alcohols from racemic mixtures involves vanadium complexes with Schiff base ligands in combination of molecular oxygen as the stoichiometric oxidant. Specifically, tridentate Schiff base vanadium catalysts derived from salicylaldehydes and *tert*-leucinol have been shown to promote the oxidative kinetic resolution of racemic α-hydroxyesters by the selective oxidation of only one enantiomer (Scheme 19).[3c]



Scheme 19. Oxidative kinetic resolution of α-hydroxy esters.

The catalytic process proceeds through the deprotonation of the *sec*-alcohol by chiral catalyst **A** followed by ligand exchange resulting diastereomeric adduct (Scheme 23). α-proton elimination of the kinetically favored adduct **B** through a two-electron oxidation process with concominant reduction of the vanadyl(V) species to the corresponding vanadium-OH would lead to the oxidized product (α-keto or ester) or the coupled product **C**. The vanadium(III) hydroxide may disproportionate with the starting vanadyl catalyst to give vanadyl(IV) complexes with release of α-keto carbonyl compounds and water. Alternatively, it may be oxidized by reaction with molecular oxygen to lead to a peroxodimer **D**, which returns the original catalyst **A**.



Scheme **23**. Proposed mechanism for asymmetric oxidation of α-hydroxy carbonyl compounds.[3d]

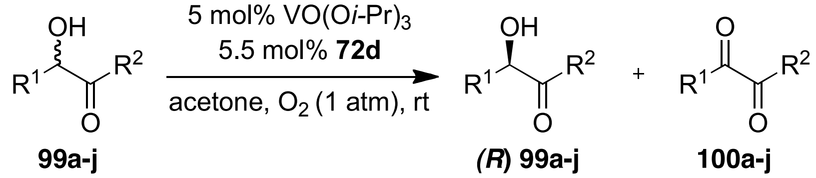
This reaction is particularly attractive not only due to the high enantioselectivity it imparts but also due to the use of molecular oxygen at atmospheric pressure as the primary oxidant. Molecular oxygen is highly abundant, low in cost, and non-toxic, which make it more attractive than other oxidants, particularly inorganic oxidants that can be expensive and potentially hazardous to dispose of after use. To the best of our knowledge, there is only one report by Shiels *et al.*[4] who used heterogeneous supported tridendate Schiff base vanadium complex for the title reaction. However, selectivities faded for those polymer supported catalysts upon recycling already in the second run.

The use of perflourinated alkyl chains as tags has been broadly applied to impose fluorous properties onto a given molecule. Arguably, the most important application of this strategy is to separate the so-tagged compound from a complex reaction mixture by fluorous biphasic separations, for example by extraction or retention of the tagged molecule with a perfluorinated solvent, fluorous silica or perfluorinated polymers.[5] As this property has provided an attractive method for catalyst recovery and recycling, consequently, perfluorinated tags were attached to several metal-based catalysts[6] including chiral Schiff base ligands[6e] and organocatalysts.[7]

4.2 Kinetic resolution of α-hydroxy esters and ketones under molecular oxygen

To evaluate the catalytic potential of the fluorous tag clicked ligand **72d**, we chose the oxidative kinetic resolution of alcohols by following a protocol initially developed by Toste *et al*.[3c] At the outset, ethyl mandelate was subjected to OKR with 5 mol% of $VO(OiPr)_3$, 5.5 mol% of **72d** at room temperature under 1 atmospheric pressure of oxygen. The reaction proceeded well and gave 55% conversion in 6 hrs, providing 41% isolated yield and 99% ee of the enantiomerically enriched α-hydroxy ester **(*R*)-99a** along with 49% yield of the corresponding α-keto ester (Table 5, entry 1). Subsequently, we investigated the asymmetric oxidation with various α-hydroxy esters and the results are summarized in table 1. Mandelate esters bearing electron donating groups gave excellent results in terms of reactivity and selectivity (Table 5, entry 3&5). In addition, electron withdrawing substituted mandelate ester provided excellent result in only 1 hour of reaction time (Table 5, entry 4). Since, α-hydroxy ketones are also viable substrates for oxidation reaction, at first we applied same reaction condition for benzoin. The reaction proceeded but the selectivity was poor (Table 5, entry 7). When the catalyst loading was increased from 5 to 10 mol%, we observed significant increase in conversion as well as the selectivity (Table 5, entry 8). Using 10 mol% of catalyst, we carried out the reaction with different benzoins. Almost in all cases, we observed good selectivity (Table 5, entries 9, 10 & 11).

Table 5. Kinetic resolution of α-hydroxy esters and ketones.

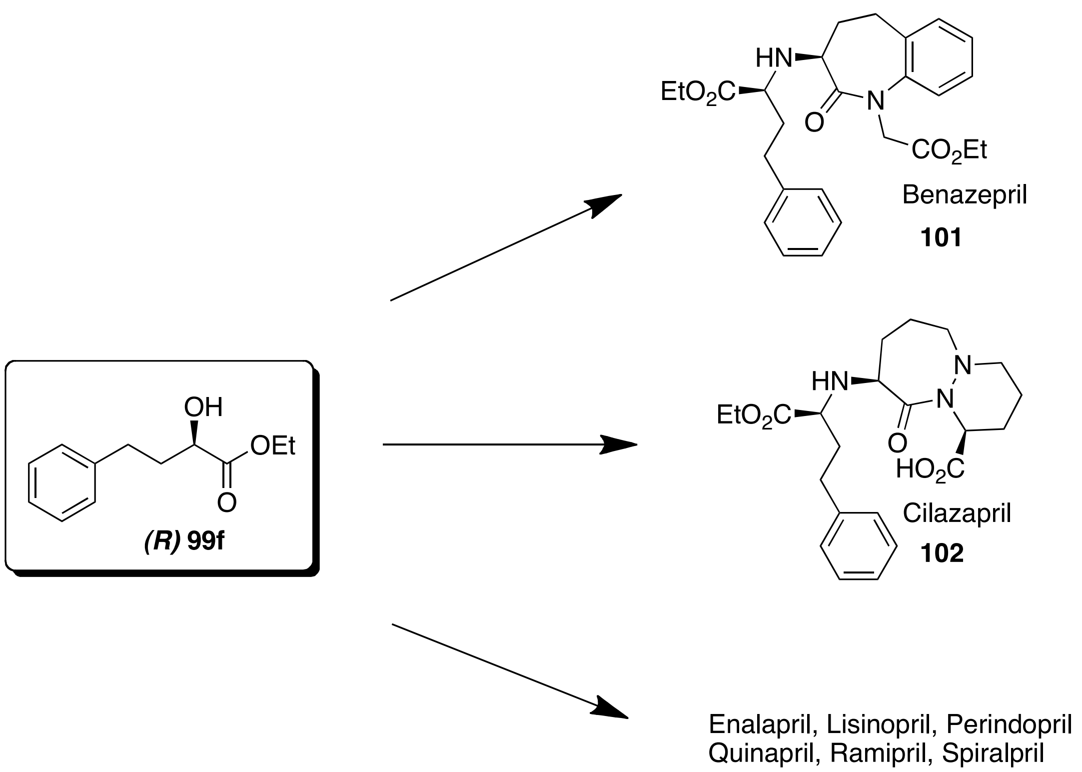


entry	R^1	R^2	substrate	time (h)	C^a	yield^b (%)	ee^c (%)	s^d
1	Ph	OEt	**99a**	6	55	41 (90)	99	49
2	Ph	OMe	**99b**	6	54	38 (84)	99	61
3	*p*-MeC_6H_4-	OMe	**99c**	5	57	37 (89)	99	35
4	*p*-$CF_3C_6H_4$-	OMe	**99d**	1	53	43 (90)	97	55
5	*p*-$OCH_3C_6H_4$	OMe	**99e**	5	54	39 (81)	99	61
6	Ph-C_2H_4	OEt	**99f**	68	50	45 (85)	95	145
7	Ph	Ph	**99g**	30	50	42 (96)	32	3
8^e	Ph	Ph	**99g**	7	65	31 (93)	99	16
9^e	*p*-MeC_6H_4-	*p*-MeC_6H_4-	**99h**	10	55	40 (90)	97	36
10^e	*p*-$OMeC_6H_4$-	*p*-$OMeC_6H_4$-	**99i**	8	59	36 (91)	99	27
11^e	*o*-$OMeC_6H_4$-	*o*-$OMeC_6H_4$-	**99j**	3.5	47	32 (77)	88	>50

[a] Conversion was determined by ^{1}H NMR analysis of crude reaction mixture. [b] Isolated yield of enantiomerically enriched α-Hydroxy carbonyl compounds; number in parentheses are the combined yield of recovered dicarbonyl and hydroxy carbonyl compound. [c] Determined by Chiral GC and HPLC. [d] $s = k_{\mathrm{rel(fast/slow)}} = \ln[(1-C)(1-\mathrm{ee})]/\ln[(1-C)(1+\mathrm{ee})]$. [e] Employed 10 mol% VO(O*i*-Pr)$_3$, 10.5 mol% Ligand **72d**.

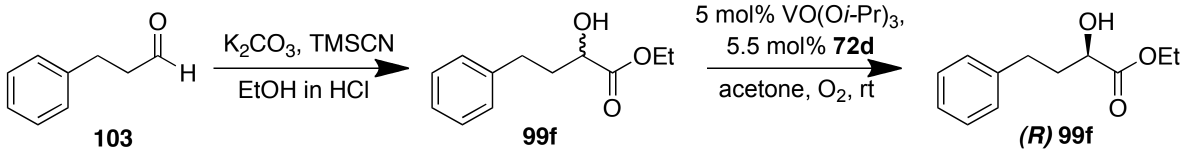
4.3 Resolution of pharmaceutical intermediates

This methodology is further applied to one of the biologically active key intermediate such as HPB ester [(*R*)-ethyl 2-hydroxy-4-phenylbutanoate], which is a valuable intermediate to synthesize many of ACE (Angiotensin Converting Enzyme) inhibitors such as Benazepril **101**, Cilazapril **102**, etc.[1b] These are widely used as antihypertensive drugs and the therapy of CHF (Congestive Heart Failure).



Scheme 24. Application of HPB ester in pharmaceutical industry.[1b]

The new synthesis of HPB ester started from inexpensive**103** (Scheme 25). Cyanosilylation of 3-phenylpropionaldehyde followed by hydrolysis afforded the racemic HPB ester which was subjected to asymmetric oxidation under the standard condition mentioned above, proceeded to 50% conversion in 68 hrs at room temperature, providing (*R*)-HPB ester **99f** in 45% yield and 95% *ee* along with the corresponding α-keto ester 40% yield (Table 6, entry 6).



Scheme 25. New synthesis of (*R*)-HPB ester.

4.4 Catalyst recovery

Furthermore, the fluorous catalyst **72d**-Vanadium makes it possible to recover itself by precipitation using hexane. The fluorous catalyst was cleanly recovered from the reaction mixture by precipitation, being repeatedly reusable. In each reuse, the recovered **72d**-vanandium complex without further purification retains its catalytic activity and same levels of enantioselectivity for upto four runs.

Table 6. Recyling of catalyst – HPB ester (3 mmol scale)

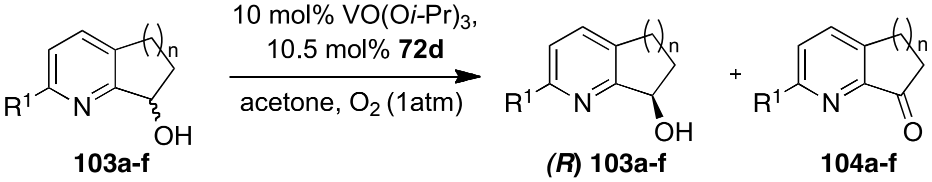
run	time (h)	C^a	yield^b(%)	ee(%)^c	s^d	cat.recovery
1	70	49	50 (92)	96	>100	128 mg
2	70	50	48 (89)	96	>100	126mg
3	96	52	43 (92)	96	65	115 mg
4	168	50	45 (87)	92	79	98 mg
5	185	60	35 (91)	92	13	90 mg

^{a} Conversion was determined by ^{1}H NMR. ^{b} Isolated yield of enantiomerically enriched α-Hydroxy carbonyl compounds. number in parentheses are the combined yield of recovered dicarbonyl and hydroxy carbonyl compound. ^{c} Determined by Chiral GC. ^{d} $s = k_{\mathrm{rel(fast/slow)}} = \ln[(1-C)(1-\mathrm{ee})]/\ln[(1-C)(1+\mathrm{ee})]$.

4.5 Kinetic resolution of pyridyl alcohols

Enantiomerically pure pyridyl alcohols are valuable intermediates for synthesis of chiral ligands and biologically active compounds.[8] Various enantioselective reductions[9] of pyridyl ketones and enzymatic approaches[10] have been reported. Recently, kinetic resolution of pyridyl alcohols *via* asymmetric benzoylation using a Cu(II)/Borabox complex has been reported by Pfaltz *et al.*[8d, 11] We were interested in this transformation in connection with our work on oxidative kinetic resolutions of α-hydroxy esters and ketones using molecular oxygen as stoichiometric oxidant. As seen before with before α-hydroxy carbonyl compounds, pyridyl alcohols could also be able to chelate with vanadium (V), which is expected to be an essential requirement for achieving high enantioselectivites. To test their suitability in the present strategy, several pyridyl alcohols were synthesized and investigated in the oxidative kinetic resolution using 1atm molecular oxygen. Initially, reactions were carried out using 10 mol% catalyst at room temperature. Reactions were sluggish at room temperature and gave little selectivity (Table 7, entry 1 & 3). Fortunately, increasing the reaction temperature to 60 °C, the reaction was accelerated and gave excellent results in terms of reactivity as well as selectivity (Table 7, entry 2 & 4). When increasing the size of the aliphatic ring markedly decreases the reactivity and selectivity in the reaction. On the other hand, pyridyl alcohols bearing Ph, Cl substituent on α-position greatly enhances the selectivity (Table 7, entries 6, 7 & 8).

Table 7. Kinetic resolution of pyridyl alcohol.



entry	R^1	n	substrate	temp (°C)	time (h)	*C* (%)[a]	yield (%)[b]	ee (%)[c]	*s*[d]
1	H	1	**103a**	rt	144	48	45 (92)	79	30.8
2	H	1	**103a**	60	5	51	43 (88)	92	53
3	H	2	**103b**	rt	98	48	42 (91)	60	8.53
4	H	2	**103b**	60	6.5	53	43 (94)	93	35.0
5	H	3	**103c**	60	11	48.5	48 (92)	34	2.9
6	Ph	1	**103d**	60	2.5	57.5	39 (90)	>99	47.6
7	Ph	2	**103e**	60	3	61	35 (93)	>99	31.5
8	Cl	2	**103f**	60	2	57	42 (97)	>99	51.2

[a] Conversion was determined by ^{1}H NMR. [b] Isolated yield of enantiomerically enriched Hydroxy compounds. number in parentheses are the combined yield of recovered carbonyl and hydroxy compound. [c] Determined by Chiral HPLC. [d] $s = k_{\mathrm{rel(fast/slow)}} = \ln[(1-C)(1-\mathrm{ee})]/\ln[(1-C)(1+\mathrm{ee})]$.

4.6 Conclusion

We have demonstrated that tagging of Schiff base ligands *via* the copper(I)-catalysed alkyne-azide cycloaddition with perfluoroalkyl moieties open the possibility to arrive at recyclable vanadium-Schiff base complex. Ligand **72d** proved to be highly efficient in the oxidative kinetic resolution of alpha hydroxy carbonyl compounds. For the first time, we realized pyridyl alcohols are also viable substrates for oxidative kinetic resolution with excellent selectivities. Moreover, the catalyst could be easily recovered and recycled in consecutive runs.

4.7 Notes and References

1. (a) Garry M. Coppola, D. H. F. S., *α-Hydroxy Acids in Enantioselective Syntheses*. VCH, Weinheim, Germany: **1997**; (b) Blaser, H. U.; Schmidt, E., *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*. VCH, Weinheim, Germany: **2003**.
2. (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988,** *18*, 249-330; (b) Keith, J. M.; Larrow, Jay F.; Jacobsen, Eric N. *Adv. Synth. Catal.* **2001,** *343*, 5-26.
3. (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001,** *123*, 7725-7726; (b) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001,** *123*, 7475-7476; (c) Radosevich,

A. T.; Musich, C.; Toste, F. D. *J. Am. Chem. Soc.* **2005,** *127*, 1090-1091; (d) Weng, S.-S.; Shen, M.-W.; Kao, J.-Q.; Munot, Y. S.; Chen, C.-T. *Proc. Natl. Acad. Sci. U. S. A.* **2006,** *103*, 3522-3527; (e) Alamsetti, S. K.; Muthupandi, P.; Sekar, G. *Chem. Eur. J.* **2009,** *15*, 5424-5427; (f) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003,** *5*, 835-837.

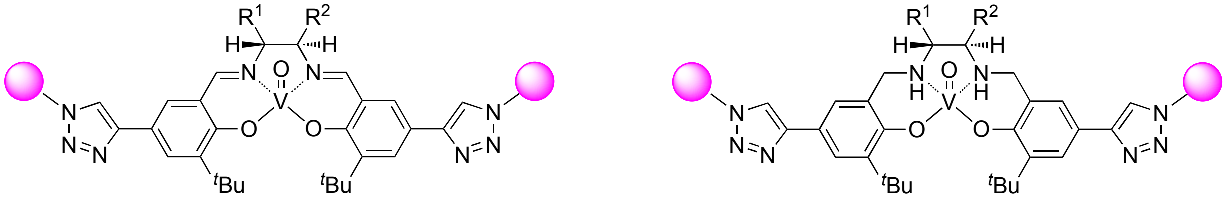
4. Shiels, R. A.; Venkatasubbaiah, K.; Jones, Christopher W. *Adv. Synth. Catal.* **2008,** *350*, 2823-2834.
5. (a) Gladysz, J. A.; Curran, D. P. *Tetrahedron* **2002,** *58*, 3823-3825; (b) Tzschucke, C. C.; Christian, M.; Willi, B.; Sebastian, R.; André, H.; Rainer, H. *Angew. Chem., Int. Ed.* **2002,** *41*, 3964-4000; (c) Zhang, W.; Curran, D. P. *Tetrahedron* **2006,** *62*, 11837-11865.
6. (a) Matsugi, M.; Curran, D. P. *J. Org. Chem.* **2005,** *70*, 1636-1642; (b) Dinh, L. V.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **2005,** *44*, 4095-4097; (c) Contel, M.; Cristina, I.; Mariano, L.; Pedro, R. V.; Pablo, J. A.; Richard, H. F. *Chem. Eur. J.* **2003,** *9*, 4168-4178; (d) Tzschucke, C. C.; Christian, M.; Heiko, G.; Willi, B. *Angew. Chem., Int. Ed.* **2002,** *41*, 4500-4503; (e) Pozzi, G.; Shepperson, I. *Coord. Chem. Rev.* **2003,** *242*, 115-124.
7. (a) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006,** *8*, 3077-3079; (b) Dalicsek, Z.; Pollreisz, F.; Gomory, A.; Soos, T. *Org. Lett.* **2005,** *7*, 3243-3246; (c) Gheorghe, A.; Cuevas-Yañez, E.; Horn, J.; Bannwarth, W.; Narsaiah, B.; Reiser, O. *Synlett* **2006,** 2767-2770.
8. (a) Iii, W. J. D.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004,** *43*, 70-74; (b) Kang, J.; Kim, H. Y.; Kim, J. H. *Tetrahedron: Asymmetry* **1999,** *10*, 2523-2533; (c) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996,** *118*, 1809-1810; (d) Mazet, C.; Roseblade, S.; Kohler, V.; Pfaltz, A. *Org. Lett.* **2006,** *8*, 1879-1882; (e) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006,** *45*, 5194-5197; (f) Xie, Y.; Huang, H.; Mo, W.; Fan, X.; Shen, Z.; Shen, Z.; Sun, N.; Hu, B.; Hu, X. *Tetrahedron: Asymmetry* **2009,** *20*, 1425-1432; (g) Bell, S.; Wustenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006,** *311*, 642-644.
9. (a) Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000,** *2*, 1749-1751; (b) Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* **2000,** *41*, 9277-9280; (c) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990,** *29*, 205-207; (d) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996,** *37*, 5675-5678.
10. (a) Uenishi, J. i.; Hiraoka, T.; Hata, S.; Nishiwaki, K.; Yonemitsu, O.; Nakamura, K.; Tsukube, H. *J. Org. Chem.* **1998,** *63*, 2481-2487; (b) Uenishi, J. i.; Hamada, M. *Tetrahedron: Asymmetry* **2001,** *12*, 2999-3006; (c) Uenishi, J.; Hamada, M. *Synthesis* **2002,** 0625-0630.
11. Roseblade, S. J.; Pfaltz, A. *Synthesis* **2007,** 3751-3753.

5 Cyanosilylation of aldehydes using Fluorous tag immobilized Schiff base V(IV) complexes

5.1 Introduction

Enantioselective addition of trimethylsilyl cyanide to prochiral aldehydes constitutes an important organic reaction because the resulting cyanohydrin trimethylsilyl ethers are versatile intermediates for the synthesis of pharmaceutical and natural products.[1] The first enantioselective synthesis of cyanohydrins was realized by Rosenthaler in 1908.[2] To date numerous methods have been developed for the addition of various cyanohydride sources to prochiral carbonyl compounds such as enzymes, Lewis acid (V, Ti, Al) or base catalysis with chiral ligands.[1,3] Excellent selectivities achieved in Ti(IV) complex catalyzed enantioselective cyanosilylation reaction in the presence of chiral Schiff base ligands such as tridentate Schiff base developed by Oguni,[3f,g] salen ligands of Belokon *et al.*[3c] and Che[3d] respectively. Salen vanadium complexes as catalysts were introduced by North *et al.*[3e] in 2000 for the cyanosilylation of prochiral aldehydes. This system is more attractive due to its simplicity of the reaction conditions requiring only 0.1 mol% of catalyst and the high enantioselectivity (upto 95% *ee*) achieved in the products. Recently, efforts have been made to develop recyclable chiral metal complexes on organic or inorganic supports[4] and ionic liquids[5] for this purpose.

Fluorous chemistry has been great potential for enantioselective transformations and recovery of the precious chiral catalyst from the reaction medium. However, the attachment of fluorous tags directly into salen ligands have not given high selectivities in asymmetric salen mediated catalysis in the past due to the electron withdrawing nature of fluorous chain.[6] To overcome this problem we introduced the fluorous tail on salen ligands *via* click chemistry[7] in order to minimize the electron withdrawing nature.



80a, $R^1 = R^2 = \text{-}(CH_2)_4\text{-}$
80b, $R^1 = R^2 = Ph$

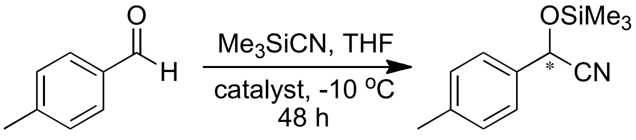
82a, $R^1 = R^2 = \text{-}(CH_2)_4\text{-}$
82b, $R^1 = R^2 = Ph$

Figure 6. Fluorous tag immobilized salen and salan vanadium(IV) complexes.

5.2 Evaluation of catalysts

To optimize the catalytic activity of complex **80a**, **80b**, **82a**, and **82b**, each complex was tested for its ability to catalyze the asymmetric addition of trimethylsilyl cyanide to 4-methylbenzaldehyde **105a** at -10 °C as shown in Table 8. As the results shown in Table 8 illustrate, the optimal catalyst was found to be complex **80a**, which is derived from the cyclohexadiamine tartrate salt. The enantiomeric excess of silyl ether was determined by chiral GC analysis. In contrast, the reduced version of complex **80a** called as salan vanadium complex **82a** and the phenyldiamine derived Vanadium complex **80b** and **82b** proved to be inferior results to complex **80a** (Table 8).

Table 8. Evaluation of catalyst on cyanosilylation of *p*-tolualdehyde.



105a **106a**

entry	catalyst[a]	yield (%)[b]	ee (%)[c]
1	**80a**	94	85
2	**80b**	89	81
3	**82a**	86	52
4	**82b**	95	49

[a] 0.1 mol% of catalyst used. [b] Isolated yield. [c] Determined by chiral GC.

Having determined that the complex **80a,** the best catalyst in the series tested, the effect of varying the catalyst to substrate ratio was investigated. As the Table 9 shows, the enantiomeric excess of silyl ether increases as the amount of catalyst used decreases. When the reaction was carried out with 5 mol% of catalyst **80a** at -10 °C, using 4-methylbenzaldehyde **105a** as representative substrate, 68% ee of trimethylsilyl ether was obtained. Whereas lowering the catalyst loading from 5 to 0.1 mol%, a dramatic increase in enantioselectivity from 68 to 85% was observed, while the yield remained almost same. The optimal amount of catalyst was found to be 0.1 mol% for cyanosilylation of aldehydes. Reducing amount of catalyst will increase the relative concentration of more active catalyst present in the reaction mixture.[3e]

Table 9. Variation of catalyst loading.

entry	**80a** (mol %)	yield (%)[a]	ee (%)[b]
1	0.1	94	85
2	0.5	95	83
3	1.0	90	75
4	1.0	92	75
5	5.0	98	68

[a] Isolated yield of enantiomerically enriched cyanosilylethers. [b] Determined by chiral GC.

The reactivity and enantioselectivity of the cyanosilylation reaction is strongly dependent on the nature of the solvent used. Therefore, the reaction was conducted in different solvents, such as dichloromethane, toluene, THF, diethyl ether using 4-methylbenzaldehyde **105a** as a representative substrate with catalyst **80a** under identical condition. Excellent yield and enantioselectivity are obtained with THF (entry 1, Table 10) while using DCM, diethylether and toluene as a solvent the yields were still high but the enantioselectivity dropped significantly ranging from 73 to 33% (entries 2,3 and 4, Table 10). We then focused on the effect of fluorous solvents on enantioselectivity; the results are summarized in Table 10. From entries 5-7, shown that the fluorous solvent had detrimental effect on enantioselectivity.

Table 10. Effect of solvent on enantioselectivity using catalyst **80a**.

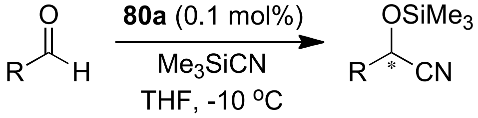
entry	solvent	yield (%)[a]	ee (%)[b]
1	THF	94	85
2	DCM	95	73
3	Et_2O	89	65
4	Toluene	90	33
5	CF_3-Ph	89	49
6	$C_2Cl_3F_3$	93	50
7	perfluorooctane	85	56

[a] Isolated yield of enantiomerically enriched cyanosilylethers. [b] Determined by chiral GC.

5.3 Substrate scope

Having the optimized catalyst structure and reaction conditions, the asymmetric addititon of trimethylsilyl cyanide to a range of aromatic aldehydes catalyzed by 0.1 mol% of catalyst **80a** was investigated. The results shown in Table 11 indicate that low to good enantioselectivities were obtained for aromatic aldehydes. In all catalytic runs, the *R*-form of V(O)salen complexes converted all aldehydes into *S*-form of cyanosilylethers.

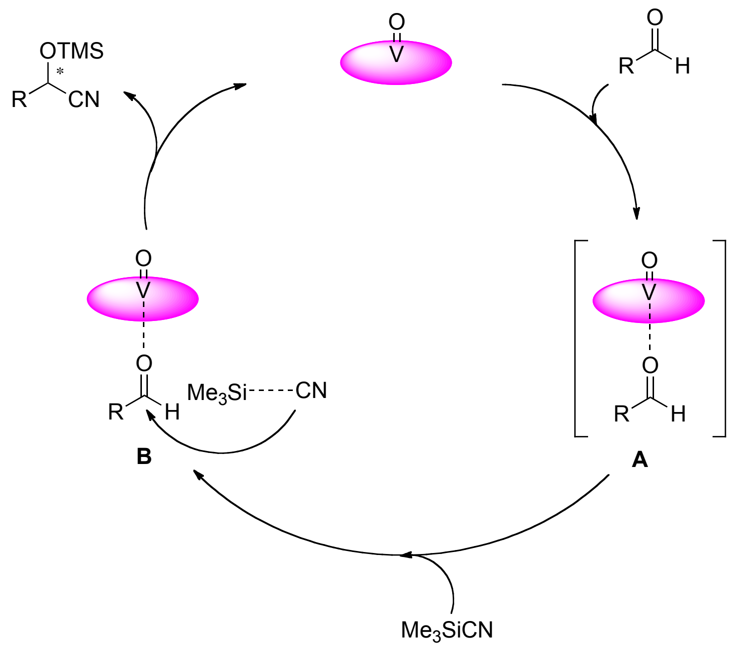
Table 11. Substrate scope



entry	substrate	product	yield (%)[a]	*ee* (%)[b]	*ee* (%)[c]
1	4-methyl benzaldehyde (**105a**)	**106a**	94	85	94
2	3-methoxy benzaldehyde (**105b**)	**106b**	92	62	-
3	3-methyl benzaldehyde (**105c**)	**106c**	85	65	95
4	4-isopropyl benzaldehyde (**105d**)	**106d**	95	62	-
5	4-hydroxy benzaldehyde (**105e**)	**106e**	79	60	-
6	2-methoxy benzaldehyde (**105f**)	**106f**	83	64	-
7	4-methoxy benzaldehyde (**105g**)	**106g**	93	38	90
8	2-methyl benzaldehyde (**105h**)	**106h**	96	33	90
9	benzaldehyde (**105i**)	**106i**	93	29	94

[a] Isolated yield of enantiomerically enriched cyanosilylethers. [b] Determined by Chiral GC. [c] literature value for non supported complex.[3e]

A probable mechanism is shown in scheme 26: In presence of the vanadium salen complex activation of the aldehyde takes place to form an intermediate **A** being the rate determination step. This intermediate reacts in a fast step with TMSCN guided by the chiral environment of the catalyst to produce trimethylsilylether of the respective cyanohydrins.



Scheme 26. Probable mechanism for catalytic cyanosilylation of aldehydes.[8]

5.4 Recycling of the catalyst

The interesting feature of this novel fluorous tag clicked V(IV) salen complex **80a** is its inherent tendency to be precipitated out in non-polar solvent such as hexane. After each catalytic cycle, the catalyst **80a** was recovered and re-used for the subsequent runs of cyanosilylation of 4-methyl benzaldehyde **105a** by adding fresh reactants. From the data in table 12, it becomes evident that the catalyst **80a** worked very well for up to four runs with a small decrease in reactivity and selectivity due to some physical loss in the work up process with retained enantioselectivity of trimethylsilylether of cyanohydrin **106a**.

Table 12. Recycling of catalyst **80a**

entry	time (h)	yield (%)[a]	ee (%)[b]
1	48	95	85
2	48	87	85
3	56	91	83
4	56	89	85

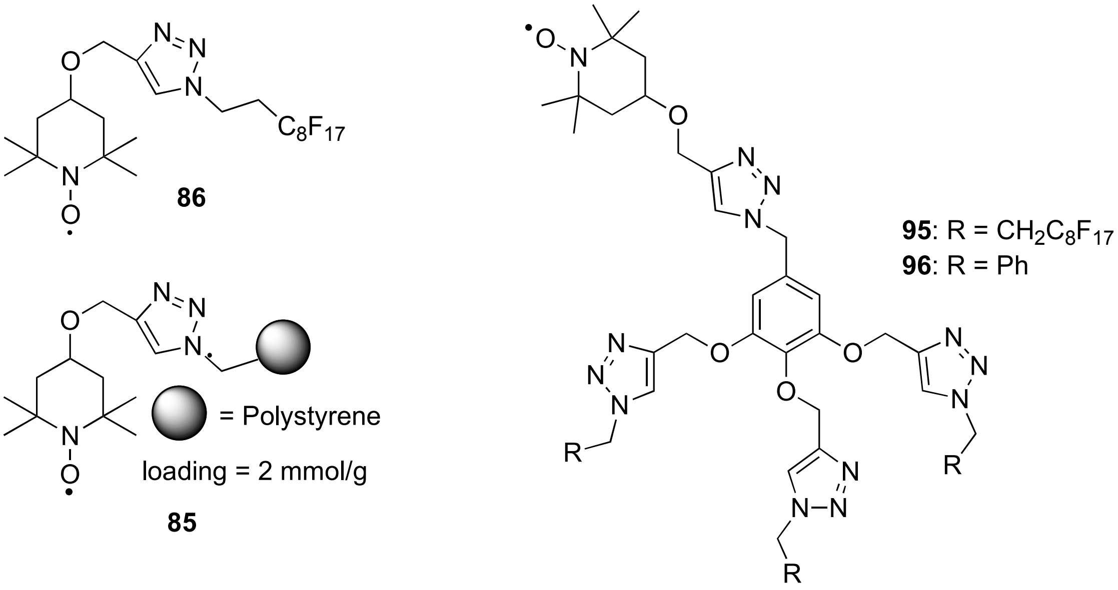
[a] Isolated yield of enantiomerically enriched cyanosilylethers. [b] Determined by chiral GC.

5.5 References

1. (a) Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004,** *43*, 2752-2778; (b) North, M. *Tetrahedron: Asymmetry* **2003,** *14*, 147-176.
2. Rosenthaler., L. *Biochem. Z.* **1908,** *14*, 238-253.
3. (a) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994,** *33*, 1555-1564; (b) North, M. *Synlett* **1993,** 807-820; (c) Belokon, Y. N.; Gutnov, A. V.; Moskalenko, M. A.; Yashkina, L. V.; Lesovoy, D. E.; Ikonnikov, N. S.; Larichev, V. S.; North, M. *Chem. Commun.* **2002**, 244-245; (d) Zhou, X.-G.; Huang, J.-S.; Ko, P.-H.; Cheung, K.-K.; Che, C.-M. *J.chem.soc., Dalton Trans.* **1999**, 3303-3309; (e) Belokon, Y. N.; North, M.; Parsons, T. *Org. Lett.* **2000,** *2*, 1617-1619; (f) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993,** *58*, 1515-1522; (g) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994,** *50*, 4385-4398.
4. (a) Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *J. Catal.* **2003,** *215*, 199-207; (b) Baleizão, C.; Gigante, B.; García, H.; Corma, A. *Tetrahedron* **2004,** *60*, 10461-10468.
5. (a) Baleizao, C.; Gigante, B.; Garcia, H.; Corma, A. *Green Chem.* **2002,** *4*, 272-274; (b) Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron Lett.* **2003,** *44*, 6813-6816.
6. (a) Pozzi, G.; Cavazzini, M.; Cinato, F.; Montanari, F.; Quici, S. *Eur. J. Org. Chem.* **1999,** 1947-1955; (b) Maillard, D.; Pozzi, G.; Quici, S.; Sinou, D. *Tetrahedron* **2002,** *58*, 3971- 3976.
7. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001,** *40*, 2004-2021.
8. Khan, N.-u. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Mayani, V. J.; Jasra, R. V. *Tetrahedron: Asymmetry* **2006,** *17*, 2659-2666.

6. Combination of perfluoroalkyl and triazoles; A new recovery strategy for TEMPO

A well-known approach for the development of recyclable catalysts is their attachment to a polymeric support that is insoluble in the solvent in which the reaction is taking place, allowing its recovery by simple filtration. An inherent disadvantage of this strategy is the generally reduced reactivity of such modified catalysts due to the heterogeneous nature of the reaction.[1] Based on our interest in developing immobilized reagents on organic and inorganic supports,[2] we recently utilized the copper-catalyzed[3] alkyne azide cycloaddition[4] (CuAAC) reaction as a versatile method for the ligation of TEMPO to polymers[5] such as **85** or **86**[6]. In this context we discovered that F_{17}-Click-TEMPO **86** showed low solubility in perfluorinated, but good solubility in organic solvents, and more strikingly, showed little affinity to fluorous silica but high affinity to conventional silica 60.[7]



86

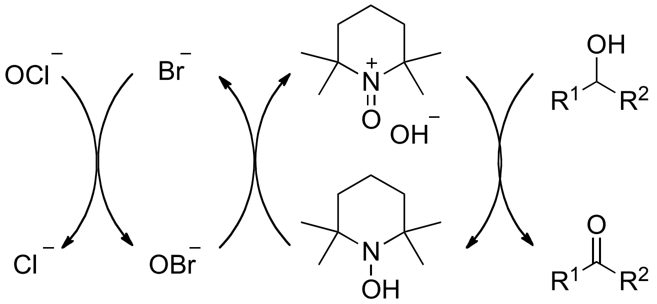
85

95: R = $CH_2C_8F_{17}$
96: R = Ph

Figure 7. Immobilized TEMPO's.

6.1 Oxidation of alcohols under Anelli's condition

The new TEMPO derivative **95** showed remarkable properties: It is largely insoluble in fluorinated or organic solvents, as well as in water; nevertheless, oxidation of alcohols using Anelli's conditions, calling for NaOCl as the terminal oxidant and KBr as the cocatalyst,[8] proceeded with high yields and selectivity (Table 13).



Scheme 27. TEMPO-catalyzed bleach-oxidation of alcohols using bromide as cocatalyst.

The active oxidant in this system is the corresponding oxoammonium cation (Scheme 27). Oxidation of the alcohol affords the corresponding carbonyl compound and the reduced form of TEMPO, the hydroxylamine, TEMPOH. The latter is then reoxidized by NaOCl to regenerate the oxoammonium cation. In general, catalytic amount of sodium bromide is used as a cocatalyst, as the reoxidation step is more favorable with hypobromite and the sodium bromide produced is readily reoxidized by hypochlorite.

All reactions were carried out at 0 °C in the presence of 1 mol % of catalyst and 1.3 equiv. NaOCl with respect to the substrate. Under these conditions, most alcohols were quantitatively oxidized within 15 min, with the exception of the more challenging cyclohexanol, which was smoothly oxidized within 1 h. In all cases, the purity of the isolated carbonyl derivatives were >95%.

Table 13. Oxidation of alcohols with **95**[a]

entry	alcohol	conversion[b] (%)	yield[c] (%)
1	4-bromobenzyl alcohol	>98	95
2	4-methylbenzyl alcohol	>98	98
3	1-octanol	>98	96
4	1-decanol	>98	92
5	cyclohexanol[d]	>98	91

[a]Alcohol (1.0 mmol) in CH_2Cl_2 (2 mL), KBr (0.2 mmol), catalyst (1.0 mol%), NaOCl (1.3 mmol), $NaHCO_3$ (0.5 mmol), 0 °C. Reaction time 15 min. [b] Determined by ^1H NMR. [c] Isolated yield. [d] Reaction time 1 h.

Notably, the activity of **95** (Table 14, entries 6-8) in the oxidation of alcohols (using 25 mmol of substrate), in CH_2Cl_2 / water is at least comparable to that of unmodified TEMPO (entries 1-2), being soluble in the solvent system, but about four times more active than polystyrene supported PS-CLICK-TEMPO **85** (entries 4-5). Like this latter catalyst, however, **95** can be recovered in a highly efficient manner by simple filtration of the reaction mixture through a standard sintered glass funnel (P40, 16-40 μm pore size) and reused without further purification. For example, the oxidation of 4-methylbenzyl alcohol to the corresponding benzaldehyde was carried out in four cycles in 92-98% yield with an initial amount of 1 mol% of catalyst **95**, from which 70% in total could still be recovered after the last cycle (Table 15).

Table 14. Activity comparison of heterogeneous and homogeneous TEMPO catalysts in the Anelli oxidation of 4-methylbenzyl alcohol[a]

entry	catalyst (mol%)	time (min)	yield[b] (%)	TON	TOF (h^{-1})
1[c]	TEMPO (0.2)	40	≥ 98	500	≥ 750
2[c]	TEMPO (0.2)	15	60	300	1200
3	86 (0.2)	40	≥ 98	500	≥ 750
4	85 (2.5)	15	68	29	116
5	85 (0.2)	40	58	300	450
6[c]	95 (1.0)	15	≥ 98	100	≥ 400
7[c]	95 (0.2)	40	97	500	≥ 750
8[c]	95 (0.2)	15	74	370	1480
9	13 (0.2)	40	96	500	≥ 750

[a] Alcohol (1.0 mmol) in CH_2Cl_2 (2 mL), KBr (0.2 mmol), catalyst (1.0 mol%), NaOCl (1.3 mmol), $NaHCO_3$ (0.5 mmol), 0 °C. Reaction time 15 min. [b] Determined by ^1H NMR. [c] 25 mmol scale.

The high activity of **95** can be most likely attributed to its behavior to act like a surfactant, suggesting a detergent effect that enhances catalysis.[9] We reason that the low solubility of **95** in dichloromethane/water is sufficient to induce the formation of an emulsion. Nevertheless, **95** must still act as a heterogeneous catalyst in this solvent system as well, judging from our attempts to reduce the amount of **95** to 0.2 mol% (Table 14, entry 8), which, although emulsion formation still occurs, resulted in reduced conversions in the oxidation of alcohols.

The combination of multiple polar triazole and perfluoro chains seems to be decisive for this property since both, **85** or with **96**, the latter being analogous to **95** but having the perfluoro alkyl chains replaced by benzyl groups, are readily soluble in dichloromethane, displaying similar activity as **95** (Table 14, entries 1 and 6) but being not recoverable by simple filtration from the reaction mixture.

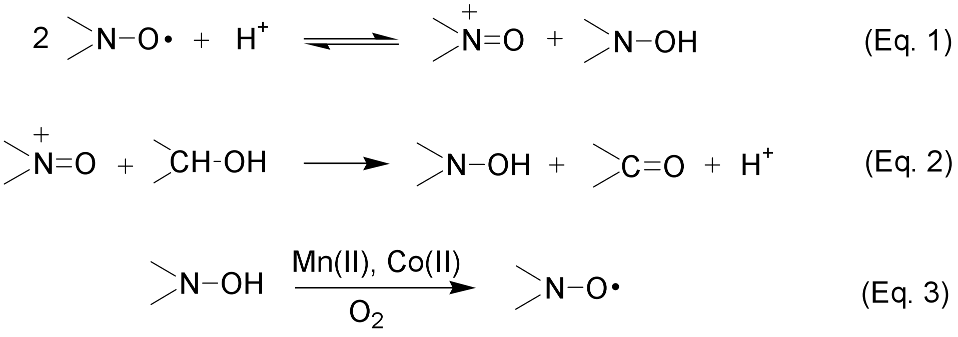
Table 15. Oxidation of 4-methylbenzyl alcohol with **95**. Recovery and recycling experiment[a]

run	conversion[b] (%)	yield (%)[c]	purity (%)[b]
1	> 98	98	> 98
2	> 98	99	> 98
3	> 98	97	> 98
4	> 98	92	> 98

[a]Alcohol (1.0 mmol) in CH_2Cl_2 (2 mL), KBr (0.2 mmol), catalyst (1.0 mol%), NaOCl (1.3 mmol), $NaHCO_3$ (0.5 mmol), 0 °C. Reaction time 15 min. [b] Determined by ^1H NMR. [c] Isolated yield.

6.2 Oxidation of alcohols under Minisci's condition

In 1984, Semmelhack reported that TEMPO/CuCl can oxidize allylic and benzylic alcohols to aldehydes using molecular oxygen.[10] This method was recently improved with the discovery of several variations of the original Cu/TEMPO catalytic systems.[11] Minisci *et al*. showed that the aerobic oxidation of both activated and unactivated alcohols can be performed under mild condition using Mn(II)-Co(II) or Mn(II)-Cu(II) nitrates in acetic acid under ambient pressure and temperature.[12] The mechanism of this transformation is depicted in Scheme 28. Acidic medium is necessary to make the catalytic system effective; the oxidation takes place selectively in acetic acid solution, but no substantial oxidation occurs in acetonitrile solution under the same condition. The actual oxidant is the oxoammonium salt, which is generated by disproportionation of TEMPO radical catalysed by the acidic medium (Eq. 1). Then, the oxoammonium salt oxidizes the alcohol to the carbonyl derivative (Eq. 2) and the TEMPO radical is regenerated by oxygen and the metal salt catalytic system (Eq. 3).



Scheme 28. Mn–Co–TEMPO-catalyzed oxidation of alcohols by oxygen.[12]

Although numerous immobilized TEMPO variants on both organic and inorganic supports were synthesized, only few examples are known where molecular oxygen is used as terminal oxidant.[13] We decided to investigate the catalytic properties of **95** under the conditions developed by Minisci, being especially attractive for industrial processes since non-chlorinated solvents and oxygen as the terminal oxidant are used.

All reactions were carried out in the presence of 1 mol% of catalyst **95** and 2 mol% $Mn(NO_3)_2 \bullet 4H_2O$ and 2 mol% $Co(NO_3)_2 \bullet 6H_2O$ with respect to the substrate under oxygen atmosphere. Under these conditions most alcohols were oxidized within 2–4 hours, with the exception of the more challenging 1-octanol, cyclohexyl alcohol and cinnamyl alcohol, which were oxidized in at most 20 hours (Table 16). In all cases, the conversion was over 90%.

Table 16. Aerobic oxidation of alchols with TEMPO **95**.[a]

entry	alcohol	time (h)	conversion[b] (%)	yield[c] (%)
1	benzyl alcohol	2	90	89
2	4-methylbenzyl alcohol	2	> 98	98
3	4-methoxybenzyl alcohol	3	> 98	96
4	4-bromobenzyl alcohol	3	95	92
5	cinnamyl alcohol	20	> 98	90
6	cyclohexyl alcohol	12	> 98	93
7	1-octanol	7	90	82
8	thiophen-2-yl-methanol	4	> 98	91
9	(4-methylthio)benzylalcohol	0.45	>98	89

[a] Alcohol (1.0 mmol) in AcOH (1 mL), $Mn(NO_3)_2.4H_2O$ (2.0 mol%), $Co(NO_3)_2.6H_2O$ (2.0mol%), **95** (1.0 mol%), 40 ^oC and at oxygen atmosphere. [b] Determined by ^1H NMR. [c] Isolated yield.

Again, the activity of **95** (Table 17) in the oxidation of 4-methyl benzyl alcohol is comparable to that of unmodified TEMPO, being soluble in the solvent system, but about four times more active than polystyrene supported PS-CLICK-TEMPO **85**.

Table 17. Activity comparison of heterogeneous and homogeneous TEMPO catalysts in the aerobic Oxidation of 4-methylbenzyl alcohol[a]

entry	catalyst	conversion[b] (%)	yield (%)
1	**TEMPO**	97	92
2	**85**	26	25
3	**95**	84	82

[a] Alcohol (1.0 mmol) in AcOH (1 mL), $Mn(NO_3)_2.4H_2O$ (2.0 mol%), $Co(NO_3)_2.6H_2O$ (2.0mol%), 3-Fluorous tagged TEMPO (1.0 mol%), 40 °C and at oxygen atmosphere, reaction time 1h. [b] Determined by ^1H NMR.

Oncemore, **95** could be recovered by simple filtration of the reaction mixture through a standard sintered glass funnel (see above) and reused without further purification. For example, the oxidation of 4-methylbenzyl alcohol to the corresponding benzaldehyde was carried out in three cycles in 96–98% yield with an initial amount of 1 mol % of catalyst **95**, from which 79% in total could still be recovered after the last cycle (Table 17).

6.3 Conclusion

We have shown a new heterogeneously supported TEMPO, acting at the same time as a surfactant between water and dichloromethane, which retains the activity of homogeneous TEMPO catalysts for the oxidation of alcohols, but nevertheless allows recovery by simple filtration.

6.4 Notes and References

---

1. (a) DeVos, D. E.; Sels, B. F.; Jacobs, P. A. *Adv. Catal.* **2002**, *46*, 1. (b) Gladysz, J. A. *Pure Appl.Chem.* **2001**, *73*, 1319; (c) Oehme, G. in *Comprehensive Asymmetric Catalysis I-III*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. 3, p 1377.
2. (a) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045 (b) Fraile, J. M.; Garcia, J. I.; Herrerias, C. I.; Mayoral, J. A.; Reiser, O.; Socuellamos, A.; Werner, H. *Chem. Eur. J.* **2004**, *10*, 2997 (c) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325 (d) Werner,H.; Herrerias, C. I.; Glos, M.; Gissibl, A.; Fraile, J. M.; Perez, I.; Mayoral, J. A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 125.
3. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596 (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

---

4. Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613.
5. *Immobilized TEMPO reagents:* (a) Bolm, C.; Fey, T. *Chem. Commun.* **1999**, 1795 (b) Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C. *J. Org. Chem.* **2001**, *66*, 8154 (c) Brunel, D.; Fajula, F.; Nagy, J. B.; Deroide, B.; Verhoef, M. J.; Veum, L.; Peters, J. A.; van Bekkum, H. *Appl. Catal. A* **2001**, *213*, 73 (d) Ciriminna, R.; Blum, J.; Avnir, D.; Pagliaro, M. *Chem. Commun.* **2000**, 1441 (e) Ciriminna, R.; Bolm, C.; Fey, T.; Pagliaro, M. *Adv. Synth. Catal.* **2002**, *344*, 159 (f) Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell'Anna, G. *Org. Lett.* **2004**, *6*, 441 (g) Ferreira, P.; Hayes, W.; Phillips, E.; Rippon, D.; Tsang, S. C. *Green Chem.* **2004**, *6*, 310 (h) Benaglia, M.; Puglisi, A.; Holczknecht, O.; Quici, S.; Pozzi, G. *Tetrahedron.* **2005**, *61*, 12058 (i) Tanyeli, C.; Gümüş, A. *Tetrahedron Lett.* **2003**, *44*, 1639-1642 (j) Holczknecht, O.; Cavazzini, M.; Quici, S.; Shepperson, I.; Pozzi, G. *Adv. Synth. Catal.* **2005**, *347*, 677 (k) Pozzi, G.; Cavazzini, M.; Holczknecht, O.; Quici, S.; Shepperson, I. *Tetrahedron Lett.* **2004**, *45*, 424 (l) Gilhespy, M.; Lok, M.; Baucherel, X. *Chem. Commun.* **2005**, 1085 (m) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **2000**, 271 (n) Weik, S.; Nicholson, G.; Jung, G.; Rademann, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 1436.
6. Gheorghe, A.; Matsuno, A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 1016.
7. Gheorghe, A.; Cuevas-Yañez, E.; Horn, J.; Bannwarth, W.; Narsaiah, B.; Reiser, O. *Synlett* **2006**, 2767.
8. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.
9. Dwars, T.; Paetzold, E.; Oehme, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 7174.
10. Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374.
11. (a) Betzemeier, B., Cavazzini, M.; Quici, S.; Knochel, P.; *Tetrahedron Lett.* **2000** *41*, 4343. (b) Ragagnin, G.; Betzemeier, B.; Quici, S.; Knochel, P. *Tetrahedron* **2002**, *58*, 3985. (c) Ansari, I. A.; Gree, R. *Org. Lett.* **2002**, *4*, 1507. (d) Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2005**, *46*, 3323. (e) Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414. (f) Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Adv. Synth. Catal.* **2004**, *346*, 1051.
12. (a) Cecchetto, A.; Fontana, F., Minisci, K.; Recupero, F. *Tetrahedron Lett.* **2001**, *42*, 6651. (b) Minisci, F.; Recupero, F.; Rodino, M.; Sala, M.; Schneider, A. *Org. Process Res. Dev.* **2003**, *7*, 794.
13. (a) Ferreira, P.; Phillips, E.; Rippon, D.; Tsang, S. C. *Appl. Catal. B* **2005**, *61*, 206. (b) Geisslmeir, D.; Jary, W. G.; Falk, H. *Monatsh. Chem.* **2005**, *136*, 1591. (c) Dijksman, A.;

Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 102. (d) Benaglia, M.; Puglisi, A.; Holczknecht, O.; Quici, S.; Pozzi, G. *Tetrahedron* **2005**, *61*, 12058. (e) Gilhespy, M.; Lok, M.; Baucherel, X. *Chem. Commun.* **2005**, 1085.

7. A recyclable TEMPO catalyst for aerobic oxidation of sulfides to sulfoxides

7.1 Introduction

The selective oxidation of sulfides into corresponding sulfoxide is one of the most important transformations in organic synthesis and is useful for the preparation of biologically and medicinally valuable intermediates.[1, 2] Reagents are available for almost every conceivable type of oxidation, but in many instances there are disadvantages associated with their use due to high cost, difficult in handling, lack of sensitivity, toxicity, instability, etc. Therefore, the development of systems displaying high atom economy using comparatively harmless oxidants such as dioxygen, hypochlorite is desired. The chemoselective oxidation of sulfides to the corresponding sulfoxides can be studied without any metal[3] however, it requires high pressure of oxygen and elevated temperature.[4] Nevertheless, there are few catalytic system available for this transformation using atmospheric oxygen as secondary oxidant.[5]

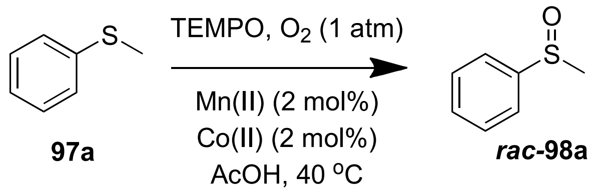
Nitric acid was the very first oxidizing agent used to convert sulfides to sulfoxides. In 1865, Marcker used this reagent to oxidize dibenzylsulfide to dibenzylsulfoxide.[6] This method was subsequently used to prepare large number of alkyl and arylsulfoxides. Fujita *et al.* studied the sulfoxidation *via* thioether cation radical formation, which was catalyzed by using stoichiometric amount of Thallium nitrate in 1977.[7] Subsequently, firouzabadi *et al.* described Fe(III) & Cu(II) montmorillonite supported metal nitrates such as clayfen and claycop[8] for the oxidation of sulfides. The drawback associated with this system is applicable only for aryl-alkyl sulfides. Various methods for the oxidation of sulfides with metal nitrates have been reported, including hydrated Fe(III) and Cu(II) nitrates under solvent free condition. In all these cases the metal nitrates were used as reagent. In addition, binary catalytic system such as hydrated $Bi(NO_3)_3$-$BiBr_3$, $Fe(NO_3)_3$-$FeBr_3$ under aerobic condition[5e,f] using 5 mol% of bromide and 10 mol% of nitrate in a redox medium were also reported.

The catalytic oxidation of sulfides to the corresponding sulfoxides by oxoammonium ion generated from TEMPO by one electron transfer mechanism was first reported by Skarzewski *et al.*[9] Oxoammonium salts are known as mild electrophilic oxidants, however their use for the oxidation of sulfides in combination with cheapest metal salts (<5 mol%) and molecular oxygen (1 atm) has not been studied.

During the course of our ongoing study on metal salt catalysed chemoselective oxidation of alcohols under Minisci's condition,[10, 11b, c] we serendipitously found that the similar reaction condition can be extended to the oxidation of sulfides to corresponding sulfoxides.

7.2 Oxidation of sulfides with TEMPO

The novel catalytic oxidation of sulfides takes place at 40 °C, in acetic acid, under one atmospheric dioxygen in combination with small amounts of $Mn(NO_3)_2.4H_2O$ (2 mol%), $Co(NO_3)_2.6H_2O$ (2 mol%) and TEMPO (1 mol%).



Scheme 29. Oxidation of Thioanisole.

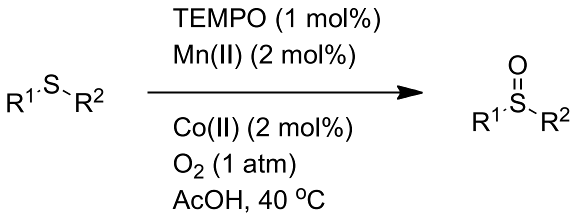
Inorder to find out the efficiency of the catalytic system, we choose thioanisole as the model substrate in our early experiments and the results are summarized in Table 17. Employing 1 mol% of TEMPO in presence of 2 mol% of $Mn(NO_3)_2.4H_2O$ and $Co(NO_3)_2.6H_2O$ afforded the corresponding sulfoxide in 58% conversion within 1.5 h (entry 1, table 17). The complete conversion was achieved by prolonging the reaction time to 4 h (entry 2, table 17). In the absence of O_2 / TEMPO or both, the conversion was only 32-40% respectively (entry 3, 5 & 4, table 17). In the absence of TEMPO and O_2 there was no control in chemoselectivity, it leads to 5% formation of sulfone as side product (entry 4, table 17). Either changing the solvent or in the absence of metal salts, there was no product formation observed (entry 6, 7, 8 & 9, table 17). Finally, the combination of TEMPO, metal salts and oxygen atmosphere under acetic acid condition proved to be very effective for the chemoselective oxidation of sulfides (entry 2, table 17). The prominent role of TEMPO in this reaction is to increase the formation of sulfoxide over sulfone and to obtain quantitative yield.

Table 17. Catalytic oxidation of methyl phenyl sulfide[a]

entry	TEMPO	metal salts	O_2	Solvent	time (h)	sulfoxide (%)[b]	sulfone (%)[b]
1	Yes	Yes	Yes	AcOH	1.5	58	-
2	Yes	Yes	Yes	AcOH	4	94	-
3	Yes	Yes	-	AcOH	1.5	40	-
4	-	Yes	-	AcOH	1.5	32	5
5	-	Yes	Yes	AcOH	1.5	35	traces
6	Yes	-	Yes	AcOH	4	<5	-
7	-	-	Yes	AcOH	4	-	-
8	Yes	-	-	AcOH	4	-	-
9	Yes	Yes	Yes	DCM	4-24	N.R	-
10	Yes	Yes	Yes	CH_3CN	4-24	N.R	-

[a] Thioanisole (1.0 mmol) in AcOH (1ml), $Mn(NO_3)_2•4H_2O$ (2.0 mol%), $Co(NO_3)_2•6H_2O$ (2.0 mol%), TEMPO (1.0 mol%) and at oxygen atmosphere, 40 °C. [b] conversion determined by ^{1}H- NMR Spectroscopy.

Under the optimized conditions, a representative spread of sulfides was evaluated. We were pleased to find that diaryl- and dialkyl- as well as arylalkylsulfides are smoothly converted to the corresponding sulfoxides in high yields. Noteworthy this was true also for electron rich sulfides, further oxidation to sulfones was not observed. It was necessary to prolong reaction times and/or catalyst loading for some, especially electron deficient sulfides (Table 1, entries 8-10) to the point that oxidation might not proceed at all (Table 18, entry 11).



Scheme 30. Oxidation of sulfides.

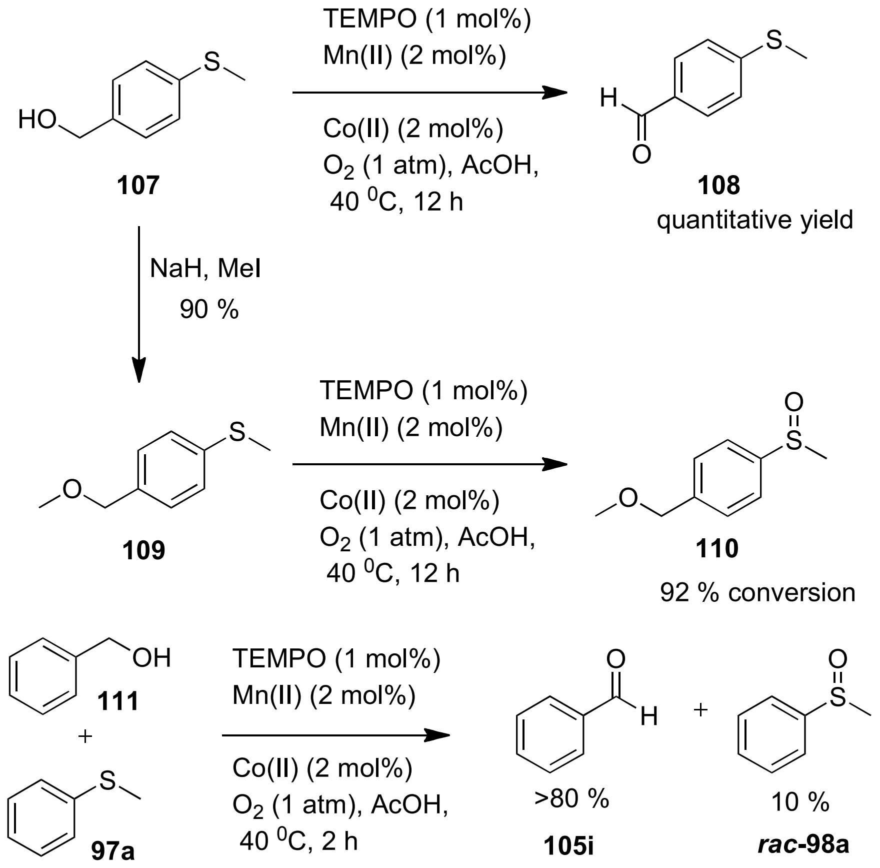
Table 18. Chemoselective oxidation of sulfides[a]

entry	R^1	R^2	time (h)	yield (%)[b]
1	Ph	Me	4	94
2	Ph	C_2H_5	4	96
3	Ph	*i*-Pr	6	91
4	2-Naphthyl	Me	5	89
5	4-Me-C_6H_4	Me	3	92
6	4-OMe-C_6H_4	Me	3	93
7	4-Cl-C_6H_4	Me	15	79
8[c]	$PhCH_2$	Ph	12	81
9[c]	Ph	Ph	24	68
10	4-CHO-C_6H_4	Me	24	0
11	C_3H_7	C_3H_7	7	98
12	C_2H_5	C_2H_5	6	92
13	*i*-Pr	*i*-Pr	6	86

[a] Sulfide (1.0 mmol) in AcOH (2 mL), $Mn(NO_3)_2•4H_2O$ (2.0 mol%), $Co(NO_3)_2•6H_2O$ (2.0 mol%), TEMPO (1.0 mol %) and at oxygen atmosphere, 40 ^oC. [b] Isolated yields. [c] Employed 5 mol% of $Mn(NO_3)_2•4H_2O$ & $Co(NO_3)_2•6H_2O$ & TEMPO.

7.3 Chemoselective oxidation with TEMPO

Since both alcohols and sulfides can be oxidized under the reaction conditions described here, we subsequently investigated issues of chemoselectivity. We found a high preference for alcohol oxidation when both functional groups were present in a substrate. For example, oxidation of **107** gave rise to **108** in quantitative yield, demonstrating that alcohol oxidation is much more facile than sulfide oxidation under the reaction conditions applied (Scheme 31). Nevertheless, after protecting **107** as methyl ether **109**, oxidation of the sulfides smoothly occurred suggesting that the hydroxymethyl group in **107** has not simply deactivated the methyl sulfide by virtue of its electron withdrawing nature. Moreover, oxidation of a mixture of benzyl alcohol **111** and phenyl methyl sulfide **97a** favored with a selectivity of at least 8:1 the oxidation of the alcohol.



Scheme 31. Chemoselectivity between alcohols and methyl phenyl sulfides in aerobic TEMPO oxidations.

Despite the high efficiency of TEMPO for the sulfide oxidation, its high cost calls for recyclable versions of this catalyst. Recently, our group reported TEMPO derivatives **85, 86,** and **95** that allow recovery either by precipitation from hexanes (**86**) or by simple filtration (**85** and **95**) due to the heterogeneous nature of the latter.[11a-c]

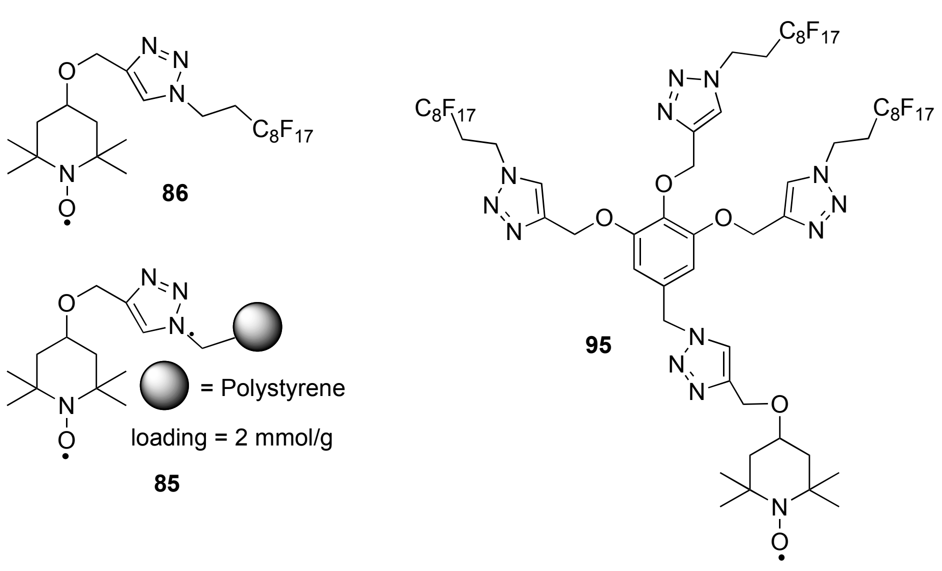


Figure 8. Immobilized TEMPOs.

Table 19. Oxidation of thioanisole[a]

entry	catalyst	sulfoxide (%)[b]
1	**TEMPO**	58
2	**86**	57
4	**85**	38
4	**95**	57

[a] Sulfide (1.0 mmol) in AcOH (1mL), $Mn(NO_3)_2{\bullet}4H_2O$ (2.0 mol%), $Co(NO_3)_2{\bullet}6H_2O$ (2.0 mol%), catalyst (1.0 mol %) and at oxygen atmosphere, 40 °C, Reaction Time = 1.5 h. [b] Determined by ^1H- NMR Spectroscopy.

Applying **86**, being soluble in acetic acid, for the oxidation of phenylmethyl sulfide under limiting conditions that allow an assessment of catalyst activity not unexpectedly revealed the same activity compared to TEMPO itself (Table 19, entry 1&2). **85** and **95**, being heterogeneously dispersed in acetic acid, showed however remarkable differences in activity: While the activity of **85** dropped roughly by a factor of two, **95** retained the activity of homogeneous TEMPO, going along with our previous observations for the oxidation of alcohols.[11c] Moreover, **95** showed also with other sulfides literally the same activity as was found with TEMPO (Table 20, cf. Table 18).

Table 20. Chemoselective oxidation of sulfides[a]

entry	R^1	R^2	time (h)	yield (%)[b]
1	Ph	Me	4	90
2	Ph	C_2H_5	4	92
3	Ph	*i*-Pr	6	92
4	2-Naphthyl	Me	5	91
5	4-Me-C_6H_4	Me	3	93
6	4-OMe-C_6H_4	Me	3	89
7	4-Cl-C_6H_4	Me	15	82
8[c]	Ph	Ph	24	61
9[c]	$PhCH_2$	Ph	12	82
10	C_3H_7	C_3H_7	7	91
11	C_2H_5	C_2H_5	6	95
12	*i*-Pr	*i*-Pr	6	90

[a] Sulfide (1.0 mmol) in AcOH (2 mL), $Mn(NO_3)_2{\bullet}4H_2O$ (2.0 mol%), $Co(NO_3)_2{\bullet}6H_2O$ (2.0 mol%), **95** (1.0 mol %) and at oxygen atmosphere, 40 °C. [b] Isolated yields. [c] Employed 5 mol% of $Mn(NO_3)_2{\bullet}4H_2O$, $Co(NO_3)_2{\bullet}6H_2O$ & **95**.

7.4 Catalyst Recovery

Catalyst **95** can be recovered by simple filtration of the reaction mixture through a standard sintered glass funnel (P40, 16-40 µm pore size) and reused without further purification. For example, the oxidation of thioanisole to the corresponding sulfoxide was this way carried out in five cycles in 92 - 98% yield (Table 21) with an initial amount of 1 mol% of catalyst **95**, of which 70% in total (i.e. >90% for each cycle) could still be recovered after the fifth run. We attribute the overall loss of catalyst due to transfer operations of the catalyst between the filter and the reaction flask.

Table 21. Oxidation of thioanisole: Recycling of catalyst **95**[a]

entry	run	conversion[b] (%)	yield (%)	recovery of catalyst (mmol)	recovery of catalyst (mg)
1	1	>98	98	0.0284	56
2	2	>98	98	0.0274	54
3	3	>98	90	0.0259	51
4	4	>98	92	0.0228	45
5	5	>98	95	0.0203	40

[a] Thioanisole (3.0 mmol) in AcOH (1mL), $Mn(NO_3)_2$•$4H_2O$ (2.0 mol%), $Co(NO_3)_2$•$6H_2O$ (2.0 mol%), catalyst (1.0 mol %) and at oxygen atmosphere, 40 °C, Reaction Time = 12 h. [b] Determined by ^{1}H- NMR Spectroscopy.

It is tempting to speculate that the fluorous chains in **95** increase the local oxygen concentration as known for fluorous media[12] to account for the superior activity in comparison to **85**, however, we have no direct experimental evidence to support this hypothesis.

7.5 Conclusion

We could develop a highly efficient protocol for the aerobic oxidation of sulfides to sulfoxides using catalytic amounts of TEMPO in combination with manganese and cobalt nitrate. Moreover, with heterogeneous **95** a readily recoverable and reusable catalyst could be identified displaying the same activity as unmodified TEMPO

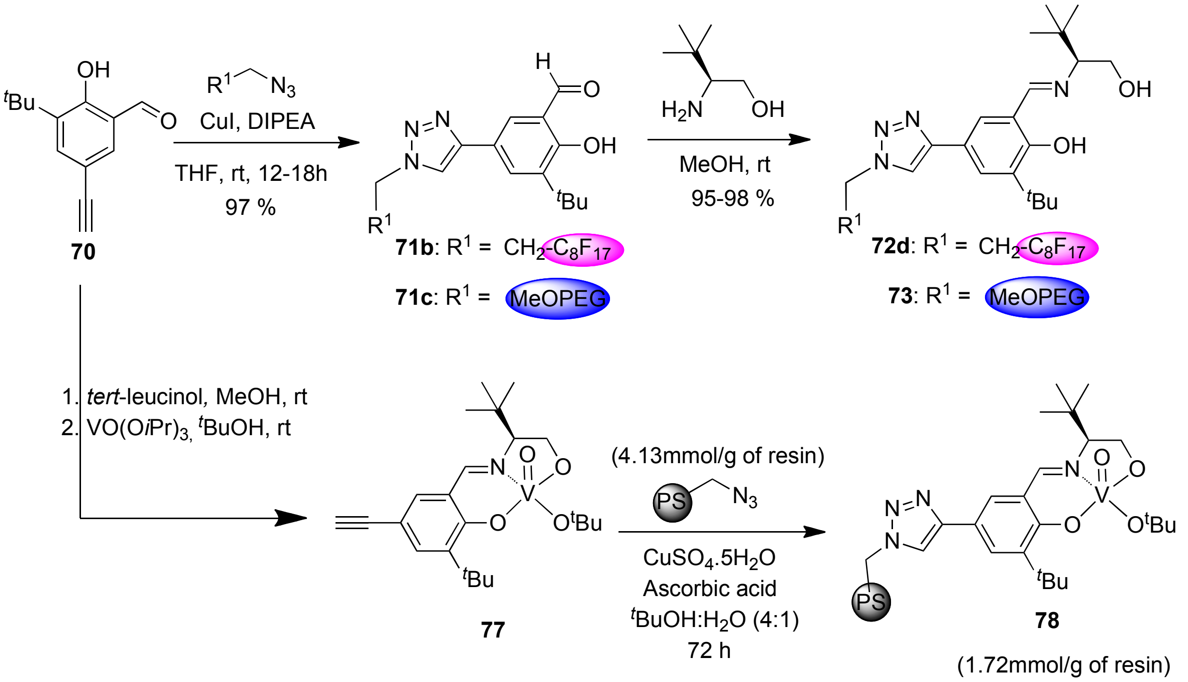
7.6 Notes and references

1. Sulfur reagents in organic synthesis; Metzner, P.; Thuillier, A.; Eds.; Academic Press: London, **1994**.

2. Drawbowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *In The chemistry of sulfones and sulfoxides;* patai, S., Rappoport, Z., Stirling, C., Eds.; Wiley: Chichester, **1988**, 233.
3. Correa, P. E.; Riley, D. P. *J. Org. Chem.* **1985**, *50*, 1787.
4. Dell'Anna, M. M.; Mastrorilli, P.; Nobile, J. *J. Mol. Catal. A*: *Chem.* **1996**, *108*, 57.
5. (a) Schoneich, C.; Aced, A.; Asmu, K. *J. Am. Chem. Soc.* **1993**, *115*, 11376; (b) Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3241; (c) Bosch, E.; Kochi, J. K. *J. Org. Chem.* **1995**, *60*, 3172; (d) Iwahama, T.; Sakaguchi, S.; Ishii, Y. P. *Tetrahedron Lett.* **1998**, *39*, 9059; (e) Komatsu, M.; Uda, M.; Suzuki, H. *Chem. Lett.* **1997**, 1229; (f) Martin, S. E.; Rossi, R. I. *Tetrahedron letters*. **2001**, *42*, 7147.
6. Marcker, C. *Ann.* **1865**, *136*, 75.
7. Nagao, Y.; Ochiai, M.; Kaneko, K.; Maeda, A,; Watanabe, K,; Fujita, E. *Tetrahedron Lett.* **1977**, *18,* 1345.
8. (a) Firouzabadi, H.; Iranpoor, N.; Zolfigol, M. A. *Synth. Commun.* **1998**, *28*, 377. (b) Firouzabadi, H.; Iranpoor, N.; Zolfigol, M. A. *Synth. Commun.* **1998**, *28*, 1179.
9. Siedlecka, R.; Skarzewski, J. *Synlett*, **1996**, 757.
10. Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* **2001**, *42,* 6651.
11. (a) Gheorghe, A.; Cuevas-Yañez, E.; Horn, J.; Bannwarth, W.; Narsaiah, B.; Reiser, O. *Synlett* **2006**, 2767; (b) Gheorghe, A.; Matsuno, A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 1016; (c) Gheorghe. A.; Chinnusamy, T.; Cuevas-Yañez. E.; Hilgers. P,; Reiser. O. *Org. Lett.* **2008**, *10*, 4171.
12. (a) R. D. Chambers, G. Sandford, A. Shah, *Synth. Commun.* **1996**, *26*, 1861. (b) S. Colonna, N. Gaggero, F. Montanari, G. Pozzi, S. Quici, *Eur. J. Org. Chem.* **2001**, 181 and references therein.

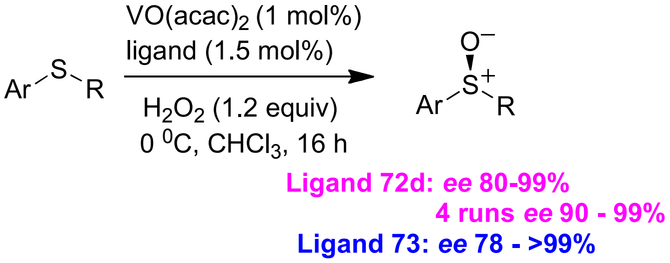
1. Asymmetric Sulfoxidation with polymer clicked vanadium complex and aq.H_2O_2

We have developed an extremely simple and practical protocol for grafting chiral Schiff bases onto polymeric support such as MeOPEG, Merrifield resin and fluorous tag from readily available and inexpensive starting materials using click chemistry as a tagging method (Scheme 32).



Scheme 32. Polymer clicked Schiff base ligands *via* click chemistry

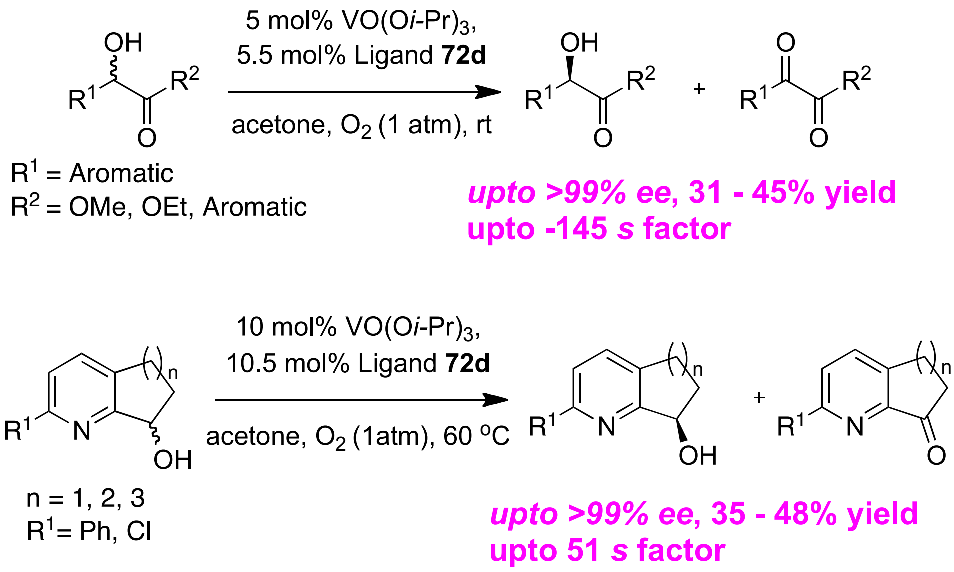
We have evaluated 'so-clicked' ligands in vanadium Schiff base catalyzed asymmetric oxidation of sulfides. Homogeneous polymer supported Schiff bases **72d** and **73** proved to be superior with respect to reactivity and selectivity than the heterogeneous supported Schiff base **78**. As exemplified by employing the catalysts **72d** in up to four runs without loss of significant enantioselectivity. Recycling of the catalyst is achieved by precipitation (Scheme 33).



Scheme 33. Asymmetric Sulfoxidation with ligand **72d** & **73**.

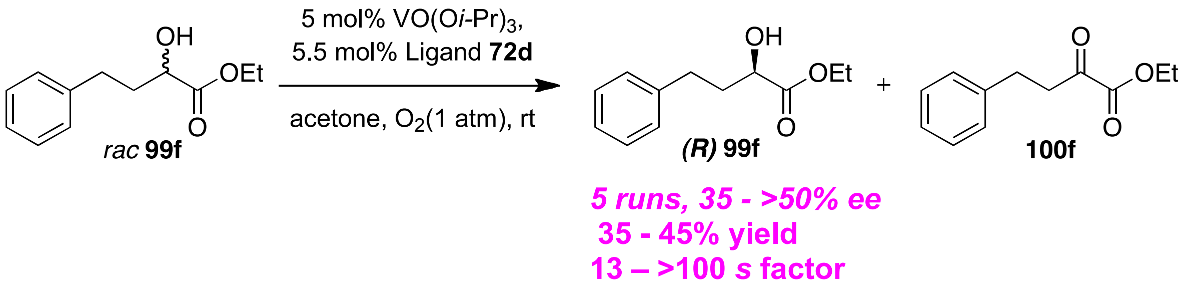
2. Vanadium catalyzed Asymmetric oxidation of α-hydroxy carbonyl compounds Using Molecular Oxygen as stoichiometric oxidant

The catalytic efficiency of the ligand **72d** was further evaluated for the kinetic resolution of α-hydroxy carbonyl compounds as well as more challenging pyridyl alcohols (Scheme 34). In both reaction, high enantioselectivities and good yields were obtained with selectivity factor 11 - >100.



Scheme 34. Kinetic Resolution of alcohols with ligand **72d**.

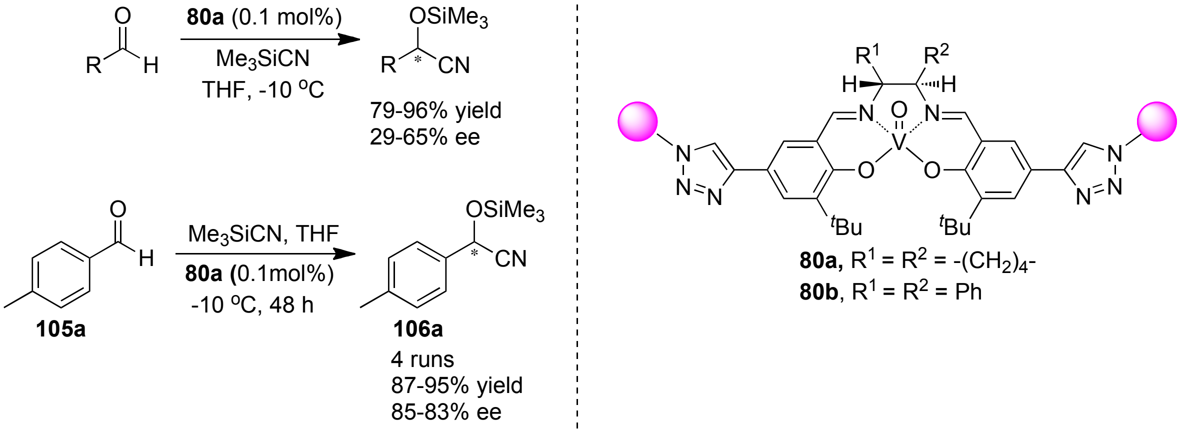
This methodology is further applied to one of the biologically active key intermediate such as **HPB ester**, which is a valuable intermediate to synthesize many of **ACE inhibitors** (Angiotensin Converting Enzyme). We could efficiently recycle the catalyst up sto 5 runs with slight loss of selectivity using HPB ester as a standard starting material in 3 mmol scale (Scheme 35).



Scheme 35. Kinetic resolution of HPB ester with **72d**.

3. Cyanosilylation of aldehydes using Fluorous tag immobilized Schiff base V(IV) complex

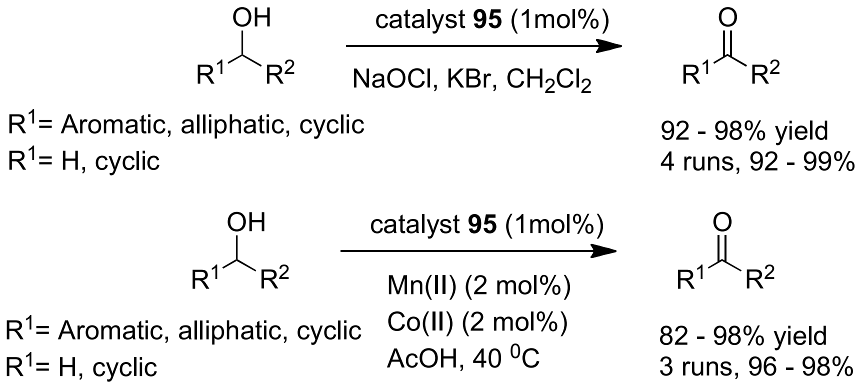
Chiral recyclable vanadium(IV) complexes were synthesized and used for the asymmetric addition of trimethylsilyl cyanide to various aldehydes at -10 °C. The catalyst **80a** performed well with 4-methyl benzaldehyde, giving excellent yield of trimehtylsilylether of cyanohydrins (95%) with good chiral induction (85%) in 48 hours with added advantage of four times recyclability.



Scheme 36. Cyanosilylation of aldehydes using catalyst **80a**.

4. Combination of perfluoroalkyl chains and triazoles: A new recovery strategy for TEMPO

We have developed new homo- and heterogeneously supported TEMPOs (Figure 8). Catalyst **86 & 95** showed similar activity like native **TEMPO** in the oxidation of alcohols under Anelli's and Minisci's condition, where as diminished reactivity observed for the same with **85**. Ultimately, catalyst **95** recovered by simple filtration due to its heterogeneous character and reused.



Scheme 37. Oxidation of alcohols using **95** under Anelli's & Minisci's condition.

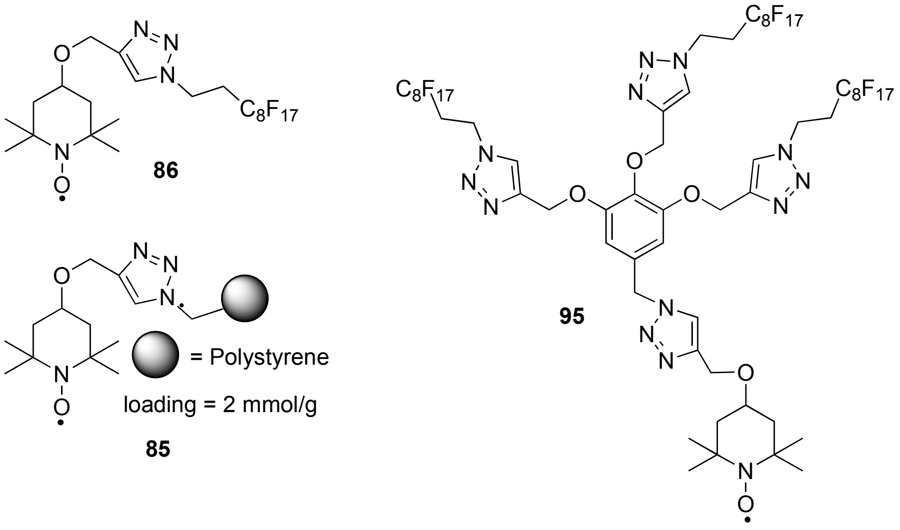
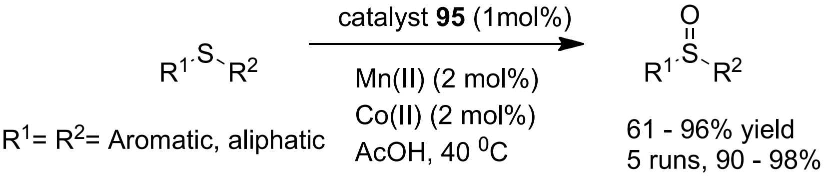


Figure 8. Immobilized TEMPOs.

5. Recyclable TEMPO for aerobic oxidation of sulfides to sulfoxides

During the course of our ongoing study on metal salt catalyzed chemoselective oxidation of alcohols under Minisci's condition, we serendipitously found that the sulfoxides themselves produced during the reaction, can be very effective catalysts for the selective oxidation of sulfides to sulfoxide. We found that a Co(II)-Mn(II), TEMPO in the presence of acetic acid was very effective for the selective aerobic oxidation of sulfides to sulfoxide under mild condition. Moreover, the catalyst **95 s**could be recycled upto 5 times without significant loss of yield.



Scheme 38. Oxidation of sulfides using **95**.

9. Experimental part

9.1 General protocol

All reactions with oxygen- and moisture sensitive reactants were performed under nitrogen atmosphere. All air or moisture sensitive liquids were transferred by syringe. Column chromatography was performed on silica gel Geduran SI 60 (0.063-0.200 mm) or flash chromatography on flash silica gel 60 (0.040-0.063) purchased from Merck.

Reagents & solvents

All commercially available reagents were used as received. Solvents were purified according to standard laboratory methods. THF was distilled over sodium/ benzophenone before use. Acetonitrile was distillated over calcium hydride.

Stereochemical assignment

The absolute configurations of the products were assigned by the comparison of their optical rotations with literature values. All other absolute configurations were assigned by analogy based on a uniform HPLC data.

NMR spectroscopy

^{1}H NMR spectrums were recorded on a Bruker Avance 600 (600 MHz) and Bruker Avance 300 (300 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 7.26 ppm). The spectra were analyzed by first order; the coupling constants are reported in Hertz (Hz). Characterization of signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = double of a doublet, dt = double of a triplet, dq = double of a quartet, ddd = double of a doublet of a doublet, Integration is determined as the relative number of atoms. ^{13}C NMR spectrums were recorded on a Bruker ARX 400 (100.6 MHz), Bruker Avance 300 (75.5 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 77.16 ppm).

Mass spectrometry

Mass spectrometry (Varian MAT 311A) was done in the Central Analytical Laboratory (Universität Regensburg). Elemental analysis (Vario EL III or Mikro-Rapid CHN) was done in microanalytical department of the University of Regensburg.

IR spectra, optical rotation and melting points

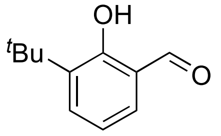
IR Spectrums were recorded on a Bio-Rad Excalibur Series FT-IR. Solid compounds were measured in KBr, liquid compounds as a neat film between NaCl-plates. The wave numbers are given in [cm^{-1}]. Melting points were measured on a Büchi SMP 20 in a silicon oil bath. Optical rotations were measured on a 241 MC Perkin-Elmer polarimeter with sodium lamp (589 nm) in the specified temperature and solvent. Either 1 dm or 0.1 dm cell was used and the concentrations are given in g/100 ml.

HPCL and GC

Chiral HPLC (335 UV detector) was performed on a Kontron Instruments 325 System. Chiracel OD/OD-H, AS and OJ columns were used (50x4.6 mm, 10 µm,) at the mentioned flowed rate and wavelength. Gas chromatography (GC) was measured on Fisons Instruments GC 8000 series (Data Jet Integrator, CP-chiralsil-DEX-CP column).

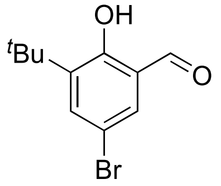
9.2 Synthesis of Schiff base ligands precursor

3-*tert*-butyl-2-hydroxybenzaldehyde (68)[1]



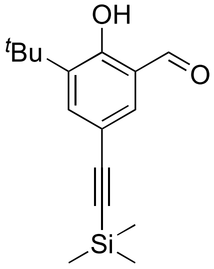
Dry paraformaldehyde (26.1 g, 0.90 mol) was added to a mixture of the phenolic derivative **67** (20 g, 0.13 mol), commercially available magnesium dichloride (19 g, 0.20 mol) and dry (over Na) triethylamine (69 mL, 0.50 mol) in acetonitrile (500 mL) and the mixture heated under reflux for 3 h. The mixture was cooled to room temperature after which 5% aq HCl was added and the product extracted with diethylether. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum. The residue purified by flash chromatography on silica gel (2% ethyl acetate in hexane). After concentration of the collected fractions gave 20.4 g (86%) as pure yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 6.95 (t, J = 7.7 Hz, 1H), 7.40 (dd, J = 7.7, 1.6 Hz, 1H), 7.53 (dd, J = 7.7, 1.6 Hz, 1H), 9.93 (s, 1H), 11.79 (s, 1H); ^{13}C-NMR (75.5 MHz,): δ = 197.2, 161.2, 138.2, 134.1, 132.0, 120.7, 119.2, 34.9, 29.2. IR (neat): $\tilde{\nu}$ = 3600-2700, 1655, 1309, 1260, 1220, 1190, 796, 750 cm^{-1}.

5-bromo-3-*tert*-butyl-2-hydroxybenzaldehyde (69)[2]



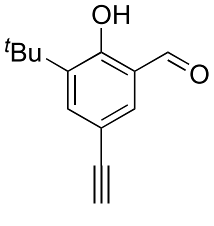
A solution of Br_2 (3 mL, 0.06 mol) in acetic acid was added drop wise at room temperature over 1 h to a solution of 3-*tert*-butyl-2-hydroxybenzaldehyde (10.3 g, 0.06 mol) in acetic acid. After 3 h the reaction mixture was diluted with dichloromethane and washed with water, saturated aqueous sodium thiosulfite, saturated aqueous $NaHCO_3$ and brine. The organic phase was dried with Na_2SO_4 and the solvents were evaporated to afford the title compound as a yellow solid 13.8 g (90%). M.P = 63-66 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 9H), 7.52 (d, *J* = 2.5 Hz, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 9.81 (s, 1H), 11.73 (br s, -OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 196.1, 160.2, 141.1, 137.0, 133.6, 121.7, 111.2, 35.2, 29.0. IR (neat) $\tilde{\nu}$ = 2968, 2956, 2660, 2657, 2605 cm^{-1}.

3-*tert*-Butyl-2-hydroxy-5-[(trimethylsilyl)ethynyl]benzaldehyde[3]



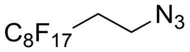
[$PdCl_2(PPh_3)_2$] (751 mg, 1.1 mmol) and CuI (204 mg, 1.1 mmol) were added to a solution of 3-*tert*-butyl-5-bromo salicylic aldehyde (9.12 g, 35.6 mmol) in triethylamine (100 mL). To this suspension a solution of ethyinyl trimethylsilane (5.59 g, 57.1 mmol) was slowly added over a period of 1 h and then refluxed under nitrogen atmosphere for 8 h. After cooling the resulting ammonium salt was filtered off and the residue was purified by column chromatography on silica gel with ethylacetate and hexane gave 9.28 g (95%) of product as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 1.41 (s, 9H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.58 (d, *J* = 2.1 Hz, 1H), 9.82 (s, 1H), 11.90 (br s, -OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 196.7, 161.4, 138.8, 137.4, 135.7, 120.3, 114.2, 104.0, 93.1, 35.0, 29.1, 0.0. IR: $\tilde{\nu}$ = 3007, 2965, 2151, 1653, 1605, 1442, 1414, 1320, 1268, 1153, 1030, 981, 930 cm^{-1}.

3-*tert*-butyl-5-ethynyl-2-hydroxybenzaldehyde (70)[3]



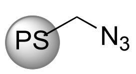
K_2CO_3 (7.5 g, 54.2 mmol) was added to a solution of trimethyl silyl derivative (9.3 g, 33.9 mmol) in methanol (80 mL). After stirring at room temperature for 4 h, the resulting precipitate was filtered off and the filtrate was dried. To the residue was added a mixture of water and dichloromethane to a two phase solution. The aqueous layer was further extracted with dichloromethane and the combined dichloromethane was dried over Na_2SO_4. The solution was concentrated under vaccum and dried to obtain the desired product as an orange yellow solid 6.1 g (89%). M.P = 58-60 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 3.02 (s, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 9.84 (s, 1H), 11.93 (br s, -OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 196.6, 161.6, 139.0, 137.5, 135.8, 120.4, 113.1, 82.7, 76.19, 35.0, 29.1. IR (neat): ν 2961, 2158, 1657, 1605, 1442, 1414, 1322, 1249, 1153, 981, 935, 843, 758, 721, 652 cm^{-1}.

1-Azido-perfluorodecane[4]



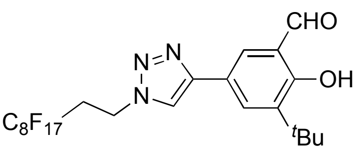
2-(n-perfluorooctyl) ethyl iodide was reacted with sodium azide in acetone: water (5:1) under reflux conditions for 7 h, resulted 2-(n-perfluorooctyl) ethyl azide in 90% yield. ^{1}H-NMR and ^{13}C-NMR spectra were identical to the ones previously reported.[4] ^{1}H-NMR (300 MHz; $CDCl_3$): δ 3.60 (t, *J* = 7.2 Hz, 2H), 2.46-2.29 (m, 2H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): 43.2, 30.7. ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.3 (t, *J* = 10.10 Hz, 3F), -114.6 (t, *J* = 13.46 Hz, 2F), -122.3 (m, 6F), -123.2 (br s, 2F), -123.9 (br s, 2F), -126.6 (m, 2F). IR (neat): $\tilde{\nu}$ = 2090 cm^{-1}.

Azidomethyl polystyrene



Merrifield resin (2.5 g, 4.3 mmol/g) in 25 mL DMSO were shaken at 50 °C with NaN_3 (2.45 g, 37.63 mmol) for 2 days. After being cooled to room temperature the suspension was filtrated and the resin was washed with MeOH (5x15 mL) and CH_2Cl_2 (5x15 mL) to give 2.4 g of resin (4.13 mmol/g). IR (neat): $\tilde{\nu}$ = 2090 cm^{-1}.

Fluorous tag clicked salicylaldehyde derivative (71b)

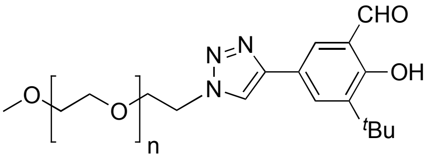


To a stirred solution of 3-*tert*-5-propargylated salicyaldehyde (0.5 g, 2.47 mmol) in degassed dry THF (15 mL), 1-azido-perfluorodecane (1.4 g, 2.47 mmol), CuI (28 mg, 6 mol%) and DIPEA (639 mg, 5 mmol) were added and the reaction mixture was stirred at rt for 12 h. Then the reaction mixture was quenched with 0.1 M EDTA solution, the product was extracted with diethylether (3 times). Then combined organic layer washed with brine and dried over Na_2SO_4. After removal of the solvent, the crude product was recrystallized from hexane and diethylether to give the pure product as a pale yellow solid 1.66 g (97%). M.P = 119-120 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9H), 2.70-3.00 (m, 2H), 4.75 (t, *J* = 7.3 Hz, 2H), 7.80 (s, 1H), 7.90-7.95 (m, 2H), 9.95 (s, 1H), 11.87 (br s, -OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 197.1, 161.3, 147.4, 139.2, 131.6, 129.1, 121.6, 120.7, 119.4, 42.5, 35.1, 31.9, 29.2; ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.3 (t, *J* = 10.10 Hz, 3F), -114.6 (t, *J* = 13.46 Hz, 2F), -122.3 (m, 6F), -123.2 (br s, 2F), -123.9 (br s, 2F), -126.6 (m, 2F); IR: $\tilde{\nu}$ = 732, 773, 812, 886, 932, 956, 987, 1049, 1088, 1117, 1146, 1199, 1268, 1298, 1327, 1368, 1395, 1414, 1447, 1637, 2349, 2966, 3120 cm^{-1}. MS (ES-MS, m/z): 692 (MH$^+$). HRMS calcd for $C_{23}H_{18}F_{17}N_3O_2$ [M$^{\bullet +}$]: 691.1128 found 691.1118.

calcd.: C: 39.96 % H: 2.62 % N: 6.08 %

found: C: 39.88 % H: 2.52 % N: 5.99 %

MeOPEG clicked salicylaldehyde derivative (71c)

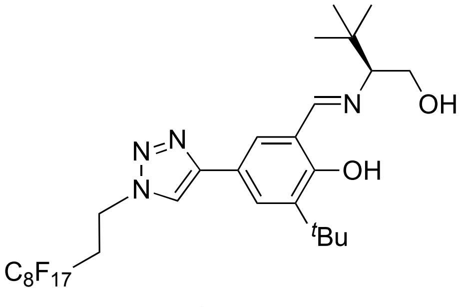


To a stirred solution of 3-*tert*-5-propargylated salicyaldehyde (21 mg, 0.104 mmol) in degassed dry DCM (10 mL), MeOPEG-azide (260 mg, 0.052 mmol), CuI (0.59 mg, 6 mol%) and TEA (18 μL, 0.13 mmol) were added and the reaction mixture was stirred at room temperature for 12 h. Then the reaction mixture was quenched with 0.1 M EDTA solution, the product was extracted with diethylether (3x10 mL). Then combined organic layer washed with brine and dried over Na_2SO_4. After removal of the solvent, the crude product was recrystallized from diethylether to give the pure product as a pale white solid in 97% yield. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 9H), 3.29 (s, 3H, PEGOC*H₃*), 3.55 (s, PEG), 3.79 (t, *J* = 4.9 Hz, 4H), 3.85 (t, *J* = 4.9 Hz, 2H), 4.5-4.56 (t, *J* = 4.8 Hz, 2H), 7.8 (s, 1H), 7.92 (s, 1H), 7.98 (s, 1H), 9.88 (s, 1H), 11.77 (s, 1H).

9.3 General procedure for the synthesis of tridendate Schiff bases:

Equivalent amounts of amino alcohol and clicked salicyaldehyde derivative were dissolved in an appropriate volume of methanol and anhydrous Na_2SO_4 stirred for 4 h. The mixture was filtered through a pad of celite and concentrated. This crude material was pure by TLC, ^{1}H- NMR and elemental analysis.

Fluorous tag clicked tridentate Schiff base (73d) derived from *tert*-leucinol



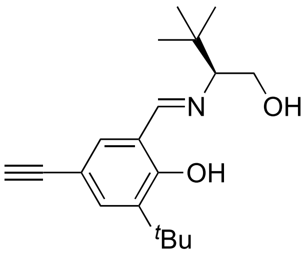
Synthesized compound **73d** according to the general procedure described above. Yellow solid. M.p = 85-88 °C. $[\alpha]_D^{20}$ = −21.3 (c 1.0, $CHCl_3$): ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.90 (s, 9H), 1.46 (s, 9H), 1.65 (br s, OH), 2.74-3.00 (m, 3H), 3.79 (dd, *J* = 11.0, 9.6 Hz, 1H), 3.97 (dd, *J* = 11.2, 2.6 Hz, 1H), 4.72 (t, *J* = 7.4 Hz, 2H), 7.66 (d, *J* = 2.1 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.74 (s, 1H), 8.40 (s,1H), 14.05

(br s, OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 166.4, 161.0, 148.2, 138.1, 127.3, 127.1, 120.0, 119.0, 118.6, 81.3, 62.4, 42.3, 35.0, 33.3, 31.9, 29.3, 27.1; ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.3 (t, *J* = 10.1 Hz, 3F), -114.6 (t, *J* = 13.7 Hz, 2F), -122.3 (m, 6F), -123.2 (br s, 2F), -123.9 (br s, 2F), -126.6 (m, 2F); IR (neat): $\tilde{v}$ = 732, 882, 1048, 1108, 1151,1203, 1365, 1396, 1440, 1461, 1602, 1632, 2349, 2871, 2965, 3114, 3320 cm^{-1}. MS (ES-MS, m/z): 791 (MH^+). HRMS calcd for $C_{29}H_{31}F_{17}N_4O_2$ [$M^{\bullet+}$]: 790.2176, found 790.2170.

calcd.: C: 44.06 % H: 3.95 % N: 7.09 %

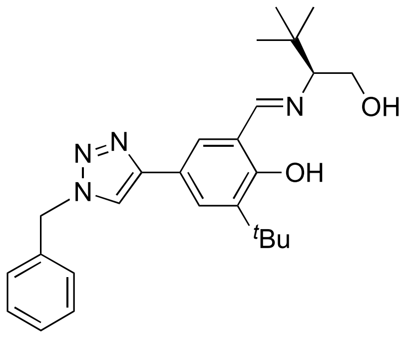
found: C: 43.88 % H: 4.23 % N: 6.86 %

(*S, E*)-2-*tert*-4-ethynyl-6-((1-hydroxy-3,3-dimethylbutan-2-ylimino)methyl) phenol (75)



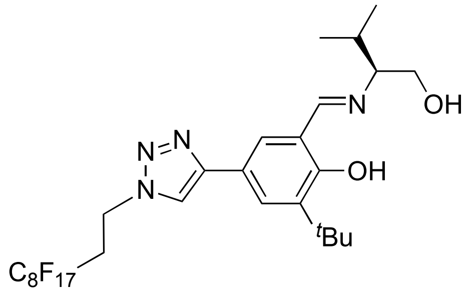
Synthesized compound **75** according to the general procedure described above. Yellow solid. M.P = 142-144 °C. $[\alpha]_D^{20}$ = −55.9 (c 1.0, $CHCl_3$): ^{1}H-NMR (300 MHz; $CDCl_3$): δ 14.24 (s, 1H), 8.30 (s, 1H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 3.95 (d, *J* = 9.4 Hz, 1H), 3.75 (dd, *J* = 11.0, 9.6 Hz, 1H), 2.98 (s, 1H), 2.94 (dd, *J* = 9.4, 2.9 Hz, 1H), 1.43 (s, 9H), 0.98 (s, 9H). ^{13}C-NMR (75.5 MHz; $CDCl_3$): 165.9, 161.5, 138.1, 133.9, 133.3, 118.3, 111.2, 83.9, 81.2, 75.1, 62.4, 34.9, 33.2, 29.2, 27.1. IR (neat): $\tilde{v}$ = 3357, 3335, 2962, 2870, 2250, 1733, 1634,1456, 1364, 1340, 1222, 1101, 1048, 895, 811, 734 cm^{-1}. MS (EI-MS, m/z): 301 ($M^{+\bullet}$). HRMS calcd for $C_{19}H_{27}NO_2$ [$M^{\bullet+}$]: 301.2042 found 301.2048.

(*S,E*)-4-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-tert-butyl-6-((1-hydroxy-3,3-dimethylbutan-2-ylimino)methyl)phenol (72)



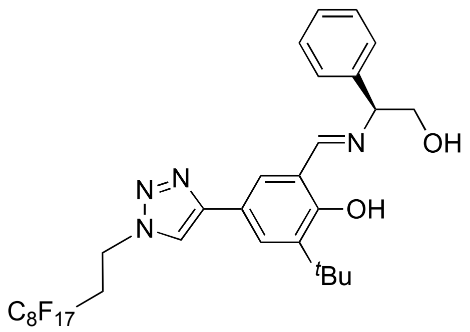
Synthesized compound **72** according to the general procedure described above. Yellow solid. $[\alpha]_D^{20}$ = −43.5 (c 1.0, $CHCl_3$): M.P = 174-176 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.98 (s, 9H), 1.44 (s, 9H), 1.85 (br. s., OH), 2.96 (dd, *J* = 9.3, 2.7 Hz, 1H), 3.78 (dd, *J* = 11.1, 9.6, 1H), 3.96 (dd, *J* = 11.2, 2.7 Hz, 1H), 5.56 (s, 2H), 7.29–7.43 (m, 5H), 7.57 (s, 1H), 7.65 (dd, *J* = 11.2, 2.0 Hz, 2H), 8.39 (s, 1H), 14.00 (br s, OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 166.5, 160.7, 148.2, 138.0, 134.8, 129.2, 128.8, 128.0, 127.2, 126.9, 120.2, 118.6, 118.5, 81.3, 62.4, 54.2, 35.0, 33.3, 29.3, 27.1; IR: $\tilde{v}$ = 727, 781, 813, 830, 895, 968, 1002, 1030, 1047, 1073, 1096, 1169, 1226, 1271, 1315, 1363, 1390, 1443, 1475, 1551, 1630, 1804, 2112, 2349, 2864, 2903, 2945, 3119, 3268 cm^{-1}. MS (ES-MS, m/z): 435 (MH$^+$). HRMS calcd for $C_{26}H_{34}N_4O_2$ [M$^{\bullet+}$]: 434.2682 found 434.2688.

Fluorous tag clicked tridentate Schiff base (73a) derived from valinol



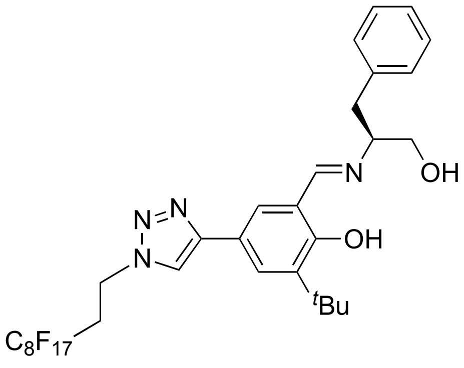
Synthesized compound **73a** according to the general procedure described above. M.p = 92-95 °C, $[\alpha]_D^{20} = -10.8$ (c 2.3, $CHCl_3$): ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.97 (dd, *J* = 6.8, 3.5 Hz, 6H), 1.46 (s, 9H), 1.7-1.8 (br s, OH), 1.9-2.1 (m, 1H), 2.75-2.98 (m, 2H), 3.01-3.12 (m, 1H), 3.76-3.92 (m, 2H), 4.72 (t, *J* = 7.4 Hz, 2H), 7.68 (dd, *J* = 15.7, 2.2 Hz, 2H), 7.75 (s, 1H), 8.40 (s, 1H), 14.00 (br s, OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 166.3, 161.0, 148.2, 138.2, 127.2, 127.1, 120.0, 119.0, 118.6, 77.8, 64.5, 42.4, 35.0, 30.1, 29.3, 19.8, 18.7; ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.3 (t, *J* = 9.8 Hz, 3F), -114.6 (t, *J* = 13.7 Hz, 2F), -122.3 (m, 6F), -123.2 (br s, 2F), -123.9 (br s, 2F), -126.6 (m, 2F); IR: $\tilde{\nu}$ = 734, 776, 908, 971, 1028, 1052, 1115, 1147, 1201, 1363, 1392, 1439, 1601, 1633, 2349, 2361, 2875, 2963, 3160, 3339 cm^{-1}. MS (ES-MS, m/z): 777 (MH$^+$). HRMS calcd for $C_{28}H_{29}F_{17}N_4O_2$ [M$^{\bullet+}$]: 776.2019 found 776.2021.

Fluorous tag clicked tridentate Schiff base (73b) derived from phenylglycinol



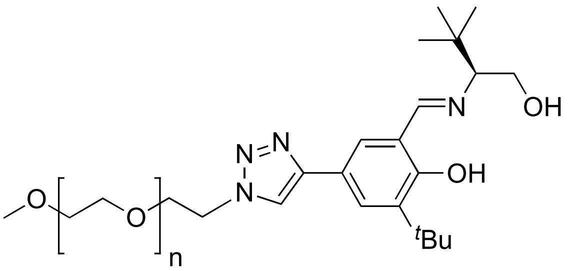
Synthesized compound **73b** according to the general procedure described above. M.p = 157-161 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 2.74-2.98 (m, 2H), 3.90-4.06 (m, 2H), 4.50 (dd, *J* = 7.6, 5.3 Hz, 1H), 4.71 (t, *J* = 7.4 Hz, 2H), 7.28-7.47 (m, 5H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.72 (t, *J* = 1.9 Hz, 2H), 8.53 (s, 1H), 13.92 (br s, OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 166.8, 160.6, 148.1, 139.2, 138.1, 128.9, 128.0, 127.5, 127.4, 127.2, 120.2, 119.0, 118.8, 75.9, 67.7, 42.3, 35.0, 31.0, 29.3; ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (t, *J* = 10.1 Hz, 3F), -114.6 (t, *J* = 13.7 Hz, 2F), -122.2 (m, 6F), -123.2 (br s, 2F), -123.9 (br. s, 2F), -126.6 (m, 2F); IR: 731, 760, 795, 874, 908, 970, 994, 1067, 1116, 1145, 1200, 1336, 1362, 1391, 1444, 1485, 1629, 2349, 2868, 2964, 3112, 3332 cm^{-1}. MS (ES-MS, m/z): 811 (MH^{+}). HRMS calcd for $C_{31}H_{27}F_{17}N_4O_2$ [M$^{\bullet+}$]: 810.1863 found 810.1872.

Fluorous tag clicked tridentate Schiff base (73c) derived from phenylalaninol



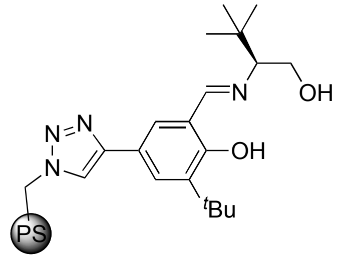
Synthesized compound **73c** according to the general procedure described above. M.p = 182-186 °C, $[\alpha]_D^{20}$ = −81.8 (c 1.1, $CHCl_3$): ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9H), 1.85-1.98 (br s, OH), 2.74–2.95 (m, 3H), 2.97 (dd, *J* = 13.6, 5.3 Hz, 1H), 3.46-3.54 (m, 1H), 3.76-3.90 (m, 2H), 4.66 (t, *J* = 7.4 Hz, 2H), 7.12-7.3 (m, 6H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.66 (d, *J* = 1.9 Hz, 2H), 8.15 (s, 1H), 14.00 (br. s, OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 166.5, 160.8, 148.2, 138.1, 137.8, 129.4, 128.5, 127.3, 127.2, 126.5, 120.0, 119.0, 118.5, 73.2, 65.8, 42.3, 39.1, 34.9, 31.0, 29.3; ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (t, *J* = 9.8 Hz, 3F), -114.7 (t, *J* = 13.7 Hz, 2F), -122.3 (m, 6F), -123.2 (br. s, 2F), -123.9 (br. s, 2F), -126.6 (m, 2F); IR: $\tilde{\nu}$ = 726, 778, 797, 855, 1020, 1049, 1068, 1170, 1226, 1282, 1427, 1455, 1595, 1630, 1733, 1981, 2349, 2866, 2965, 3135, 3399 cm^{-1}. MS (ES-MS, m/z): 825 (MH^{+}). HRMS calcd for $C_{32}H_{29}F_{17}N_4O_2$ [M$^{\bullet+}$]: 824.2019 found 824.2009.

MeOPEG clicked tridentate Schiff base ligand (74)



Synthesized compound **74** according to the general procedure described above. ^{1}H-NMR (600 MHz; $CDCl_3$): δ 14.03 (s, OH), 8.35 (s, 1H), 7.86 (s, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.59 (s, 1H), 4.52 (t, *J* = 5.0 Hz, 2H), 3.88 (dd, J = 11.7, 0.6 Hz, 2H), 3.85 (t, *J* = 5.0 Hz, 2H), 3.68-3.71 (m, 5H), 3.58 (s, PEG), 3.31 (s, 3H), 2.86-2.91 (dd, *J* = 9.3, 2.2 Hz, 1H), 2.15 (s, 1H), 1.41 (s, 9H), 0.93 (s, 9H).

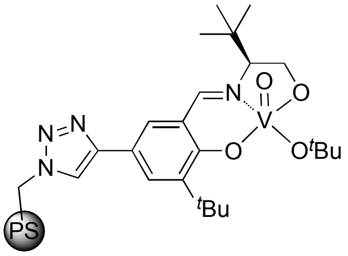
Polystyrene clicked tridentate Schiff base ligand (76)



To a suspension of Merrifield supported azide (estimated loading 4.13 mmol/g of azide, 48 mg, 0.2 mmol) in degassed DCM (10 mL), 4-propargyltridentate Schiff base (90 mg, 0.3 mmol), DIPEA (154 µL, 0.93 mmol) and CuI (3.3 mg, 6 mol%) were added. The resulting mixture was shaken at room temperature for 3 days. The reaction was monitored by IR spectroscopy and once the signal of the azide group had completely disappeared, the reaction mixture was quenched with 0.1 M EDTA/sat. NH4Cl solution. The resin was filtered and washed with CH_2Cl_2 (5x5 mL) and dried under vacuum to afford PS-CLICK-tridentate Schiff base with an estimated catalyst loading of 1.59 mmol/g, yield: 55 mg. The loading was determined by elemental analysis. IR: $\tilde{\nu}$ = 3310, 2961, 2870, 2689, 2359, 1631, 1600, 1466, 1440, 1392, 1364, 1326, 1275, 1206, 1152, 1102, 1049, 1020, 919, 897, 801, 750, 650, 585 cm^{-1}

found: C: 72.74 % H: 6.33 % N: 8.88 %

Synthesis of preformed clicked tridentate Schiff base ligand (78)



To a solution of Schiff base (1 mmol) in 1mL *tert*-butanol, VO(O-*i*-Pr)$_3$ (0.24 mL, 1.0 mmol) was added at room temperature. The mixture was stirred for 1 h and the solvent was removed under reduced pressure to give a quantitative yield of the product, which was directly subjected for the click reaction without further purification.

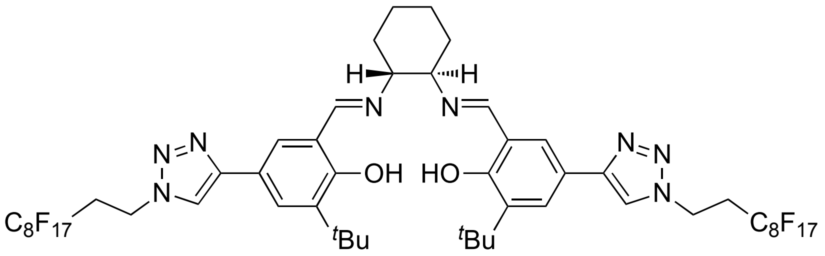
20 mL Schlenk tube was charged with Merrifield supported azide (0.30 mmol, 1 equiv) and 6 ml of a degassed 1:1 mixture of H_2O and ^{t}BuOH. To this solution was added the pre-metallated Schiff base ligand (1.5 equiv). After the subsequent addition of ascorbic acid (0.2 equiv) and $CuSO_4 \bullet 5H_2O$ (6 mol%) the solution was allowed to shaken at ambient temperature. The reaction was monitored by IR spectroscopy and once the signal of the azide group had completely disappeared, the resin was collected by filtration and sequentially washed with sat. NH_4Cl, water and diethylether. The solid (1.76 mmol/g of resin) was dried in vacuo for 24 hours. IR: $\tilde{\nu}$ = 2962, 2930, 2868, 1620, 1528, 1436, 1361, 1275, 1201 1169, 1020, 989, 779 cm^{-1}

Found: C: 70.23% H: 7.34 % N: 9.84 %

Resolution of *cis*/*trans*-1,2-diaminocyclohexane

A 100 mL beaker equipped with a magnetic stir bar, was charged with L-(+)-tartaric acid (1.5 g, 9.9 mmol) and distilled water (5 mL). The mixture was stirred at room temperature until complete dissolution occurred, at which point a mixture of *cis* and *trans*-1,2-diaminocyclohexane (2.4 mL, 19.4 mmol) was added slowly. The resulting solution was added glacial acetic acid (1 mL, 1.75 mmol). A white precipitate formed immediately upon addition of the acid and the slurry was vigorously stirred as it was cooled to room temperature over 1 h. The mixture was then cooled to <5 °C in an ice bath for 2 h and the precipitate was collected by vaccum filteration. The wet cake was washed with cold water and then rinsed with methanol. The product was then dried at 40 °C under reduced pressure to yield (*R, R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt as a white solid (1.5 g, 93% yield).

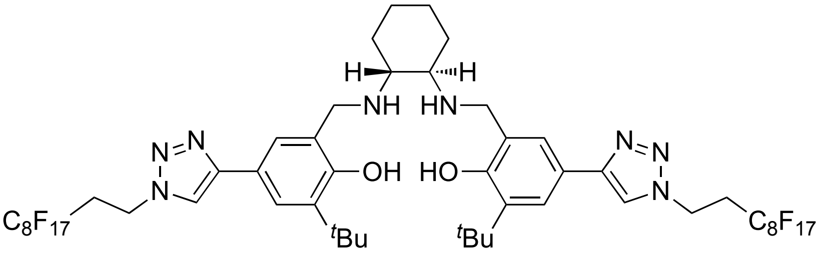
Fluorous tagged salen ligand derived from cyclohexyldiamine tartarate (79a)



A 250 mL three necked flassk equipped with a magnetic stir bar, a reflux condenser and an additional funnel was charged with tartatic acid diammine (222.7 mg, 0.844 mmol), K_2CO_3 (232.8 mg, 1.69 mmol) and distilled water (5 mL). The mixture was stirred until dissolution was achieved and then ethanol (50 mL) was added. The resulting cloudy mixture was heated to reflux and a solution of aldehyde (1.17 g, 1.69 mmol) in ethanol (10 mL) was added in a steady stream over 15 min. The funnel was rinsed with ethanol and the yellow slurry was stirred at reflux for 2 h before heating was discontinued. Water was added and the stirred mixture was cooled to <5 °C over 1h and maintained at that temprature for one additional hour. The product was collected by vaccum filteration and washed with ethanol. The crude solid was redissolved in dichloromethane and washed with water and brine. After drying over Na_2SO_4, the solvent was removed under vaccum and desired product was isolated as a yellow crystalline solid (1.14 g, 93% yield).

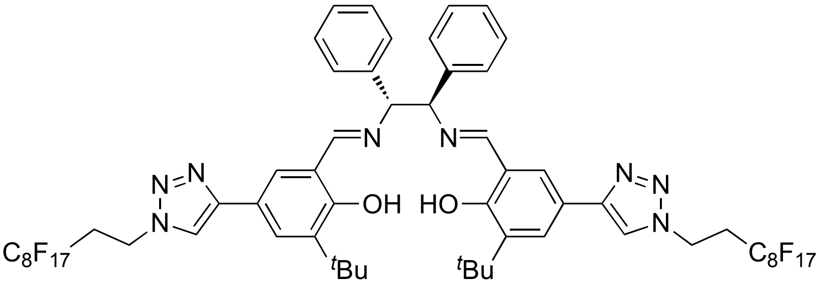
$[\alpha]_D^{20} = -43.3$ (c =1, $CHCl_3$). ^{1}H-NMR (300 MHz; $CDCl_3$): δ 14.07 (br s, 2-OH), 8.24 (s, 2H), 7.62 (d, J = 2.2 Hz, 2H), 7.58 (s, 2H), 7.37 (d, J = 2.1 Hz, 2H), 4.68-4.61 (m, 4H), 3.33-3.28 (m, 2H), 2.87-2.70 (m, 4H), 2.00-1.40 (m, 10H), 1.40 (s, 18H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.38, 160.78, 148.20, 137.95, 127.09, 119.98, 118.93, 118.58, 72.26, 42.28, 34.89, 32.93, 31.90, 29.26, 24.24. ^{19}F-NMR (282 MHz; $CDCl_3$): δ -81.30 (t, *J* = 10.10 Hz, 6F), -114.62 (t, *J* = 13.5 Hz, 4F), -122.11--122.43 (m, 12F), -123.21--123.35 (m, 4F), -123.93 (d, *J* = 8.4 Hz, 4F), -126.57--126.71 (m, 4F). IR (Neat): 2959, 1631, 1437, 1362, 1200, 1115, 1029, 974, 890, 804, 704 cm^{-1}. LRMS (ES-CI, MH$^+$): 1461 Anal. calcd for $C_{46}H_{25}F_{51}N_{12}O_3$: C, 42.75; H, 3.17; N, 7.67. Found: C, 42.89; H, 3.19; N, 7.57.

Fluorous tagged salan ligand derived from cyclohexyldiamine tartarate (81a)



To a stirred solution of salen (150 mg, 0.103 mmol) in refluxing ethanol (15 mL) was added $NaBH_4$ (13.6 mg, 0.36 mmol). This initially yellow solution was allowed to reflux for five minutes before becoming colourless, at which point water (8 mL) was added leading to the formation of a white precipitate. The mixture was allowed to stir for 1 h at 25 °C filtered and washed with portions of hexane yielding 154 mg of product. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.80 (s, 2H), 7.51 (d, *J* = 2.0 Hz, 2H), 7.32 (d, *J* = 1.9 Hz, 2H), 4.68 (t, *J* = 7.5 Hz, 4H), 3.95 (q, *J* = 15.2 Hz, 4H), 2.90-2.73 (m, 4H), 2.43-2.41 (m, 2H), 2.12-2.07 (m, 2H), 1.64-1.63 (m, 2H), 1.31 (s, 18H), 1.21-1.16 (m, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.49, 148.91, 137.47, 124.08, 123.89, 123.58, 120.43, 119.13, 59.40, 49.50, 42.31, 34.76, 30.88, 29.39, 24.29. ^{19}F-NMR (282 MHz; $CDCl_3$): δ -81.31 (t, *J* = 10.10Hz, 6F), -114.63 (t, *J* = 13.4 Hz, 4F), -122.12--122.44 (m, 12F), -123.24 (t, *J* = 4.4 Hz, 4F), -123.91 (s, 4F), -126.64 (m, *J* = 15.7, 9.1 Hz, 2F). LRMS (ES-CI, MH$^+$): 1465.8. IR (neat): 2934, 2864, 1615, 1442, 1359, 1199, 1145, 1115, 1048, 1027, 800, 787, 705, 658.

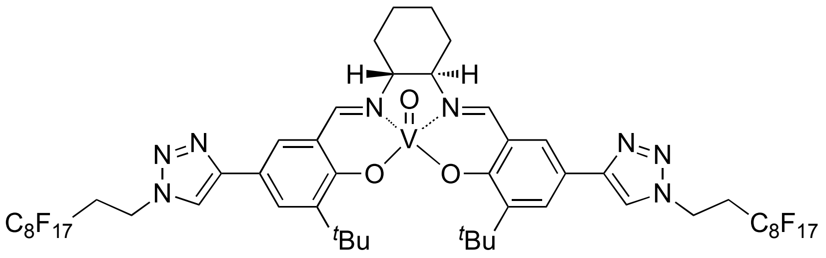
Fluorous tagged salen ligand derived from diphenyldiamine (79b)



Aldehyde (400 mg, 0.58 mmol) was dissolved in hot ethanol under N_2. To the stirred solution was added (*R,R*)-1,2-diphenylethylenediamine (61.4 mg, 0.29 mmol). The mixture was heated at reflux for 4 h and then cooled slowly to 0

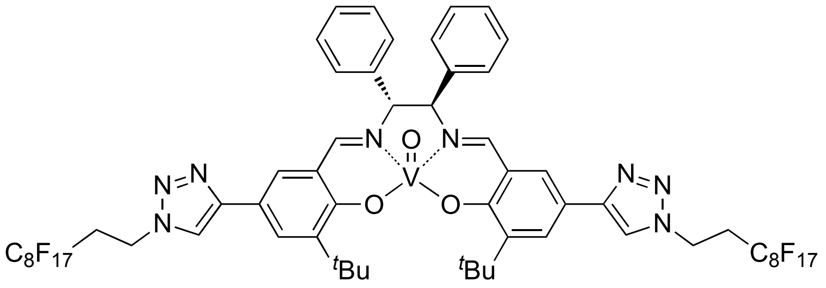
°C. The title compound precipitated as a yellow solid that was recovered by filtration and washed with cold ethanol (154 mg, quant.). ^{1}H-NMR (300 MHz; CDCl$_3$): δ 14.00 (s, 2-OH), 8.36 (s, 2H), 7.67 (d, *J* = 2.1 Hz, 2H), 7.63 (s, 2H), 7.44 (d, *J* = 2.0 Hz, 2H), 7.24 (s, 10H), 4.76 (s, 2H), 4.70 (t, *J* = 7.4 Hz, 4H), 2.93-2.76 (m, 4H), 1.43 (s, 18H). ^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.71, 160.65, 148.15, 139.08, 138.00, 128.47, 127.99, 127.75, 127.41, 120.12, 118.97, 118.59, 80.07, 76.60, 42.30, 34.94, 31.90, 30.58, 29.23. ^{19}F-NMR (282 MHz; CDCl$_3$): δ -81.26 (d, *J* = 19.8 Hz, 3F), -114.52--114.75 (m, 2F), -122.08--122.54 (m, 6F), -123.13--123.32 (m, 2F), -123.89--123.99 (m, 2F), -126.56--126.70 (m, 2F). LRMS (ES-CI, MH$^+$): 1559. IR (neat): 2960, 2906, 2876, 1721, 1627, 1602, 1453, 1438, 1392, 1362, 1200, 1145, 1115, 1047, 1029,878, 777, 703 cm^{-1}.

Synthesis of fluorous tagged salen vanadium(IV) complex (80a)



To a stirring solution of (*R,R*)-salen ligand (1 equiv) in dichloromethane was added VO(acac)$_2$ (1 equiv) at room temperature. The resulting mixture was stirred at rt until complete disapperance of salen ligand by TLC. After removal of the solvent, the green solid was recrystallized from dichloromethane and hexane to afford VO salen complex **80a** as a green solid. LRMS (ES-CI, MH$^+$): 1526.6. IR (Neat): 2957, 1615, 1542, 1392, 1313, 1260, 1201, 1145, 1104, 1045, 987, 887, 816, 749, 704.

Synthesis of fluorous tagged salen vanadium(IV) complex (80b)

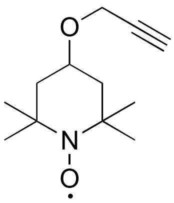


To a stirring solution of (*R,R*)-salen ligand (1 equiv) in dichloromethane was added VO(acac)$_2$ (1 equiv) at room temperature. The resulting mixture was stirred at rt until complete disapperance of salen ligand by TLC. After removal of the solvent, the green solid was recrystallized from dichloromethane and hexane to afford VO salen complex **80b** as a green solid. LRMS (ES-CI, MH$^+$): 1624.6. HRMS $C_{60}H_{46}F_{34}N_8O_3V$ found 1623.25875. Calculated: 1623.25897. IR

(Neat): 2957, 2916, 2875, 1719, 1606, 1541, 1455, 1428, 1409, 1391, 1311, 1200, 1145, 986, 888, 816, 787, 746, 701, 657, 572.

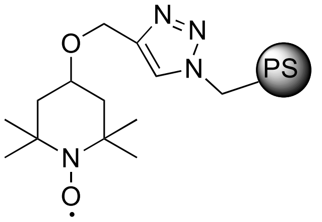
9.4 Synthesis of polymer supported TEMPO catalyst

Propargyl ether TEMPO (84)



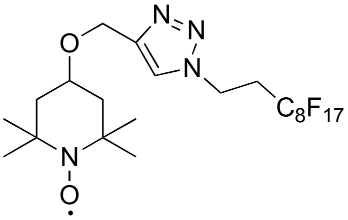
To a stirring suspension of NaH (60 % in mineral oil, 850 mg, 22.0 mmol) in dry DMF (100 mL) 4-hydroxy TEMPO **83** (3.0 g, 17.44 mmol) was added portionwise at 0 °C and stirred at rt for 30 min. Propargyl bromide (2.0 mL, 22.0 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 3 h at rt. Water (100 mL) was added and the solution was extracted with EtOAc (5x50 mL). The combined organics were washed with water (10x50 mL) and dried over $MgSO_4$, filtered and evaporated under reduced pressure and purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give the title compound **84** (80 %) as an orange solid. m.p. 58-59 °C; MS (PI-EIMS 70 eV) *m/z* 210.2 (M^+); Anal. calcd for $C_{12}H_{20}NO_2$: C, 68.54; H, 9.59; N, 6.66. Found: C, 68.21; H, 9.89; N, 6.33.

PS-CLICK-TEMPO (85)



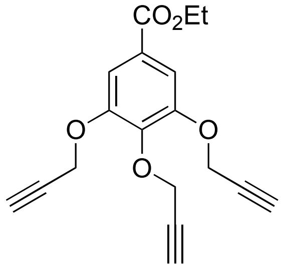
To a suspension of Merrifield supported azide (estimated loading 4.3 mmol/g of azide, 1.10 g, 4.76 mmol) in degassed DCM (100 mL), 4-propargyloxy-TEMPO 38 (1.87 g, 8.58 mmol) and CuI (27 mg, 3 mol%) were added. The resulting mixture was shaken at room temperature for 3 days. The resin was filtered and washed with CH_2Cl_2 (5x50 mL) and dried under vacuum to afford PS-CLICK-TEMPO **85** with an estimated TEMPO loading of 2.0 mmol/g; yield: 1.40 g. The loading was determined by measurement the quantity of unreacted propargyl ether TEMPO **84**, elemental analysis and IR.

F_{17}-CLICK-TEMPO (86)



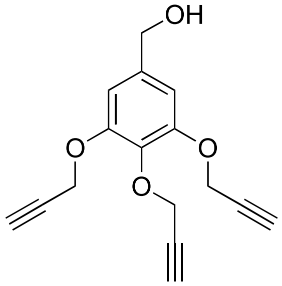
To a stirred mixture of 1-azidoperfluorodecane (1.19 g, 2.43 mmol) and propargyl ether TEMPO **84** (0.95 g, 4.54 mmol) in degassed THF (15 mL), CuI (27 mg, 6 mol%) was added. The resulting mixture was stirred under nitrogen atmosphere at rt for 1 day. Then, the solvent was removed *in vacuo* and the residue was purified by column chromatography (silica, from 20% to 50% EtOAc in hexanes) to give the recovered **84** (0.4 g, 42%) and the title compound **86** (1.35g, 80%) as a light orange solid. Mp. 105-107 °C; IR (KBr): 2984, 1468, 1371, 1410, 1177, 1142, 1084, 1045, 989, 957, 661 cm^{-1}. MS (PI-EIMS 70 eV) *m/z* 699 (M^+); HRMS calc. for $C_{22}H_{24}F_{17}N_4O_2$ [MH^+]: 699.1628, found 699.1620.

3,4,5-Tris-prop-2-ynloxy-benzoic acid ethyl ester (88)



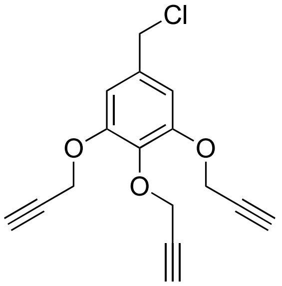
To a stirred solution of 3,5-dihydroxy-benzoic acid ethyl ester **87** (5.0 g, 25.25 mmol) and propargyl bromide (80% wt, 8.43 mL, 78.28 mmol) in acetone (75 mL) were added K_2CO_3 (10.8 g, 11.0 mmol) and 18-crown-6 (26 mg, 0.10 mmol). The reaction mixture was refluxed for 24 h, filtered and evaporated to dryness. Water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3x30 mL). The organic phases were joined, dried over Na_2SO_4 and the solvent was evaporated *in vacuo.* The crude product was crystallized in CH_2Cl_2-hexane to afford the title compound **88** (7.87 g, 83%) as a white solid, mp 64-65 °C. ^{1}H-NMR (300 MHz, [D$_4$] MeOH): δ = 1.38 (t, *J* = 7.11, 3H), 2.86 (t, *J* = 2.44, 1H), 3.00 (t, *J* = 2.39, 2H), 4.34 (q, *J* = 7.12, 2H), 4.77 (d, *J* = 2.49, 2H), 4.82-4.85 (m, 4H), 7.46 (s, 2H). ^{13}C-NMR (75 MHz, [D$_4$] MeOH): δ = 14.70, 58.08, 61.11, 62.48, 77.06, 77.61, 79.34, 79.75, 110.99, 127.21, 142.50, 152.82, 167.30. IR (KBr): 2997, 2125, 1701, 1588 cm^{-1}. LRMS (CI, MH^+): 313. HRMS calc. for $C_8H_{16}O_5$ [MH^+]: 312.0998, found 312.0994.

3,4,5-Tris-(propargyloxy)benzyl alcohol (89)



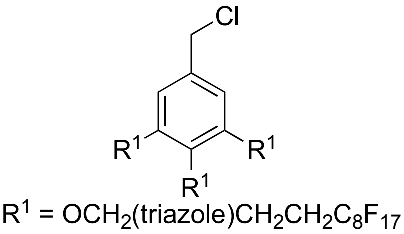
To a stirred solution of ester **88** (6.59 g, 21.12 mmol) in dry THF (63 mL) $LiAlH_4$ (0.99 g, 26.19 mmol) was added in small fractions. The reaction mixture was cooled to 0 °C and quenched with NH_4Cl saturated aqueous solution (50 mL). The mixture was acidified with 10 % HCl to pH= 2 and concentrated *in vacuo*. The mixture was extracted with CH_2Cl_2 (5x20 mL). The organic phases were joined, dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to afford the title compound **89** (1.35 g, 81 %) as a white solid, mp 99-100 °C. ^{1}H-NMR (300 MHz, [D$_4$] MeOH): δ = 2.82 (t, *J* = 2.44, 1H), 2.95 (t, *J* = 2.39, 2H) 4.54 (s, 2H), 4.66 (d, *J* = 2.39, 2H), 4.77 (d, *J* = 2.20, 4H), 4.86 (s, 2H), 6.80 (s, 2H). ^{13}C-NMR (75 MHz, [D$_4$] MeOH): δ = 57.95, 61.07, 65.05, 76.58, 77.15, 79.78, 80.19, 108.14, 137.30, 139.39, 153.01. IR (KBr): 3539, 3289, 2928, 2119, 1595 cm^{-1}. LRMS (CI, M$^+$): 270. HRMS calc. for $C_{16}H_{14}O_4$ [MH$^+$]: 270.0892, found 270.0898.

3,4,5-Tris-(propargyloxy)benzyl chloride (90)



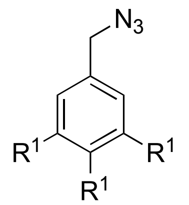
A mixture of PPh_3 (5.97 g, 22.82 mmol), CCl_4 (19.0 mL) in dry THF (100 mL) was stirred at reflux for 30 min. The reaction mixture was cooled down to rt and alcohol **89** (5.13 g, 19.05 mmol) was then added. The resulting mixture was refluxed for 24 h. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford the chloride **90** (2.84 g, 52%) as a white solid, mp 61 ^{o}C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.47 (t, *J* = 2.44, 1H), 2.53 (t, *J* = 2.38, 2H), 4.54 (s, 2H), 4.72 (d, *J* = 2.45, 2H), 4.76 (d, *J* = 2.42, 4H), 6.79 (s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 46.36, 57.10, 60.36, 75.37, 76.10, 78.27, 79.06, 109.02, 133.49, 137.21, 151.65. IR (KBr): 2945, 2122, 1580 cm-1. LRMS (CI, M$^+$): 288. HRMS calc. for $C_{16}H_{13}ClO_3$ [MH$^+$]: 288.0553, found 288.0553.

3-Ponytails perfluorinated chloride (91)



To a stirred solution of **90** (144 mg, 0.5 mmol) in dry THF (25 mL), 1-azido-perfluorodecane (1.46 g, 3.00 mmol), CuI (17 mg, 0.09 mmol) and DIPEA (1.25 mL) were added and the reaction mixture was stirred at rt (26-27 ^{o}C) for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and the solvent was evaporated *in vacuo.* The suspension was filtrated and the residue was washed with ether (5x15 mL), CH_2Cl_2 (5x15 mL) and water (5x15 mL). Drying of the residue in vacuum afforded the title compound **91** as a white solid (492 mg, 56%), mp 165-166 ^{o}C (Dec.). ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 100 °C): δ = 2.75-2.89 (m, 6H), 4.46 (s, 2H), 4.63 (m, 6H), 5.12 (s, 2H), 5.19 (s, 4H), 6.73 (s, 2H), 7.77 (s, 2H), 7.81 (s, 1H). ^{13}C-NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 32.02, 32.24, 32.47, 42.64, 46.28, 64.12, 66.63, 110.24, 123.61, 124.26, 133.89, 139.35, 144.55, 145.16, 152.68. IR (KBr): 2963, 1598, 1442, 1203, 1147 cm^{-1}. LRMS (ES, MH$^+$): 1756.

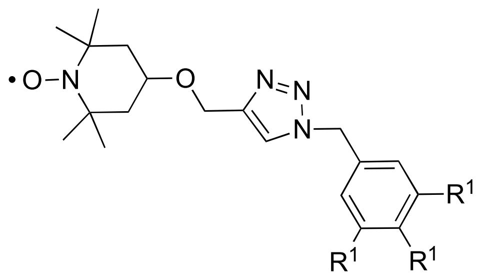
3-Ponytails perfluorinated azide (93)



$R^1 = OCH_2(triazole)CH_2CH_2C_8F_{17}$

To a suspension of chloride **91** (490 mg, 0.280 mmol) in DMSO (7.7 mL) was added NaN_3 (182 mg, 2.80 mmol) and the reaction mixture was heated at 60 °C for 24 h. Then, the solution was cooled to rt and water (20 mL) was added. The precipitate was filtered and washed with water and cold ether and dried *in vacuo* to afford the azide **93 (**432 mg, 93%) as a white solid, mp 167-169 °C (Dec.). ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 100 °C): δ = 2.73-2.89 (m, 6H), 4.22 (s, 2H), 4.64 (m, 6H), 5.14 (s, 2H), 5.20 (s, 4H), 6.64 (s, 2H), 7.77 (s, 2H), 7.81 (s, 1H). ^{13}C-NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 32.00, 32.22, 32.44, 42.65, 55.03, 64.09, 66.55, 109.79, 123.61, 124.28, 131.90, 139.17, 144.54, 145.16, 152.85. IR (KBr): 2105, 1597, 1203, 1148 cm^{-1}. LRMS (ES, MH$^+$): 1763. Anal. calcd for $C_{46}H_{25}F_{51}N_{12}O_3$: C, 31.34; H, 1.43; N, 9.54. Found: C, 31.63; H, 1.77; N, 9.37.

3-Ponytails perfluorinated TEMPO (95)



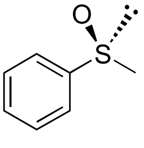
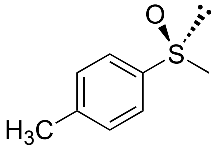
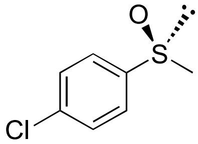
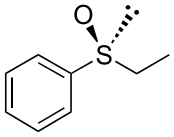
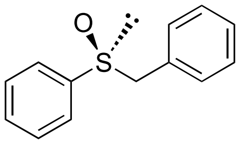
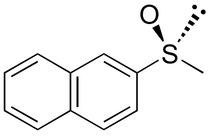
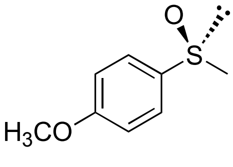
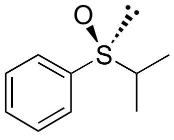
$R^1 = OCH_2(triazole)CH_2CH_2C_8F_{17}$

To a stirred mixture of azide **93** (250 mg, 0.141 mmol) and propargyl ether TEMPO **84** (56 mg, 0.26 mmol) in THF (2.5 mL), DIPEA (0.25 mL) and CuI (2 mg, 6 mol%) were added. The resulting mixture was stirred under nitrogen atmosphere at rt (26-27 °C) for 72 h and then quenched with a saturated aqueous solution of NH_4Cl (5 mL). The precipitate was filtered and washed with water and cold ether and dried *in vacuo* to afford the TEMPO **95 (**236 mg, 84%) as a pale yellow solid, mp 198 °C (Dec.). IR (KBr): 3138, 2982, 1600, 1202, 1148 cm^{-1}. LRMS (ES, MH$^+$): 1973.

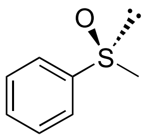
9.5 Asymmetric sulfoxidation

General procedure for asymmetric sulfoxidation

$VO(acac)_2$ (2.6 mg, 0.01 mmol) and the ligand (0.015 mmol) were dissolved in a Schrank tube in $CHCl_3$ and the solution stirred for 30 min. After the addition of sulfide (1 mmol), the reaction mixture was cooled to 0 °C and added 30% H_2O_2 drop by drop. The mixture was stirred for 16 h at 0 °C. The aqueous layer was separated off and the solvent removed *in vaccuo* from the remaining mixture. The crude product was purified by chromatography on silicagel (hexane/ethylacetate). The enantioselectivities were determined by chiral HPLC [Daicel UV detector (254 nm), flow rate 0.5 mL / min] unless otherwise stated.

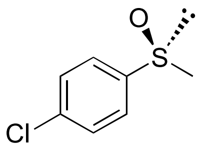
sulfoxide	column	conditions	t_r (min)	t_r (min)
	OD	Heptane / i-PrOH 80 / 20	18.10 (minor)	20.00 (major)
	OD	Heptane / i-PrOH 85 / 15	20.20 (minor)	21.80 (major)
	OD	Heptane / i-PrOH 97 / 3	76.30 (minor)	81.00 (major)
	OD	Heptane / i-PrOH 90 / 10	24.80 (minor)	28.6 (major)
	OD	Heptane / i-PrOH 98 / 2	12.60 (minor)	16.70 (major)
	OD	Heptane / i-PrOH 90 / 10	46.80 (minor)	51.30 (major)
	OD	Heptane / i-PrOH 90 / 10	44.80 (minor)	46.90 (major)
	OD	Heptane / i-PrOH 96/4	28.04 (minor)	34.68 (major)

(*S*)-Phenyl methyl sulfoxide (98a)



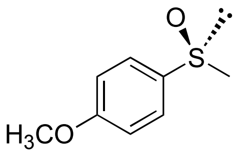
^{1}H-NMR (300 MHz, CDCl$_3$): δ 7.65-7.61 (m, 2H), 7.54-7.47 (m, 3H), 2.70 (s, 3H). ^{13}C-NMR (75 MHz, CDCl$_3$): δ 145.73, 131.04, 129.36, 123.49, 43.99. 80% *ee*; $[\alpha]_D^{23} = -130$ (c 1.3, DCM)

(*S*)-4-chlorophenyl methyl sulfoxide (98b)



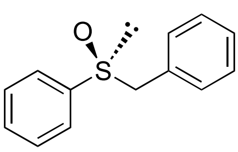
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.46-7.41 (m, 2H), 2.65 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 144.21, 137.25, 129.67, 125.00, 44.06. >99% *ee*; $[\alpha]_D^{23} = -165$ (c 1.0, DCM)

(*S*)-4-methoxyphenyl methyl sulfoxide (98c)



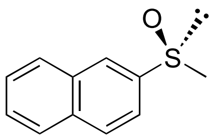
^{1}H-NMR (300 MHz, CDCl3): δ 7.55-7.50 (m, 2H), 6.98-6.93 (m, 2H), 3.77 (s, 3H), 2.64 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 162.02, 136.22, 125.57, 114.89, 55.56, 43.80. 80% *ee*; $[\alpha]_D^{23} = -147$ (c 1.1, DCM)

(*S*)-Benzyl phenyl sulfoxide (98d)



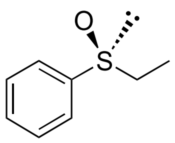
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45-7.34 (m, 5H), 7.27-7.20 (m, 3H), 6.98-6.95 (m, 2H), 4.03 (q, *J* = 14.2 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 142.78, 131.18, 130.38, 129.15, 128.87, 128.46, 128.26, 124.44, 63.57.

(*S*)-2-Naphthyl methyl sulfoxide (98e)



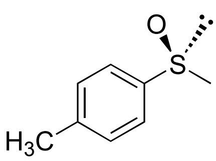
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.00-7.89 (m, 3H), 7.59 (ddd, *J* = 7.1, 3.6, 2.1 Hz, 3H), 2.79 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 142.78, 134.44, 132.93, 129.63, 128.53, 128.08, 127.81, 127.38, 124.06, 119.46, 43.84. 96% *ee*; $[\alpha]_D^{23} = -136$ (c 1.0, DCM)

(*S*)-Phenyl ethyl sulfoxide (98f)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.59-7.44 (m, 5H), 2.93-2.66 (m, 2H), 1.16 (t, *J* = 7.4 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 143.34, 130.93, 129.15, 124.19, 50.32, 5.98. 88% *ee*; $[\alpha]_D^{23} = -193$ (c 1.0, DCM)

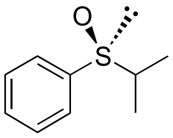
(*S*)-*p*-tolyl methyl sulfoxide (98g)



^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.47-7.44 (m, 2H), 7.26-7.23 (m, 2H), 2.62 (s, 3H), 2.33 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 142.52, 141.47, 130.03, 123.52, 44.02, 21.41. 80% *ee*; $[\alpha]_D^{23} = -141$ (c 0.6, acetone)

(*S*)-Phenyl isopropyl sulfoxide (98h)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 6.6, 3.2 Hz, 2H), 7.50 (dd, *J* = 5.0, 1.9 Hz,



3H), 2.83 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 141.78, 131.01, 128.91, 125.05, 54.64, 15.92, 13.99. 80% *ee*; $[\alpha]_D^{23} = -136$ (c 1.05, DCM)

General procedure for asymmetric sulfoxidation using polymer supported ligand

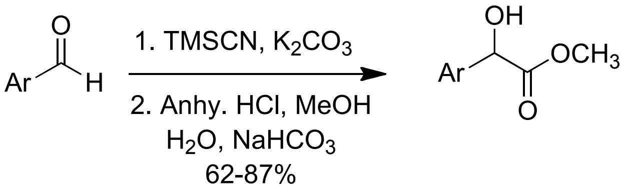
Polystyrene supported Schiff base ligand was allowed to swollen in chloroform for an hour. A solution of $VO(acac)_2$ (2.6 mg, 0.01 mmol) in chloroform was added and the mixture was shaken for 1 h. The solution was filtered and the resin washed with chloroform (5x2 mL) and transferred into a reaction test tube. Thioanisole in chloroform was added, followed by 30% H_2O_2. The reaction mixture was stirred for 16 h at 0 °C. The washed the reaction mixture with sat.NaCl, extracted the organic layer twice with DCM. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography on silicagel (hexane/ethylacetate). The enantioselectivities were determined by chiral HPLC [Daicel UV detector (254 nm), flow rate 0.5 mL/min] unless otherwise stated.

Recycling Experiment: Asymmetric sulfoxidation

$VO(acac)_2$ (5.3 mg, 0.02 mmol) and **72d** (20 mg, 0.025 mmol) were dissolved in a Schrank tube in $CHCl_3$ and the solution stirred for 30 min. After the addition of sulfide (317 mg, 2 mmol), reaction mixture was cooled to 0 °C and added 30% H_2O_2 (1.2equ.) slowly. The mixture was stirred for 16-18 h at 0 °C and then washed with water, extracted with DCM twice. The combined organic layer dried over Na_2SO_4, filtered and concentrated. The complex was precipitated out using combination of diethylether and hexane and filterated. Washed the precipitate twice with hexane and then the collected organic layer was concentrated under vaccuo. The crude product was purified by chromatography on silicagel (hexane/ethylacetate). The filtered complex was dried and used for further runs without further activation.

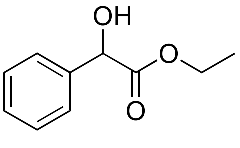
9.6 Kinetic Resolution of alcohols

General procedure for synthesis of α-hydroxy esters



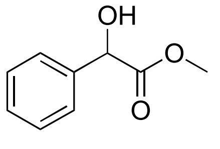
All reactions were performed at room temperature with 3 mol% K_2CO_3, 1.2 equiv. TMSCN. To a stirred solution of aldehyde (1 equiv) and potassium carbonate (3 mol%) was added dropwise TMSCN (1.5 equiv). The resulting heterogeneous solution was stirred continuously and the progress of the reaction monitored by TLC. After complete disappearance of starting material, the filtrate was diluted with DCM and washed by brine solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure afforded pure cyanosilylethers, which could be used directly for further reactions. The crude trimethylsilyloxy acetonitrile was dissolved in ether and the solution was cooled to 0 °C. Then HCl-MeOH was added dropwise and the solution left to stand at 0 to -10 °C for 24 h. The precipitated solid was separated by decantation, washed with cold ether, dissolved in distilled water and extracted with ether. After washing with sat.$NaHCO_3$, distilled water and saturated brine, the combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the pure of α-hydroxy esters.

Ethyl -2-hydroxy-2-phenylacetate (99a)



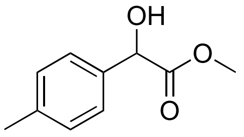
^{1}H-NMR (300 MHz; CDCl3): δ 7.45-7.30 (m, 5H), 5.16 (s, 1H), 4.28-4.08 (m, 2H), 4.01 (s, br., 1H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 173.68, 138.56, 128.57, 128.39, 126.62, 73.02, 62.14, 14.04. IR (neat): $\tilde{\nu}$ = 3480, 2984, 1728, 1494, 1454, 1368, 1258, 1209, 1181, 1094, 1065, 939, 915, 867, 765, 732, 697, 599 cm^{-1}. MS (EI-MS, m/z): 180.1 ($M^{+\bullet}$).

Methyl -2-hydroxy-2-phenylacetate (99b)



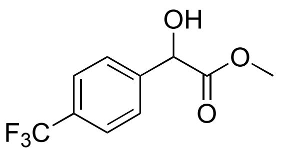
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.41-7.34 (m, 5H), 5.19 (s, 1H), 4.2 (br. s, 1H), 3.74 (s, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ174.16, 138.26, 128.68, 128.57, 126.67, 72.99, 53.07. IR (neat): $\tilde{\nu}$ = 3484, 2955, 1733, 1494, 1437, 1213, 1180, 1091, 1065, 979, 927, 850, 784, 731, 696, 605 cm^{-1}. MS (EI-MS, m/z): 166.1 ($M^{+\bullet}$). HRMS calcd for $C_9H_{10}O_3$ [$M^{\bullet+}$]: 166.0630 found 166.0632.

Methyl-2-hydroxy-2-(p-tolyl)acetate (99c)



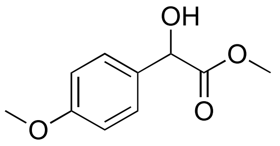
^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.15 (s, 1H), 3.74 (s, 3H), 2.36 (s, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): 174.31, 138.39, 135.42, 129.37, 126.62, 72.85, 52.99, 21.24. IR (neat): $\tilde{\nu}$ = 3483, 2953, 2923, 1730, 1514, 1438, 1219, 1175, 1078, 1022, 979, 908, 821, 791, 737, 576 cm^{-1}. MS (EI-MS, m/z): 180.1 ($M^{+\bullet}$). HRMS calcd for $C_{10}H_{12}O_3$ [$M^{\bullet+}$]: 180.0786, found 180.0788.

Methyl -2-hydroxy-2-(4-(trifluoromethyl)phenyl)acetate (99d)



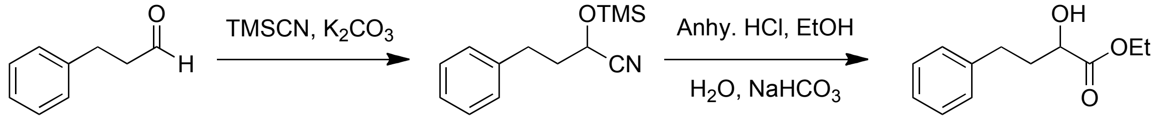
1H-NMR (300 MHz; CDCl$_3$): δ 7.63-7.54 (m, 4H), 5.25 (d, *J* = 3.6 Hz, 1H), 3.85 (d, *J* = 4.3 Hz, 1H), 3.75 (s, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): 173.43, 142.05, 130.85, 130.41, 126.96, 125.52, 72.35, 53.27. ^{19}F-NMR (282 MHz, CDCl$_3$): -63.22. IR (neat): $\tilde{\nu}$ = 3483, 2961, 1738, 1621, 1440, 1419, 1323, 1163, 1114, 1087, 1065, 1018, 979, 912, 831, 787, 755, 723, 596 cm^{-1}. MS (EI-MS, m/z): 234.0 ($M^{+\bullet}$). HRMS calcd for $C_{10}H_9F_3O_3$ [$M^{\bullet+}$]: 234.0504, found 234.0506.

Methyl-2-hydroxy-2-(4-methoxyphenyl)acetate (99e)

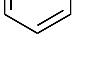


^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.31-7.26 (m, 2H), 6.86-6.81 (m, 2H), 5.09 (s, 1H), 4.07 (br. s, 1H), 3.73 (s, 3H), 3.66 (s, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): 174.23, 159.70, 130.65, 128.01, 114.01, 72.60, 55.24, 52.75. IR (neat): $\tilde{\nu}$ = 3483, 3009, 2953, 2838, 1733, 1612, 1511, 1439, 1247, 1173, 1076, 1030, 979, 909, 832, 796, 729, 584, 528 cm^{-1}. MS (EI-MS, m/z): 196.1 ($M^{+\bullet}$). HRMS calcd for $C_{10}H_{12}O_4$ [$M^{\bullet+}$]: 196.0736, found 196.0734.

Synthesis of HPB Ester

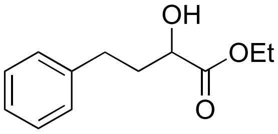


Ethyl-4-phenyl-2-((trimethylsilyl)oxy)butanoate



^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.36-7.20 (m, 5H), 4.39 (t, *J* = 6.5 Hz, 1H), 2.82 (t, *J* = 7.8 Hz, 2H), 2.18-2.13 (m, 2H), 0.23 (s, 9H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 140.23, 129.10, 128.86, 126.76, 120.25, 60.97, 37.98, 30.97, 0.00.

Ethyl 2-hydroxy-4-phenylbutanoate (99f)

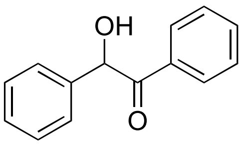


^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.33-7.20 (m, 5H), 4.12-4.26 (m, 3H), 3.02 (br. s, 1H), 2.78 (td, *J* = 8.0, 3.2 Hz, 2H), 1.90-2.19 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 175.26, 141.26, 128.62, 128.47, 126.07, 69.75, 61.79, 36.06, 31.10, 14.27. IR (neat): $\tilde{\nu}$ = 3472, 3027, 2933, 1727, 1603, 1497, 1455, 1369, 1209, 1178, 1097, 1021, 912, 863, 735, 699, 576 cm^{-1}. MS (EI-MS, m/z): 208.1 (M$^{+•}$). HRMS calcd for $C_{12}H_{16}O_3$ [M$^{•+}$]: 208.1099 found 208.1097.

General procedure for synthesis of α-hydroxy ketones

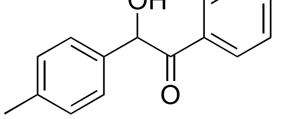
Mixing of the solutions of appropriate benzaldehyde (12 mmol) in alcohol and NaCN (5 mmol) in water was followed by refluxing for 1 h. The reaction mixture was washed with sodium bicarbonate solution and extracted with ether. Removal of ether and column chromatography of the residue using ethyl acetate and hexane as eluent provided the pure benzoins.

2-hydroxy-1,2-diphenylethanone (99g)



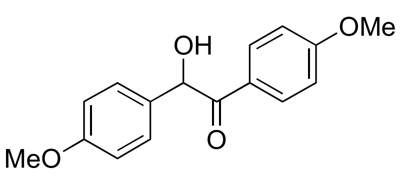
^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.94-7.91 (m, 2H), 7.54-7.49 (m, 1H), 7.42-7.26 (m, 7H), 5.97 (s, 1H), 4.60 (s, 1H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 198.99, 139.06, 133.96, 133.52, 129.17, 129.16, 128.73, 128.62, 127.83, 76.27. IR (neat): $\tilde{\nu}$ = 3372, 3061, 3029, 2934, 1678, 1595, 1491, 1449, 1386, 1337, 1308, 1262, 1203, 1091, 1068, 1028, 1004, 976, 928, 856, 830, 753, 694, 672, 594, 510 cm^{-1}. MS (EI-MS, m/z): 212.1 (M$^{+•}$).

2-hydroxy-1,2-di-p-tolylethanone (99h)



^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.26-7.17 (m, 4H), 7.12 (d, *J* = 7.9 Hz, 2H), 5.90 (d, *J* = 5.9 Hz, 1H), 4.58 (d, *J* = 6.1 Hz, 1H), 2.35 (s, 3H), 2.28 (s, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 198.59, 144.95, 138.37, 136.42, 130.97, 129.83, 129.41, 129.32, 127.69, 75.85, 21.78, 21.21. IR (neat): $\tilde{\nu}$ = 3470, 3328, 3028, 2920, 1673, 1605, 1570, 1512, 1215, 1396, 1311, 1273, 1168, 1095, 971, 852, 802, 778, 666, 503 cm^{-1}. MS (EI-MS, m/z): 240.1 (M$^{+•}$).

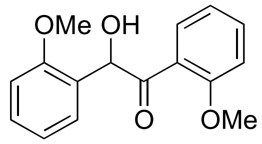
2-hydroxy-1,2-bis(4-methoxyphenyl)ethanone (99i)



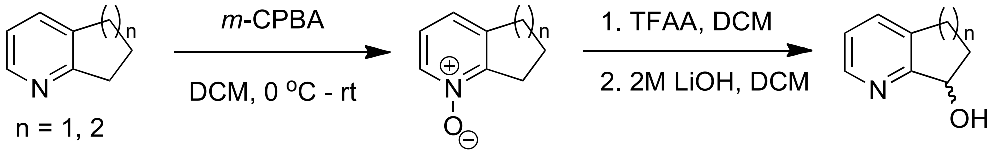
^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.89 (d, *J* = 9.0 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.83 (dd, *J* = 8.9, 3.0 Hz, 4H), 5.84 (s, 1H), 4.57 (s, 1H), 3.78 (s, 3H), 3.72 (s, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 197.36, 164.00, 159.65, 131.88, 131.60, 129.05, 126.32, 114.52, 113.95, 75.26, 55.52, 55.26. IR (neat): $\tilde{\nu}$ = 3465, 2921, 2842, 1664, 1595, 1511, 1467, 1386, 1311, 1261, 1238,1177, 1116, 1075, 1021, 977, 829, 794, 567 cm^{-1}. MS (EI-MS, m/z): 272.1 (M$^{+•}$).

2-hydroxy-1,2-bis(2-methoxyphenyl)ethanone (99j)

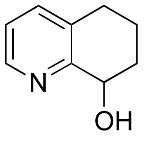
^{11}H-NMR (300 MHz; CDCl$_3$): δ 7.68 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.35 (ddd, *J* = 8.4, 7.3, 1.8 Hz, 1H), 7.20-7.13 (m, 2H), 6.91 (td, *J* = 7.5, 0.8 Hz, 1H), 6.82 (td, *J* = 7.5, 1.0 Hz, 1H), 6.75 (dd, *J* = 8.1, 4.7 Hz, 2H), 6.10 (d, *J* = 5.6 Hz, 1H), 4.49 (d, *J* = 5.7 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 201.66, 158.16, 157.22, 133.96, 130.65, 130.01, 129.63, 127.53, 125.21, 121.21, 120.67, 111.25, 110.89, 75.93, 55.27, 55.17. IR (neat): $\tilde{\nu}$ = 3469, 2941, 2838, 1673, 1598, 1489, 1464, 1437, 1386, 1290, 1238, 1185, 1163, 1116, 1076, 1048, 1023, 976, 754 cm^{-1}. MS (EI-MS, m/z): 272.1 (M$^{+•}$).



Synthesis of Pyridyl alcohols[5]



5,6,7,8-tetrahydroquinolin-8-ol (103b)

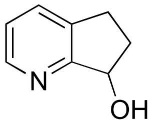


To the cold solution of *m*-CPBA (1.2 equiv) in dichloromethane (15 mL), 5,6,7,8-tetrahydroquinoline (1 g, 7.5 mmol) in dichloromethane was added dropwise. After removing the ice bath the reaction mixture was stirred at rt overnight. An additional 0.6 equiv *m*-CPBA was added and stirred for 5 h. The organic layer was washed with dilutes NaOH to remove remaining peroxides. The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was used for next step without further purification.

Trifluoroacetic anhydride (4 mL) was added slowly to cold solution of crude 5, 6, 7, 8-tetrahydroquinoline-*N*-oxide in 10 mL of dichloromethane. The reaction mixture was allowed to warm up to rt and was stirred overnight. The volatile compounds were removed under reduced pressure and remaining organic phase was dissolved in dichloromethane and 2M LiOH solution was added to it. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography. (Triethylamine/ethyl acetate 1:9, $R_f = 0.4$). Yield: 78 %.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.30-8.29 (m, 1H), 7.31 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.01 (dd, *J* = 7.7, 4.8 Hz, 1H), 5.15 (s, 1H), 4.68 (dd, *J* = 7.2, 5.4 Hz, 1H), 2.79-2.60 (m, 2H), 2.16-2.06 (m, 1H), 1.98-1.65 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.03, 146.46, 137.05, 131.90, 122.19, 67.85, 31.03, 28.44, 18.84. IR (neat): $\tilde{\nu}$ = 3193, 3069, 2965, 2926, 2876, 2839, 2701, 1578, 1440, 1331, 1289, 1188, 1159, 1117, 1082, 1054, 1001, 968, 884, 849, 799, 780, 723, 700 cm^{-1}. MS (EI-MS, m/z): 149.1 ($M^{+\bullet}$).

6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (103a)

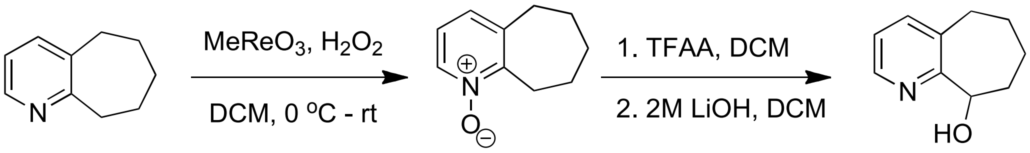


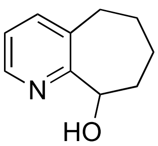
To the cold solution of *m*-CPBA (1.2 equiv.) in dichloromethane (15 mL), 6,7-dihydro-*5H*-[1] pyridine (1 g, 8.4 mmol) in dichloromethane was added dropwise. After removing the ice bath the reaction mixture was stirred at rt overnight. An additional 0.6 equiv *m*-CPBA was added and stirred for 5 h. The organic layer was washed with dilutes NaOH to remove remaining peroxides. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used for next step without further purification.

Trifluoroacetic anhydride was added slowly to cold solution of crude 6,7-dihydro-*5H*-[1] pyridine-*N*-oxide in dichloromethane. The reaction mixture was allowed to warm up to rt and stirred overnight. The volatile compounds were removed under reduced pressure and remaining organic phase was dissolved in dichloromethane and 2M LiOH solution was added to it. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography. Yield: 62 %.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.32 (dt, *J* = 5.0, 0.7 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.06 (dd, *J* = 7.6, 5.0 Hz, 1H), 6.50 (br s, 1H), 5.20 (t, *J* = 6.7 Hz, 1H), 2.98 (m, 1H), 2.73 (m, 1H), 2.46 (m, 1H), 2.01 (m, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 165.18, 147.55, 136.66, 133.57, 122.68, 73.19, 32.78, 27.54. IR (neat): $\tilde{\nu}$ = 3224, 3068, 2979, 2941, 2857, 1587, 1402, 1330, 1295, 1219, 1155, 1074, 943, 793, 735, 700, 620 cm^{-1}. MS (EI-MS, m/z): 135 ($M^{+\bullet}$).

6,7,8,9-tetrahydro-5H-cyclohepta [b] pyridin-9-ol (103c)

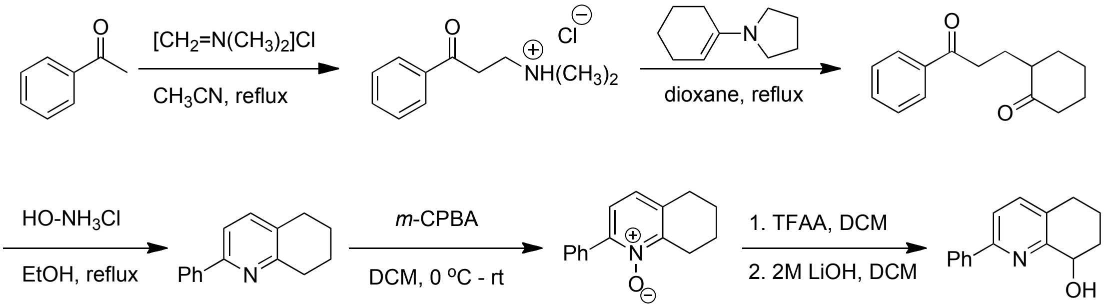




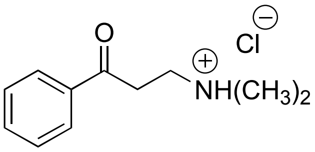
To stirred solution of 6,7,8,9-tetrahydro-5H-cycloheptapyridine (500 mg, 3.4 mmol) and methyltrioxorhenium (42.4 mg, 5 mol%) in dichloromethane (5 mL) was slowly added hydrogen peroxide 0.7 mL (30% aq) at 0 °C. The reaction mixture was allowed to warm to rt and catalytic amount of MnO_2 was added to destroy the remaining hydrogen peroxide. The mixture was filtered and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was used for next step without further purification.

Acetic anhydride (10 mL) was added slowly to cold solution of crude 6,7,8,9-tetrahydro-5H-cycloheptapyridine-*N*-oxide in dichloromethane. The reaction mixture was refluxed for 1 hour while the clor changed from yellow to brown. The reaction mixture was poured on ice and diluted with 20% NaOH and extracted with three times with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The brown oil was dissolved in 50 mL of MeOH. 25 mL of 10% NaOH was added and the reaction mixture stirred for 1 h at rt. The reaction mixture was extracted five times with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography. Yield: 54%. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.25 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.35-7.32 (m, 1H), 7.02 (dd, *J* = 7.4, 4.9 Hz, 1H), 5.81 (s, 1H), 4.66 (dd, *J* = 11.2, 2.3 Hz, 1H), 2.71-2.55 (m, 2H), 2.17-2.09 (m, 1H), 2.01-1.66 (m, 3H), 1.31 (m, 1H), 1.19-1.05 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.03, 29.01, 34.32, 36.31, 72.17, 122.08, 135.67, 137.20, 144.35, 160.93. IR (neat): $\tilde{\nu}$ = 3360, 3055, 2924, 2852, 1582, 1455, 1439, 1402, 1296, 1259, 1059, 1019, 941, 796, 773, 737 cm^{-1}. MS (CI-MS, m/z): 146.1 (MH^+).

Synthesis of 2-phenyl-5,6,7,8-tetrahydroquinolin-8-ol (103e)

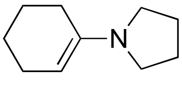


3-dimethylamino-1-phenyl-propan-1-one hydrochloride



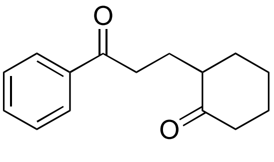
A mixture of *N*,*N*-dimethyleneiminium chloride (2 g, 22 mmol) and acetophenone (4.2 mL, 22 mmol) in acetonitrile (11 mL) was refluxed for 1 h. After cooling to rt the product was recrystallized immediately. Yield: 82%. ^{1}H-NMR (300 MHz; DMSO-d$_6$): δ 10.95 (br s, 1H), 8.03-8.00 (m, 2H), 7.71-7.66 (m, 1H), 7.59-7.54 (m, 2H), 3.66 (t, J = 7.4 Hz, 2H), 3.42-3.38 (m, 2H), 2.79 (s, 6H). ^{13}C-NMR (75.5 MHz; DMSO-d$_6$): δ 196.65, 135.83, 133.65, 128.74, 127.94, 51.61, 42.04, 33.07. IR (Neat): 3487, 3398, 2949, 2666, 2570, 2471, 1674, 1628, 1597, 1467, 1426, 1385, 1334, 1223, 1137, 1078, 1037, 1003, 958,754, 688, 652. LRMS (ES-CI, M-H$^+$): 177.

1-(Cyclohex-1-en-1-yl)pyrrolidine



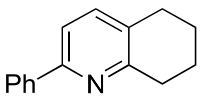
The solution of cyclohexanone (26 mL, 0.25 mol), pyrrolidine (32 mL, 0.38 mol) in toluene (75 mL) was refluxed using dean-stark trap until water formation stopped. The solvent was removed under vacuum and crude product was purified by distillation. Yield: quantitative. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.47–1.58 (m, 2H), 1.6–1.73 (m, 2H), 1.81 (q, J = 6.6 Hz, 4H), 2.02–2.12 (m, 2H), 2.13–2.21 (m, 2H), 2.97 (t, J = 6.3 Hz, 4H), 4.26 (s, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 23.00, 23.35, 24.52, 27.02, 27.52, 47.40, 93.51, 143.36.

2-(3-Oxo-3-phenylpropyl)cyclohexanone



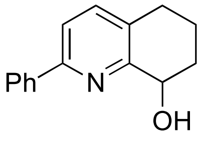
3-dimethylamino-1-phenyl-propan-1-one hydrochloride (4 g, 16.4 mmol) was suspended in dioxane (40 mL). After addition of cyclohexanone pyrrolidine enamine (2.5 g, 16.4 mL) the reaction mixture was refluxed for 16 h. After cooling to rt, water was added and refluxed for additional one hour. The aqueous phase was extracted with dichloromethane and the combined organic layers were washed with diluted HCl, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography. Yield: 31%. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.98-7.94 (m, 2H), 7.53-7.50 (m, 1H), 7.43 (td, *J* = 7.3, 1.4 Hz, 2H), 3.17-3.06 (m, 1H), 2.95 (ddd, *J* = 17.0, 8.3, 6.6 Hz, 1H), 2.48-2.23 (m, 3H), 2.18-1.99 (m, 3H), 1.90-1.80 (m, 1H), 1.75-1.58 (m, 3H), 1.50-1.37 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.51, 25.13, 28.19, 34.68, 36.36, 42.32, 49.9, 128.1, 128.6, 133.0, 136.8, 200.4, 213.4.

2-phenyl-5,6,7,8-tetrahydroquinoline



The solution of 2-(3-oxo-3-phenyl-propyl)-cyclohexanone (2.6 g, 11 mmol) and hydroxylamine hydrochloride (0.8 g, 11 mmol) in ethanol (20 mL) was refluxed for 3 h. After 3 h, the reaction mixture was neutralized by sodium carbonate solution and water and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated to yield crude brown oil, which was purified by column chromatography. Yield: 38%. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.99-7.95 (m, 2H), 7.49-7.36 (m, 5H), 3.03 (t, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.3 Hz, 2H), 1.99-1.81 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.86, 23.27, 28.60, 32.92, 117.94, 126.86, 128.30, 128.67, 130.75, 137.47, 139.95, 154.68, 157.26.

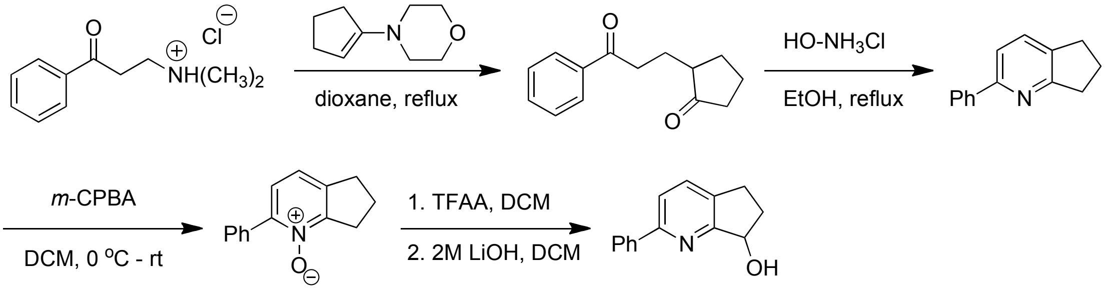
2-Phenyl-5,6,7,8-tetrahydroquinolin-8-ol (103e)



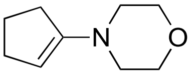
To the cold solution of *m*-CPBA (2.47 gm, 14.3 mmol) in dichloromethane (10 mL), 2-phenyl-5,6,7,8-tetrahydroquinoline (2.50 g, 12 mmol) in dichloromethane was added dropwise. After removing the ice bath the reaction mixture was stirred at rt overnight. An additional 0.6 equiv *m*-CPBA was added and stirred for 5 h. The organic layer was washed with dilutes NaOH to remove remaining peroxides. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used for next step without further purification.

Trifluoroacetic anhydride was added slowly to cold solution of 2-phenyl-5, 6, 7, 8-tetrahydroquinoline-*N*-oxide (1.4 g, 6.2 mmol) in dichloromethane (20 mL). The reaction mixture was allowed to warm up to rt and was stirred overnight. The volatile compounds were removed under reduced pressure and remaining organic phase was dissolved in dichloromethane and 2M LiOH solutions was added to it. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography. Yield: 87%. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.00 (dq, *J* = 6.3, 1.9 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.50-7.38 (m, 4H), 4.74 (dd, *J* = 9.1, 5.6 Hz, 1H), 4.37 (s, 1H), 2.88-2.83 (m, 2H), 2.41-2.34 (m, 1H), 2.08-2.00 (m, 1H), 1.93-1.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.65, 154.21, 138.91, 137.76, 129.91, 128.88, 128.73, 126.69, 119.19, 69.20, 30.67, 28.02, 19.71. IR (neat): $\tilde{\nu}$ = 3216, 3061, 2927, 2827, 1593, 1567, 1461, 1263, 1189,1157, 1076, 1010, 963, 933, 851, 769, 733, 696, 594 cm^{-1}. MS (EI-MS, m/z): 225.2 ($M^{+\bullet}$).

2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (103d)

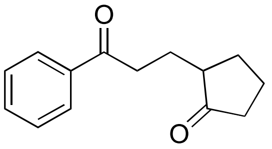


4-(Cyclopent-1-en-1-yl)morpholine



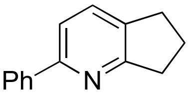
The solution of cyclopentanone (25 g, 0.30 mol), morpholine (39 mL, 0.45 mol) in toluene (75 mL) was refluxed using dean-stark trap until water formation stopped. The solvent was removed under vacuum and crude product was purified by distillation. Yield: 70%. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 4.40 (s, 1H), 3.68 (t, *J* = 4.9 Hz, 4H), 2.83 (t, *J* = 4.9 Hz, 4H), 2.33-2.25 (m, 4H), 1.88-1.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 151.71, 98.28, 66.64, 49.04, 31.33, 30.29, 22.50.

2-(3-Oxo-3-phenylpropyl)cyclopentanone



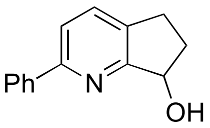
3-Dimethylamino-1-phenyl-propan-1-one hydrochloride (2.5 g, 11.7 mmol) was suspended dioxane (15 mL). After addition of cyclopentanone morpholine enamine (1.79 g, 11.7 mmol) the reaction mixture was refluxed for 16 h. After cooling to rt, water was added and refluxed for additional one hour. The water phase was extracted with dichloromethane and the combined organic layers were washed with diluted HCl, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography. Yield: 1.06 g, 42%. ^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.94 (dd, *J* = 7.1, 1.5 Hz, 2H), 7.55-7.50 (m, 1H), 7.46-7.40 (m, 2H), 3.09 (m, 2H), 2.27-1.92 (m, 6H), 1.83-1.68 (m, 2H), 1.61-1.48 (m, 1H). ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 220.96, 199.86, 136.82, 133.07, 128.62, 128.08, 48.23, 38.15, 36.20, 29.94, 24.28, 20.70.

2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine



The solution of 2-(3-oxo-3-phenyl-propyl)-cyclopentanone (1.0 g, 4.63 mmol) and hydroxylamine hydrochloride (0.321 g, 4.63 mmol) in ethanol (20 mL) was refluxed for 3 h. After 3 h, the reaction mixture was neutralized by sodium carbonate solution and water and the water phase was extracted with dichloromethane. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to yield crude brown oil, which was purified by column chromatography. Yield: 787 mg, 87%. ^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.92 (d, *J* = 6.9 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.45-7.32 (m, 4H), 3.06 (t, *J* = 7.7 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.13 (quintet, *J* = 7.5 Hz, 2H). ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 165.90, 155.92, 140.07, 135.47, 132.62, 128.69, 128.40, 126.96, 118.29, 34.51, 30.57, 23.32.

2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (103d)

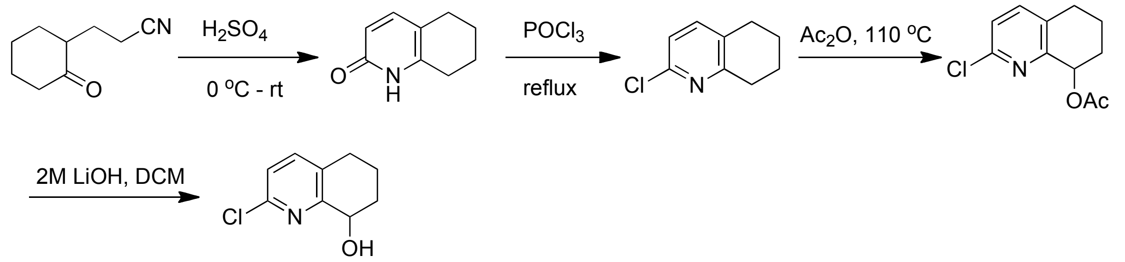


To the cold solution of *m*-CPBA (1.2 equiv) in dichloromethane (10 mL), 2-phenyl-6,7-dihydro-*5H*-[1]pyridine (0.5 g, 2.56 mmol) in dichloromethane was added dropwise. After removing the ice bath the reaction mixture was stirred at rt overnight. An additional 0.6 equiv *m*-CPBA was added and stirred for 5 h. The organic layer was washed with dilutes NaOH to remove remaining peroxides. The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was used for next step without further purification.

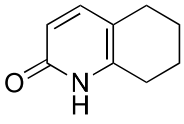
Trifluoroacetic anhydride (0.7 mL) was added slowly to cold solution of crude 2-phenyl-6,7-dihydro-*5H*-[1]pyridine-*N*-oxide in dichloromethane (20 mL). The reaction mixture was allowed to warm up to rt and was stirred overnight. The volatile compounds were removed under pressure and remaining organic phase was dissolved in dichloromethane and 2M LiOH solution was added to it. The combined organic layers were washed with water, dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography. Yield: 84%. ^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.94-7.90 (m, 2H), 7.54 (q, *J* = 7.6 Hz, 2H), 7.46-7.35 (m, 3H), 5.25 (t, *J* = 6.7 Hz, 1H), 4.80-4.72 (br s, 1H), 3.04-2.94 (m, 1H), 2.82-2.71 (m, 1H), 2.50 (m, 1H), 2.05 (m, 1H). ^{13}C-NMR (75.5 MHz; CDCl$_3$): δ

164.96, 156.51, 139.48, 134.98, 133.83, 128.67, 127.12, 120.13, 74.58, 33.13, 27.29. IR (neat): $\tilde{\nu}$ = 3162, 3073, 2971, 2941, 2852, 2738, 2717, 1590, 1573, 1447, 1433, 1398, 1315, 1238, 1157, 1111, 1053, 1022, 961, 909, 852, 767, 692 cm^{-1}. MS (EI-MS, m/z): 211.2 (M$^{+\bullet}$).

Synthesis of 2-chloro-5,6,7,8-tetrahydroquinolin-8-ol (103f)

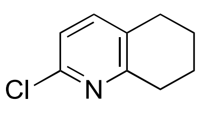


5,6,7,8-tetrahydroquinolin-2(1H)-one



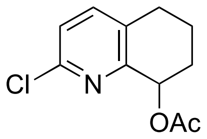
To a cold solution of sulfuric acid (20 mL) was added dropwise 3-(2-oxocyclohexyl)propanenitrile (3g, 19.4 mmol). After the addition, the reaction mixture was stirred at rt for 3 h. The reaction mixture was poured into cold water and extracted with chloroform to remove polymeric impurities and unaromatized material, The resulting aqueous solution was neutralized with aqueous ammonia. A white solid precipitated which was extracted with chloroform. The organic layers were dried over Na2SO4 and concentrated under vaccum to obtain white solid product.The pure product was obtained after column chromatography (49% yield). ^{1}H-NMR (300 MHz; CDCl$_3$): δ 13.33 (s, 1H), 7.10 (d, *J* = 9.1 Hz, 1H), 6.29 (d, *J* = 9.1 Hz, 1H), 2.62 (t, *J* = 5.7 Hz, 2H), 2.39 (t, *J* = 5.5 Hz, 2H), 1.71-1.64 (m, 4H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 165.07, 143.73, 143.21, 116.64, 114.44, 26.67, 26.05, 22.51, 21.55.

2-Chloro-5,6,7,8-tetrahydroquinoline



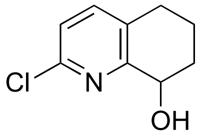
A mixture of POCl$_3$ (6.6 mL, 19.8 mmol) and 5,6,7,8-tetrahydro-2-quinolone (1 g, 6.6 mmol) was refluxed under nitrogen overnight. The mixture was cooled, poured into 2M cold NaOH and extracted with dichloromethane. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography. Yield: Quantitative. ^{1}H-NMR (300 MHz; CDCl$_3$): δ 7.20 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 2.77 (t, *J* = 6.1 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 1.78-1.67 (m, 4H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 22.34, 22.62, 27.98, 32.19, 121.1, 131.0, 139.5, 147.6, 158.0.

2-chloro-5,6,7,8-tetrahydroquinolin-8-yl acetate



To 2-chloro-5,6,7,8-tetrahydro-2-quionoline (526 mg, 3.5 mmol) was added glacial acetic acid (2.5 mL) and the mixture was stirred at 82 °C. 30% aqueous hydrogen peroxide (0.53 mL) was added slowly to the reaction mixture and stirred further for 5 h at 82 °C, after which additional hydrogen peroxide (0.09 mL) was added. The resulting mixture was stirred for 12 h at this temperature and then cooled to room temperature. The excess hydrogen peroxide was destroyed by adding catalytic manganese dioxide and stirred for one more hour at room temperature. Water and acetic acid were removed under pressure. The residue was poured into water and neutralized with Na_2CO_3 and then extracted with dichloromethane. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated in vacuum to afford corresponding pyridine *N*-oxide, which was used directly for the next step without further purification. The crude pyridine *N*-oxide was dissolved in acetic anhydride (4 mL) and stirred at 85 °C for 5 h. The resulting reaction mixture was then cooled to room temperature and concentrated under reduced pressure to afford crude acetate product. Column chromatography afforded the desired compound in 77% yield as colorless oil. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.34 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 5.77 (t, *J* = 4.5 Hz, 1H), 2.81-2.59 (m, 2H), 2.13-2.10 (m, 1H), 2.02 (s, 3H), 1.99-1.70 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.05, 21.4, 27.7, 28.6, 70.4, 123.9, 132.5, 140.0, 148.8, 153.7, 170.2.

2-Chloro-5,6,7,8-tetrahydroquinolin-8-ol (103f)



To a stirred solution of 2-chloro-5,6,7,8-tetrahydro-2-quionoline-8-acetate (153 mg, 0.67 mmol) in ethanol (0.4 mL), a solution of KOH (54 mg) in ethanol (1 mL) was added. The resulting mixture was stirred at rt for 30 min and then the solvent was removed under vacuum to yield dark solid, which was treated with water and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to obtain 8-hydroxy-2-chloro-5,6,7,8-tetrahydro-2-quionoline. Yield: 93%. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.31 (d, *J* = 8.1 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 4.62 (dd, *J* = 7.6, 5.4 Hz, 1H), 3.80 (s, 1H), 2.69 (t, *J* = 9.5 Hz, 2H), 2.18-2.09 (m, 1H), 1.97-1.87 (m, 1H), 1.83-1.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.59, 147.30, 138.91, 129.66, 121.95, 67.37, 29.33, 26.79, 18.03. IR (neat): $\tilde{\nu}$ = 3237, 2951, 2896, 2837, 2689, 1570, 1419, 1340, 1294, 1200, 1132, 1107, 1078, 1008, 958, 862, 841, 814, 786, 678, 637, 534 cm^{-1}. MS (EI-MS, m/z): 183 ($M^{+\bullet}$).

General Procedure for the oxidative kinetic resolution of *sec* alcohols

To a solution of ligand **6** (5.5 mol%) in acetone (1.5 mL), was added $VO(OiPr)_3$ (2.95 μL, 5 mol%). The resulting solution was stirred under an atmosphere of oxygen for 15 min. The alcohol (0.25 mmol) was then added and allowed the reaction mixture to stir at room temperature. Aliquots of the reaction mixture were removed *via* syringe at intervals to monitor for percent conversion and enantiomeric excess. Each aliquot was filtered over a pipette silica gel column and the filtrate was analyzed by TLC, GC, and HPLC as necessary. After completion of the reaction (~50% conversion), the reaction mixture was concentrated and the resulting residue was purified by silica gel column chromatography using hexane, ethylacetate combination.

General Procedure for the oxidative kinetic resolution of pyridyl alcohols

To a solution of ligand **72d** (10.5 mol%) in acetone (1.5 mL), was added $VO(OiPr)_3$ (10 mol%). The resulting solution was stirred under an atmosphere of oxygen for 15 min. The alcohol (0.125 mmol) was then added and allowed the reaction mixture to stir at 60 °C. Aliquots of the reaction mixture were removed *via* syringe at intervals to monitor for percent conversion and enantiomeric excess. Each aliquot was filtered over a pipette silica gel column and TLC, GC, and HPLC analyzed the filtrate as necessary. After completion of the reaction (~ 50 % conversion), the reaction mixture was concentrated and the resulting residue was purified by silicagel column chromatography using hexane, ethylacetate and triethylamine combination.

General Procedure for the oxidative kinetic resolution of *sec* alcohols

To a solution of ligand **72d** (5.5 mol%) in acetone (1.5 mL), was added $VO(OiPr)_3$ (2.95 µL, 5 mol%). The resulting solution was stirred under an atmosphere of oxygen for 15min. The alcohol (0.25 mmol) was then added and allowed the reaction mixture to stir at room temperature. Aliquots of the reaction mixture were removed via syringe at intervals to monitor for percent conversion and enantiomeric excess. Each aliquot was filtered over a pipette silica gel column and the filtrate was analyzed by TLC, GC, and HPLC as necessary. After completion of the reaction (~ 50% conversion), the reaction mixture was concentrated and the resulting residue was purified by silicagel column chromatography using hexane, ethylacetate combination.

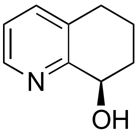
Kinetic resolution of HPB ester (99f)-Recycling Experiment

To a solution of ligand **72d** (5.5 mol%) in acetone (5 mL), was added VO(O*i*Pr)$_3$ (5 mol%). The resulting solution was stirred under an atmosphere of oxygen for 15min. The alcohol (3 mmol) was then added and allowed the reaction mixture to stir at room temperature. Aliquots of the reaction mixture were removed via syringe at intervals to monitor for percent conversion and enantiomeric excess. Each aliquot was filtered over a pipette silica gel column and the filtrate was analyzed by TLC, GC, and HPLC as necessary. After completion of the reaction (~ 50 % conversion), the reaction mixture was concentrated and the resulting residue was precipitated by adding hexane. The catalyst was collected by filteration and dried. The mother liquor was concentrated and purified by silicagel column chromatography using hexane, ethylacetate combination. **(R)-99f;** 97% *ee*; $[\alpha]_D^{20} = -18.0$ (c 1.0, chloroform)

The absolute configuration of alpha hydroxy esters, ketones were determined by comparison of α_D values and HPLC with those previously reported.[5]

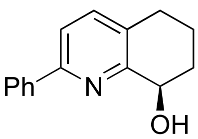
The stereochemistries of pyridyl alcohols were determined by comparison with literature data.[6]

***(R)*-5,6,7,8-tetrahydroquinolin-8-ol (*R*-103b)**



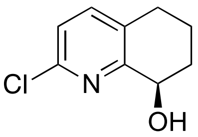
93% *ee*; $[\alpha]_D^{20} = -58$ (c 0.95, chloroform)

(*R*)-2-Phenyl-5,6,7,8-tetrahydroquinolin-8-ol (*R*-103e)



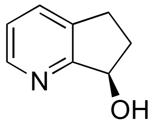
>99% *ee*; $[\alpha]_D^{20} = -135$ (c 1.0, chloroform)

(*R*)-2-Chloro-5,6,7,8-tetrahydroquinolin-8-ol (*R*-103f)



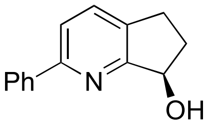
>99% *ee*; $[\alpha]_D^{20} = -54.2$ (c 0.61, chloroform)

(*R*)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (*R*-103a)



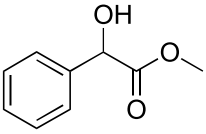
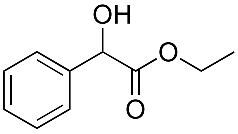
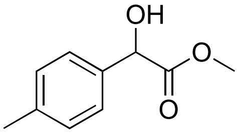
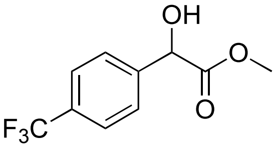
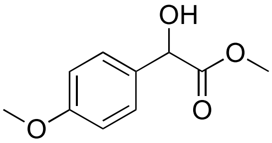
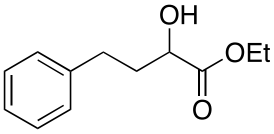
92% *ee*; $[\alpha]_D^{20} = -73$ (c 0.95, chloroform)

***R*-2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (*R*-103d)**



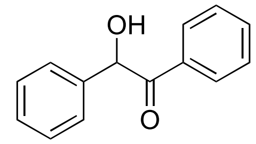
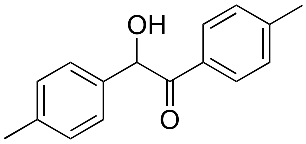
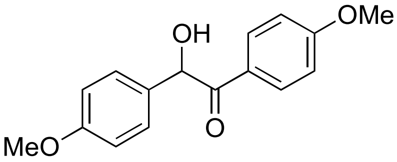
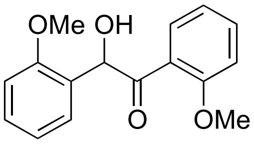
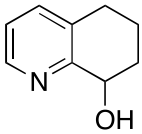
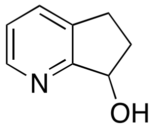
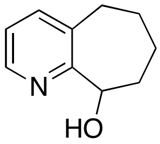
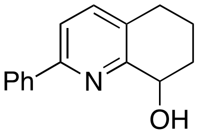
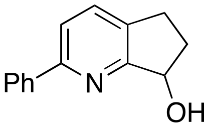
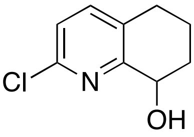
>99% *ee*; $[\alpha]_D^{20} = -36$ (c 0.3, chloroform)

***Table 22*. Methods for the determination of enantiomeric excess using chiral GC**

Substrate	Condition	Retention times
	90 °C – 5 min 100 °C – 5 min 110 °C – 30 min	24.19-major (*R*) 25.54-minor (*S*)
	90 °C – 5 min 100 °C – 5 min 110 °C – 30 min	28.41 major (*R*) 29.52 minor (*S*)
	110 °C isothermal	29.16 major (*R*) 32.45 minor (*S*)
	110 °C isothermal	24.03 major (*R*) 31.20 minor (*S*)
	130 °C isothermal	26.43 major (*R*) 28.09 minor (*S*)
	120 °C isothermal	35.0 major (*R*) 38.8 minor (*S*)

Methods for the Determination of Enantiomeric Excess using chiral HPLC

Detection wavelength 254nm

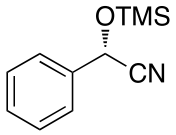
Substrate	Column	Heptane: *i*PrOH	Flow (mL/min)	Retention Times (min)
	OD-H	80/20	0.5	19.96 (*S*) 27.18 (*R*)
	OD-H	80/20	0.5	15.90 (*S*) 19.29 (*R*)
	OD-H	80/20	0.5	33.68 (*S*) 36.99 (*R*)
	OD-H	90/10	1	20.47 (*S*) 22.17 (*R*)
	OD-H	99 / 1	1	9.91 (*R*) 13.99 (*S*)
	OD-H	99/1	0.5	26.19 (*R*) 30.20 (*S*)
	AS	99/1	0.5	28.49 (*R*) 36.50 (*S*)
	OD-H	99/1	1	17.48 (*R*) 20.19 (*S*)
	OD-H	99 / 1	1	35.66 (*R*) 60.25 (*S*)
	OD-H	99/1	0.5	26.19 (*R*) 30.20 (*S*)

9.7 Cyanosilylation of aldehydes

General procedure for the asymmetric synthesis of cyanohydrin trimethylsilyl ethers

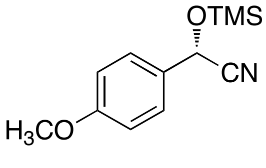
The aldehyde (1 mmol) and catalysts (0.1 mol%) were dissolved in distilled THF (2 mL). Trimethylsilyl cyanide (1.2 mmol) was added dropwise, and the reaction mixture was left to stir at -10 °C for 32 h. After the reaction was completed (as shown by TLC) the mixture was concentrated and the compound purified by flash column chromatography on silica gel (eluted with hexane/ethylacetate 95:5). The enantiomeric excess of cyanohydrin trimethylsilyl ethers were determined by chiral GC.

(*S*)-α-(trimethylsilyoxyl)phenylacetonitrile



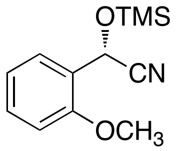
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.51-7.48 (m, 2H), 7.43-7.41 (m, 3H), 5.53 (s, 1H), 0.25 (s, 9H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 136.56, 129.63, 129.23, 126.64, 119.51, 63.94, 0.04. GC condition: GC: CP-Chirasil-Dex CB, 25 m x 0.25 mm Di, 0.25 μm Film, Inj. 250 °C, Det. 90 °C (isothermal), retention time: 52.01 min (major), 53.12 min (minor).

(*S*)-2-(4-methoxyphenyl)-2-((trimethylsilyl)oxy)acetonitrile



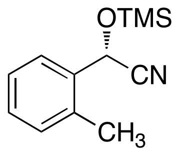
^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.38 (dd, J = 8.9, 0.4 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 5.43 (s, 1H), 3.79 (s, 3H), 0.20 (s, 9H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 160.60, 128.73, 128.20, 119.65, 114.52, 63.60, 55.57, 0.04. GC condition: CP-Chirasil-Dex CB, 25 m x 0.25 mm Di, 0.25 μm Film, Inj. 250 °C, Det. Initial temperature 110 °C - 20 min, then 130 °C – 30 min, retention time: 45.03 min (minor), 45.54 min (major).

(*S*)-2-(2-methoxyphenyl)-2-((trimethylsilyl)oxy)acetonitrile



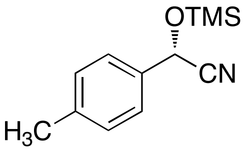
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.61 (d, J = 11.4 Hz, 1H), 7.28–7.36 (t, J = 5.8 Hz, 1H), 6.99–7.07 (t, J = 0.9 Hz, 1H), 6.89–6.92 (d, J = 11.7 Hz, 1H), 5.80 (s, 1H), 3.75 (s, 3H), 0.158 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 130.2, 126.9, 126.7, 124.6, 120.5, 110.3, 57.9, 55.2, −2.18. GC condition: CP-Chirasil-Dex CB, 25 m x 0.25 mm Di, 0.25 μm Film, Inj. 250 °C, Det. Initial temperature 110 °C - 20 min, then 130 °C – 30 min, retention time: 32.82 min (major), 34.69 min (minor).

(*S*)-2-(o-tolyl)-2-((trimethylsilyl)oxy)acetonitrile



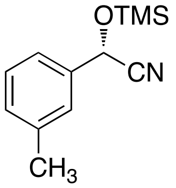
^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.21 (s, 9 H, 3 CH$_3$), 2.40 (s, 3 H, CH$_3$), 5.56 (s, 1 H), 7.18-7.29 (m, 3 H), 7.50-7.53 (m, 1 H). ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = -0.30, 18.7, 61.9, 118.8, 126.4, 127.0, 129.4, 131.0, 134.0, 135.6. GC condition: CP-Chirasil-Dex CB, 25 m x 0.25 mm Di, 0.25 *μ*m Film, Inj. 250 °C, Det. 90 ^{o}C (isothermal), retention time: 76.37 min (major), 80.71 min (minor).

(*S*)-2-(p-tolyl)-2-((trimethylsilyl)oxy)acetonitrile



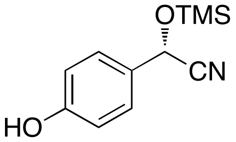
Obtained as yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.22 (9H, s), 2.37 (3H, s), 5.45 (1H, s), 7.0–7.2 (4H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.23, 128.78, 127.58, 119.47, 114.66, 63.87, 55.78, -0.28. GC condition: CP-Chirasil-Dex CB, 25 m x 0.25 mm Di, 0.25 *μ*m Film, Inj. 250 °C, Det. 90 ^{o}C (isothermal), retention time: 56.65 min (minor), 57.46 min (major).

(*S*)-2-(m-tolyl)-2-((trimethylsilyl)oxy)acetonitrile



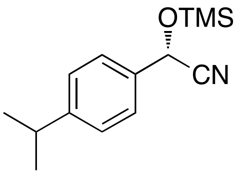
Obtained as a yellow oil (86% conversion, 81% ee). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.24 (9H, s), 2.39 (3H, s), 5.46 (1H, s), 7.0–7.3 (4H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ 138.74, 136.07, 130.02, 128.74, 126.93, 123.41, 119.21, 63.72, 21.46, -0.12. GC condition: CP-Chirasil-Dex CB, 25 m x 0.25 mm Di, 0.25 μm Film, Inj. 250 °C, Det. 90 ^{o}C (Isothermal), retention time: 86.17 min (minor), 87.71 min (major).

(S)-2-(4-hydroxyphenyl)-2-((trimethylsilyl)oxy)acetonitrile



GC condition: CP-Chirasil-Dex CB, 25m x 0.25mm Di, 0.25 μm Film, Inj. 250 °C, Det. 110 ^{o}C (Isothermal), retention time: 46.16 min (minor), 46.83 min (major).

(S)-2-(4-isopropylphenyl)-2-((trimethylsilyl)oxy)acetonitrile



GC condition: CP-Chirasil-Dex CB, 25m x 0.25mm Di, 0.25 μm Film, Inj. 250 °C, Det. 110 ^{o}C (Isothermal), retention time: 34.75 min (minor), 35.19 min (major).

9.8 Oxidation of alcohols by 3-ponytails perfluorinated TEMPO 95\bleach

Alcohol (1.0 mmol) in 2 mL CH_2Cl_2, KBr (24 mg, 0.2 mmol) and TEMPO **95** (20 mg, 1.0 mol%) were added to a round-bottom flask. The reaction mixture was stirred at 0 °C before addition of 0.8 mL NaOCl (10%) and $NaHCO_3$ (40 mg, 50 mg/mL bleach). The resulting suspension was stirred at 0 °C for 15 min. The reaction mixture was filtered off using a sintered glass funnel (P40, 16-40 μm pore size) and the solid washed with water (5 mL) and CH_2Cl_2 (2x5 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated to give pure carbonyl compound.

Oxidation of 4-methylbenzyl alcohol by -ponytails perfluorinated TEMPO 95\bleach; recycling experiments

4-methylbenzyl alcohol (305 mg, 2.50 mmol) in 5 mL CH_2Cl_2, KBr (60 mg, 0.50 mmol) and TEMPO **95** (50 mg, 0.025 mmol) were added to a round-bottom flask. The reaction mixture was stirred at 0 °C before addition of 2.0 mL NaOCl (10%) and $NaHCO_3$ (100 mg, 50 mg/mL bleach). The resulting suspension was stirred at 0 °C for 15 min. The reaction mixture was filtered off using a sintered glass funnel (P40, 16-40 pore size) and the solid washed with water (5 mL) and CH_2Cl_2 (2x5 mL), dried *in vacuo* and re-used without further purification. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated to give 4-methylbenzaldehyde.

General procedure for the aerobic oxidation of sulfides to sulfoxide by native TEMPO

Sulfide (1.0 mmol), $Mn(NO_3)_2{\bullet}4H_2O$ (0.02 mmol), $Co(NO_3)_2{\bullet}6H_2O$ (0.02 mmol), TEMPO **95** (20 mg, 1 mol%) and glacial acetic acid (1 mL) were added to a schlenk flask and heated at 40 °C under an oxygen atmosphere until completion. Then, the reaction mixture was washed by water and extracted with CH_2Cl_2. The organic layer was washed with water (2x10 mL), dried over Na_2SO_4 and concentrated under vacuum to afford the corresponding sulfoxide.

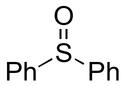
General procedure for the aerobic oxidation of sulfides to sulfoxide by 95

Sulfide (1.0 mmol), $Mn(NO_3)_2{\bullet}4H_2O$ (0.02 mmol), $Co(NO_3)_2{\bullet}6H_2O$ (0.02 mmol), catalyst **95** (20 mg, 1 mol%) and glacial acetic acid (1 mL) were added to a schlenk flask and heated at 40 °C under an oxygen atmosphere until completion. Then, the reaction mixture was filtered, washed with water and CH_2Cl_2. The organic layer was washed with water (2x10 mL), dried over Na_2SO_4 and concentrated under vacuum to afford the corresponding sulfoxide.

Aerobic oxidation of thioanisole by catalyst 95; recycling experiment

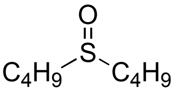
Thioanisole (366 mg, 3 mmol), $Mn(NO_3)_2$•$4H_2O$ (15 mg, 0.06 mmol), $Co(NO_3)_2$•$6H_2O$ (18 mg, 0.06 mmol), TEMPO **95** (60 mg, 1 mol%) and glacial acetic acid (3 mL) were added to a schlenk flask and heated at 40 °C under an oxygen atmosphere. After 4 h the reaction mixture was filtered, washed with water and CH_2Cl_2. The organic layer was washed with water (2x10 mL), dried over Na_2SO_4 and concentrated under vacuum to afford sulfoxide. Catalyst **95** was washed with water and CH_2Cl_2 and reused without further purification. Fresh portions of $Mn(NO_3)_2$•$4H_2O$ (15 mg, 0.06 mmol) and $Co(NO_3)_2$•$6H_2O$ (18 mg, 0.06 mmol) were added to each run.

Diphenylsulfoxide



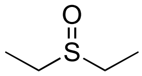
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.66-7.61 (m, 4H), 7.48-7.39 (m, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 145.63, 131.10, 129.37, 124.81.

Dibutylsulfoxide



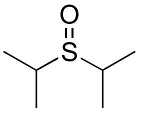
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.64-2.56 (m, 4H), 1.74-1.63 (m, 4H), 1.42 (dquintet, J = 14.7, 7.3 Hz, 4H), 0.90 (t, J = 7.3 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 52.05, 24.55, 22.01, 13.64

Diethylsulfoxide



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.82-2.68 (m, 4H), 1.27 (t, J = 7.5 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 43.18, 5.79.

Diisopropylsulfoxide



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.71 (dt, J = 13.7, 6.9 Hz, 2H), 1.22 (dd, J = 12.2, 6.9 Hz, 12H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 46.64, 17.25, 14.15.

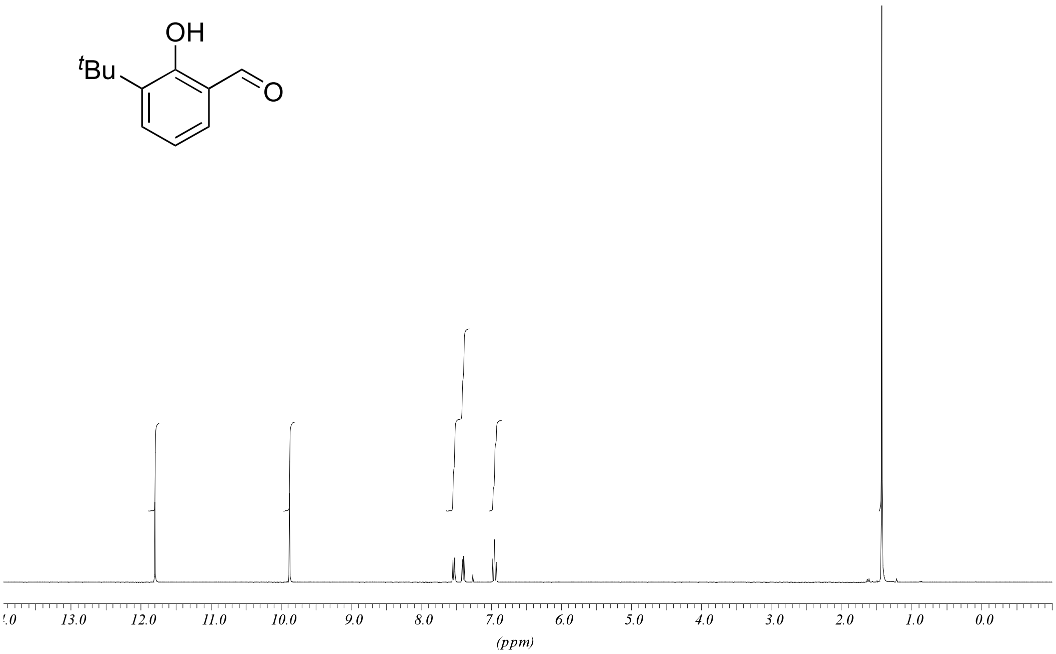
References

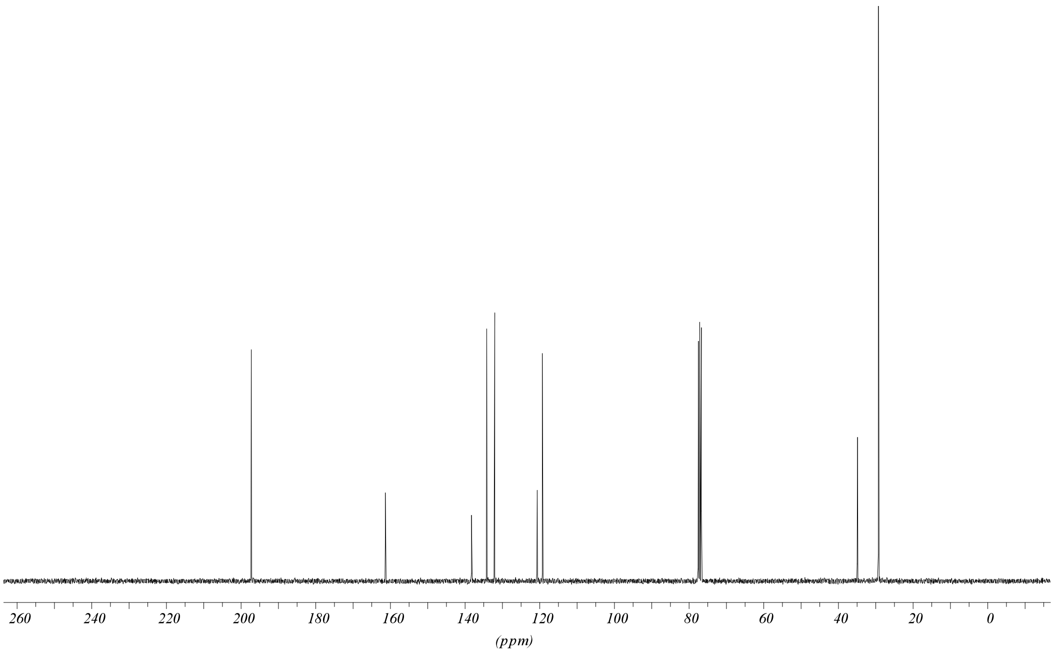
1. N.U. Hofsløkken, L. Skattebøl, *Acta Chemica Scandinavica.* **1999**, *53*, 258-262.
2. M. Cavazzini, A. Manfredi, F. Montanari, S. Quici, G. Pozzi *Eur. J. Org. Chem.* **2001**, 4639.
3. Chang, K.-H.; Huang, C.-C.; Liu, Y.-H.; Hu, Y.-H.; Chou, P.-T.; Lin, Y.-C., *Dalton Trans.* **2004**, 1731-1738.
4. Szonyi, F.; Cambon, A. *J. Fluorine Chem.* **1989**, *42*, 59.
5. a) Tang, L.; Deng, L., *J. Am. Chem. Soc.* **2002,** *124*, 2870-2871. b) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G., *Tetrahedron: Asymmetry* **1998,** *9*, 4117-4122. b) Alamsetti, S. K.; Muthupandi, P.; Sekar, G., *Chem. Eur. J.* **2009,** *15*, 5424-5427.
6. a) Mazet, C.; Roseblade, S.; Kohler, V.; Pfaltz, A., *Org. Lett.* **2006,** *8*, 1879-1882. b) Kaiser, S.; Smidt, S. P.; Pfaltz, A., *Angew. Chem., Int. Ed.* **2006,** *45*, 5194-5197.

10 Appendix

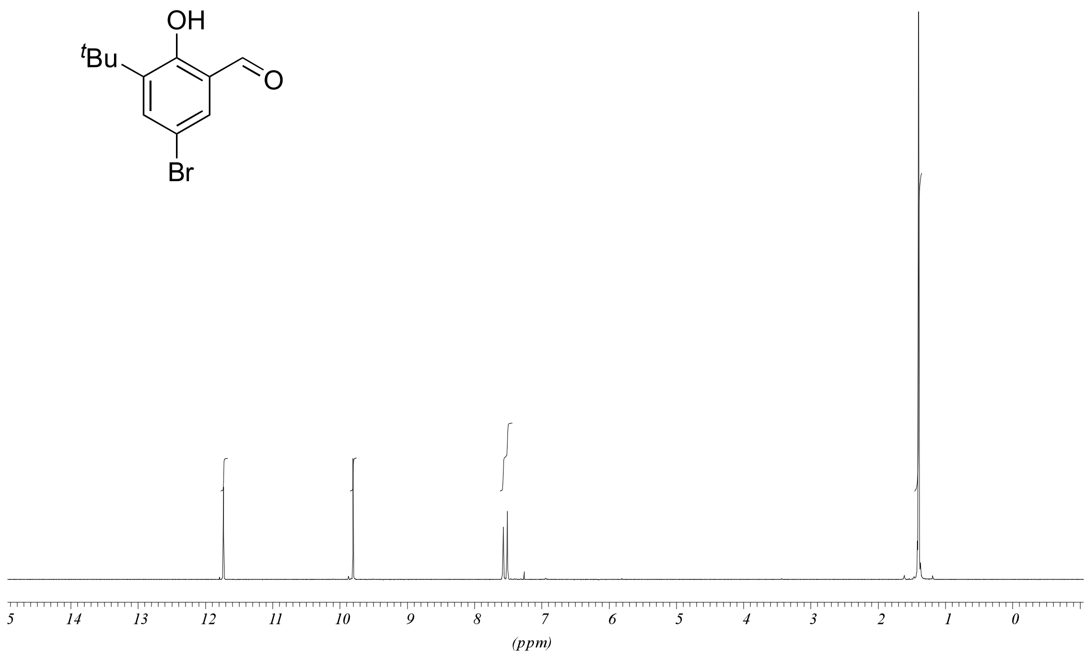
10.1 ^{1}H and ^{13}C NMR spectra

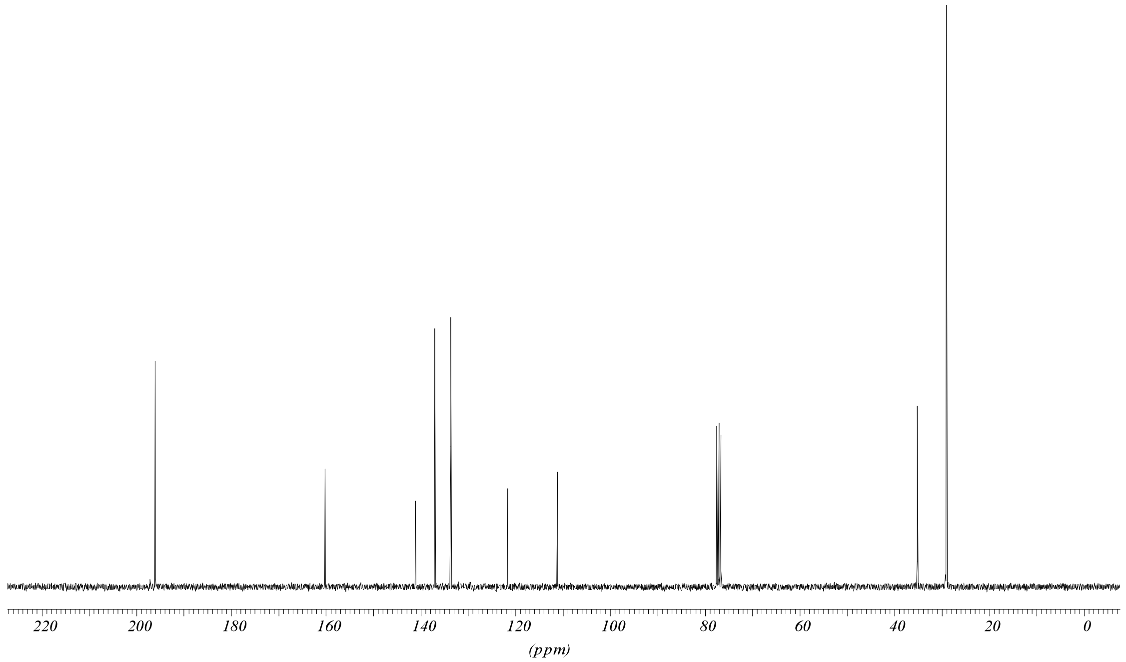
3-*tert*-Butyl-2-hydroxybenzaldehyde (68)



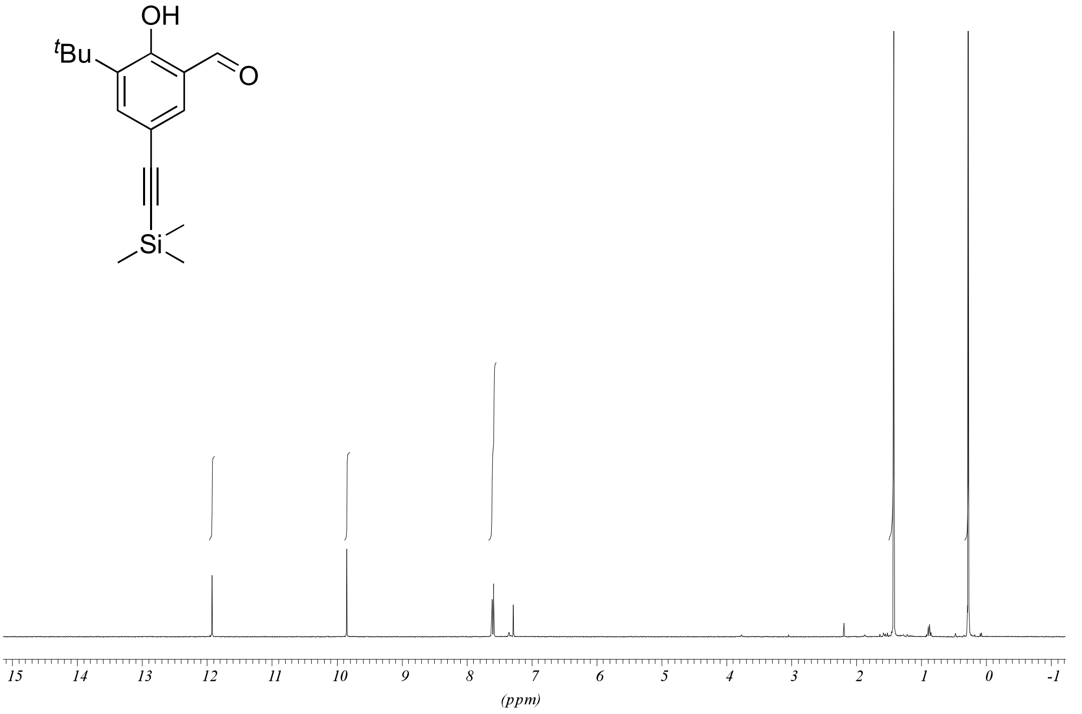


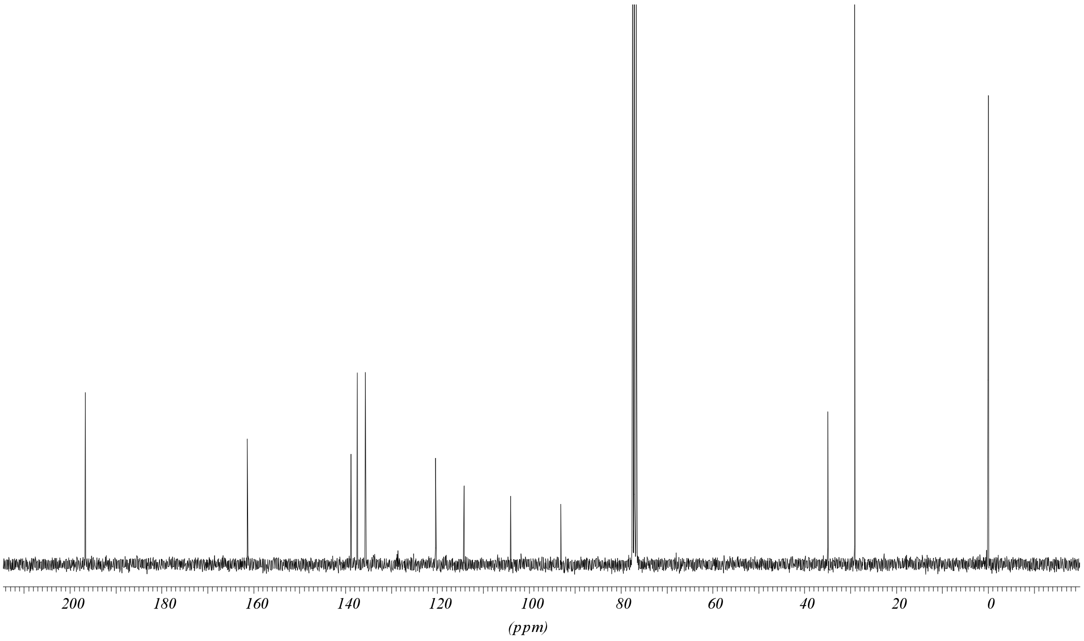
5-bromo-3-*tert*-butyl-2-hydroxybenzaldehyde (69)



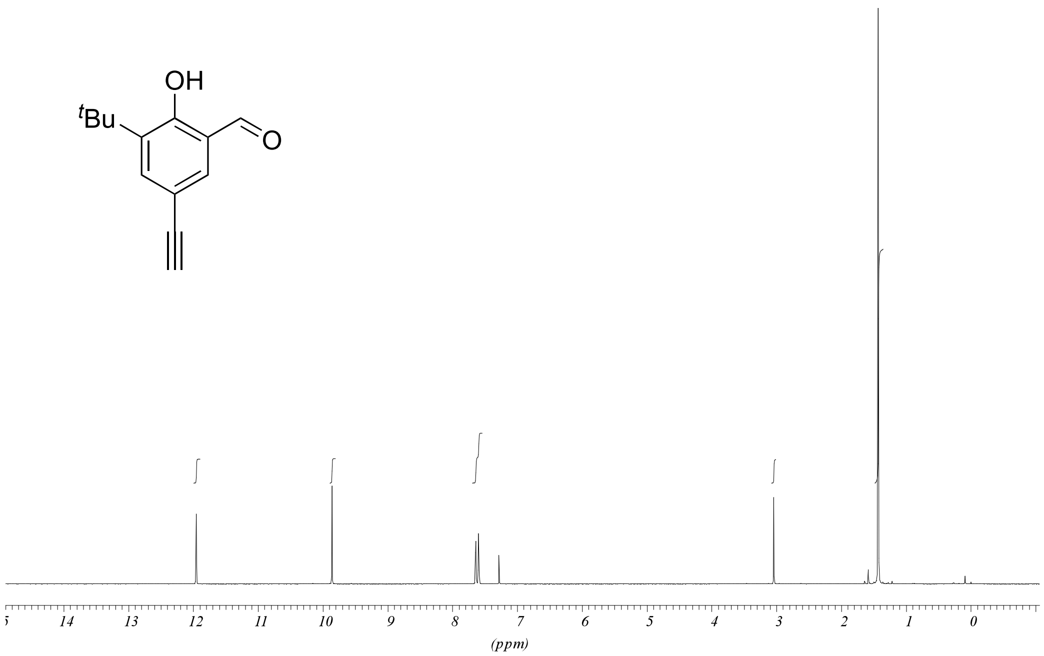


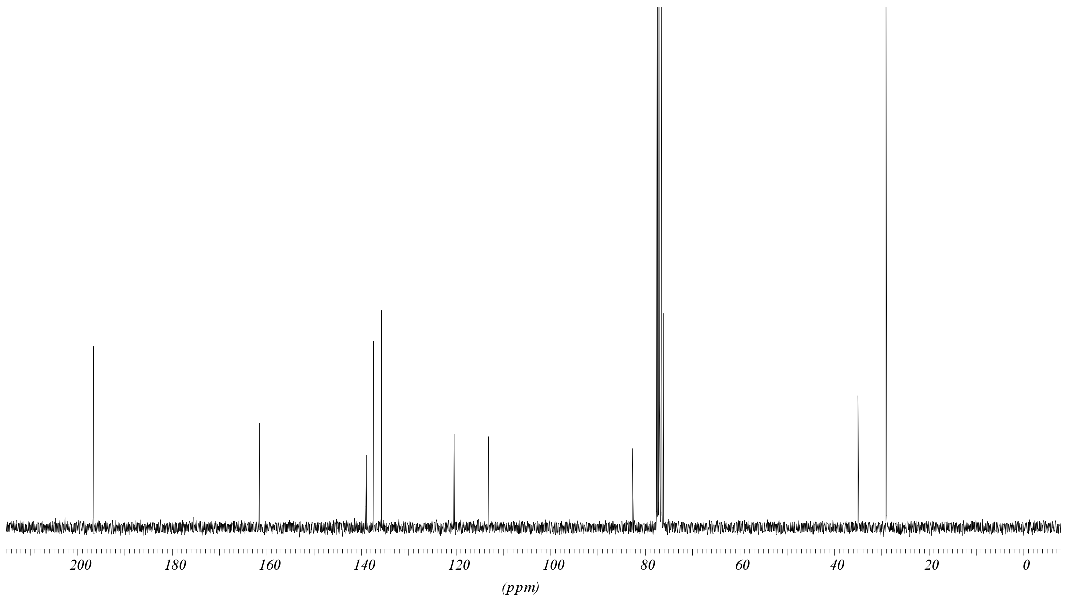
3-*tert*-butyl-2-hydroxy-5-[(trimethylsilyl)ethynyl]benzaldehyde



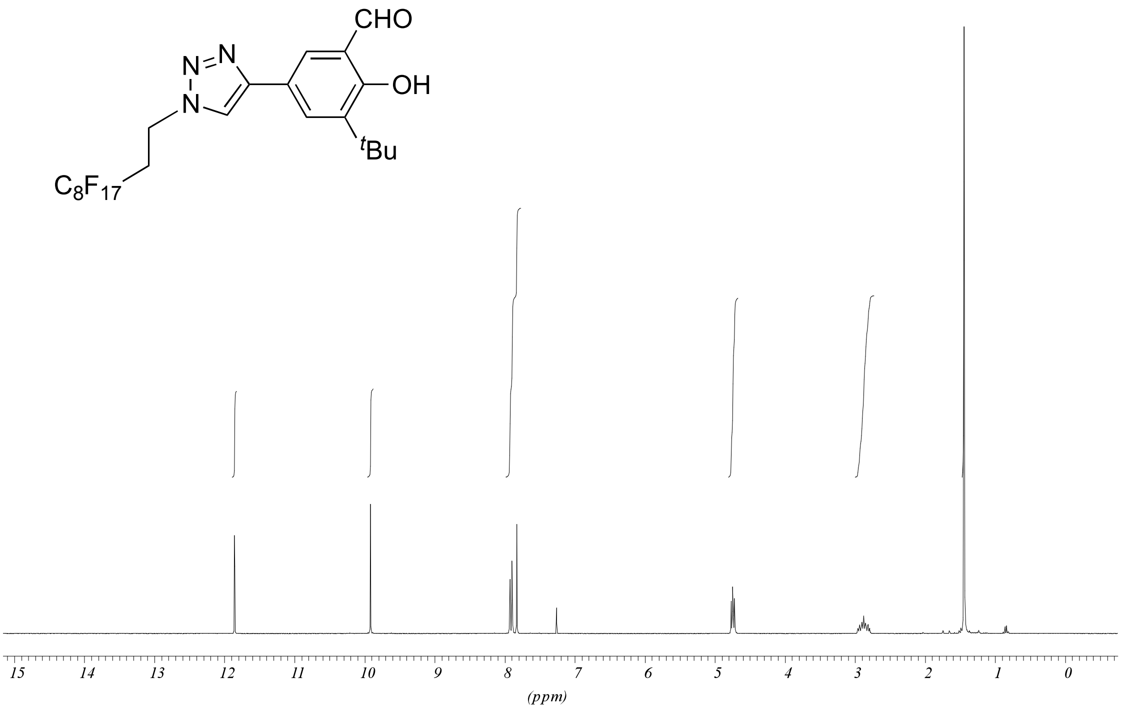


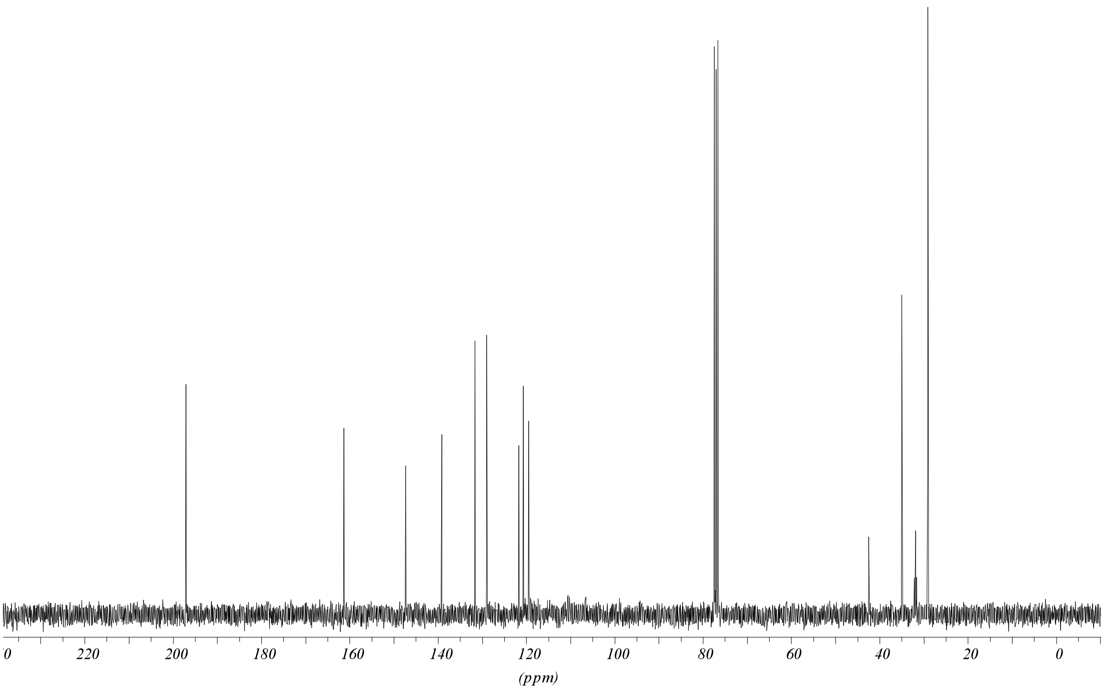
3-*tert*-butyl-5-ethynyl-2-hydroxybenzaldehyde (70)

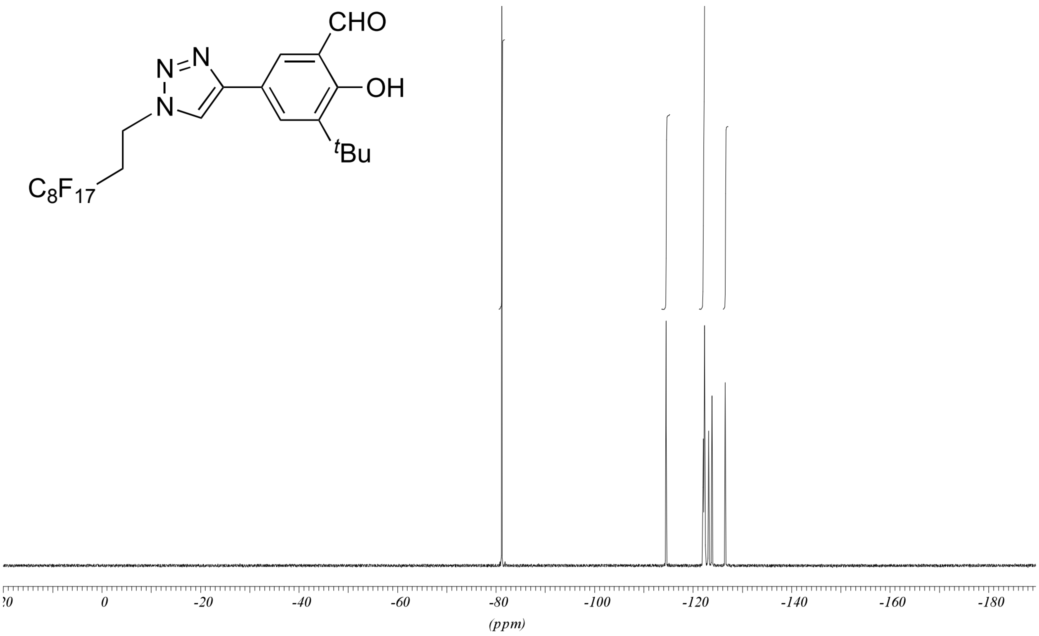




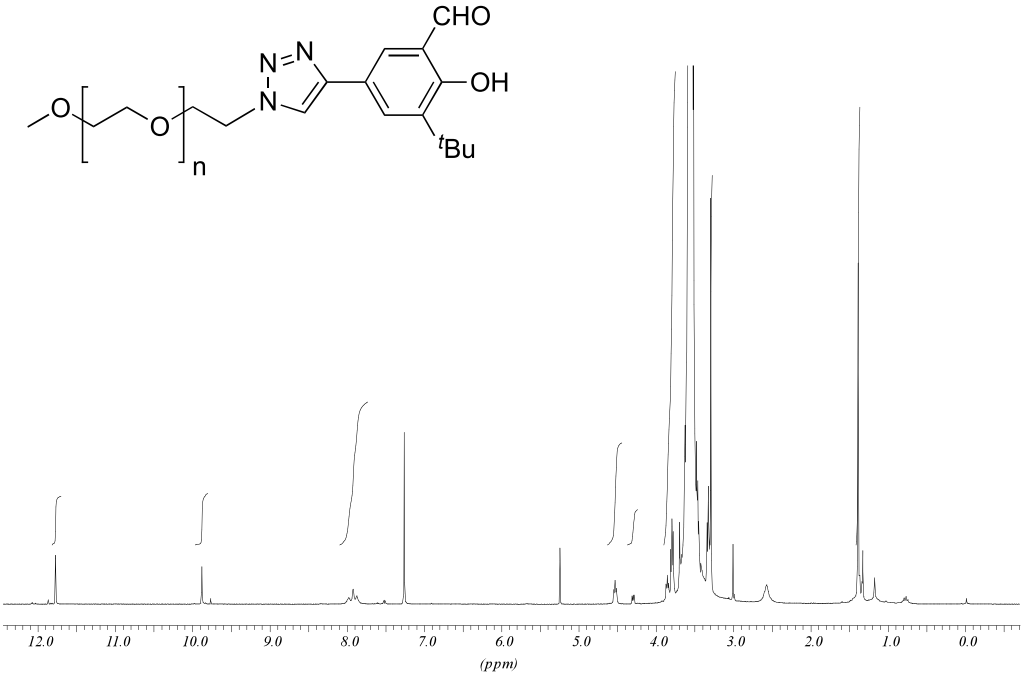
Fluorous tag clicked salicylaldehyde derivative (71b)



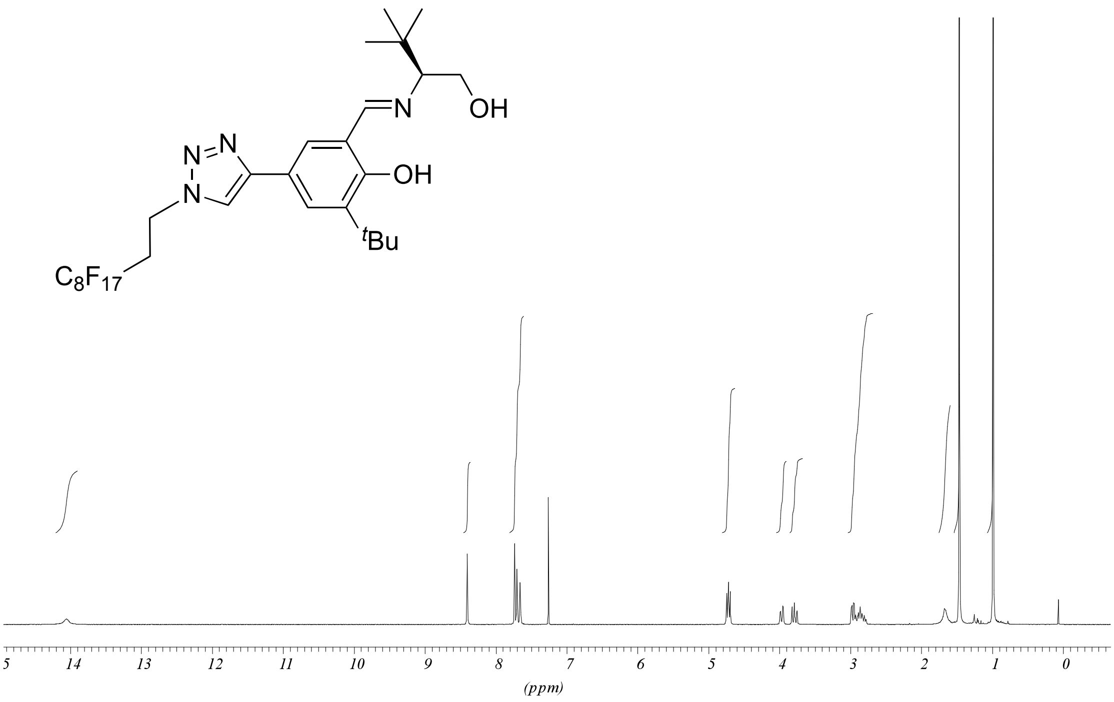


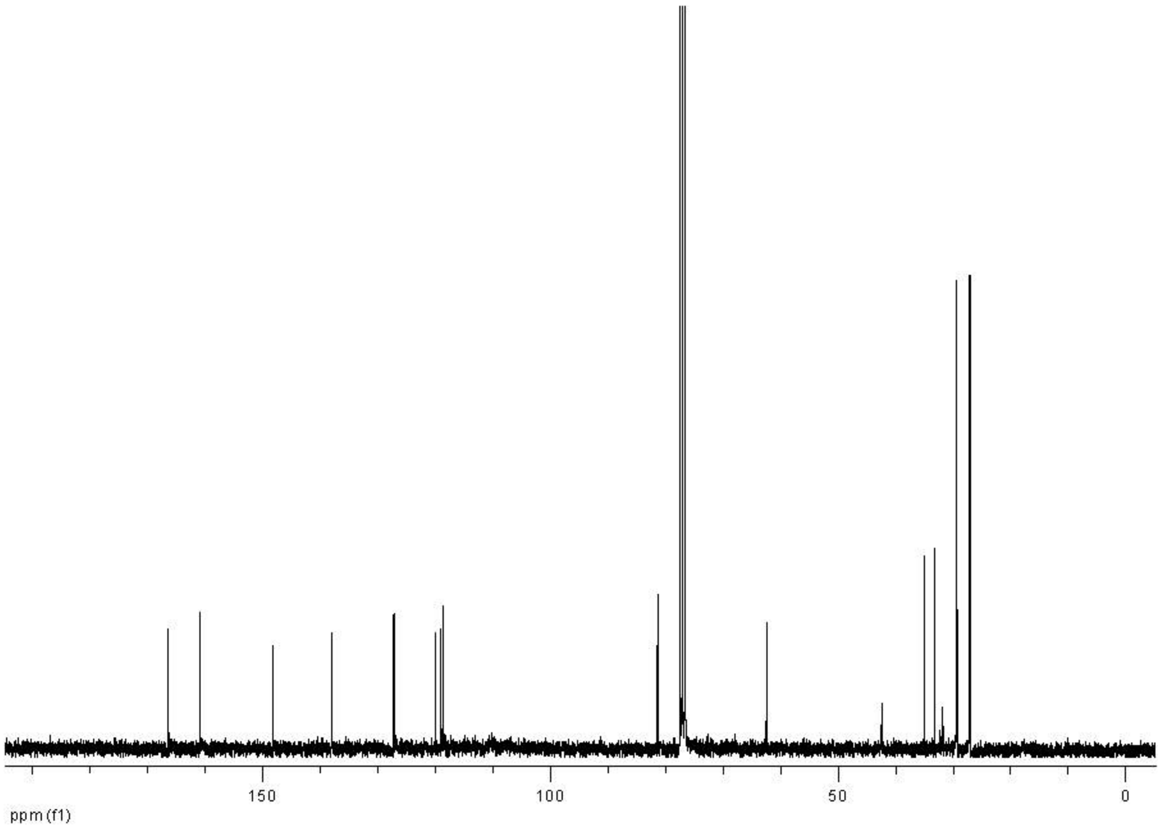


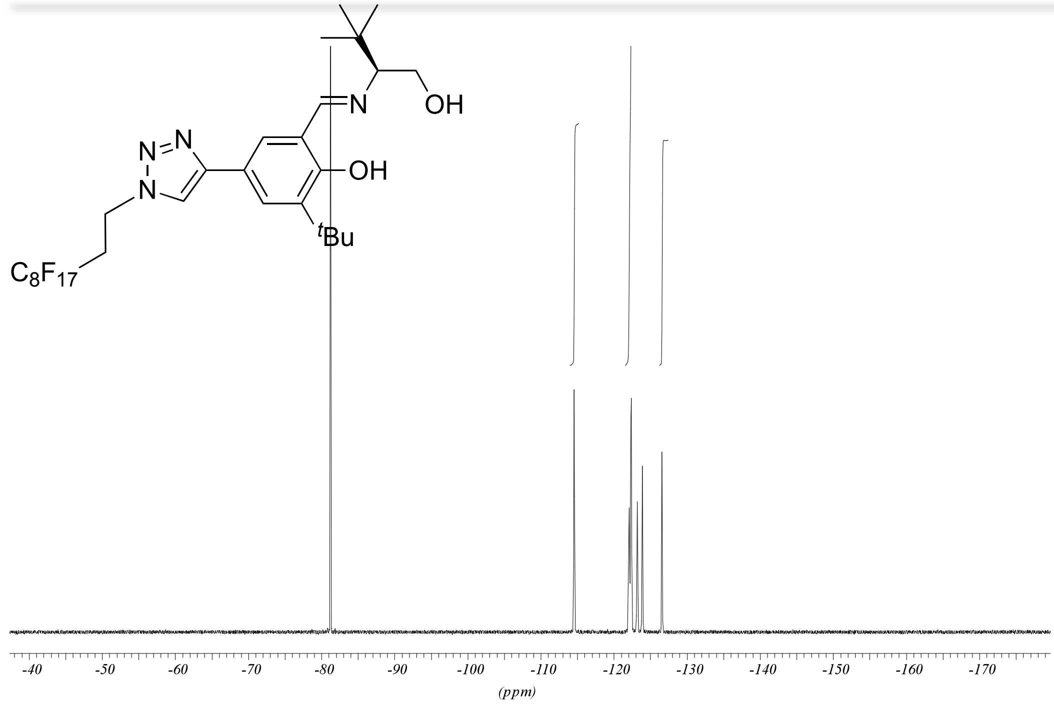
MeOPEG clicked salicylaldehyde derivative (71c)



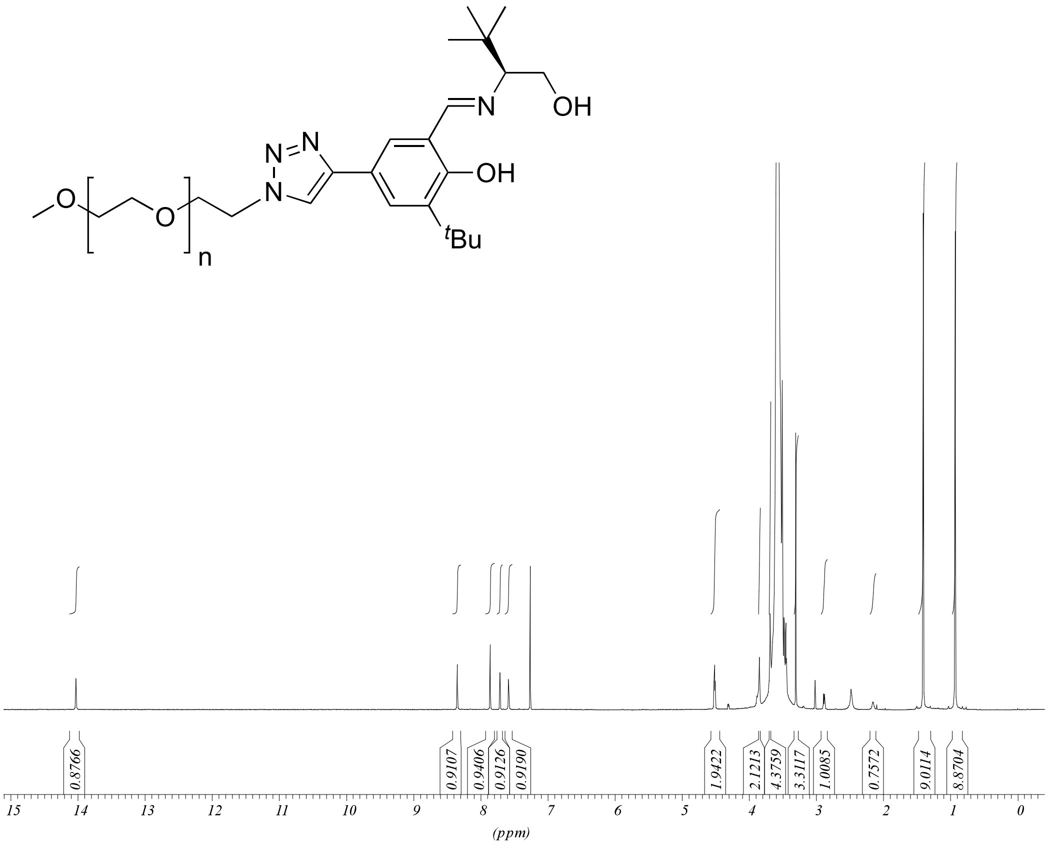
Fluorous tag clicked tridentate Schiff base (73d) derived from *tert*-leucinol



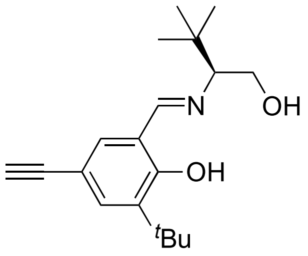


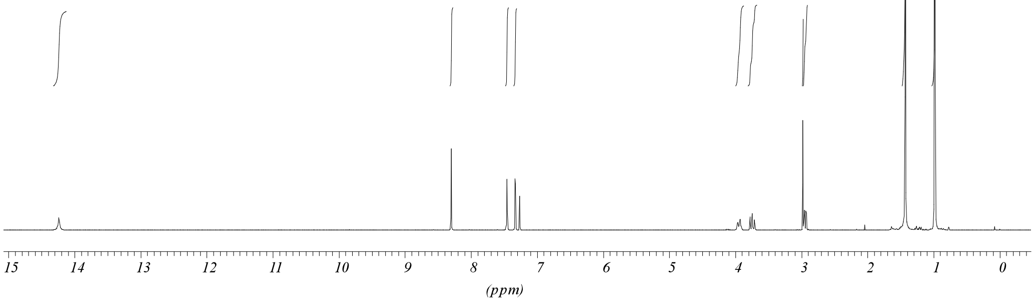


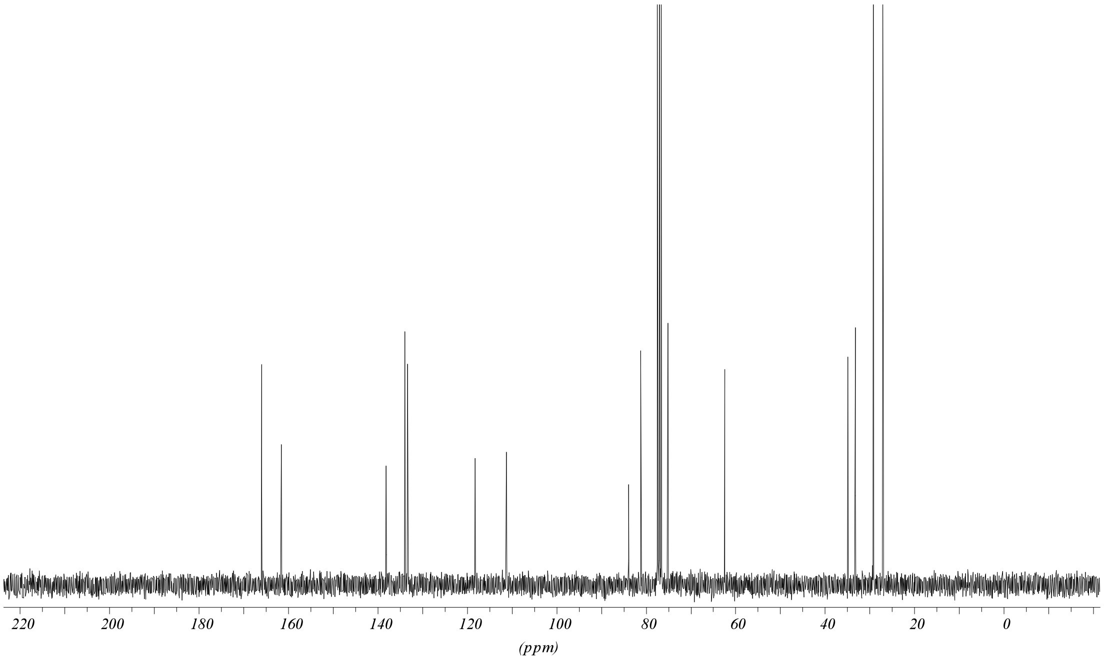
MeOPEG clicked tridentate Schiff base ligand (74)- 600 MHz, CDCl$_3$



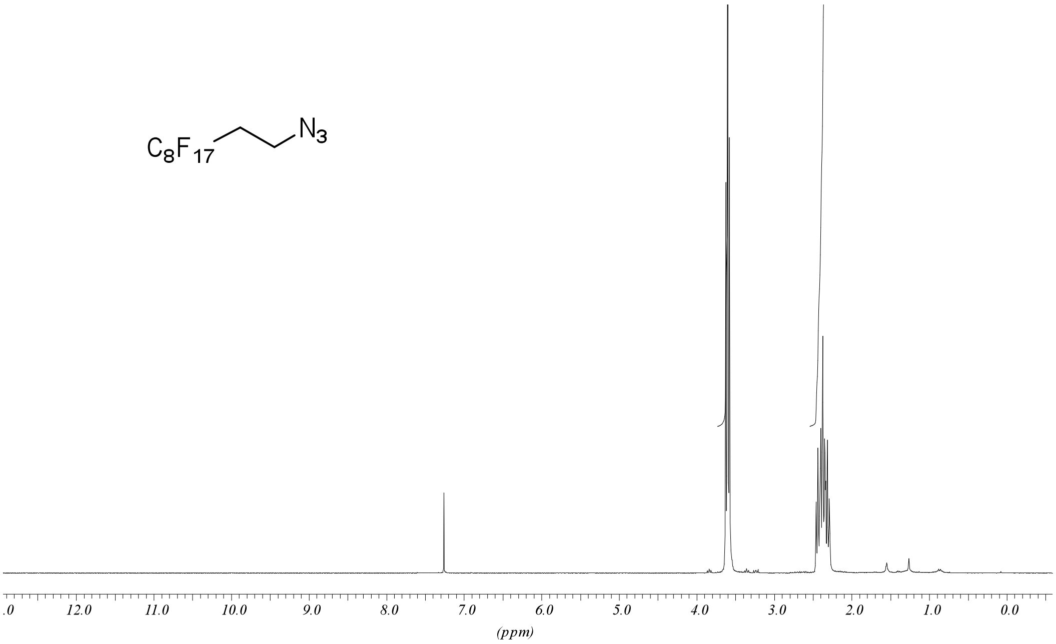
(*S, E*)-2-*tert*-4-ethynyl-6-((1-hydroxy-3,3-dimethylbutan-2-ylimino)methyl) phenol (75)

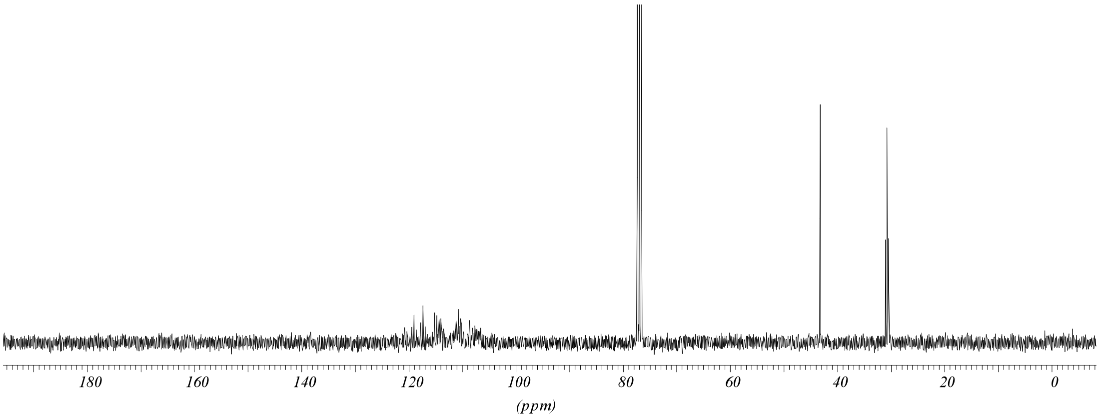


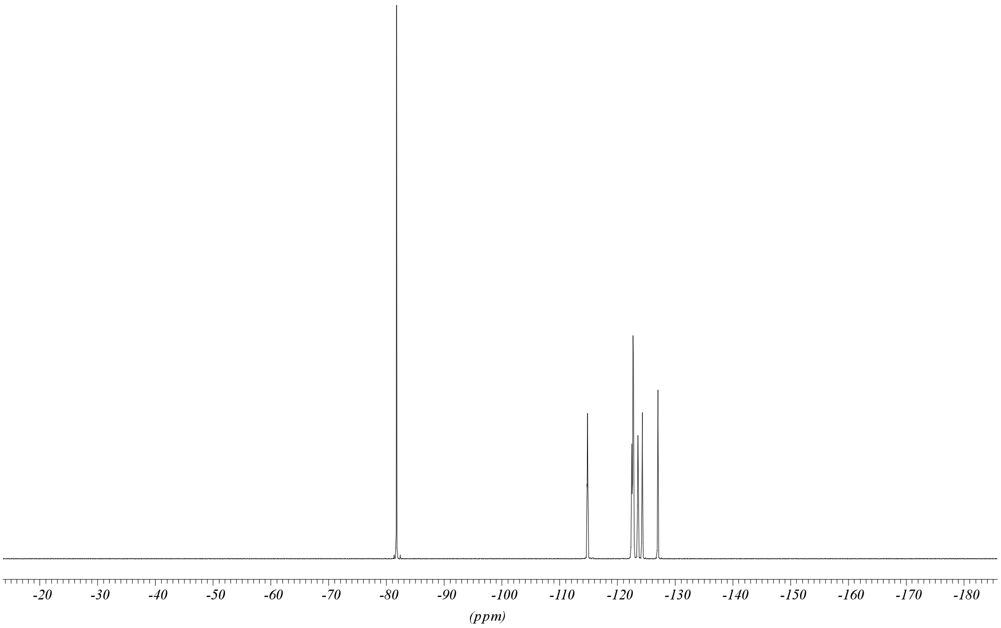




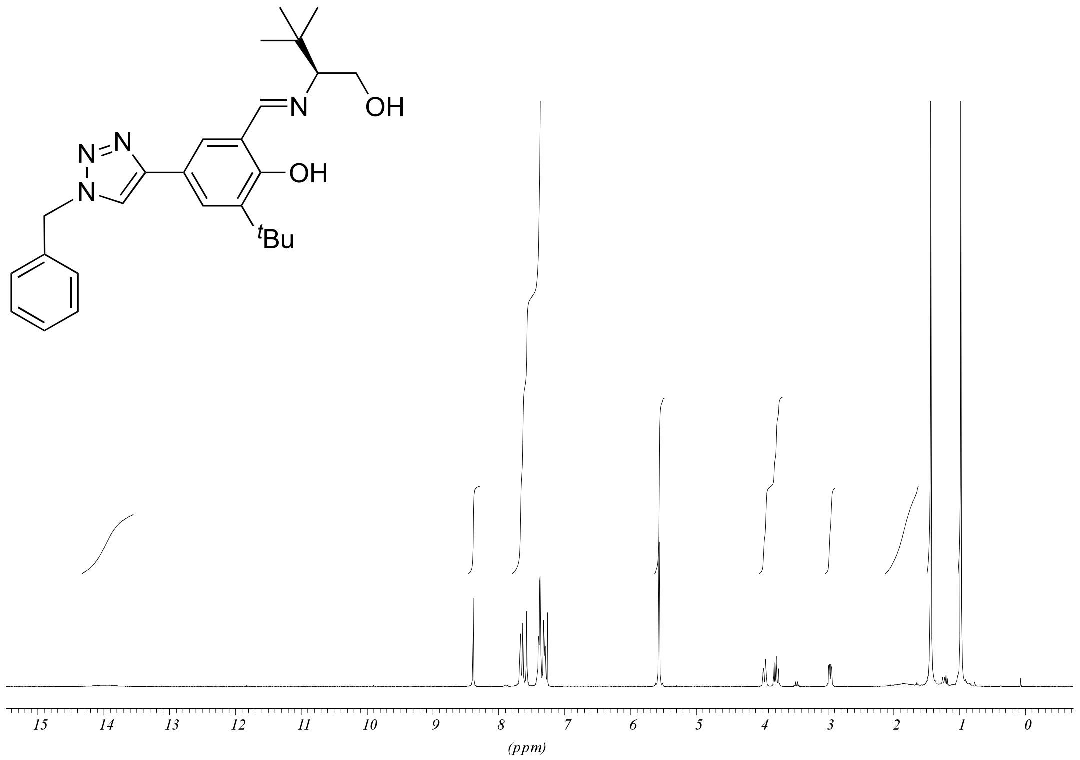
1-Azido-perfluorodecane

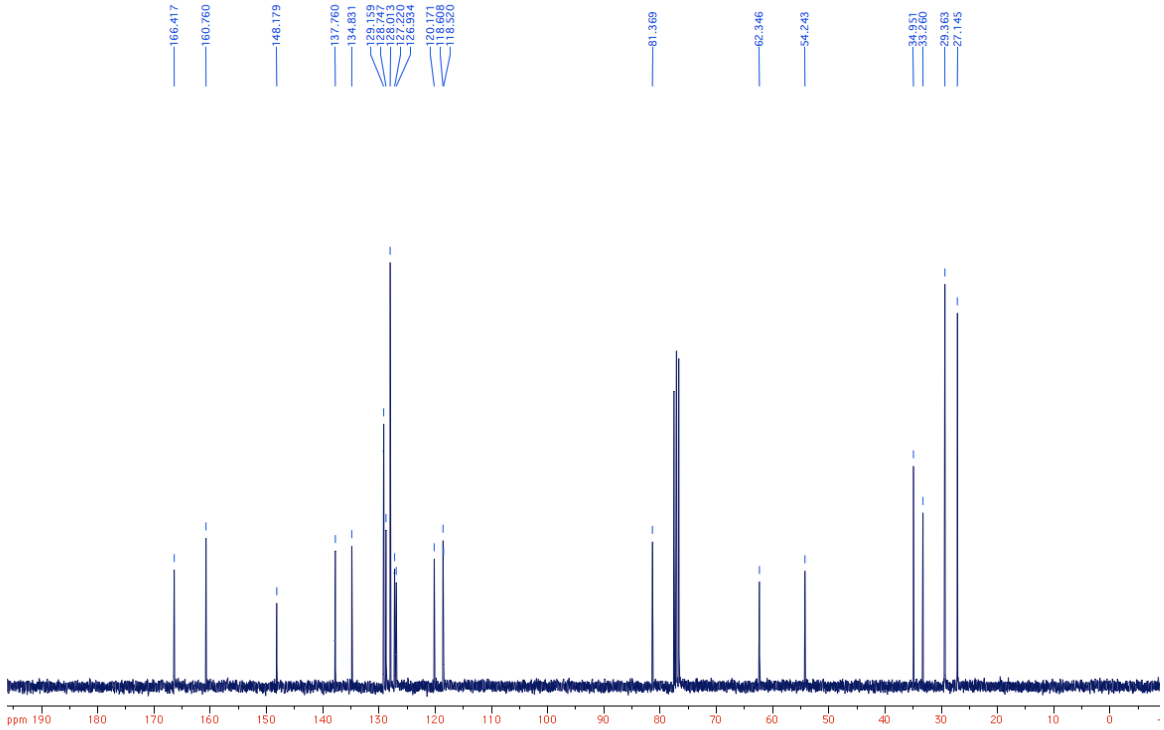




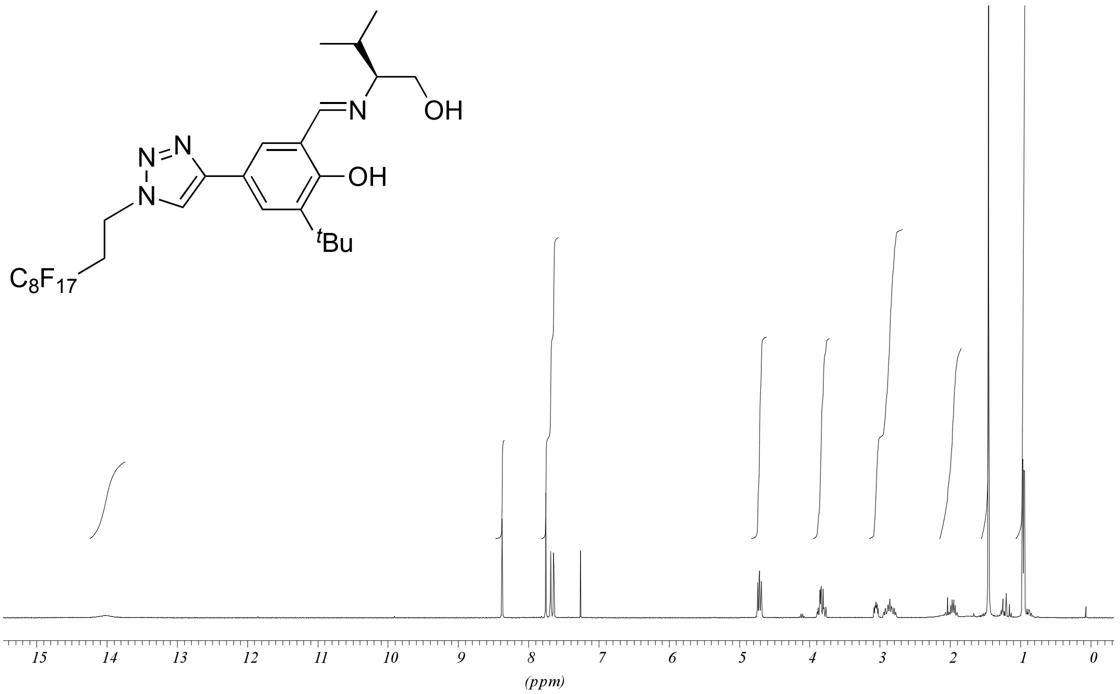


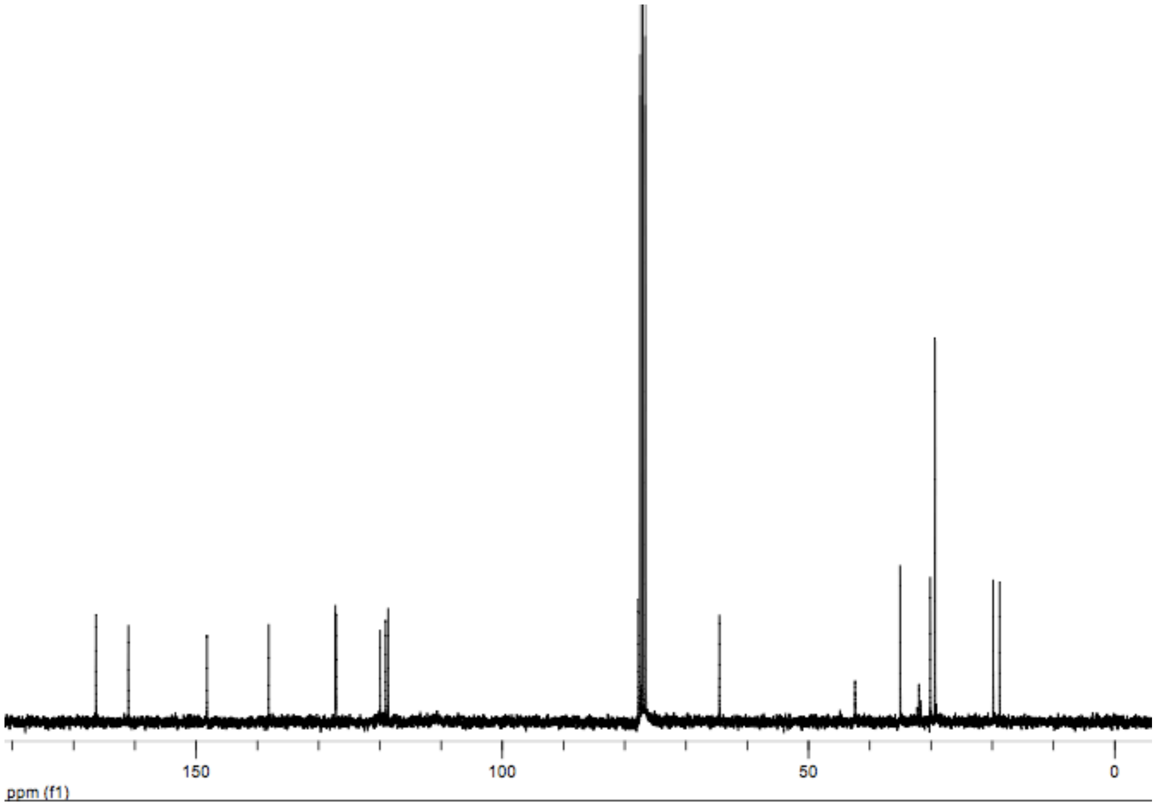
(*S,E*)-4-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-tert-butyl-6-((1-hydroxy-3,3-dimethylbutan-2-ylimino)methyl)phenol (72)

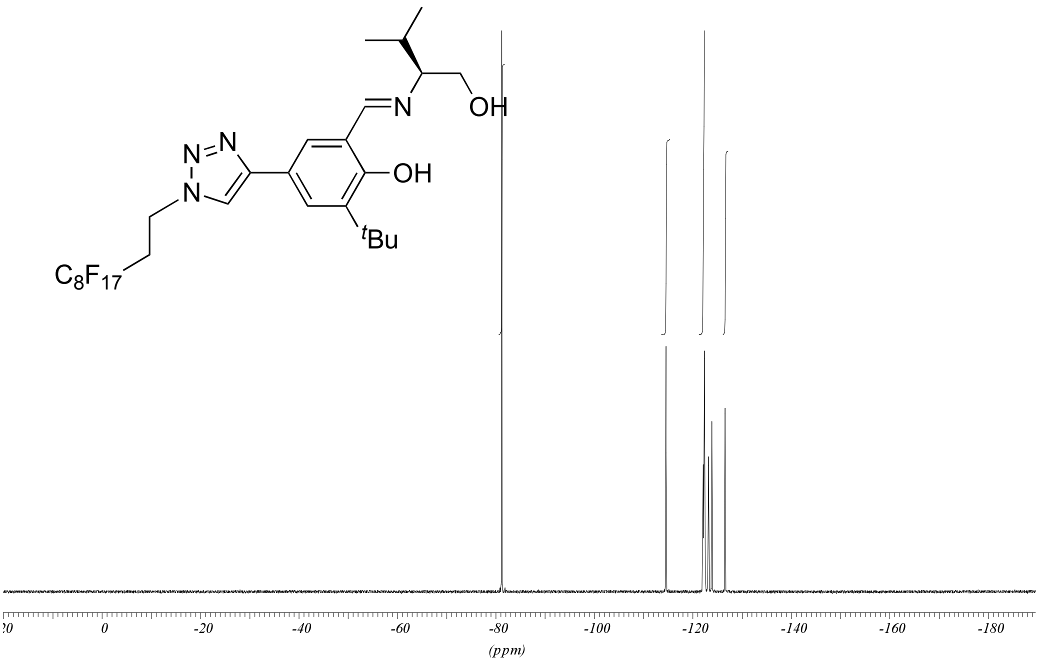




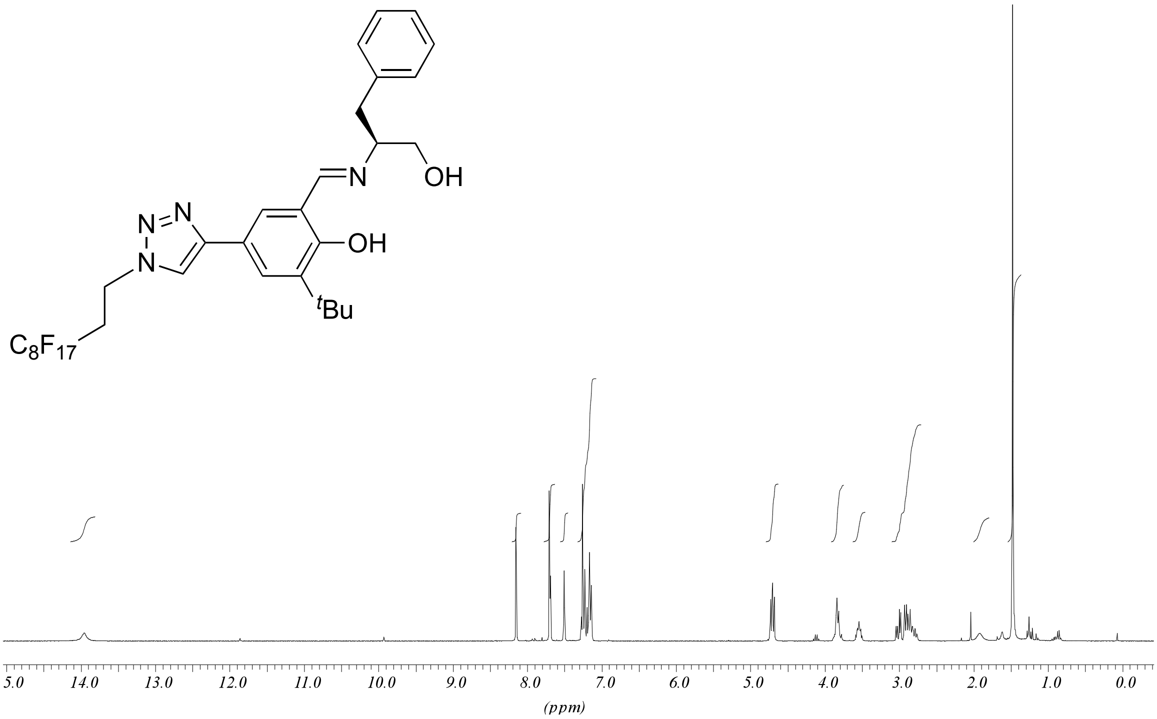
Fluorous tag clicked tridentate Schiff base (73a) derived from valinol

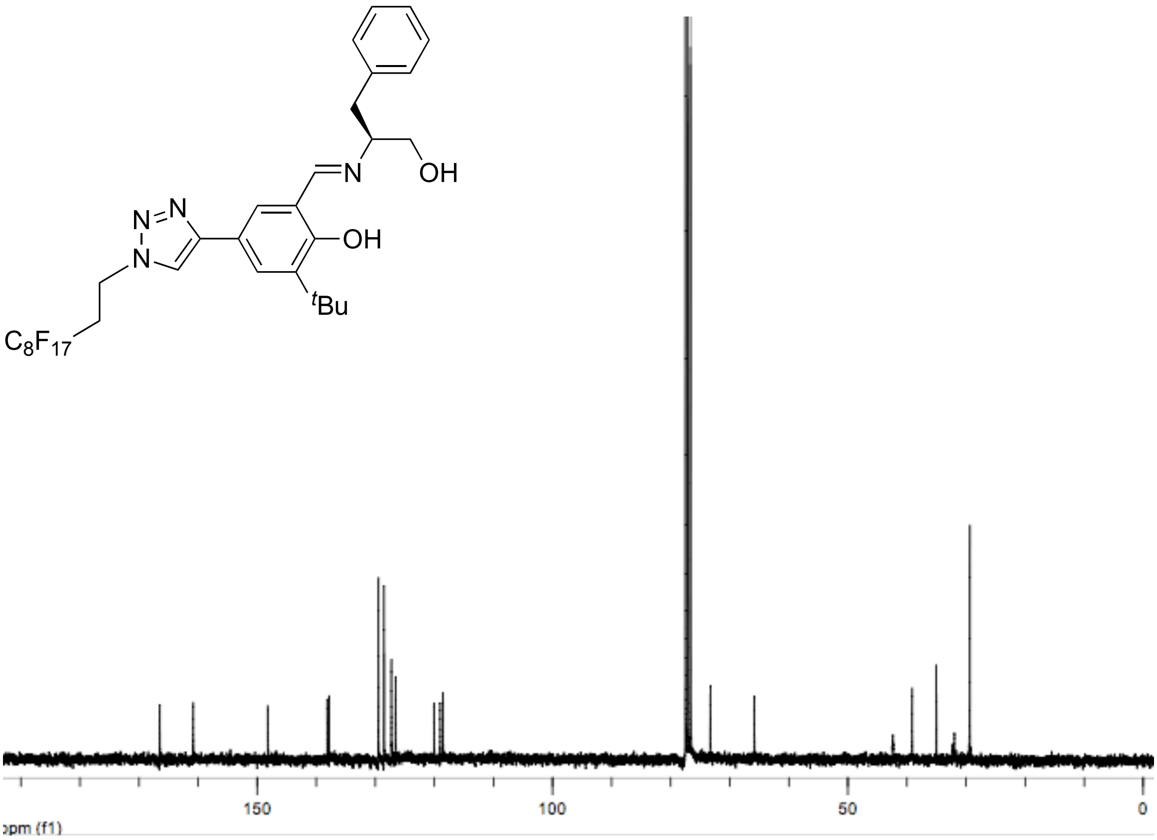


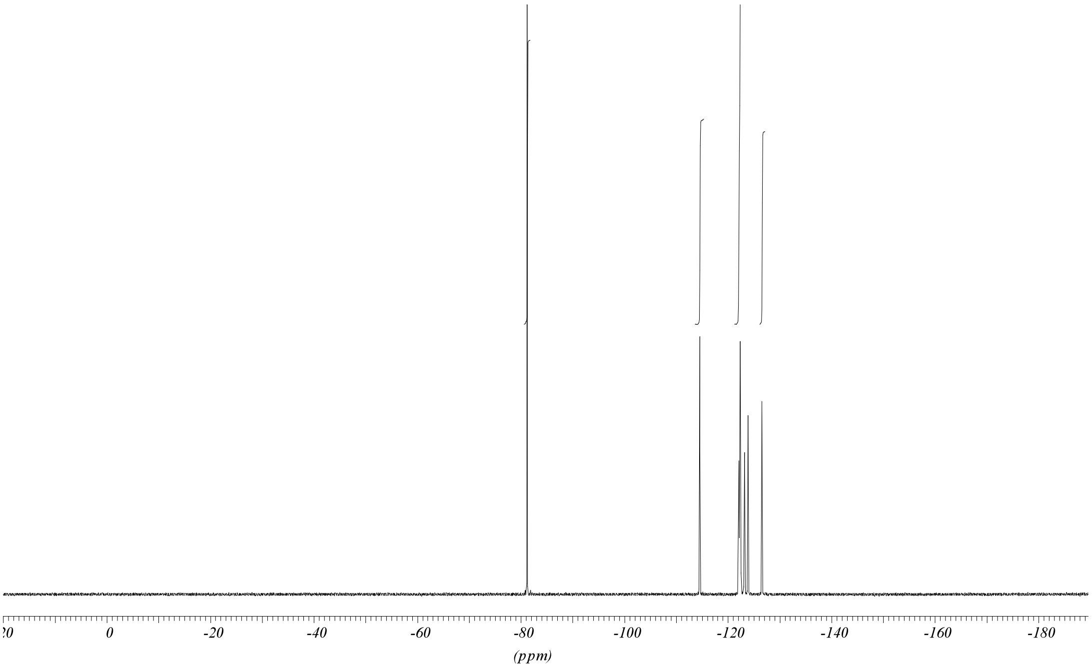




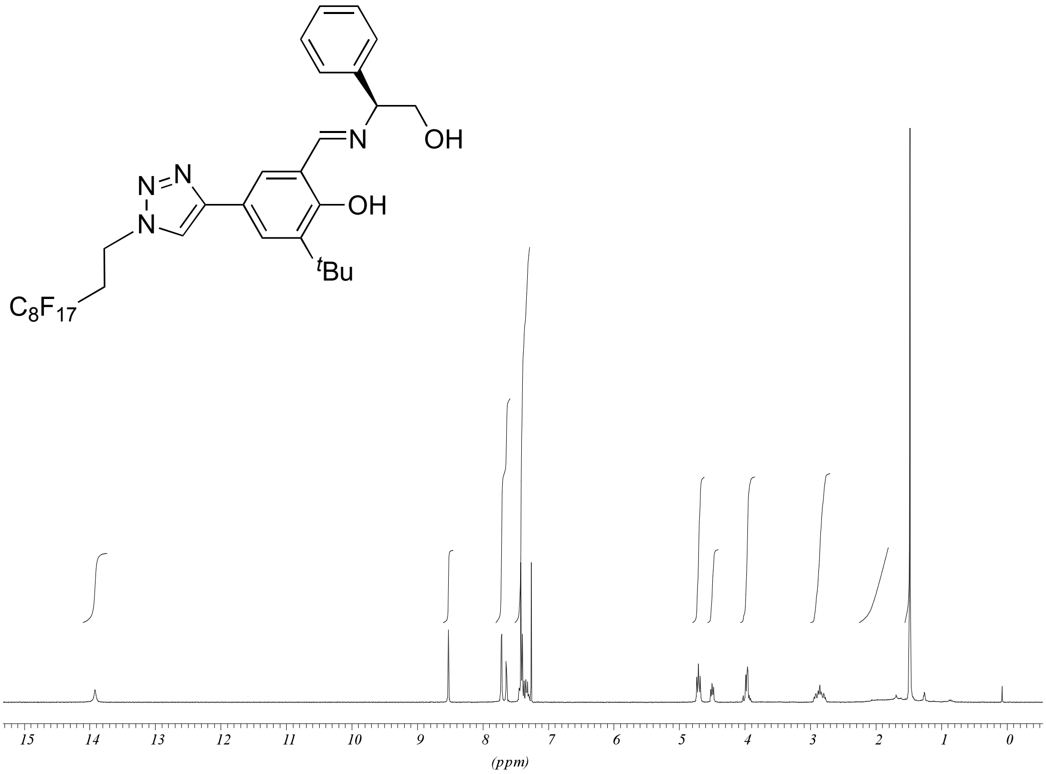
Fluorous tag clicked tridentate Schiff base (73c) derived from phenylalaninol

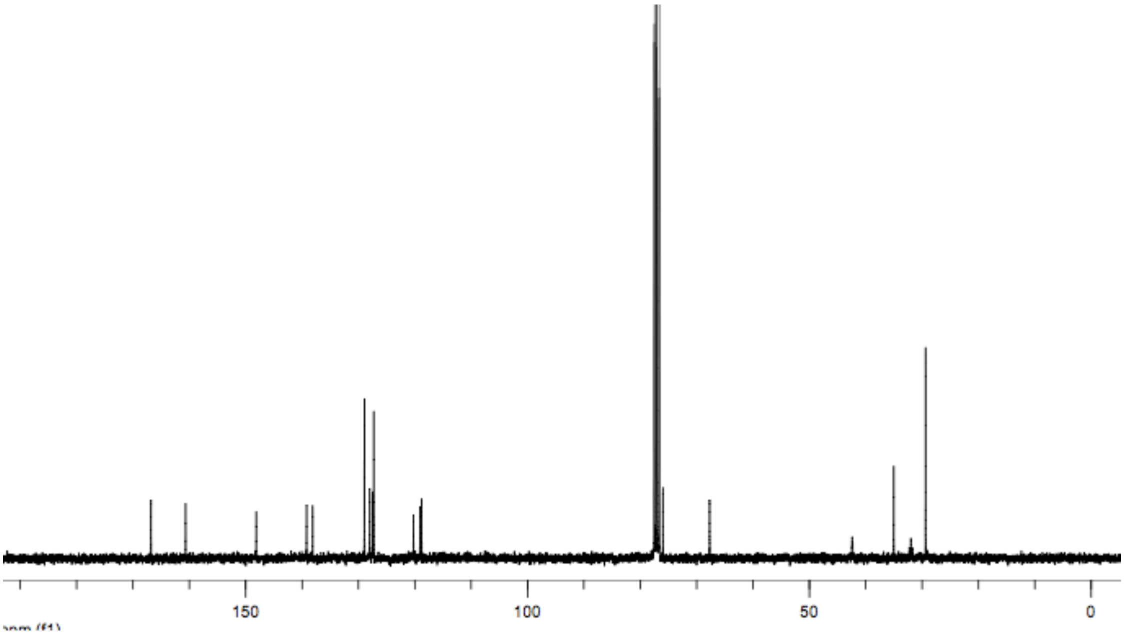



N
N
N
N
OH
OH
tBu
C8F17
150
100
50
0
pm (f1)

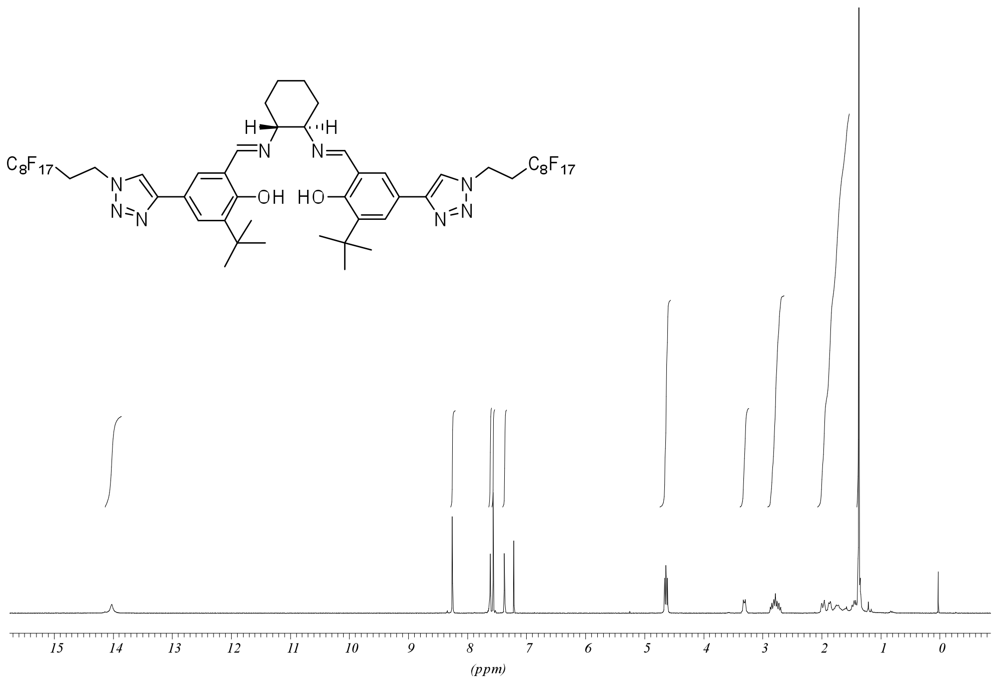

0
-20
-40
-60
-80
-100
-120
-140
-160
-180
(ppm)

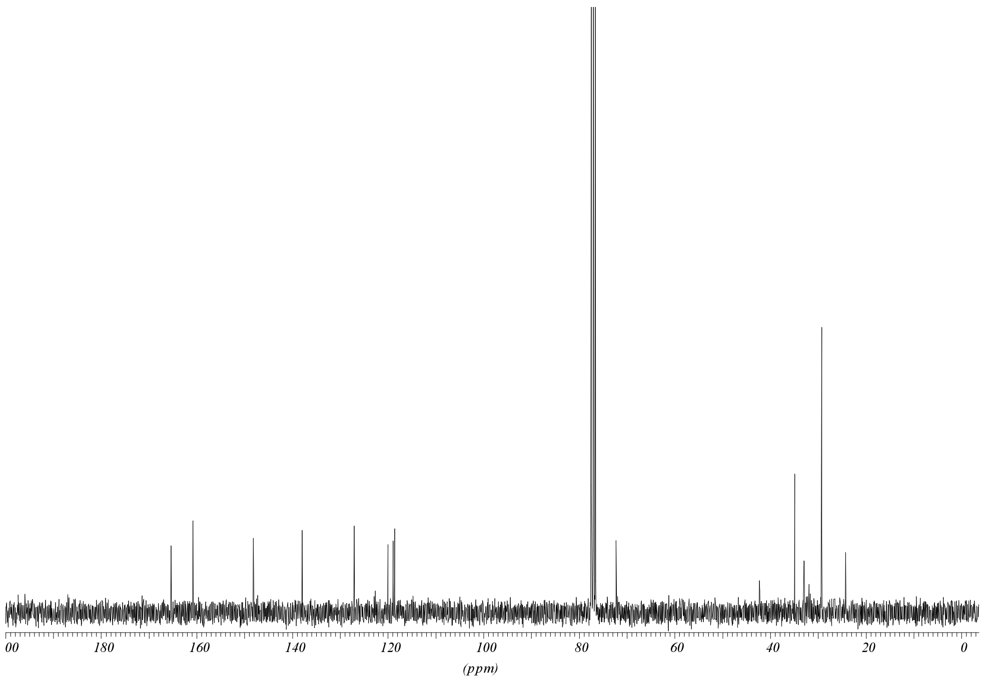
Fluorous tag clicked tridentate Schiff base (73b) derived from phenylglycinol

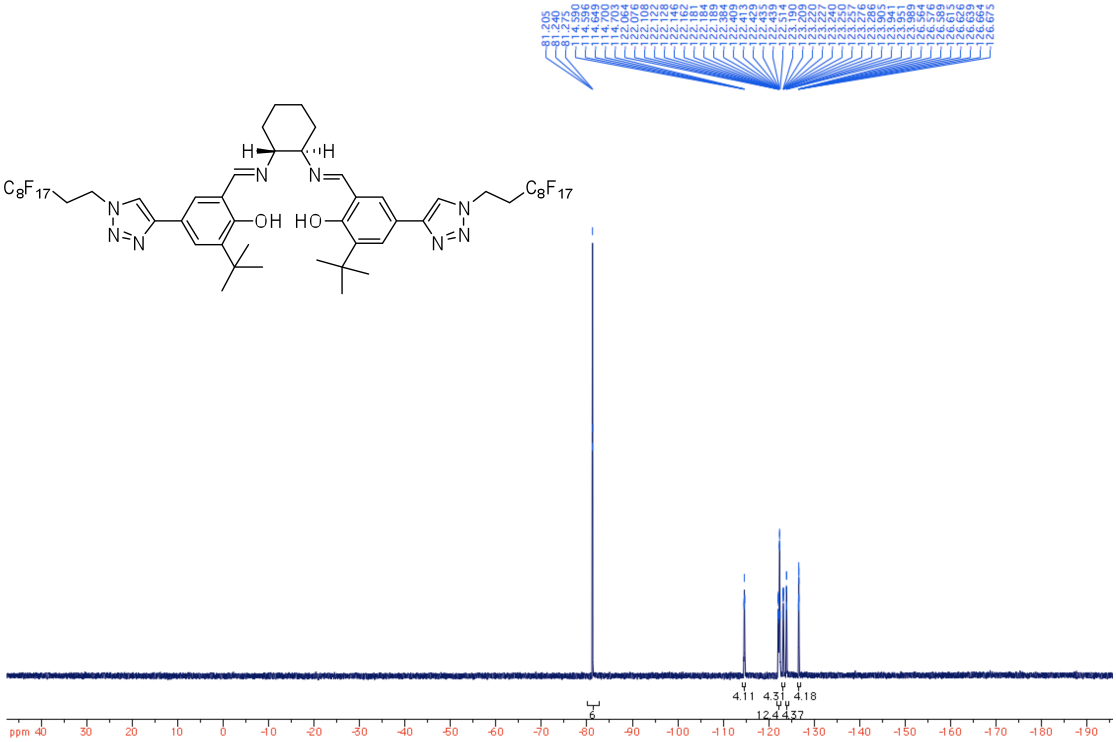




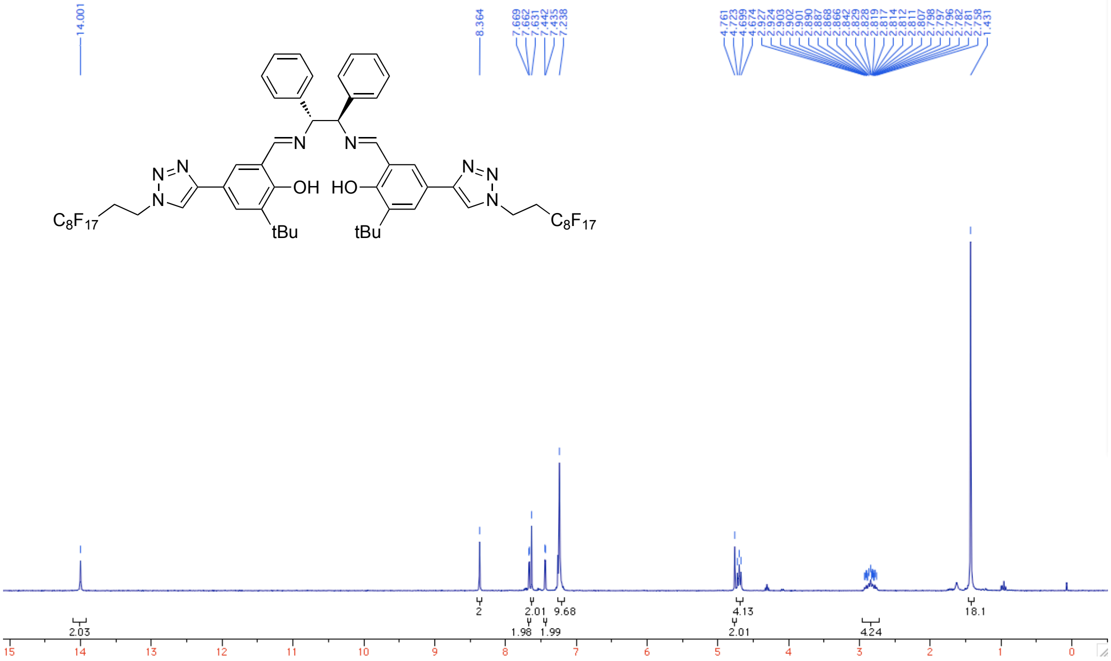
Fluorous tagged salen ligand derived from cyclohexyldiamine tartarate (79a)

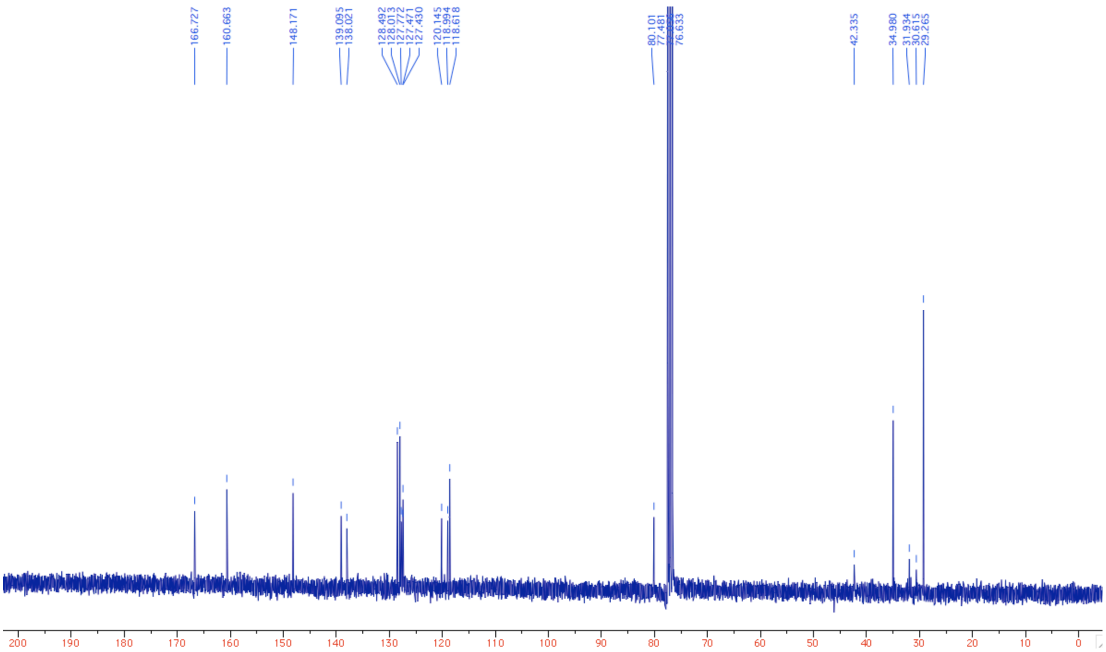


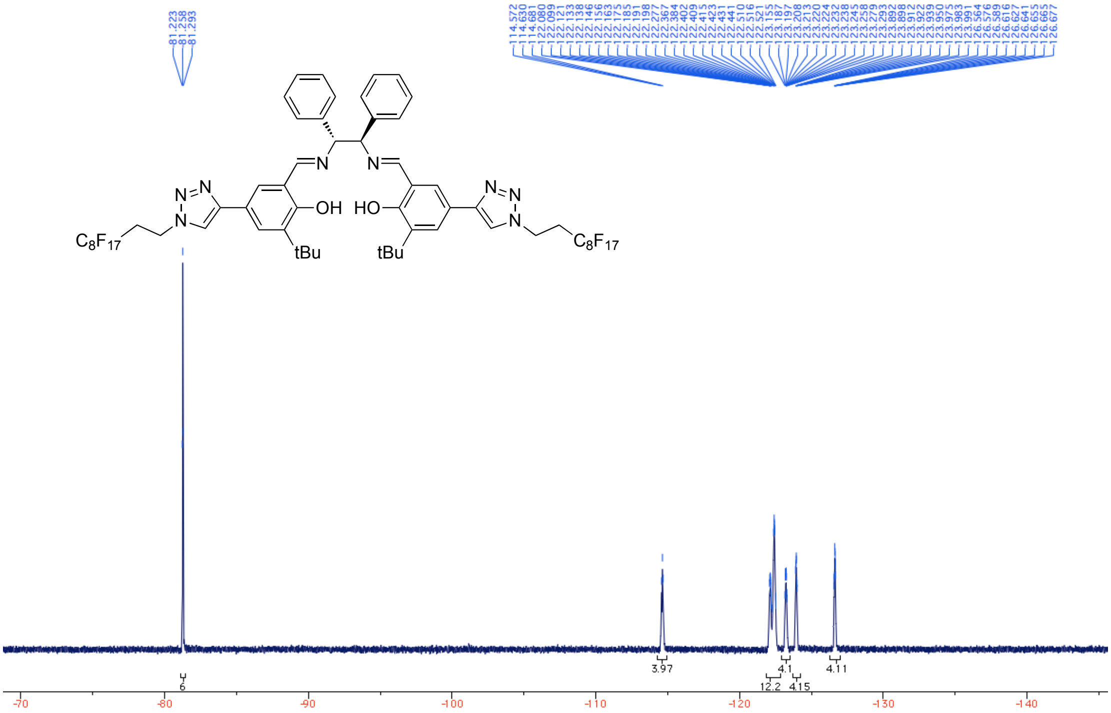




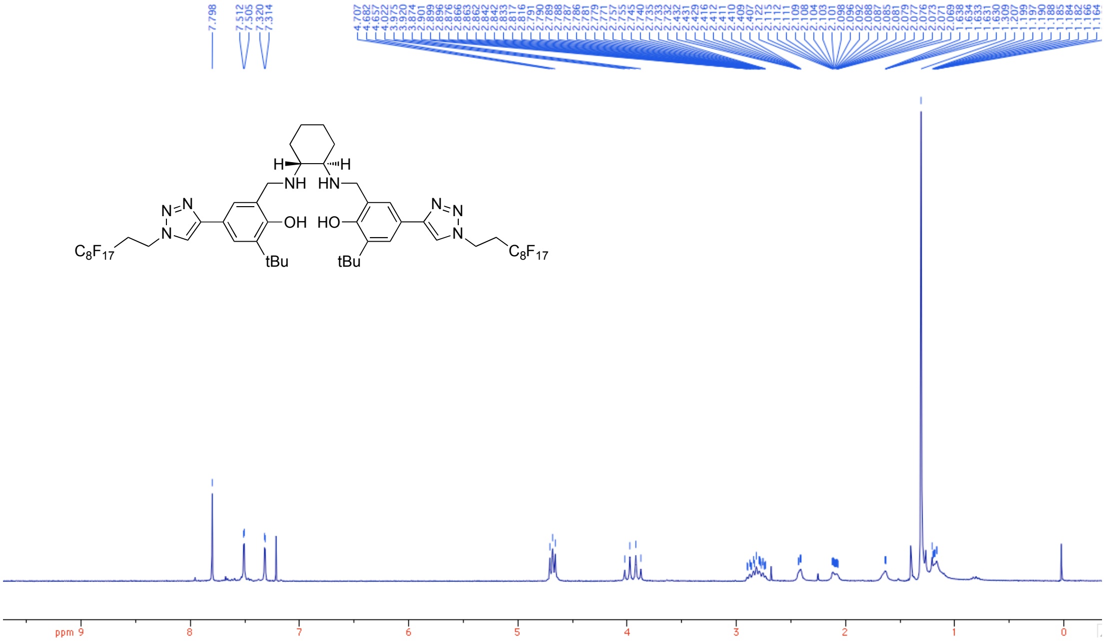
Fluorous tagged salen ligand derived from diphenyldiamine (79b)

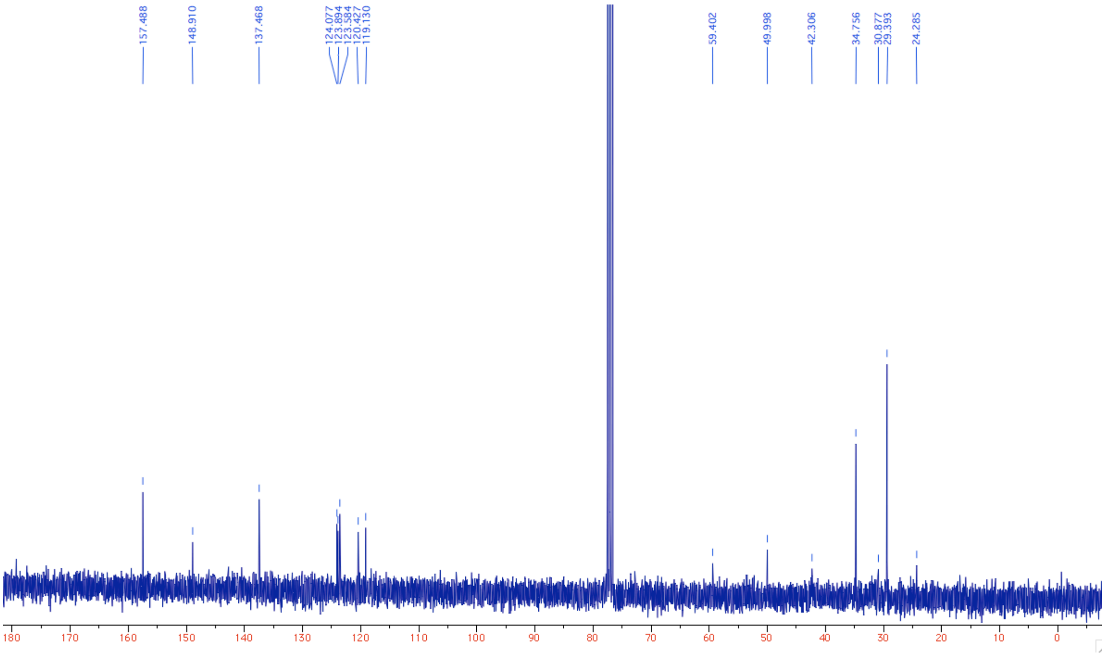


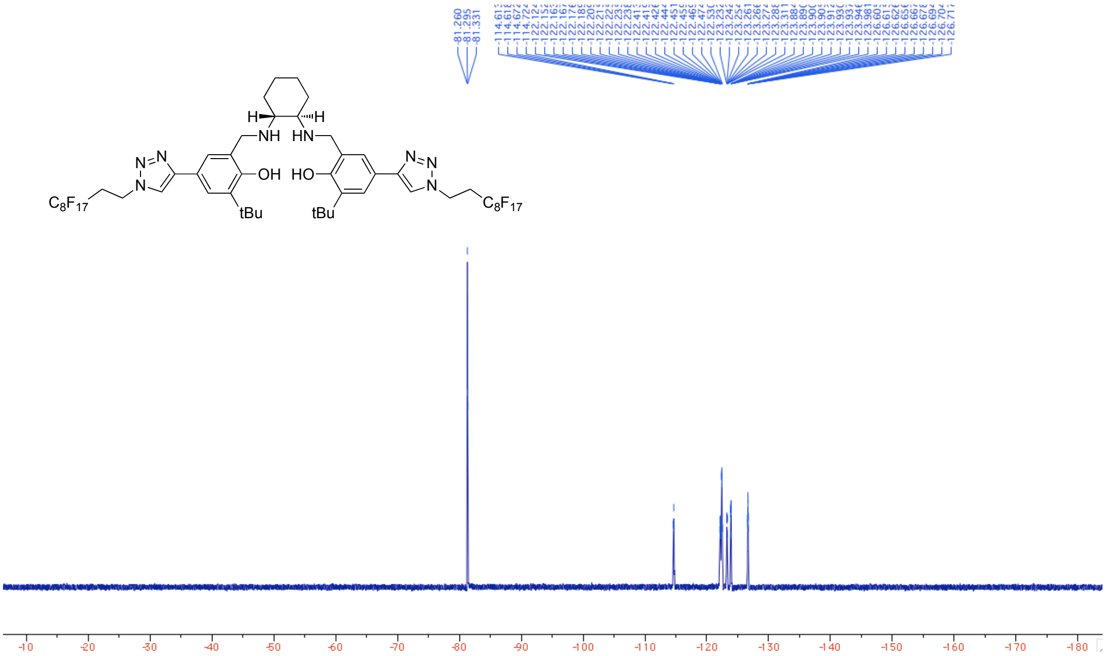

166.727
160.663
148.171
139.095
138.021
128.492
128.013
127.772
127.471
127.430
120.145
118.994
118.618
80.101
77.481
77.057
76.633
42.335
34.980
31.934
30.615
29.265
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


-81.223
-81.258
-81.293
-114.572
-114.630
-114.681
-122.080
-122.099
-122.121
-122.133
-122.138
-122.146
-122.156
-122.163
-122.175
-122.185
-122.191
-122.198
-122.277
-122.367
-122.384
-122.402
-122.409
-122.415
-122.423
-122.431
-122.441
-122.510
-122.516
-122.521
-123.155
-123.187
-123.197
-123.208
-123.213
-123.220
-123.224
-123.232
-123.238
-123.245
-123.258
-123.279
-123.293
-123.892
-123.898
-123.912
-123.922
-123.939
-123.950
-123.975
-123.983
-123.991
-126.564
-126.576
-126.589
-126.616
-126.627
-126.641
-126.655
-126.665
-126.677
N
N
N=N
N
OH
HO
N=N
N
tBu
tBu
C8F17
C8F17
6
3.97
4.1
12.2
4.15
4.11
-70
-80
-90
-100
-110
-120
-130
-140

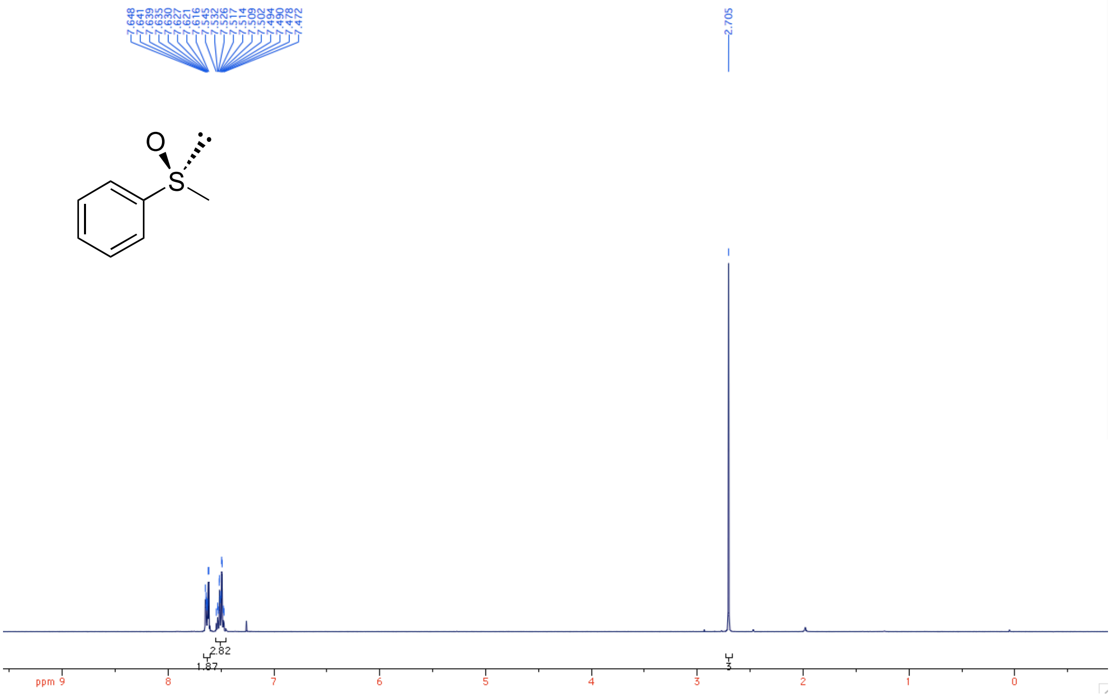
Fluorous tagged salan ligand derived from cyclohexyldiamine tartarate (81a)

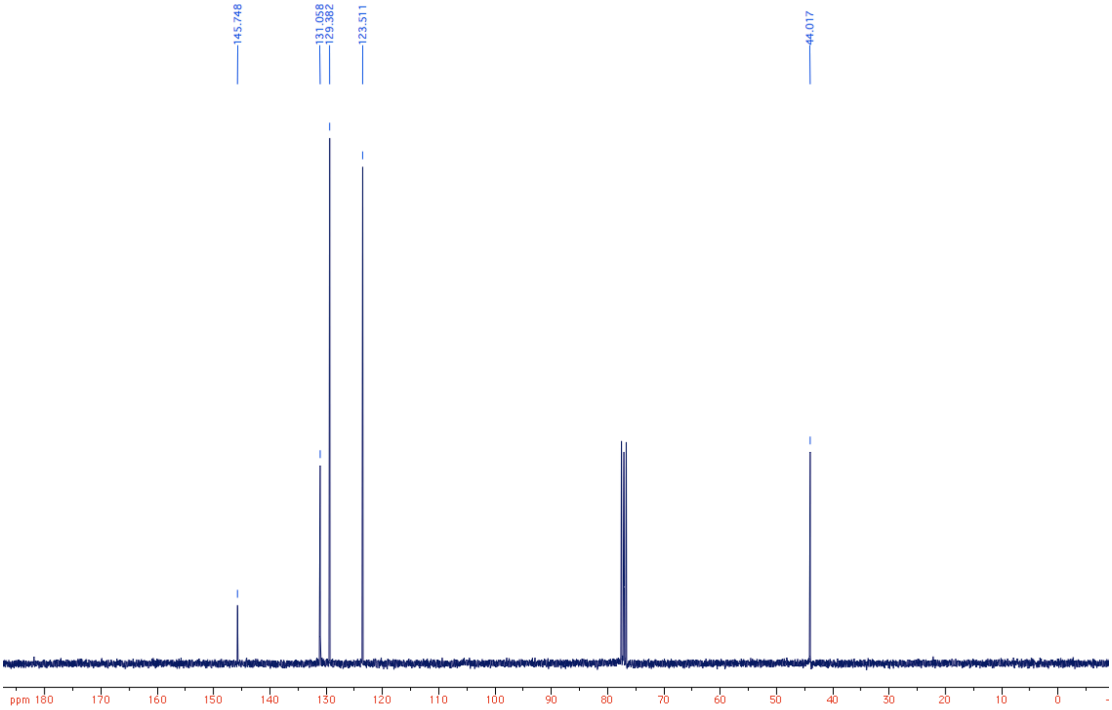




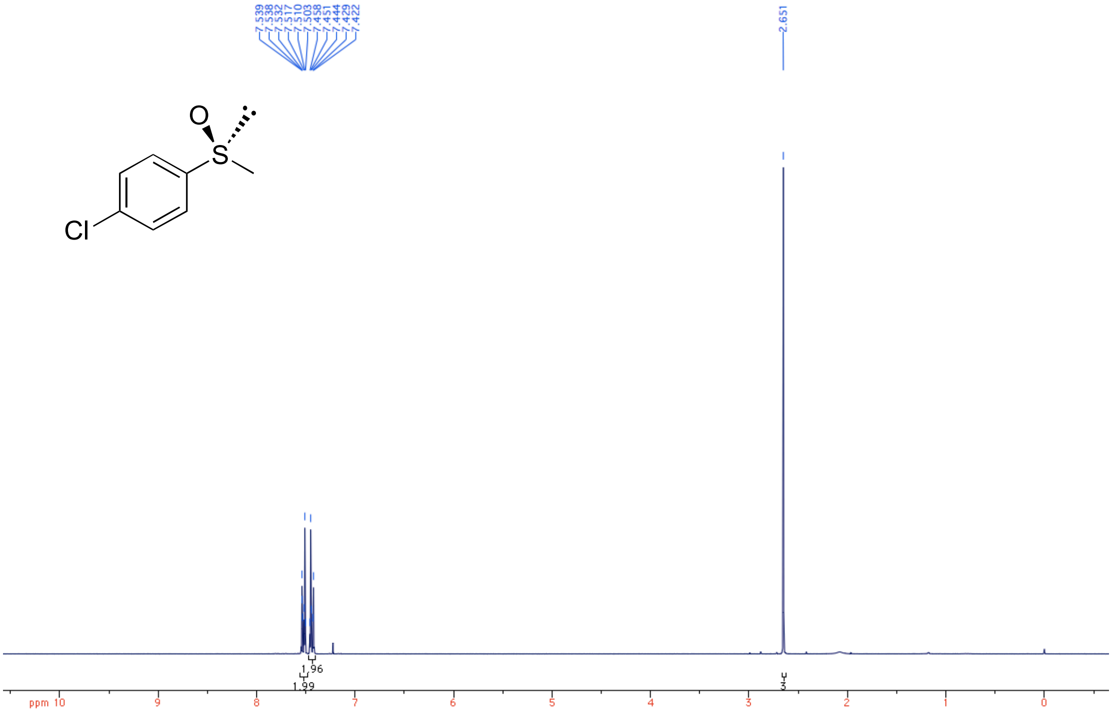

-81.260
-81.295
-81.331
H
NH
HN
H
N=N
N
OH
HO
N=N
N
C8F17
tBu
tBu
C8F17
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180

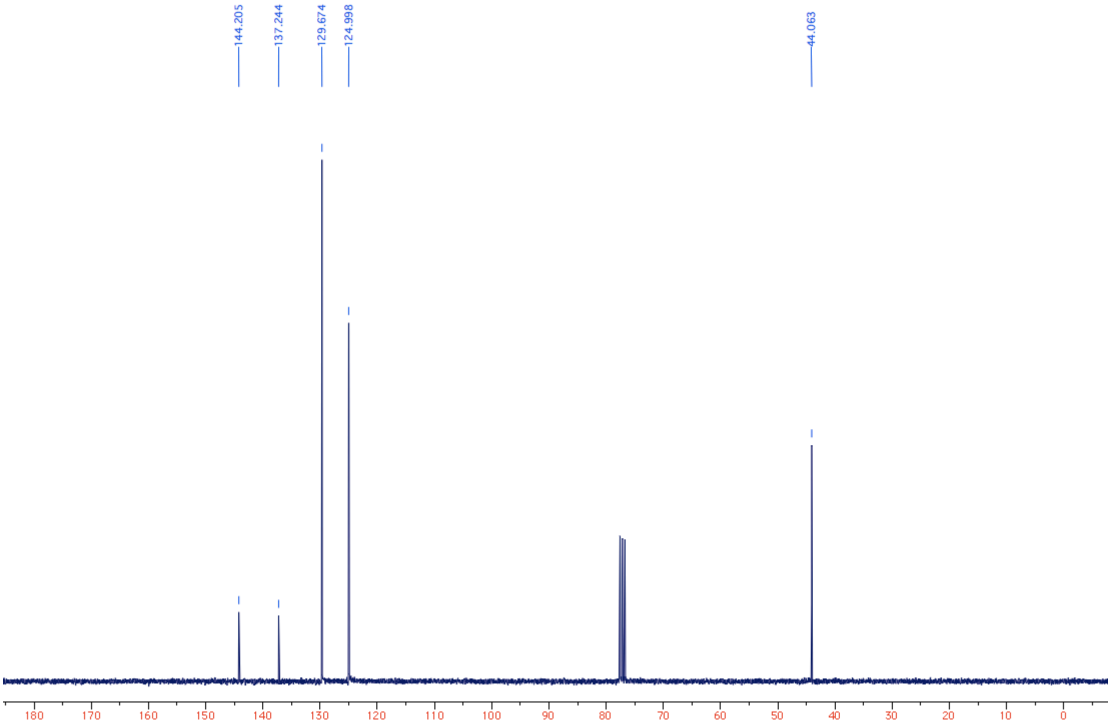
(*S*)-Phenyl methyl sulfoxide (98a)



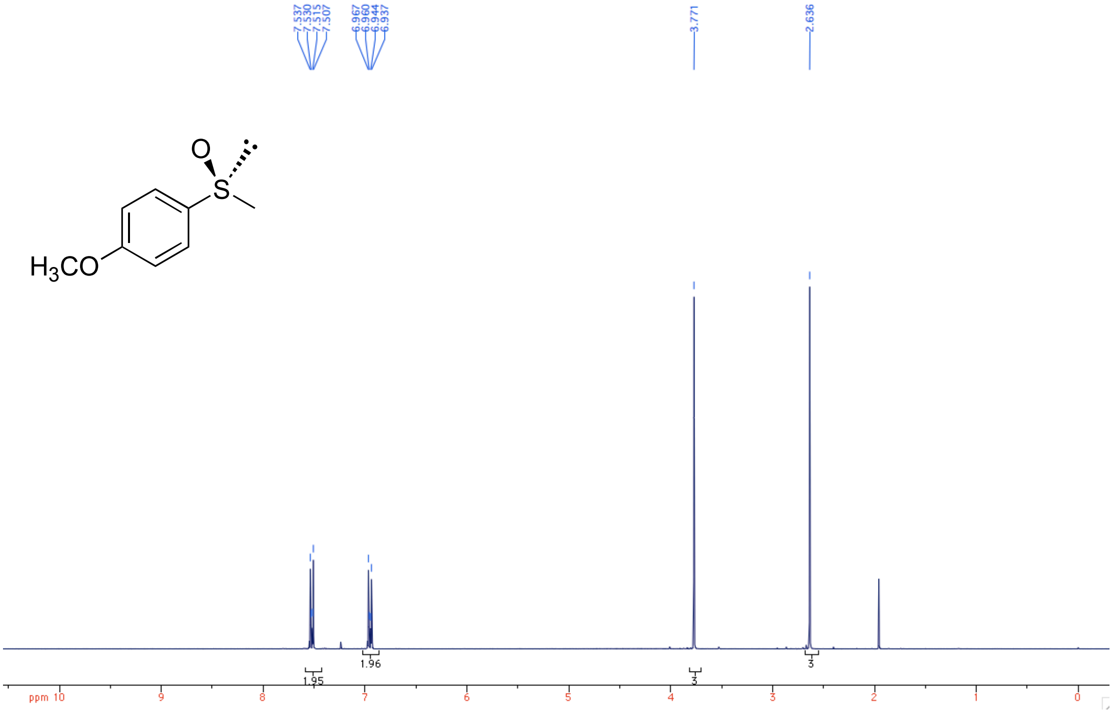


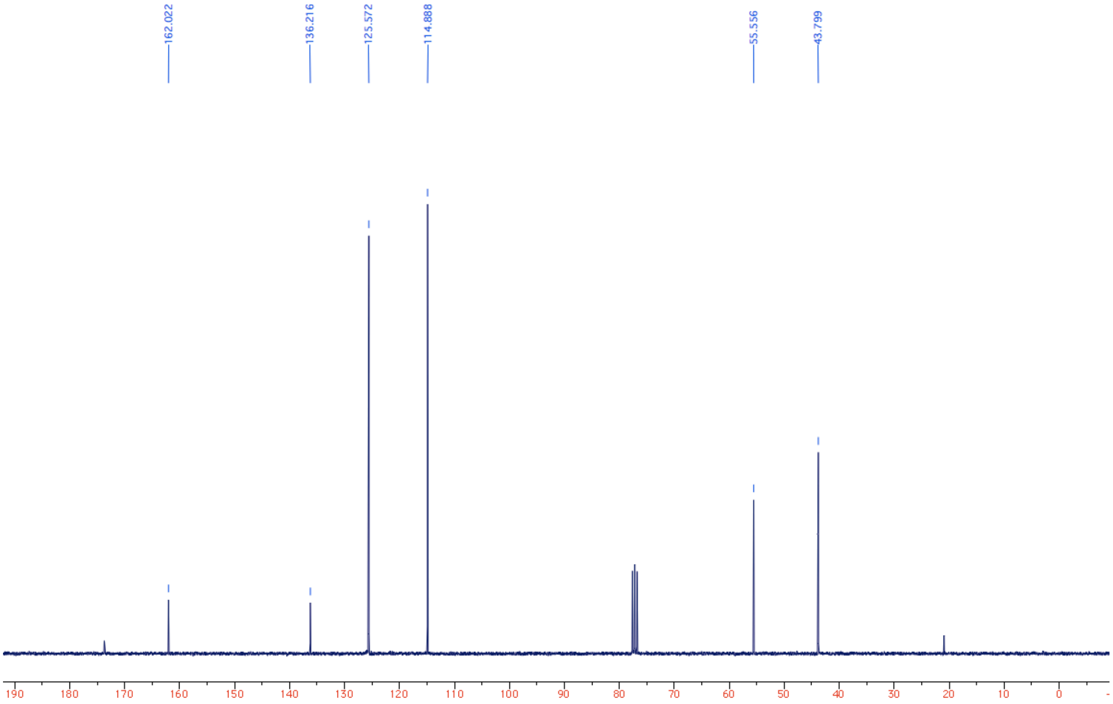
(*S*)-4-chlorophenyl methyl sulfoxide (98b)



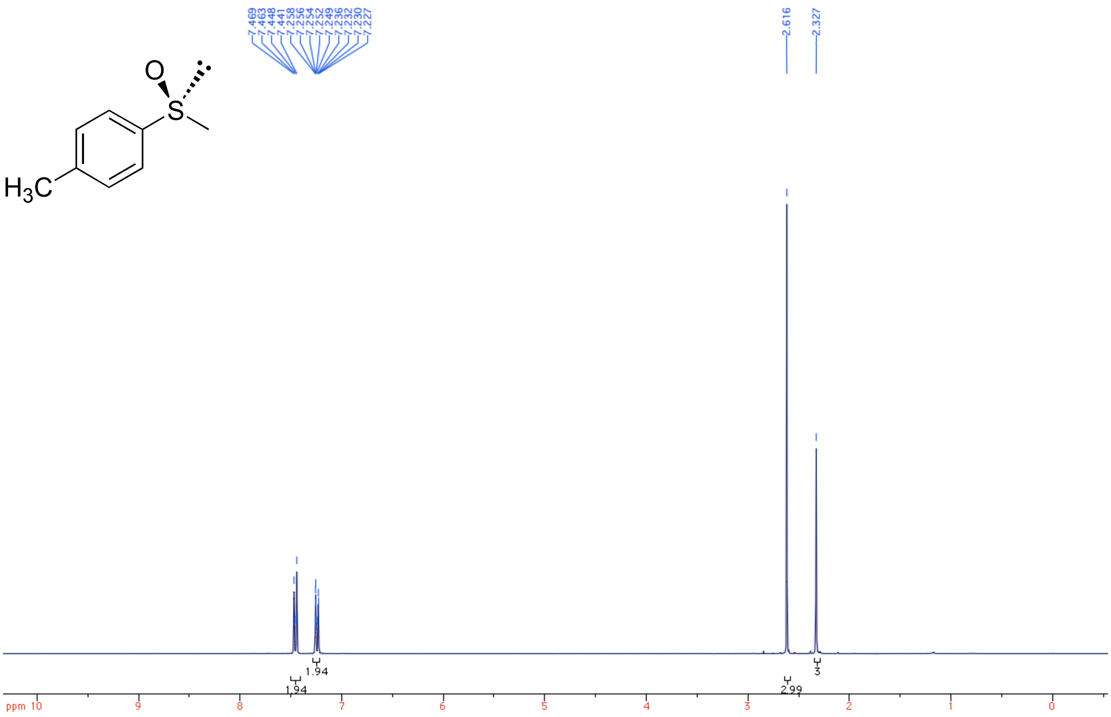


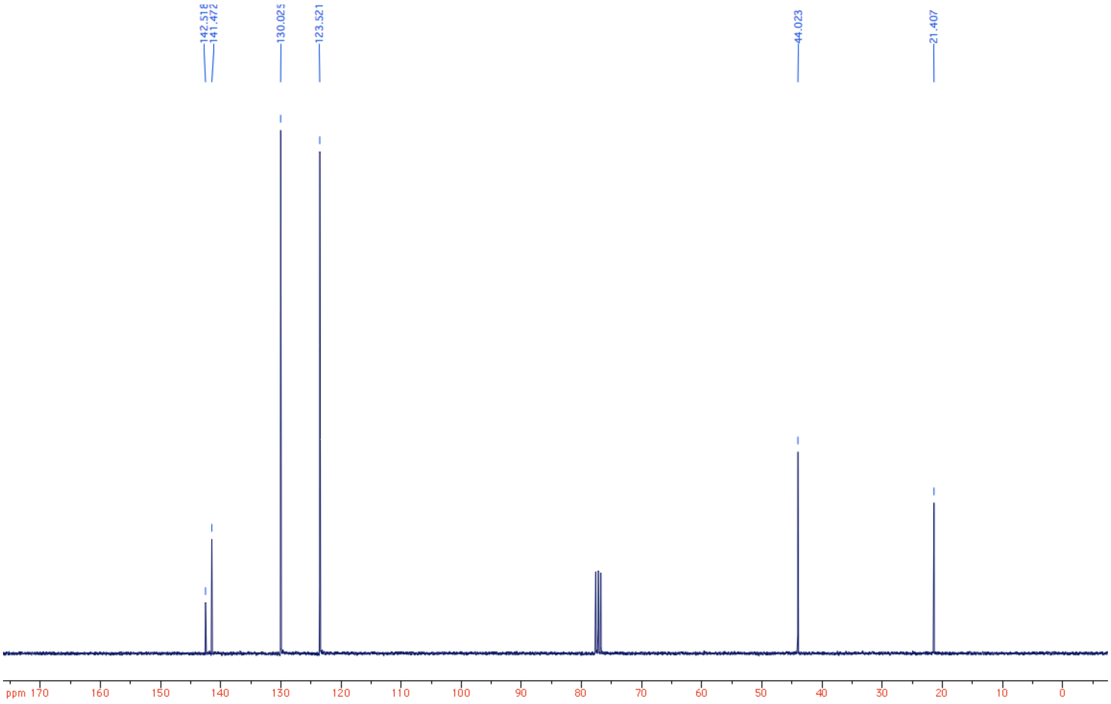
(*S*)-4-methoxyphenyl methyl sulfoxide (98c)



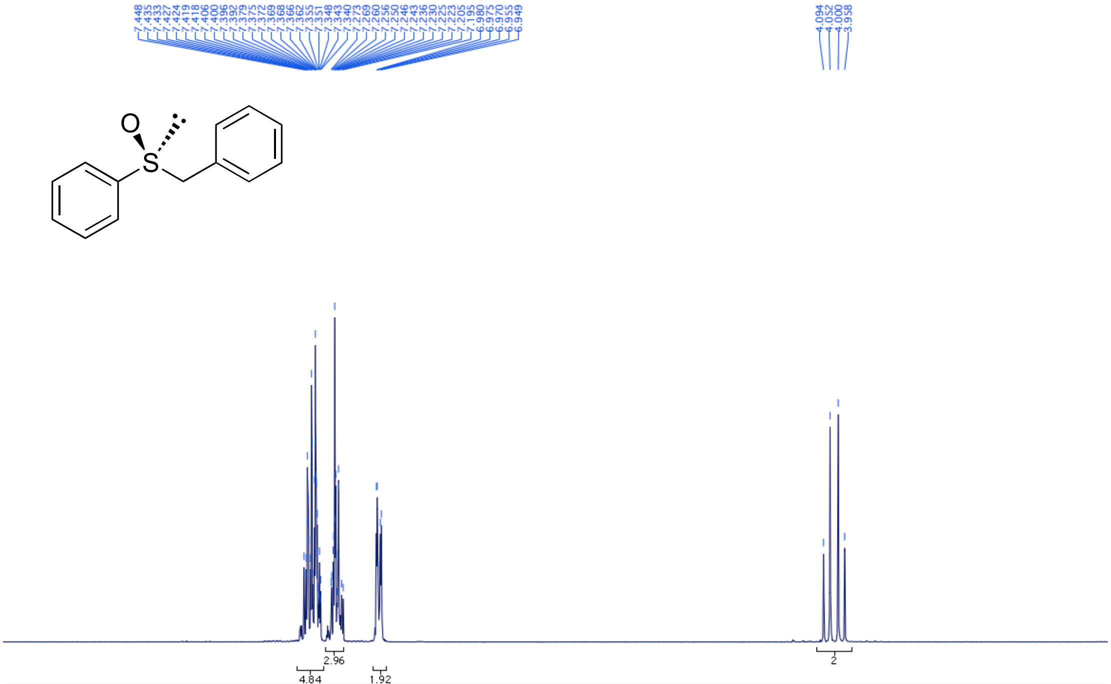


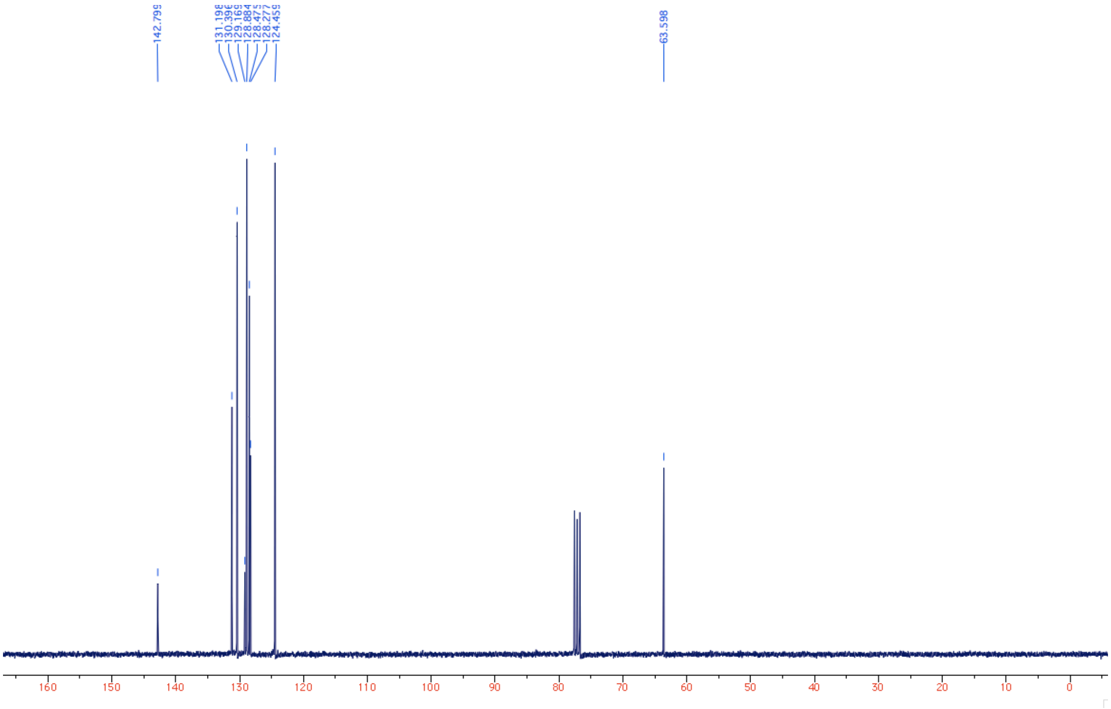
(*S*)-*p*-tolyl methyl sulfoxide (98g)



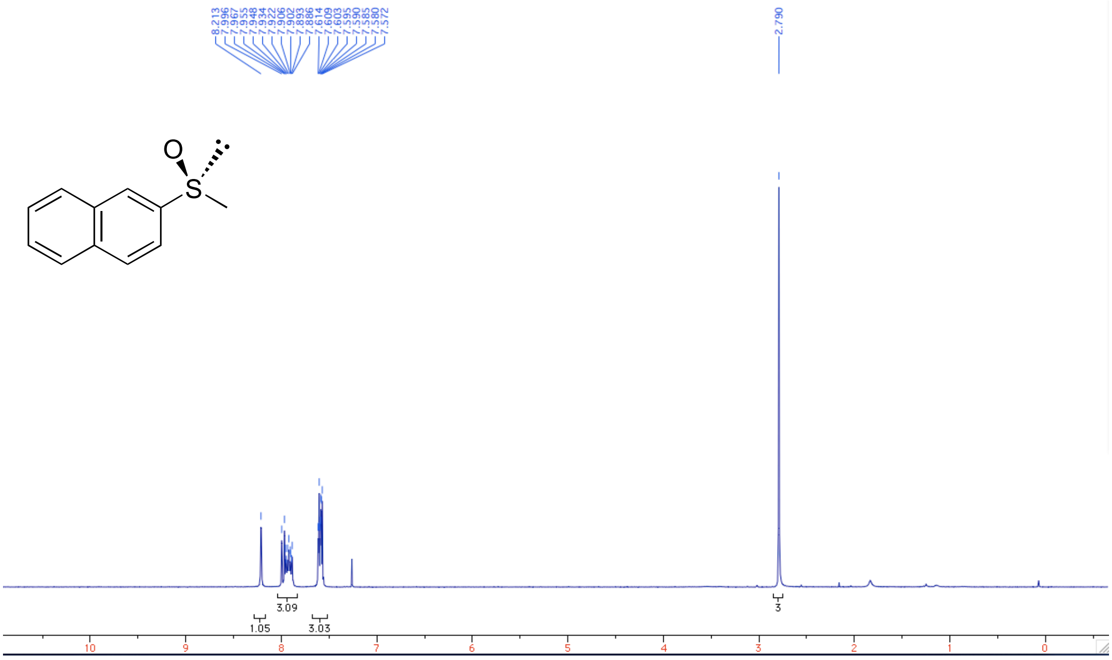


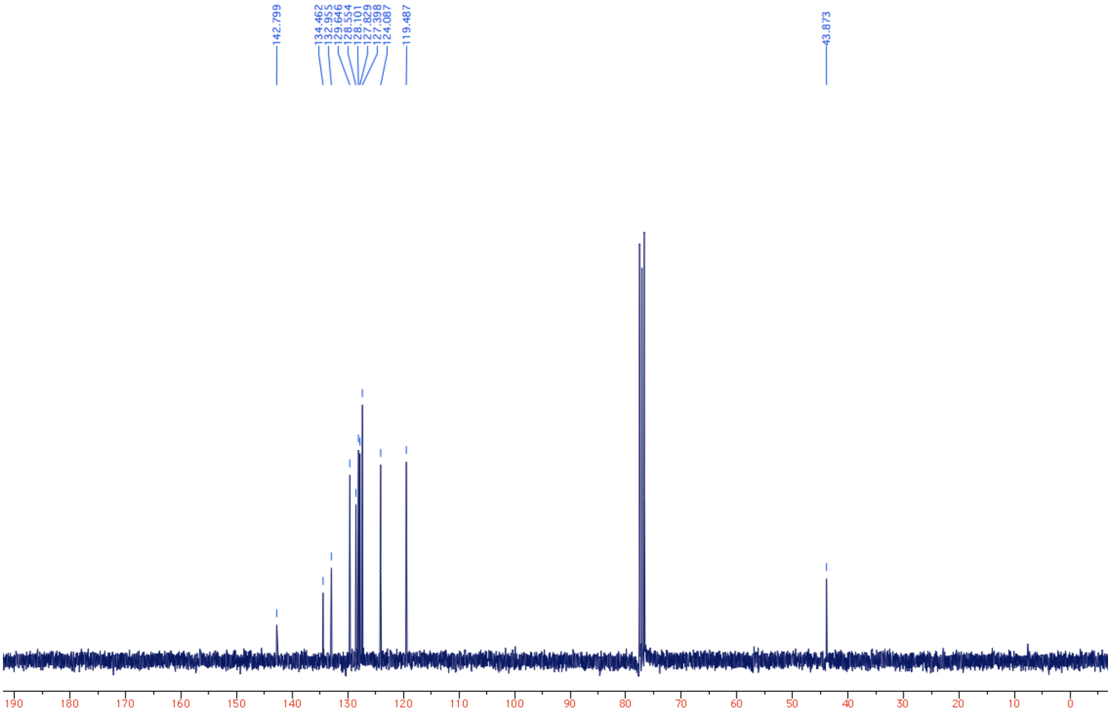
(*S*)-Benzyl phenyl sulfoxide (98d)



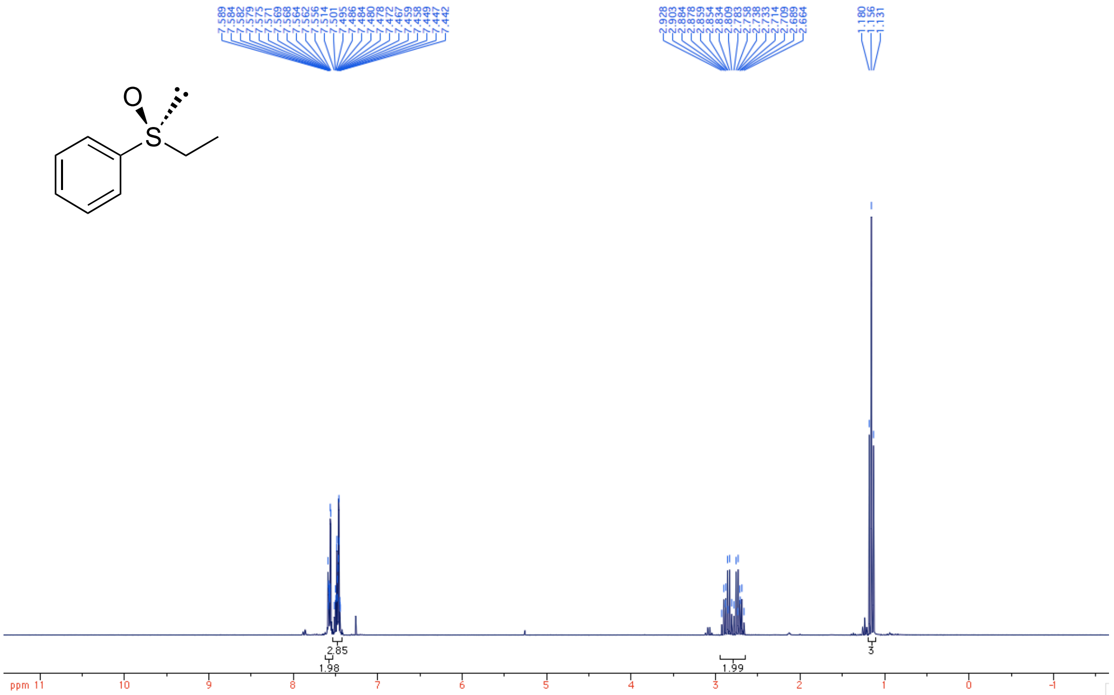


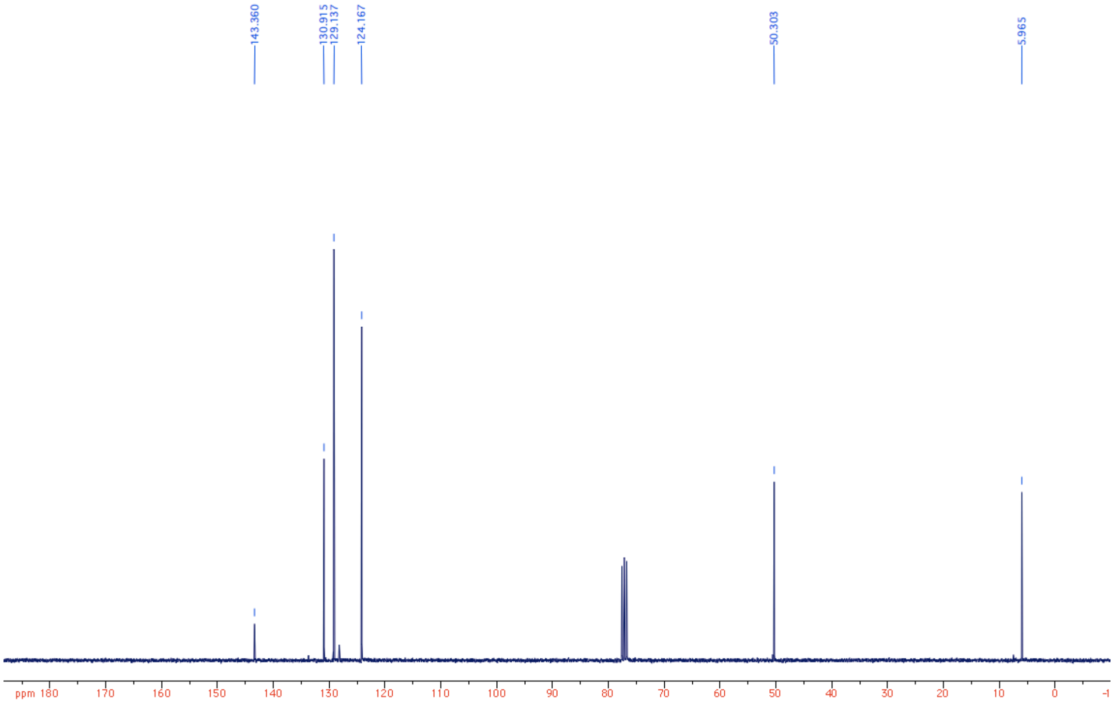
(*S*)-2-Naphthyl methyl sulfoxide (98e)



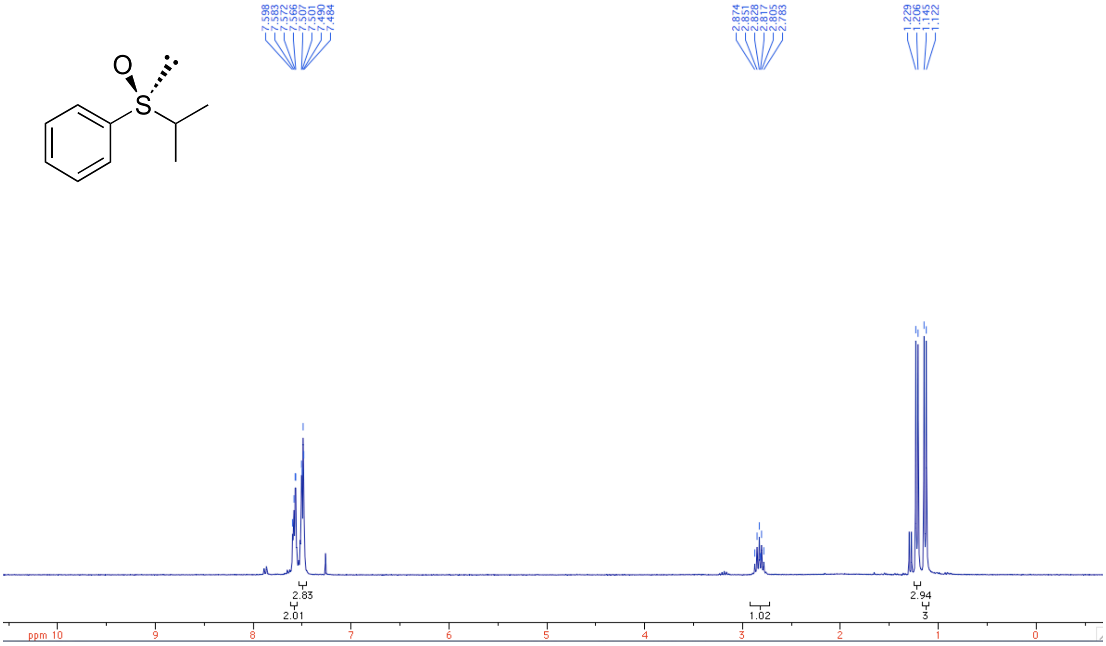


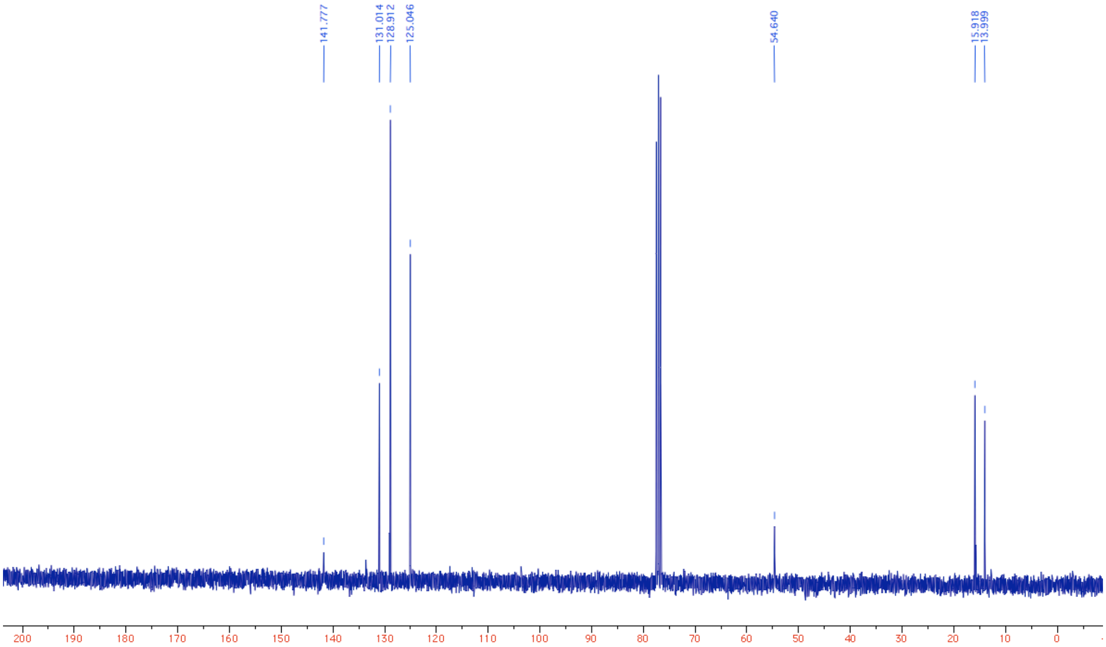
(*S*)-Phenyl ethyl sulfoxide (98f)



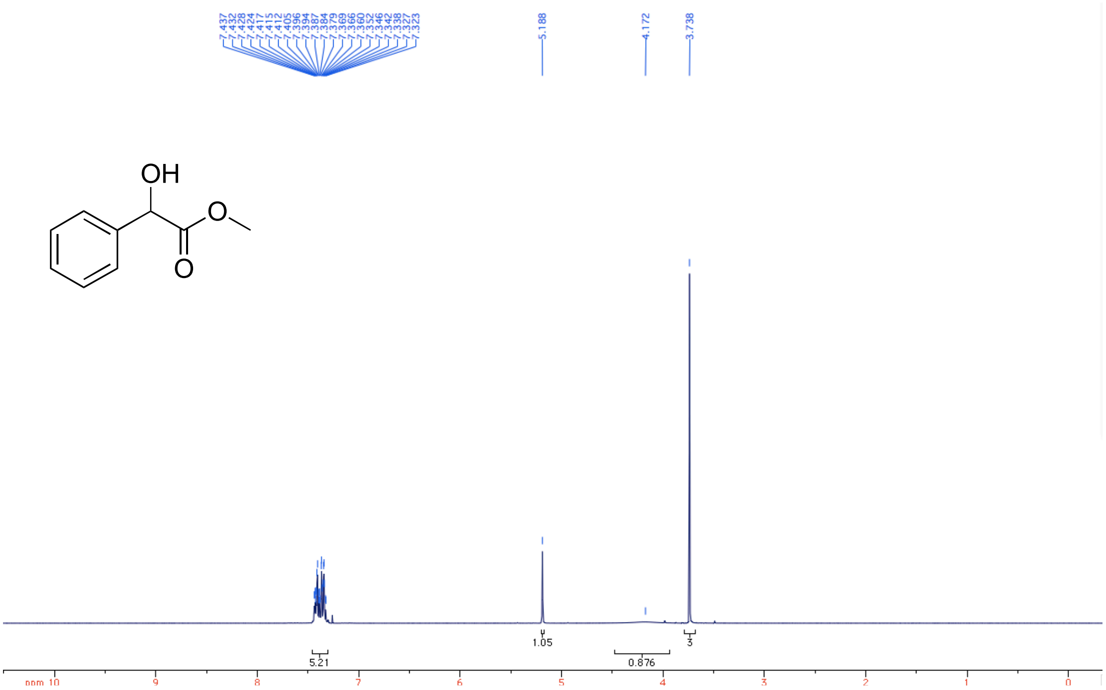


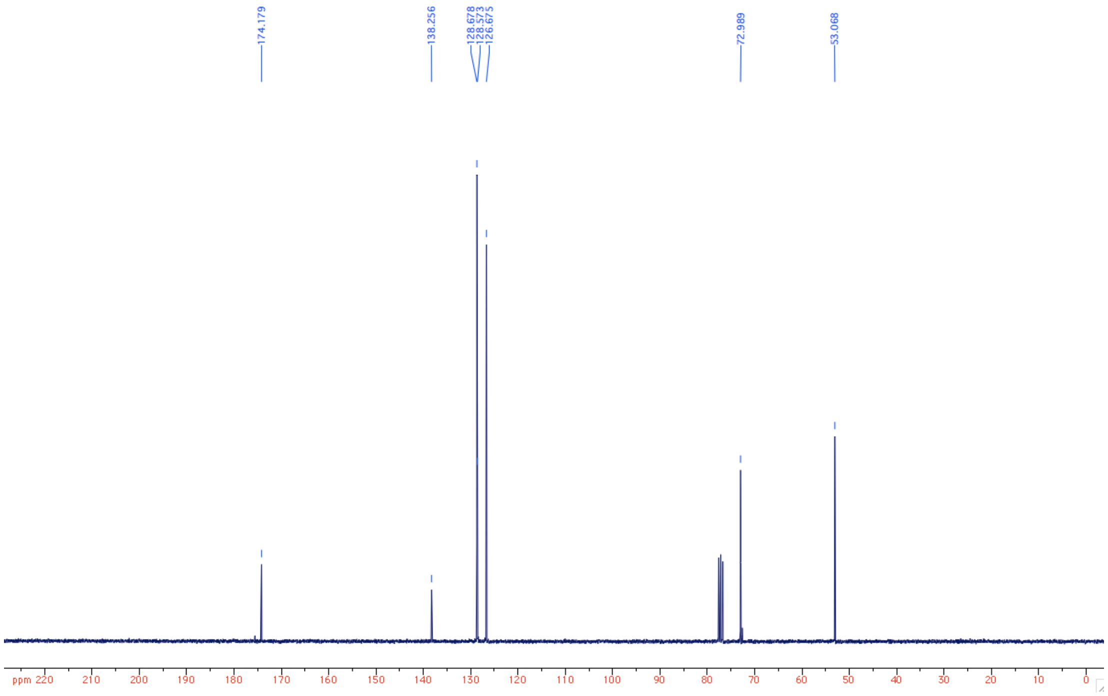
(*S*)-Phenyl isopropyl sulfoxide (98h)



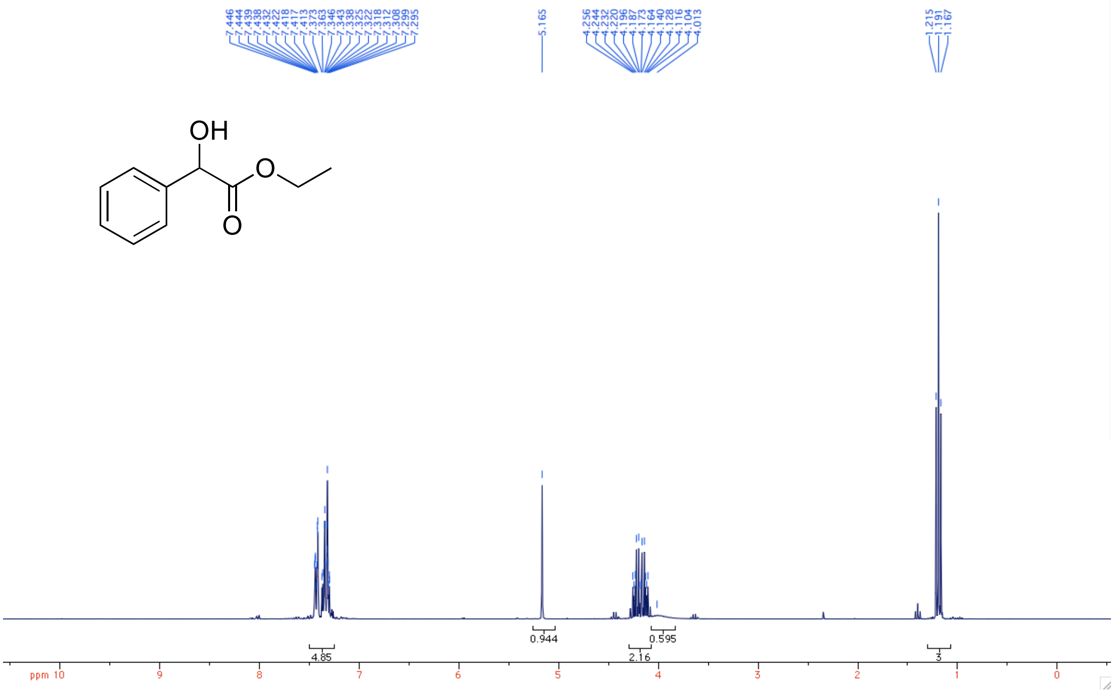


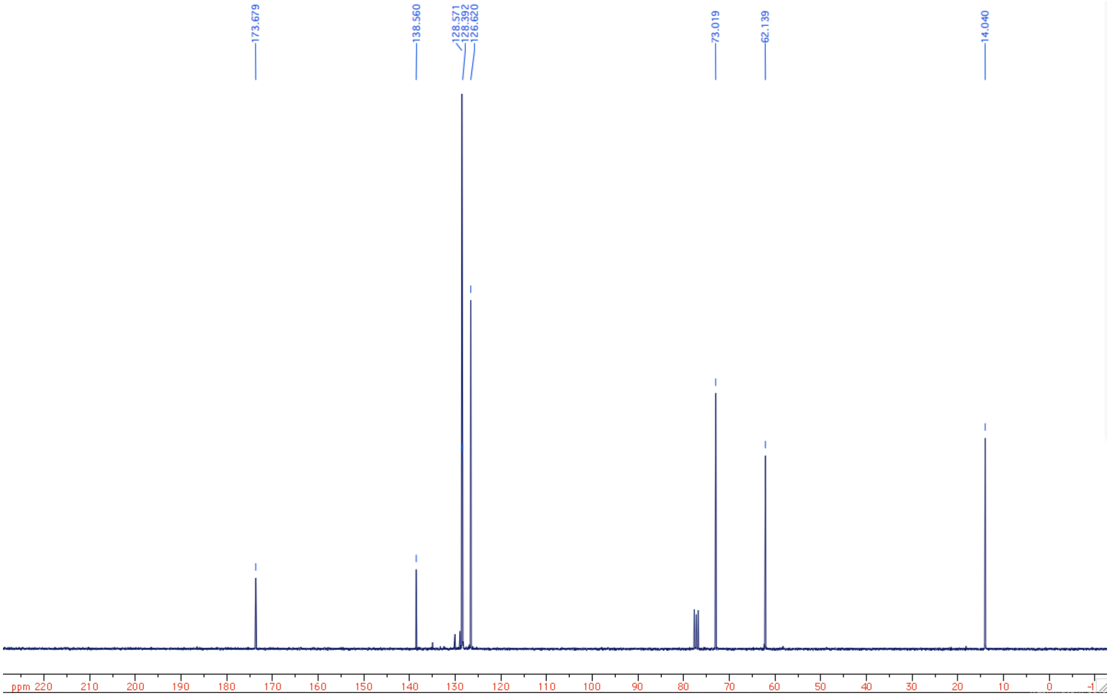
Methyl-2-hydroxy-2-phenylacetate (99b)



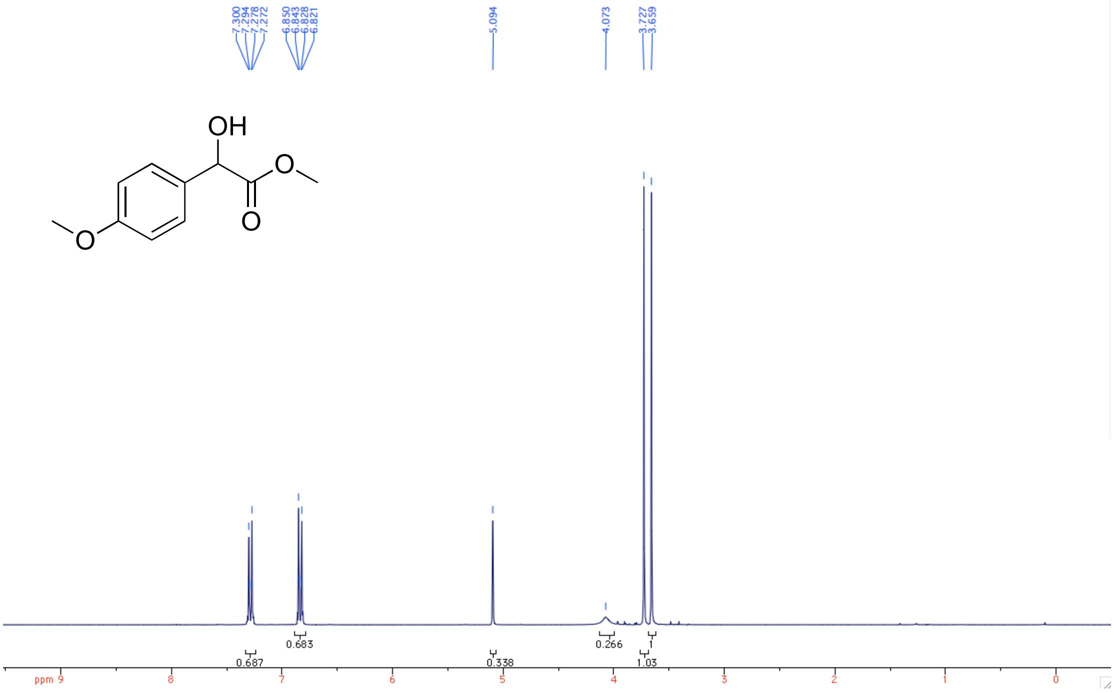


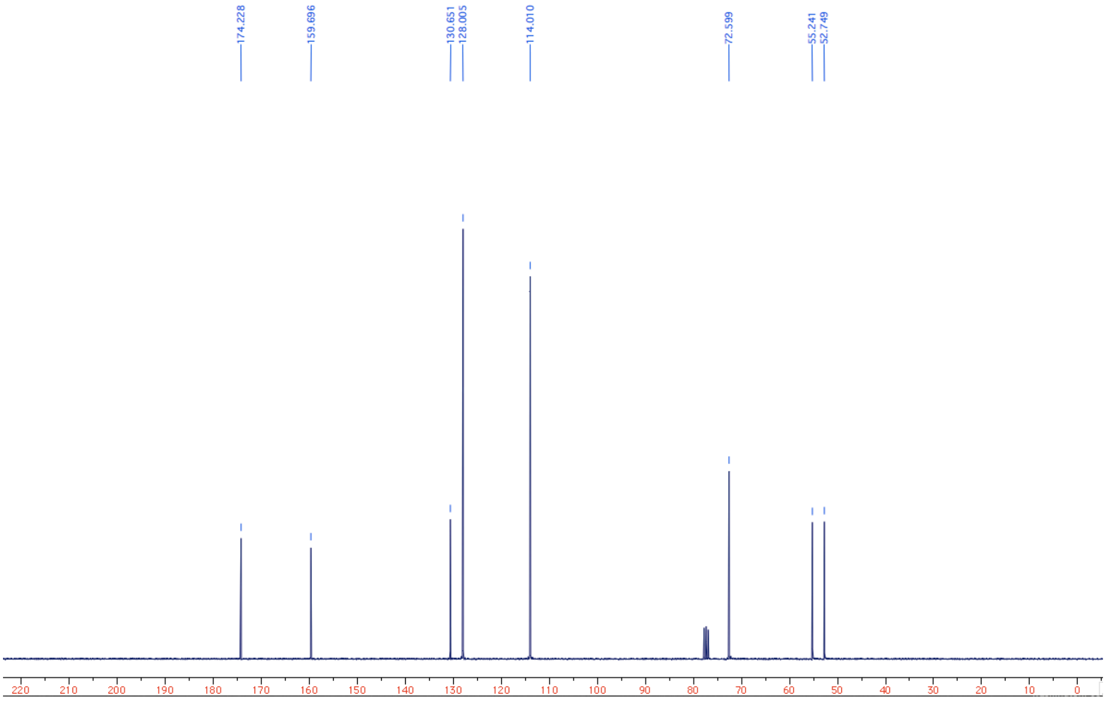
Ethyl-2-hydroxy-2-phenylacetate (99a)



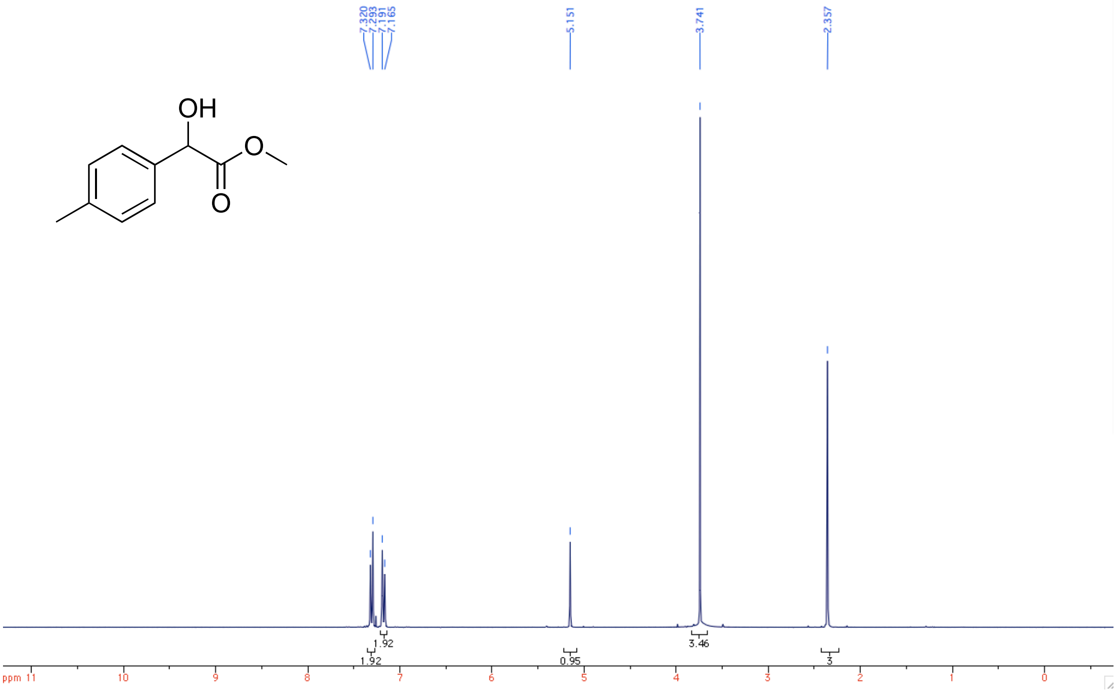


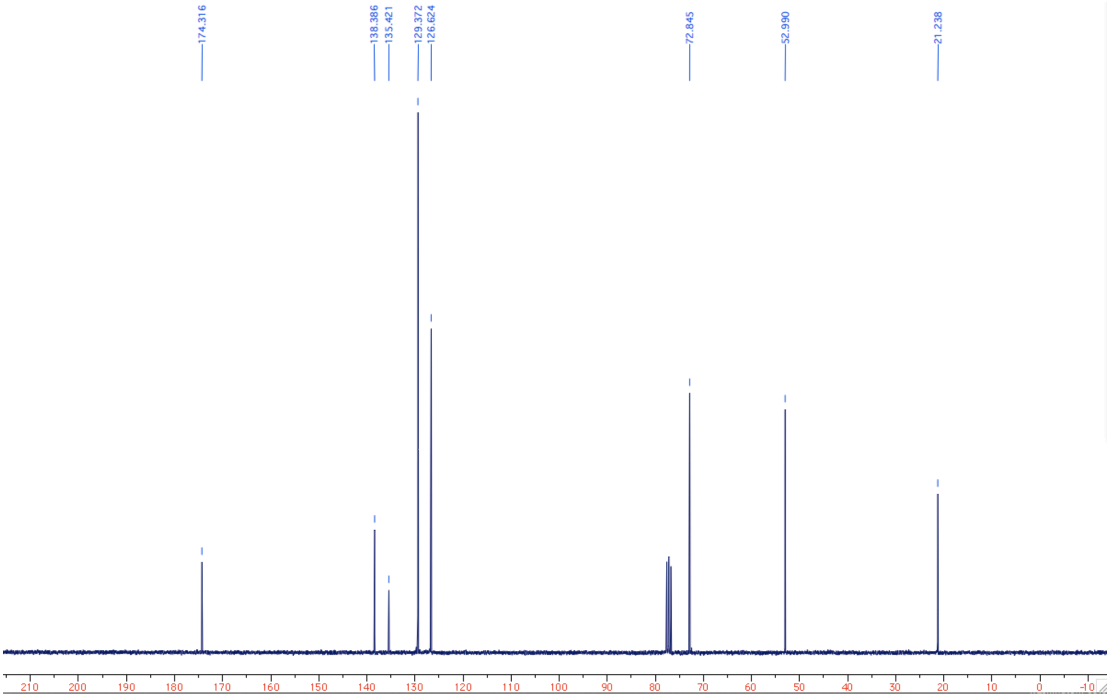
Methyl-2-hydroxy-2-(4-methoxyphenyl)acetate (99e)



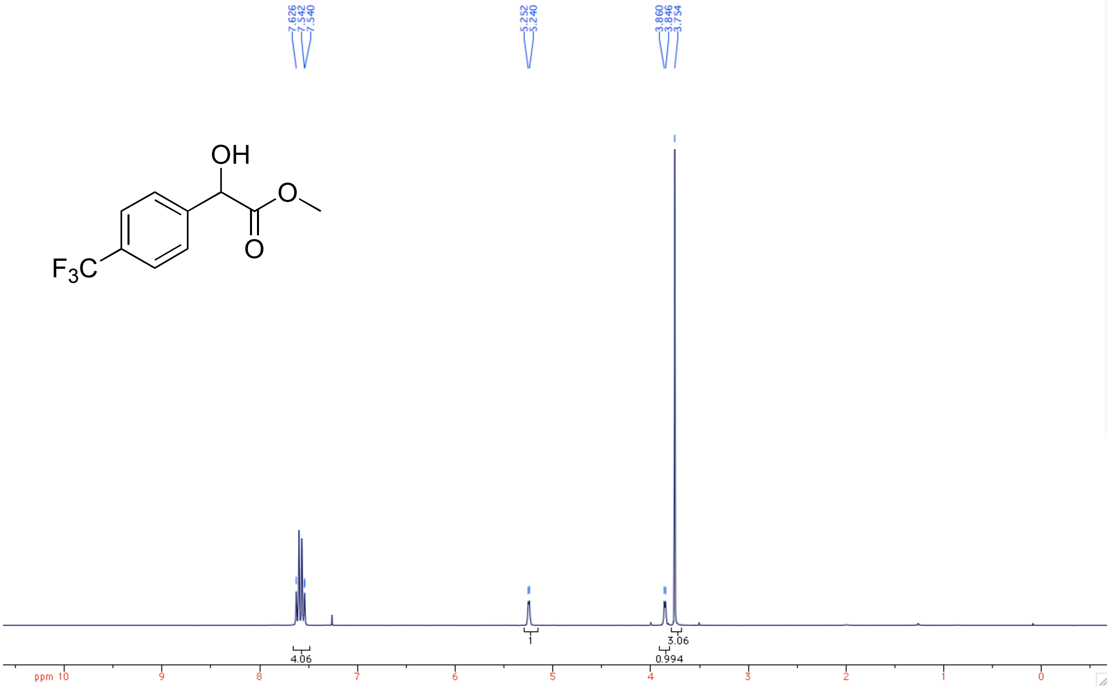


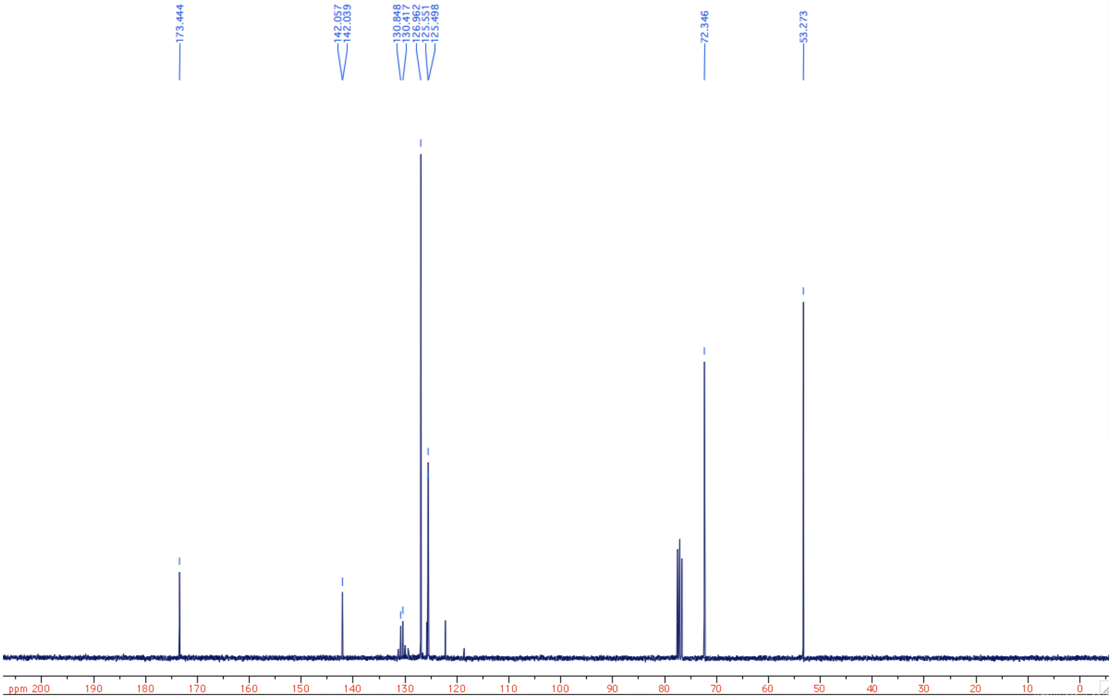
Methyl-2-hydroxy-2-(p-tolyl)acetate (99c)



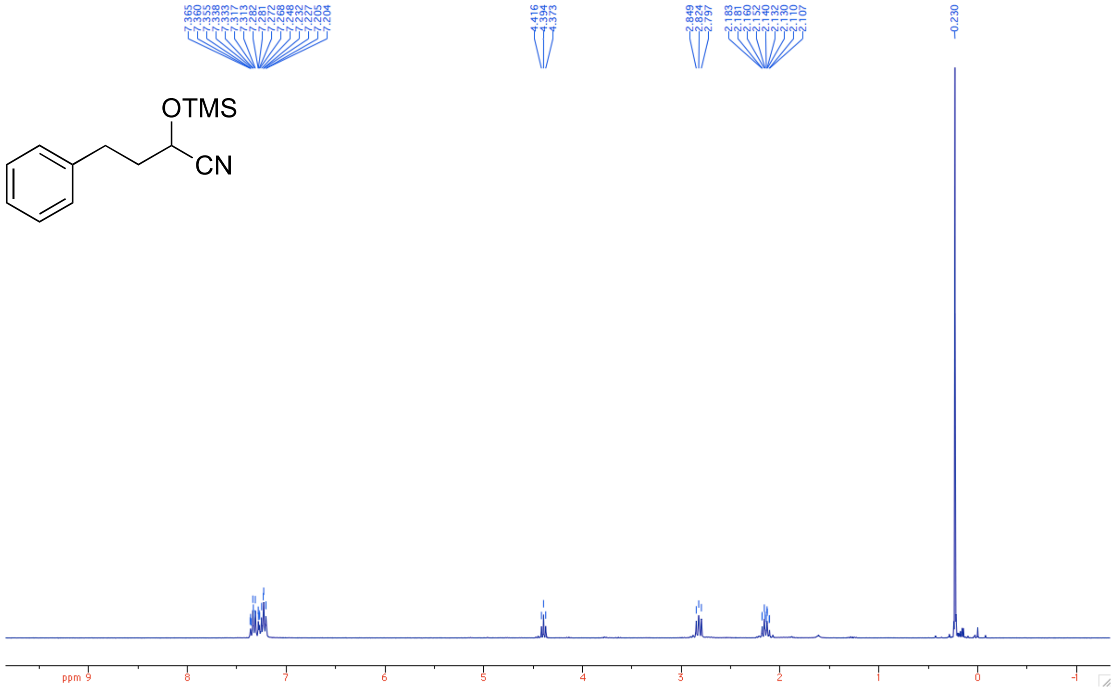


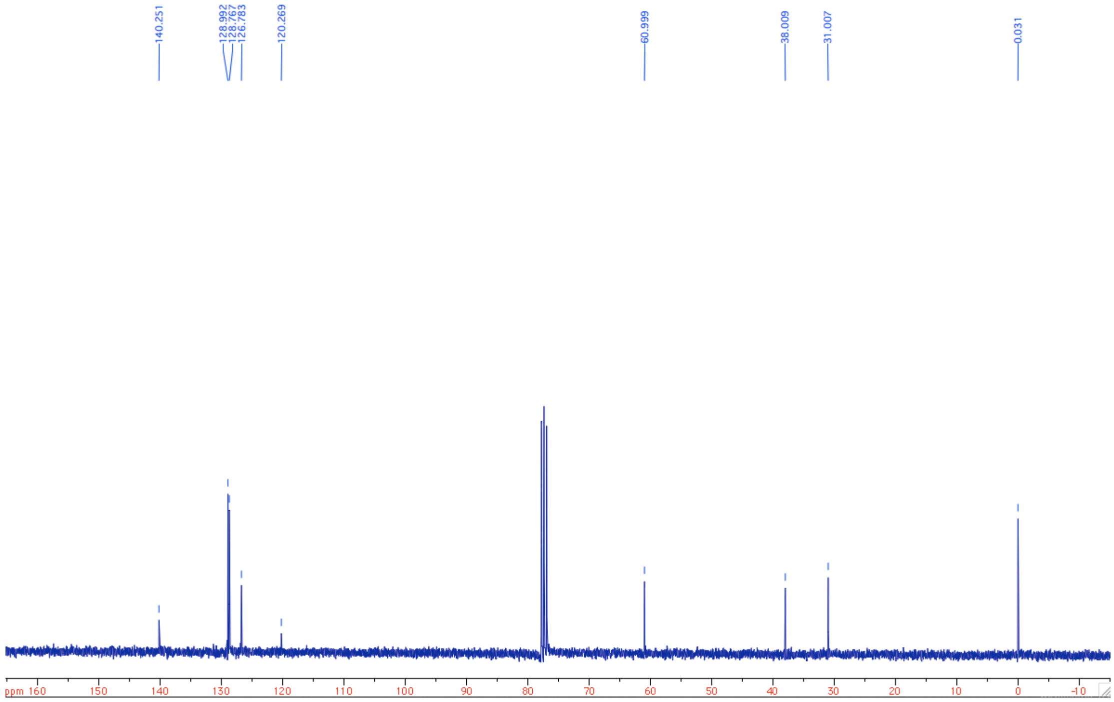
Methyl-2-hydroxy-2-(4-(trifluoromethyl)phenyl)acetate (99d)



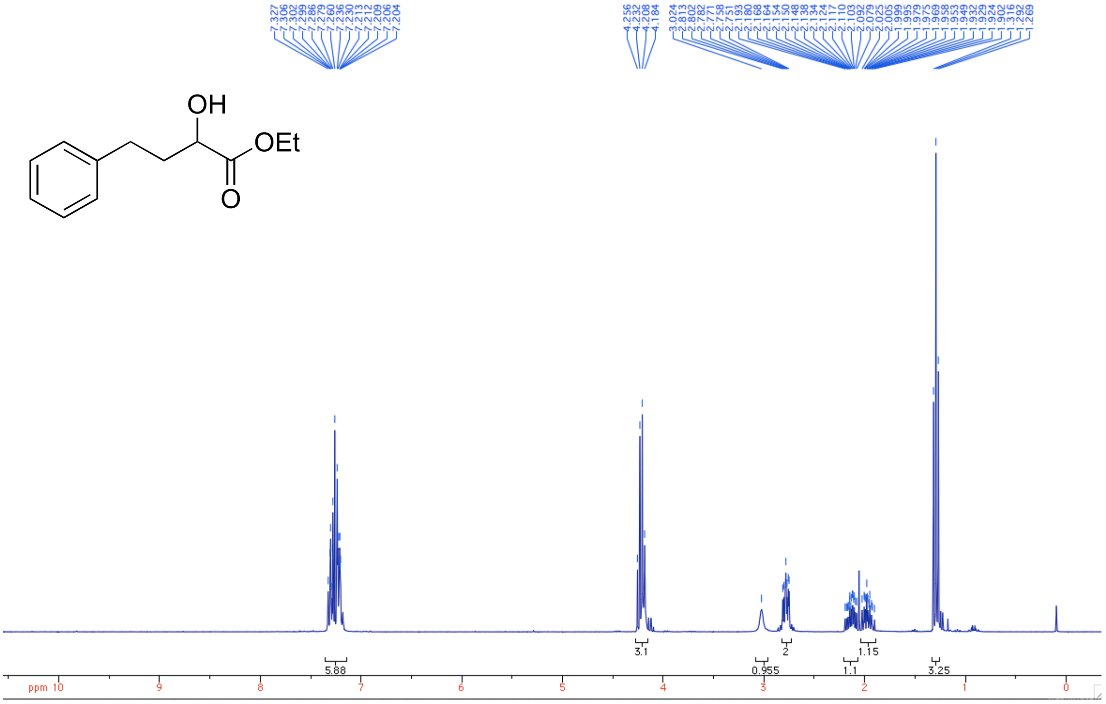


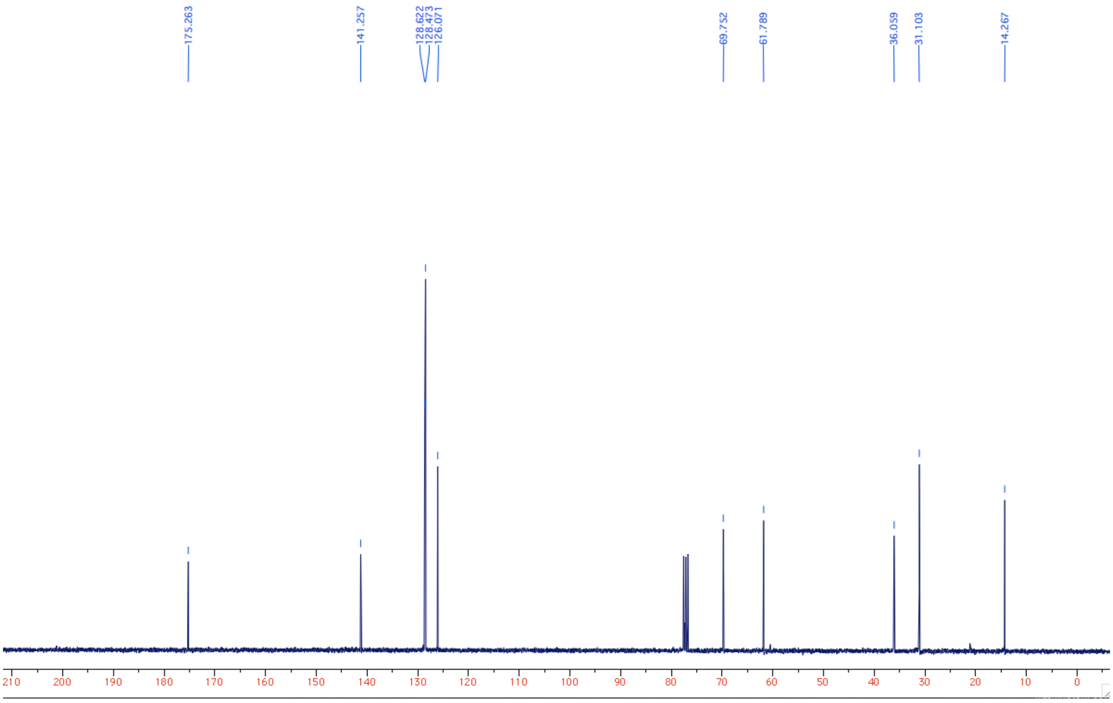
Ethyl-4-phenyl-2-((trimethylsilyl)oxy)butanoate



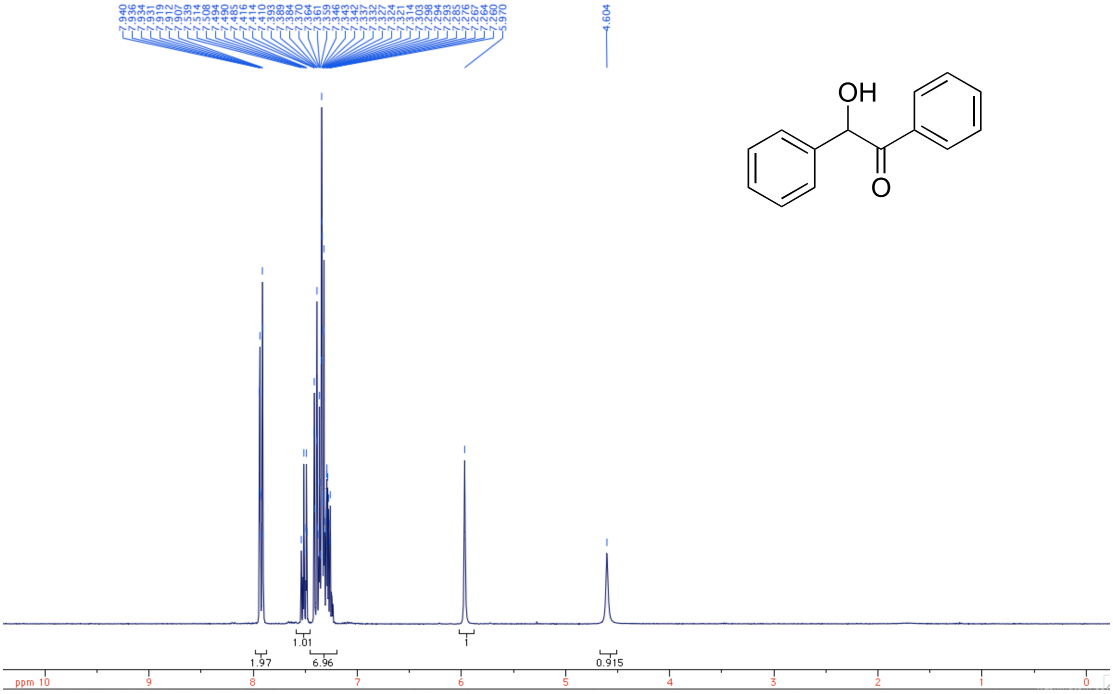


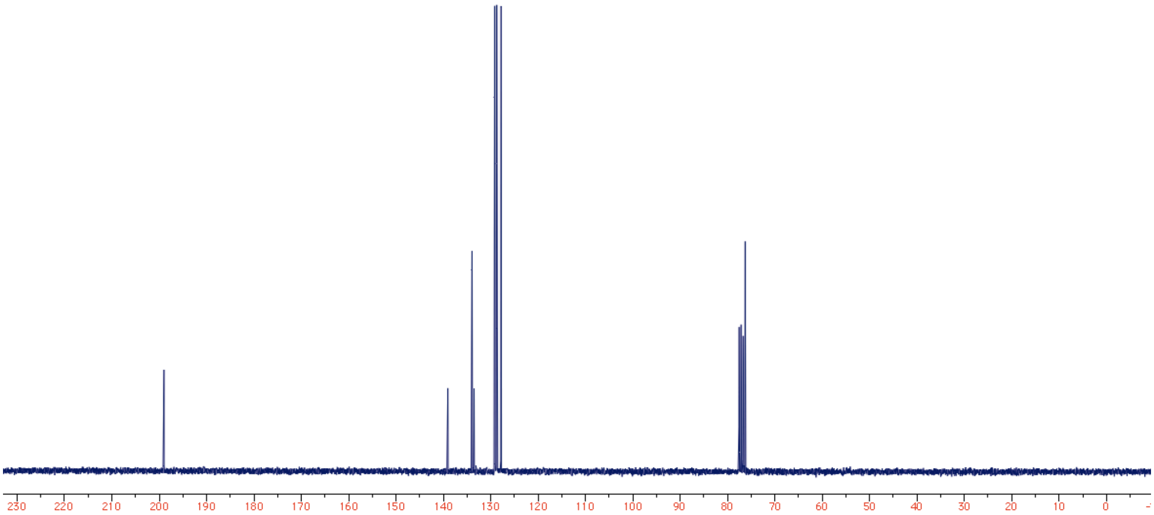
Ethyl 2-hydroxy-4-phenylbutanoate (99f)



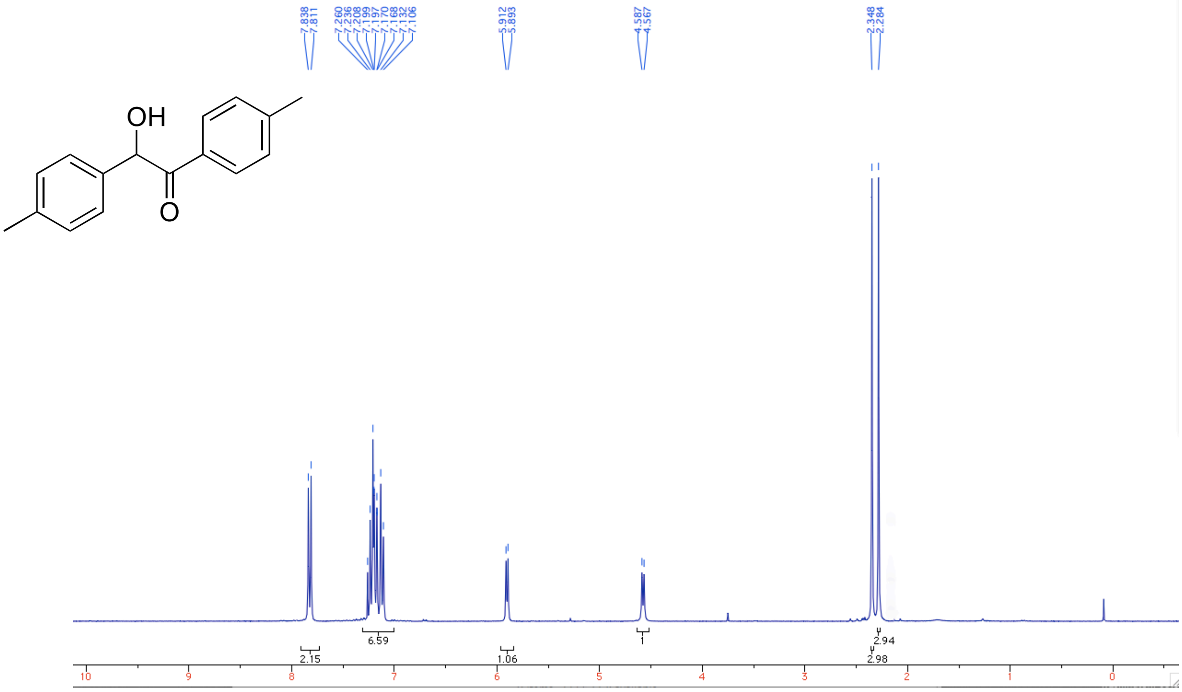


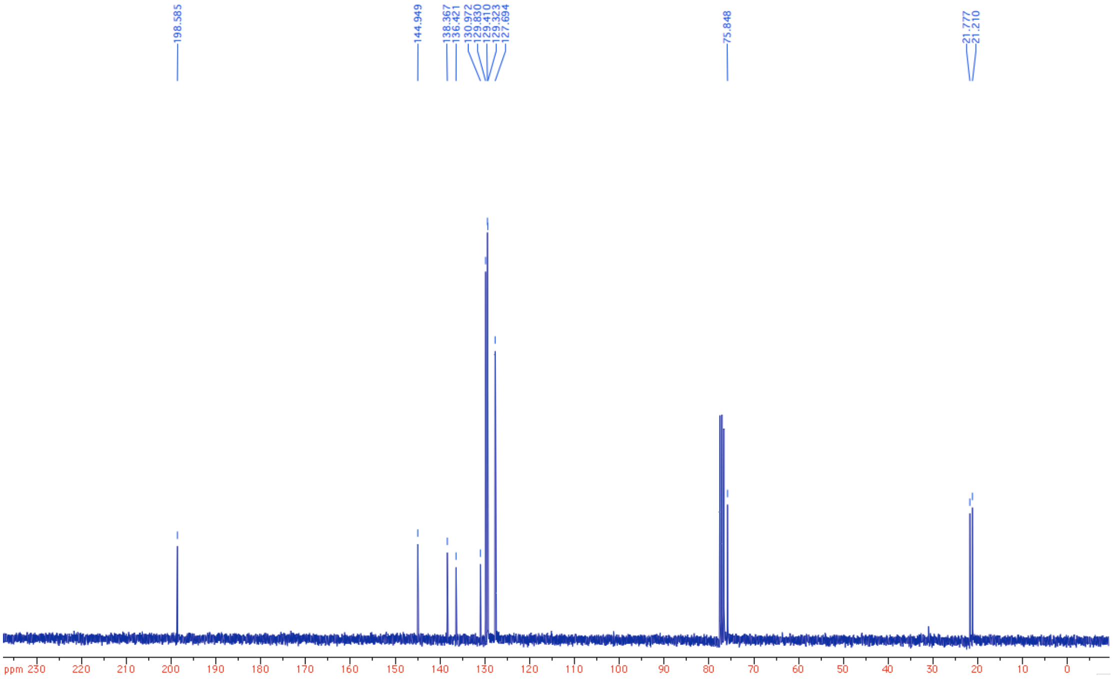
2-hydroxy-1,2-diphenylethanone (99g)



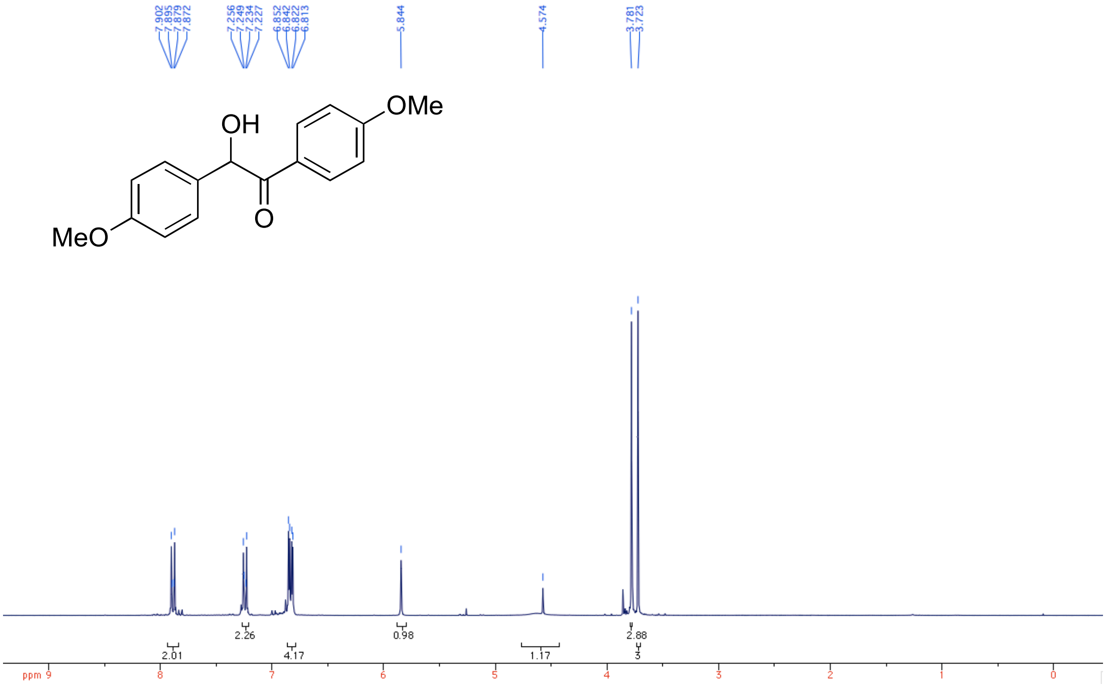


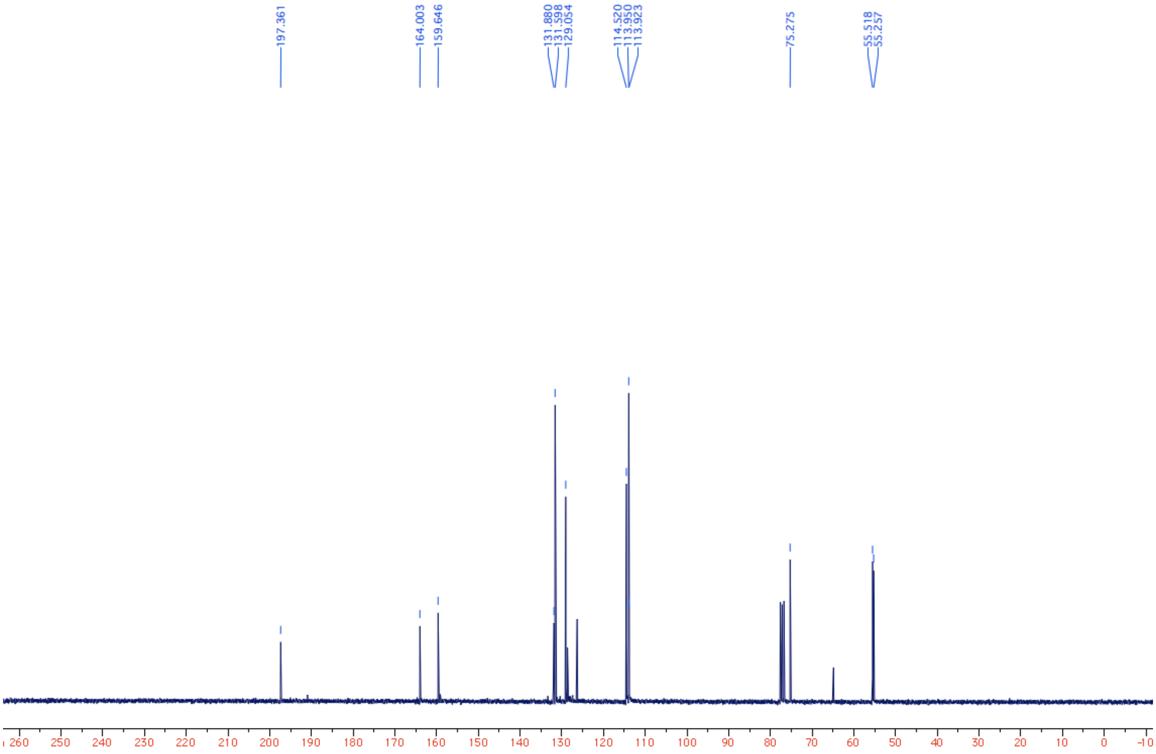
2-hydroxy-1,2-di-p-tolylethanone (99h)



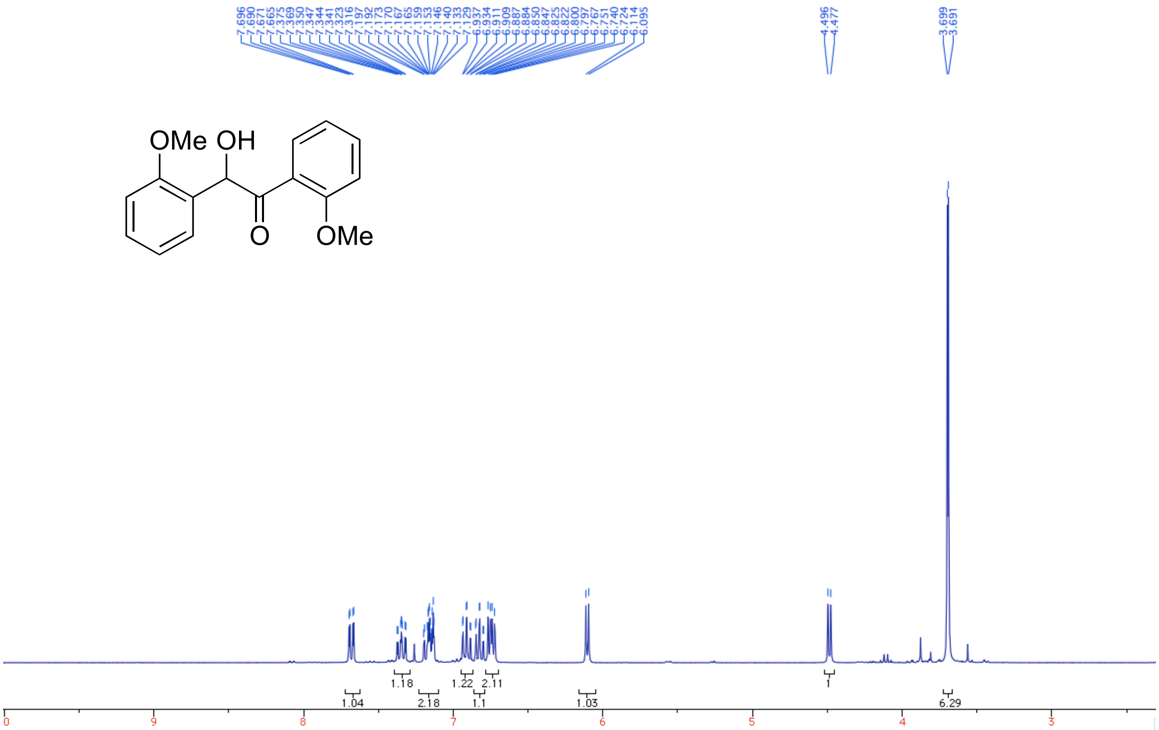


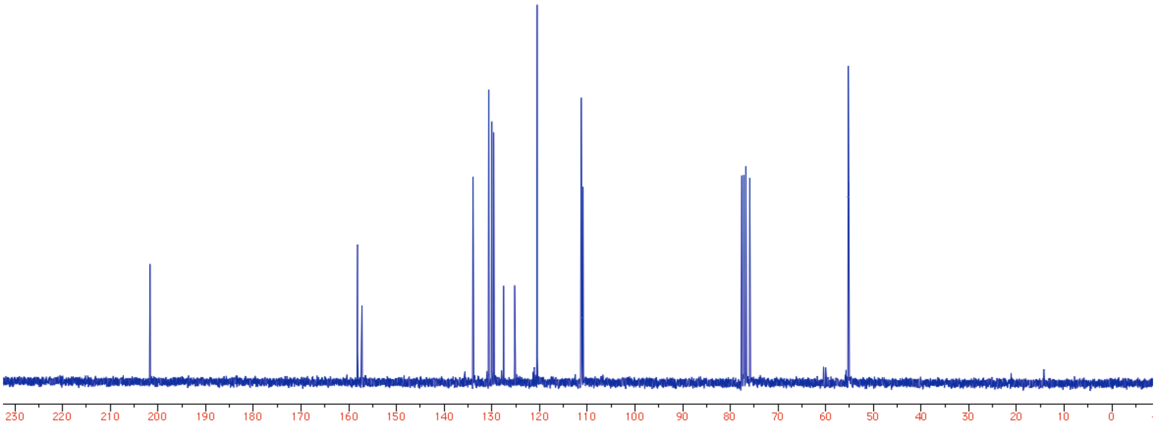
2-hydroxy-1,2-bis(4-methoxyphenyl)ethanone (99i)



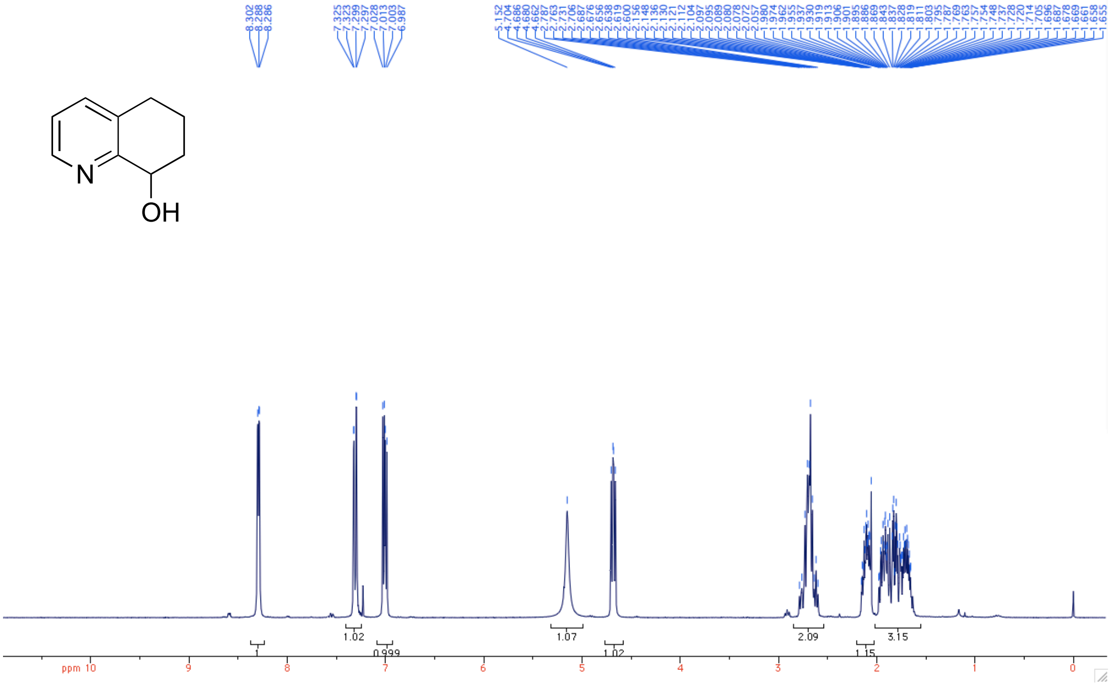


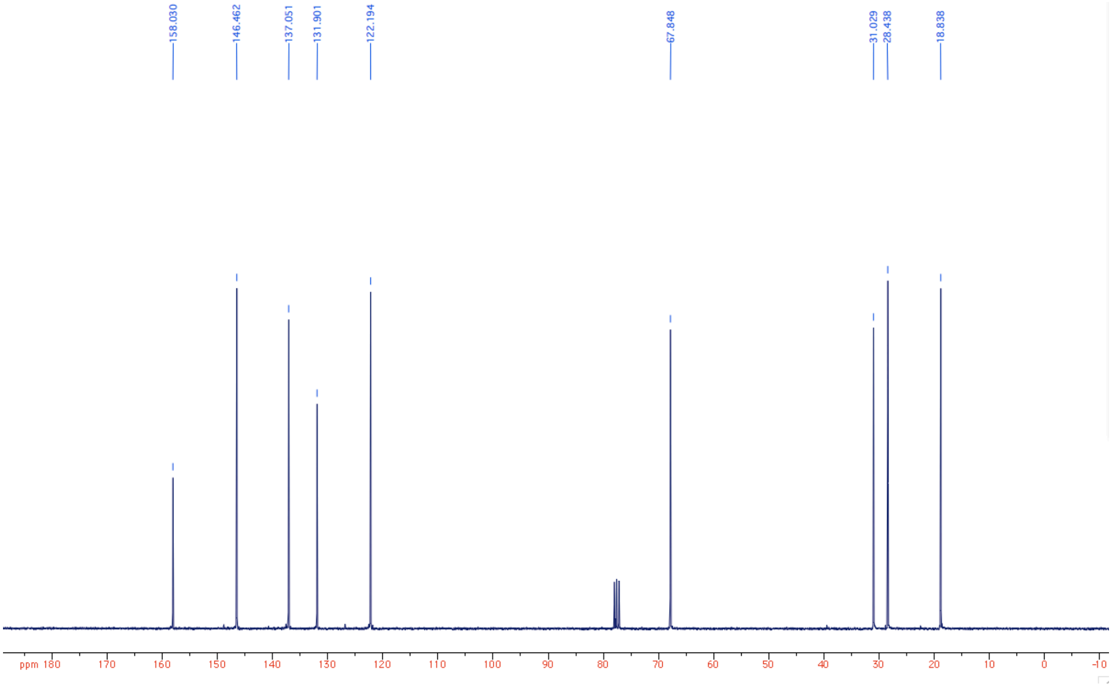
2-hydroxy-1,2-bis(2-methoxyphenyl)ethanone (99j)



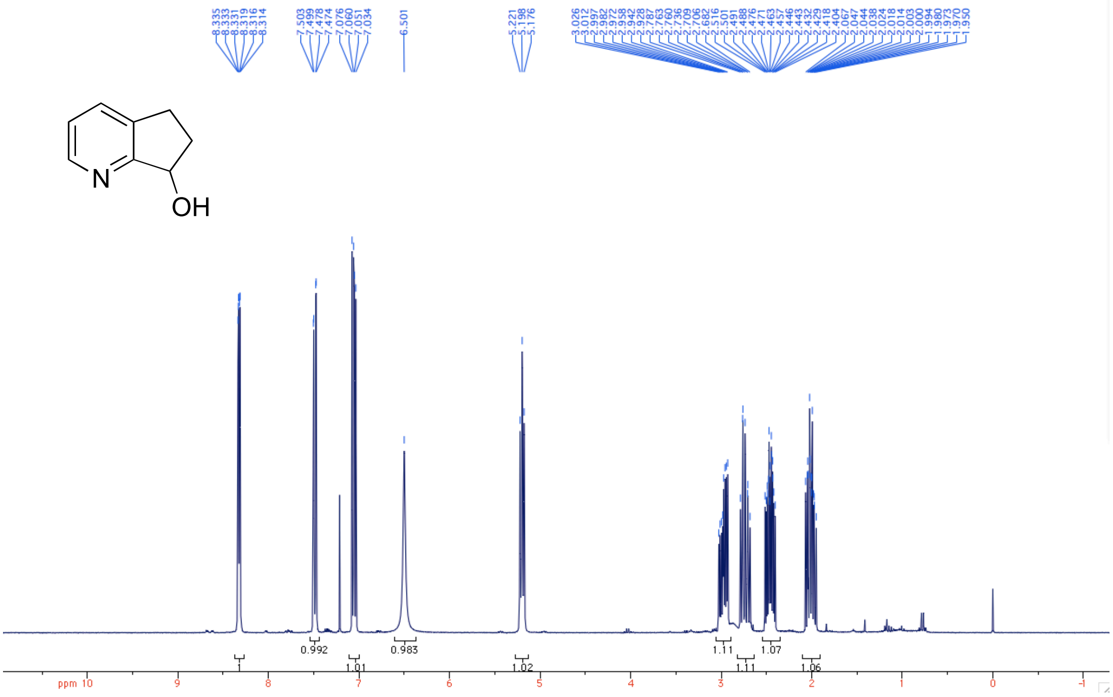


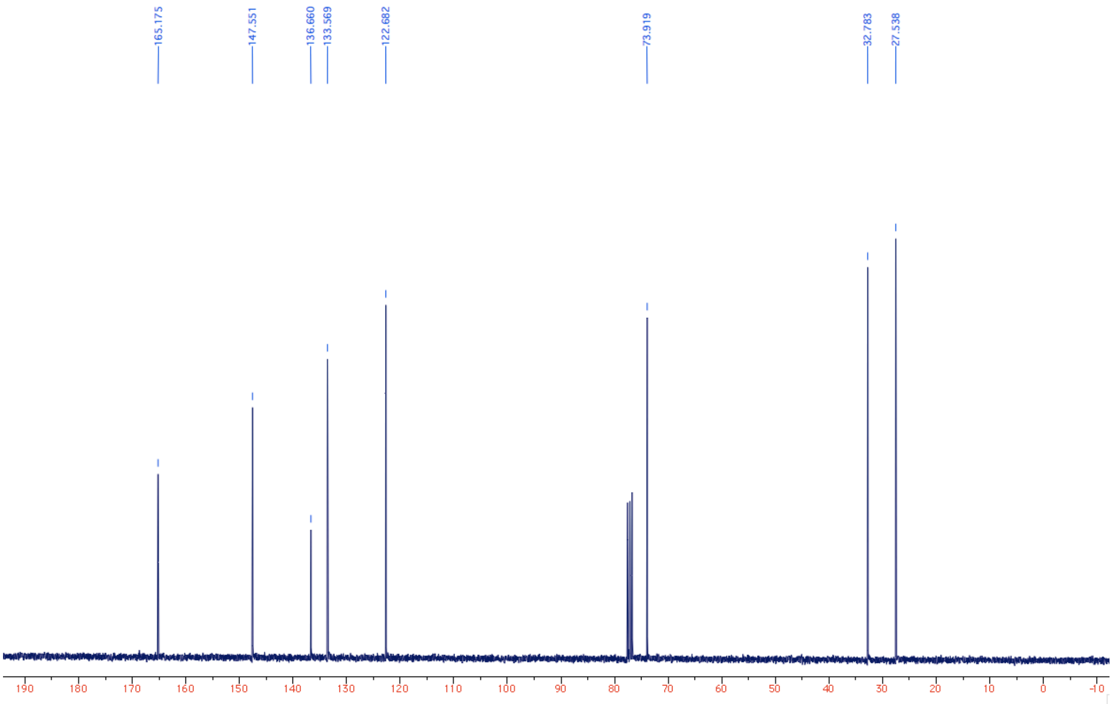
5,6,7,8-tetrahydroquinolin-8-ol (103b)



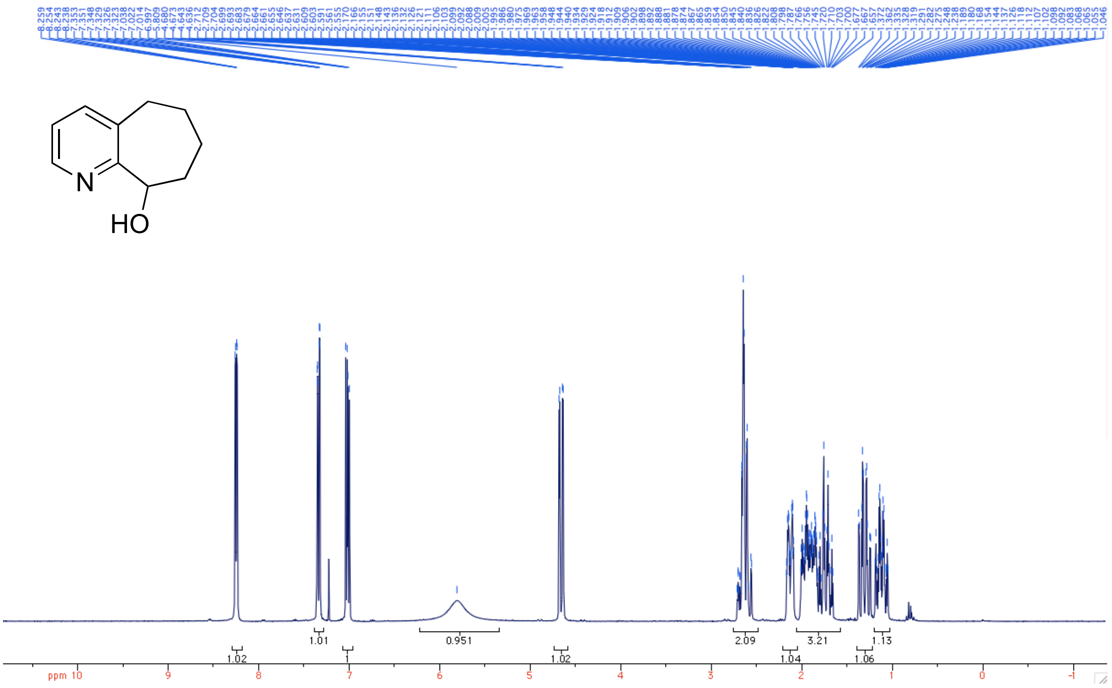


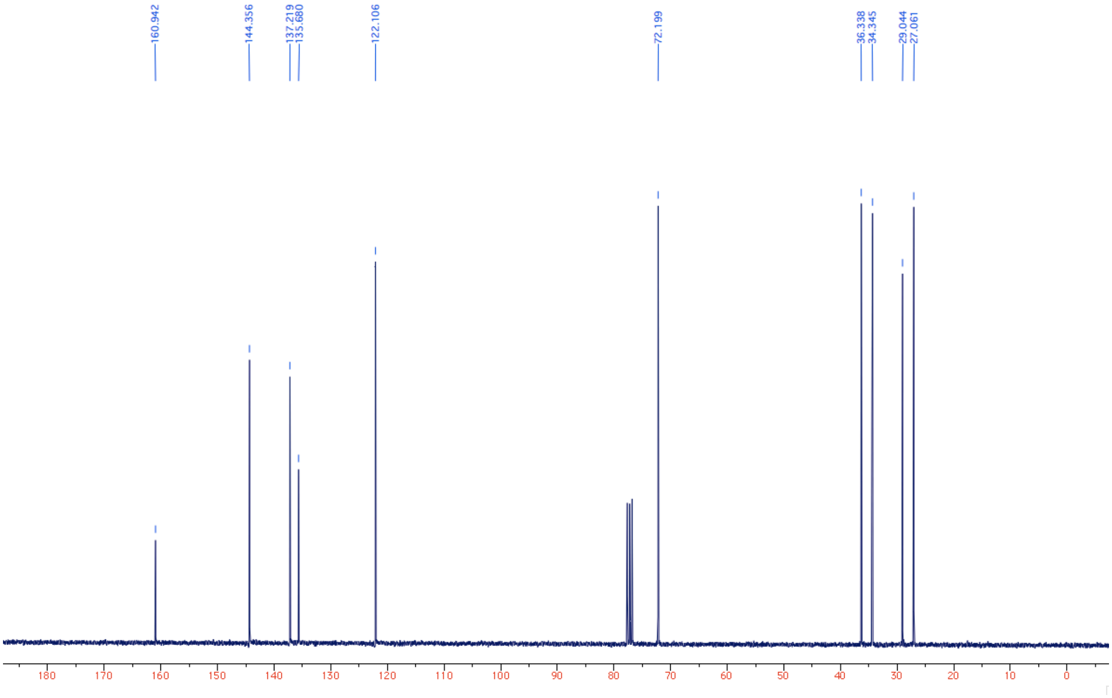
6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (103a)



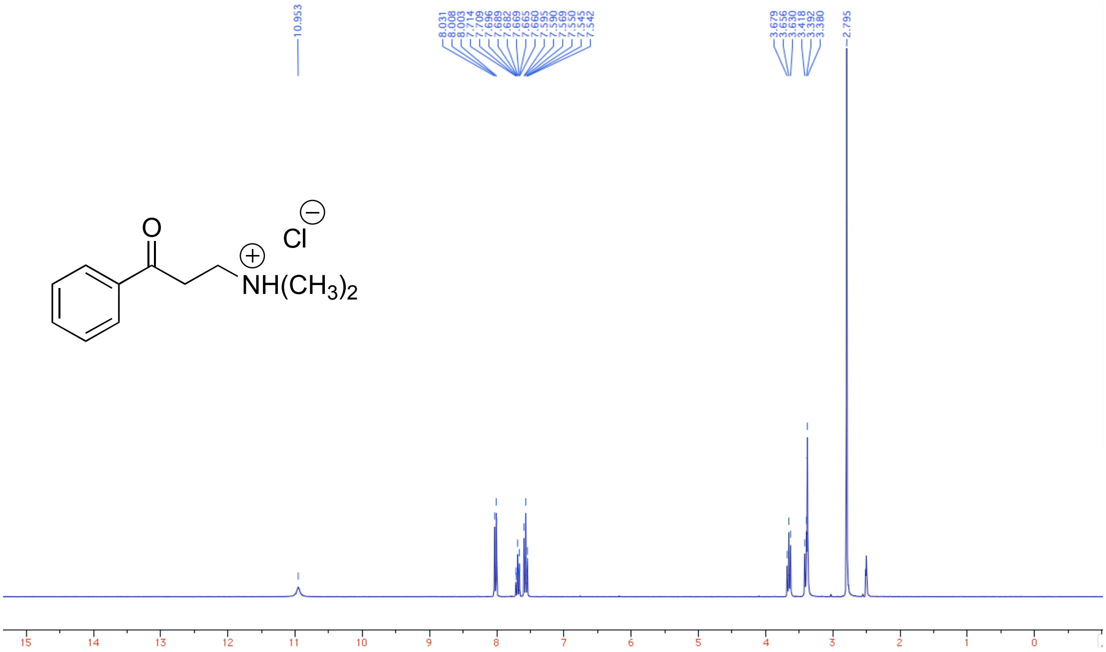


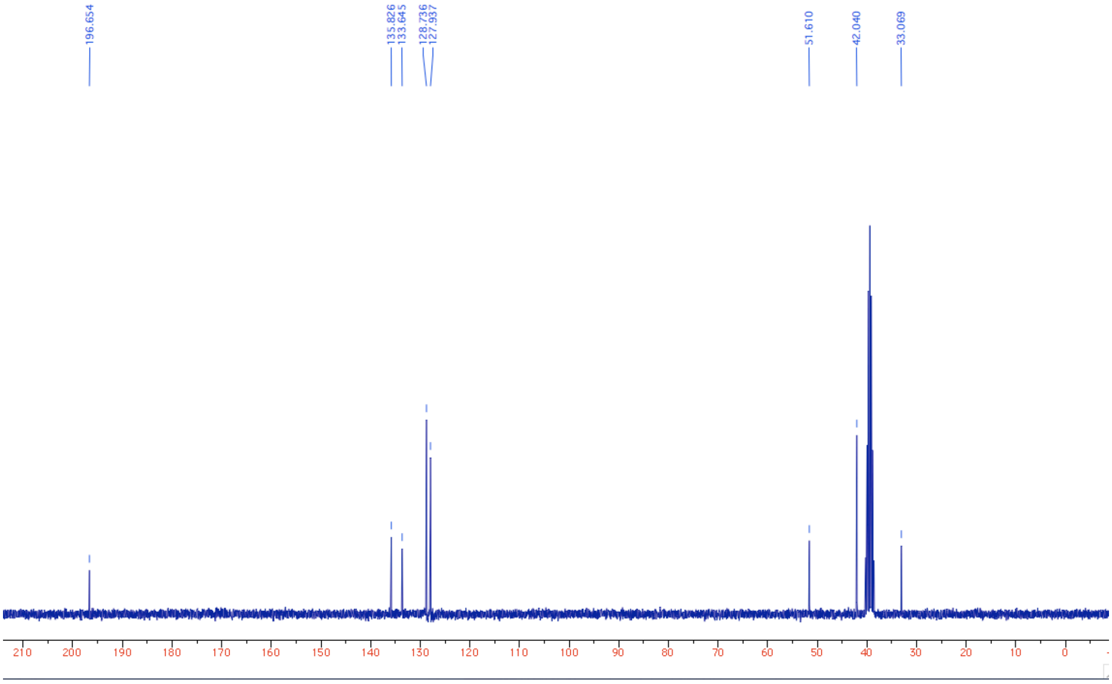
6,7,8,9-tetrahydro-5H-cyclohepta [b] pyridin-9-ol (103c)



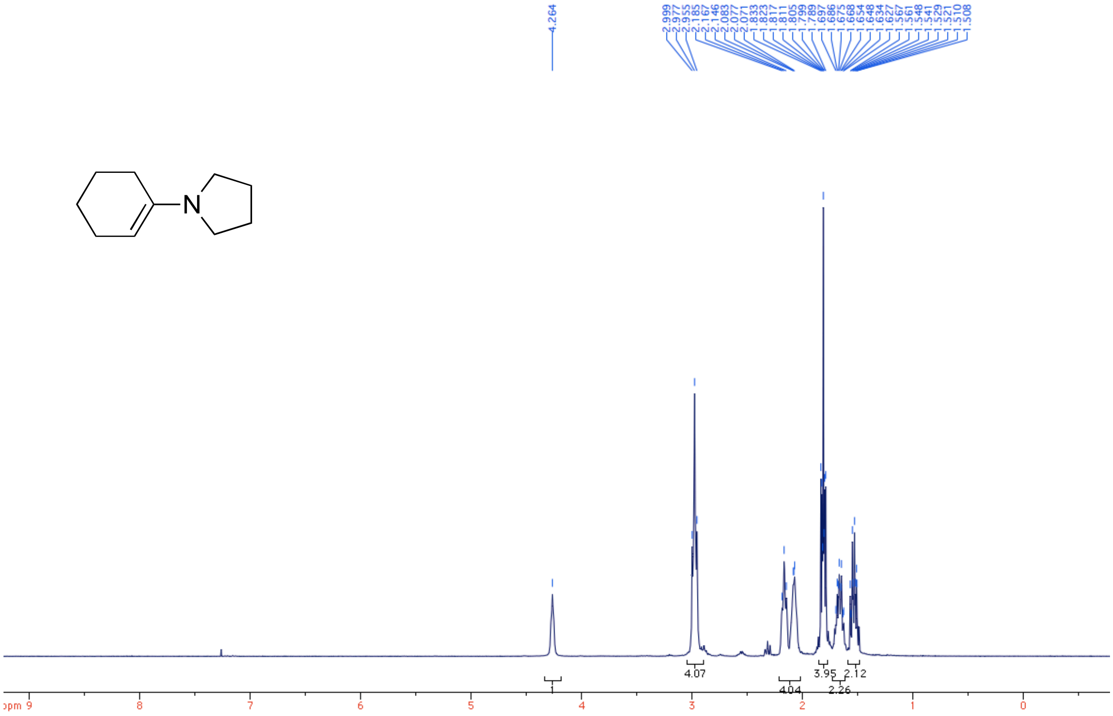


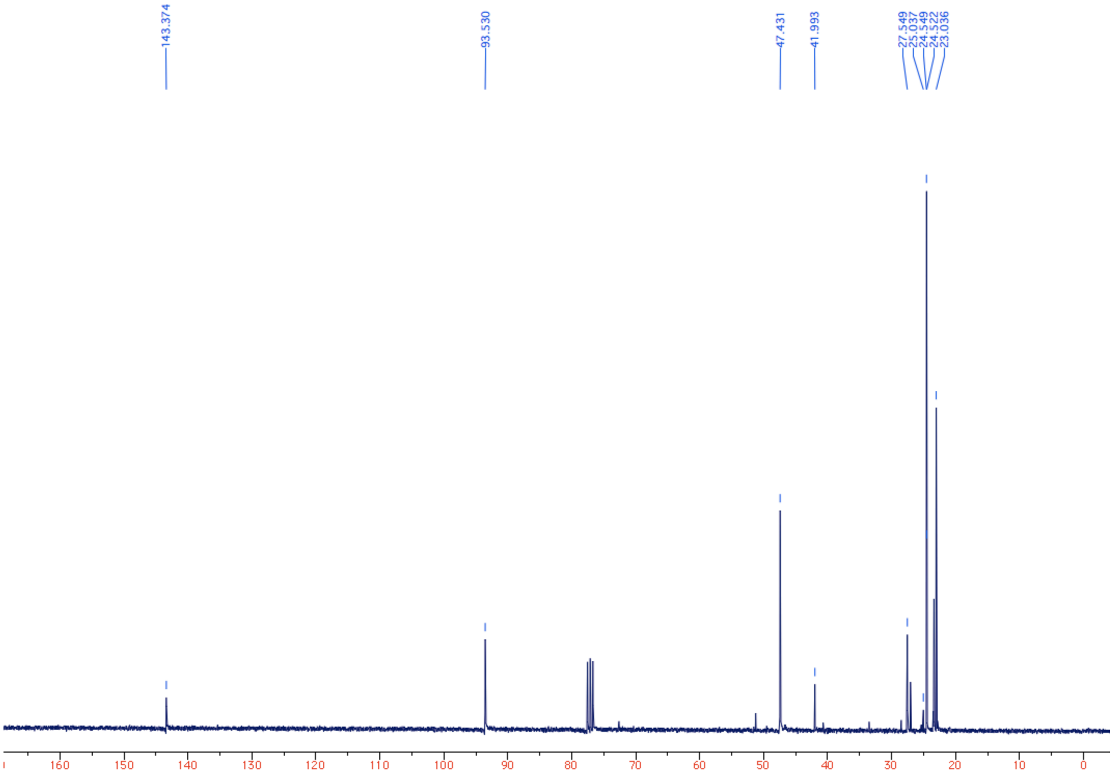
3-dimethylamino-1-phenyl-propan-1-one hydrochloride



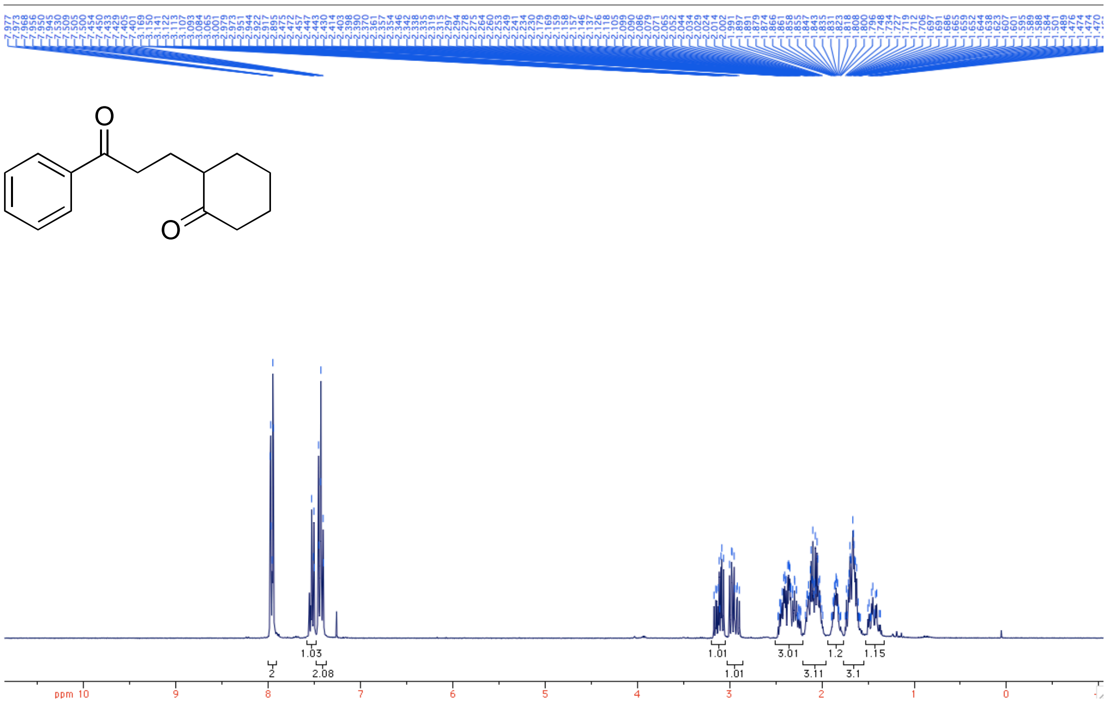


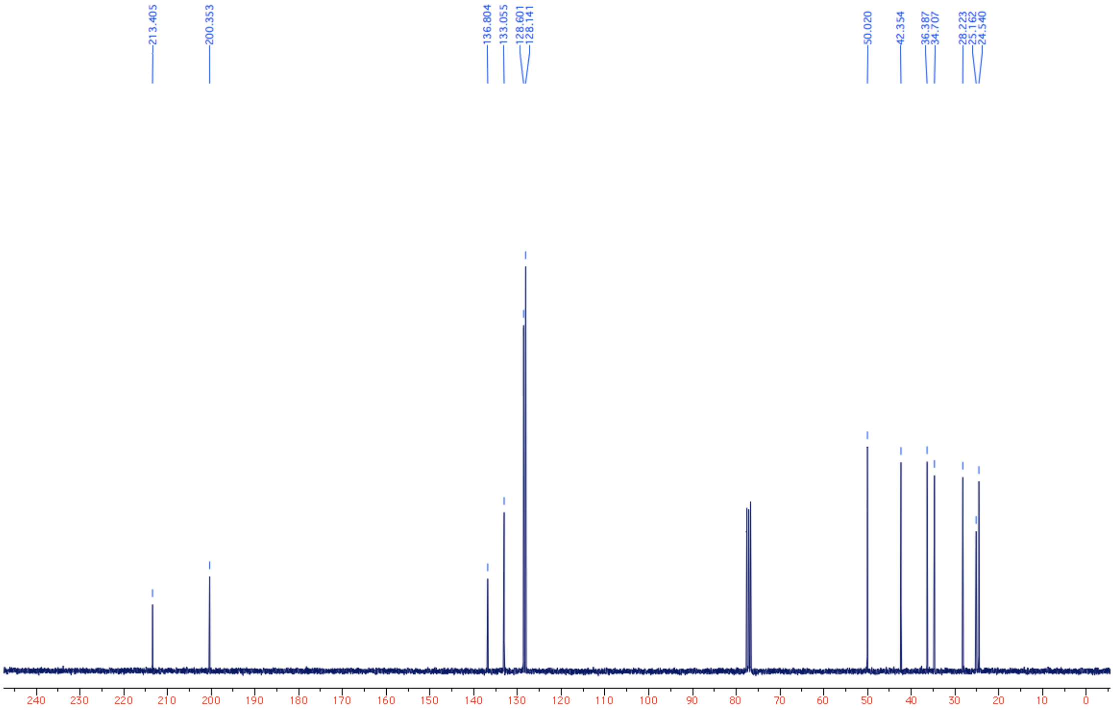
1-(Cyclohex-1-en-1-yl)pyrrolidine



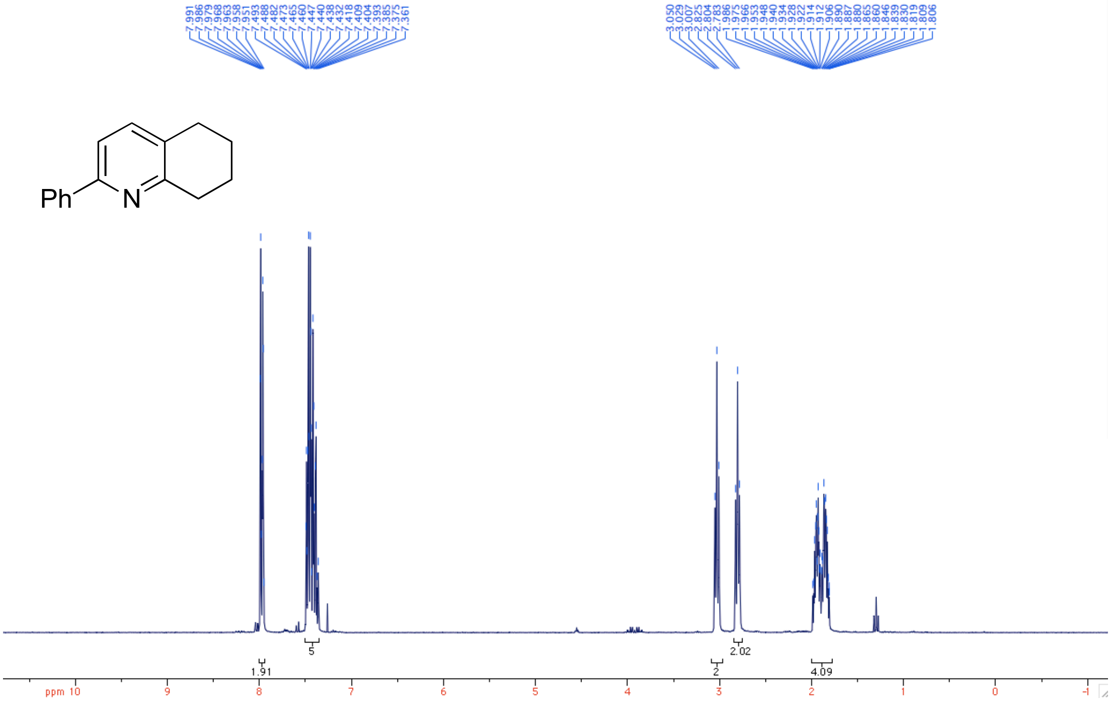


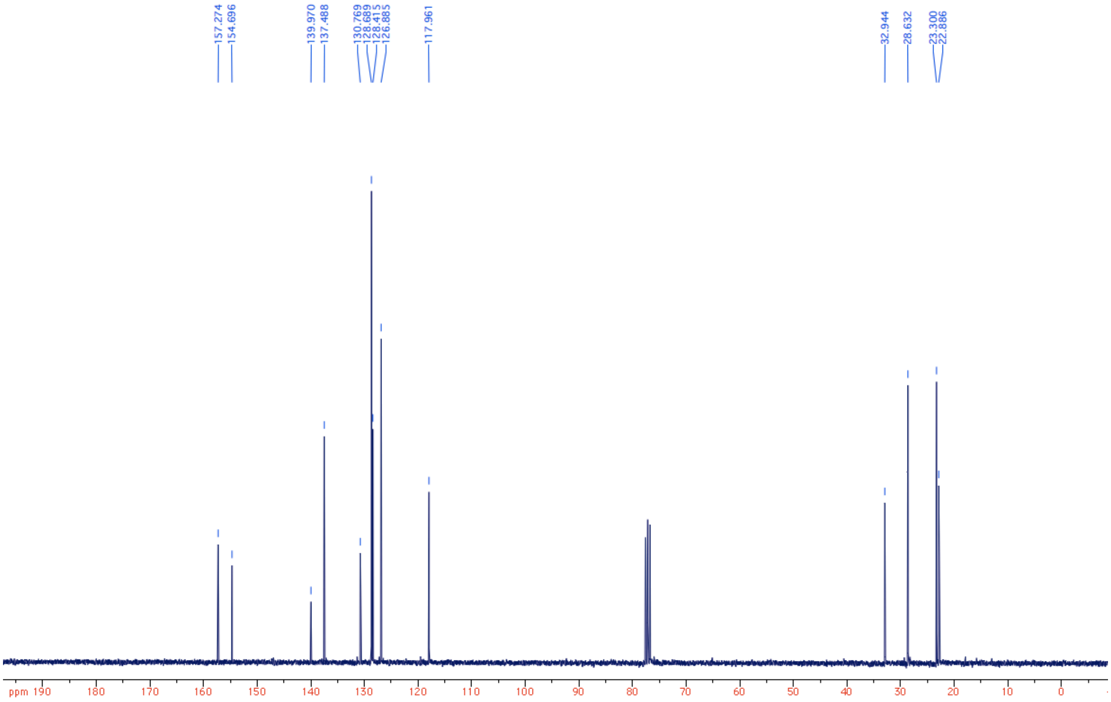
2-(3-Oxo-3-phenylpropyl)cyclohexanone



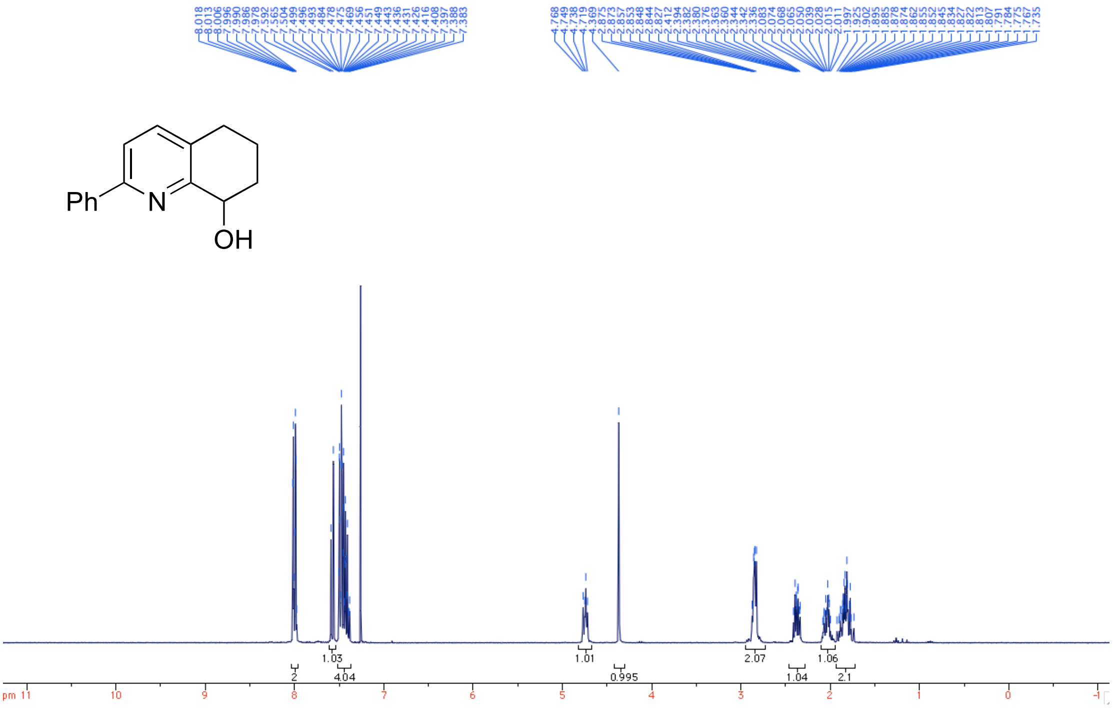


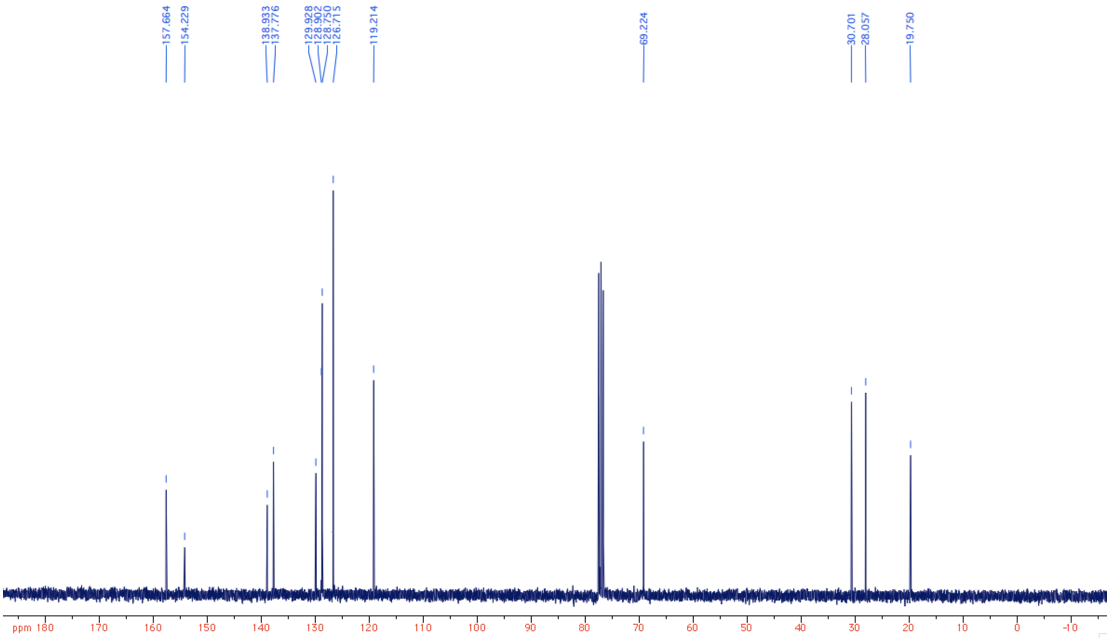
2-phenyl-5,6,7,8-tetrahydroquinoline



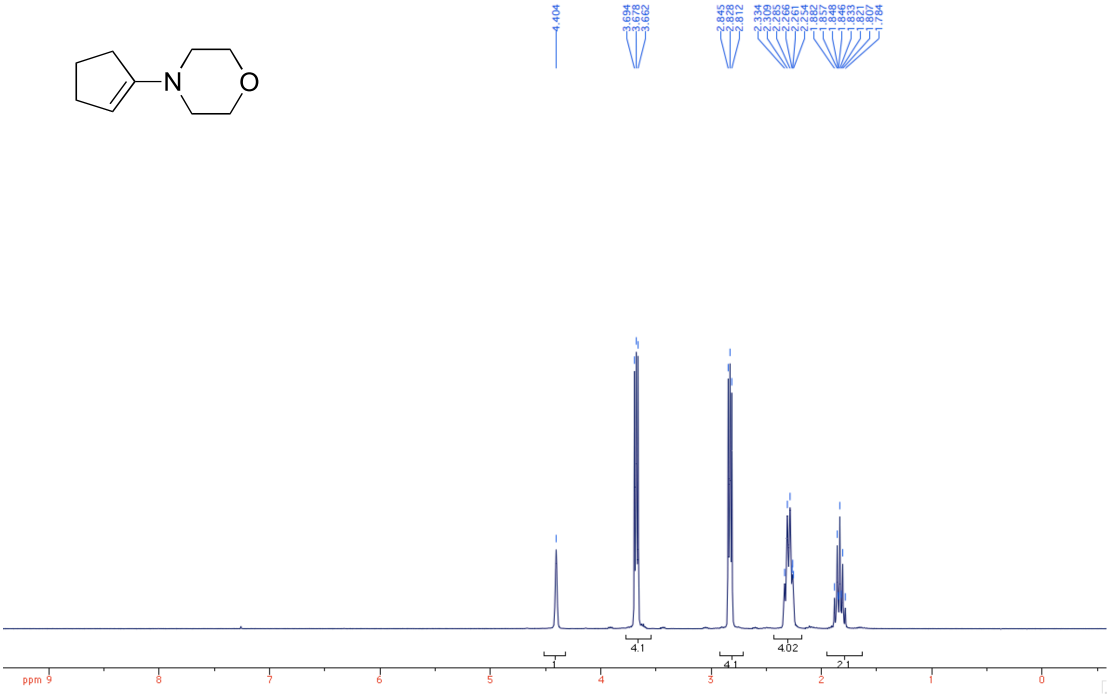


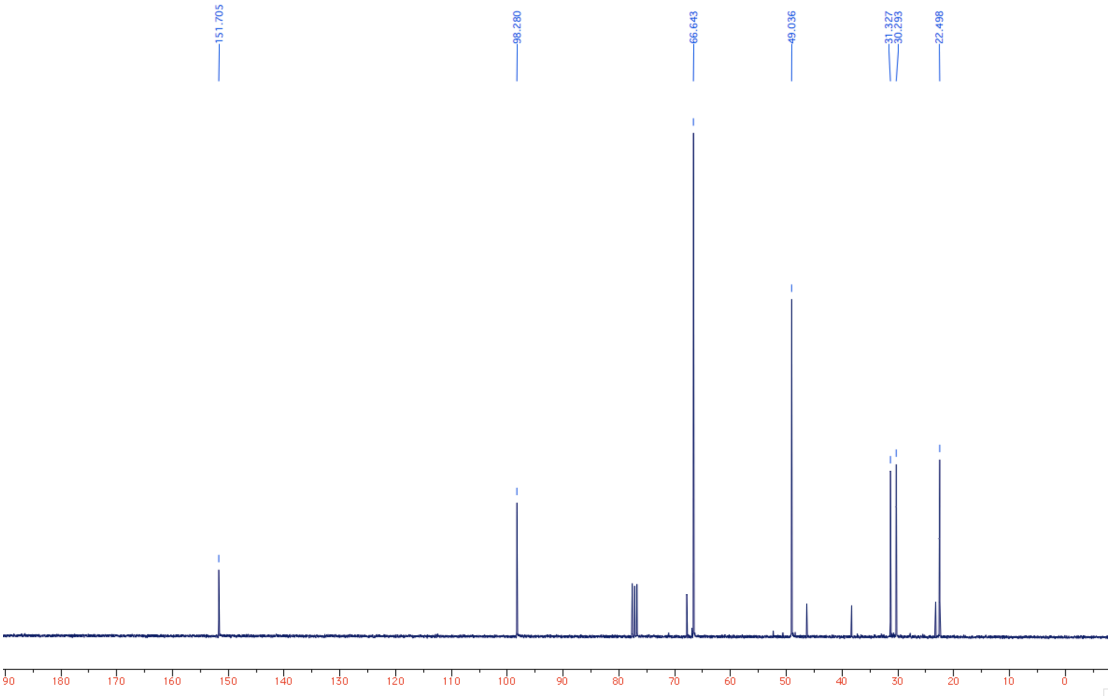
2-Phenyl-5,6,7,8-tetrahydroquinolin-8-ol (103e)



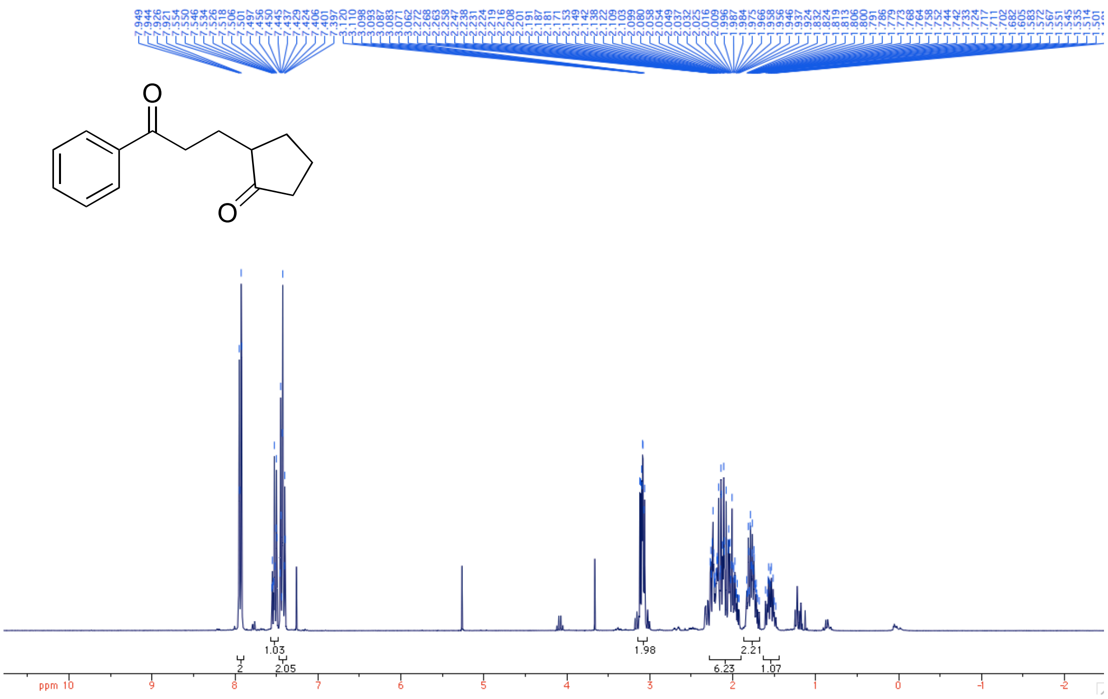


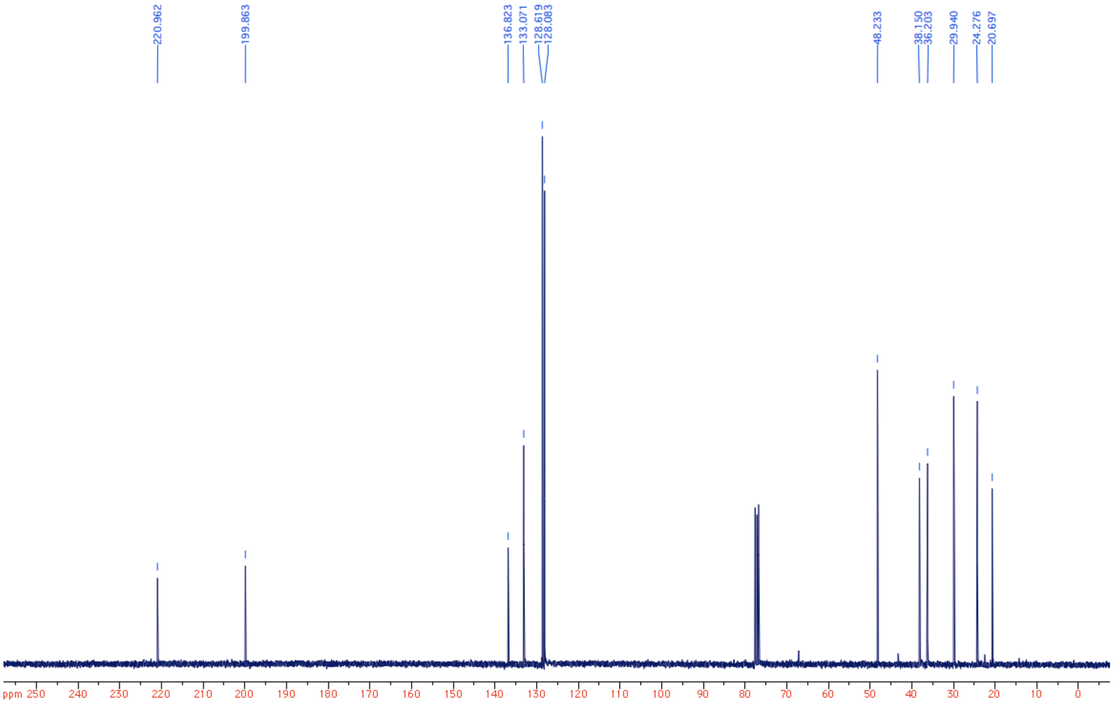
4-(Cyclopent-1-en-1-yl)morpholine



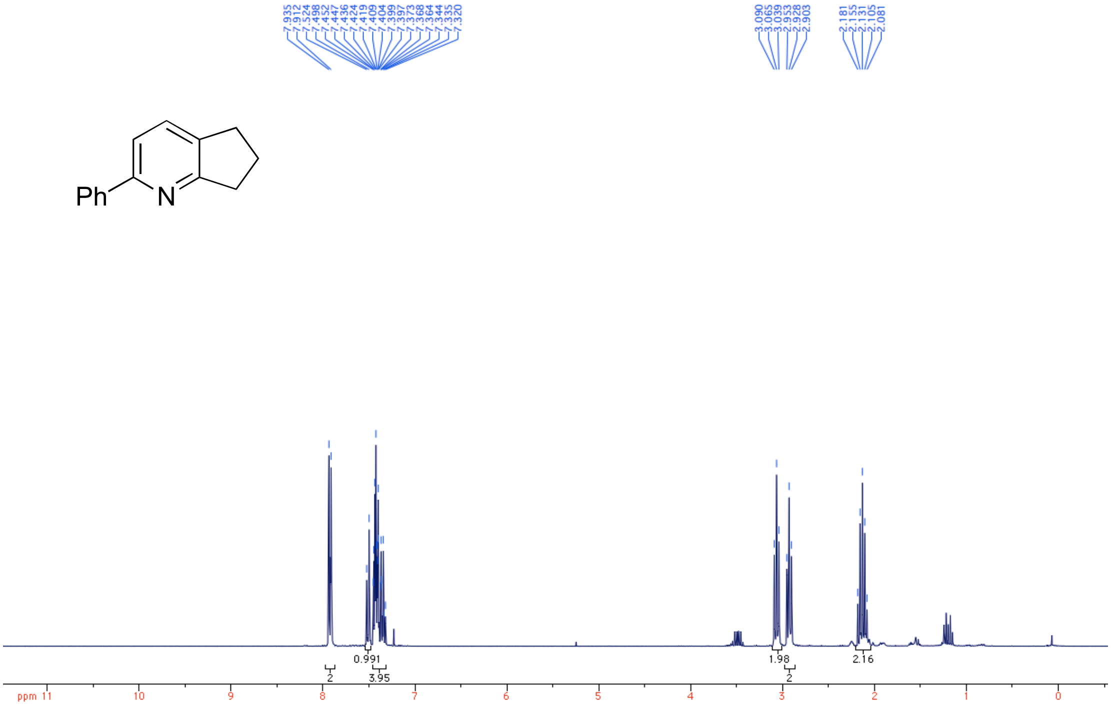


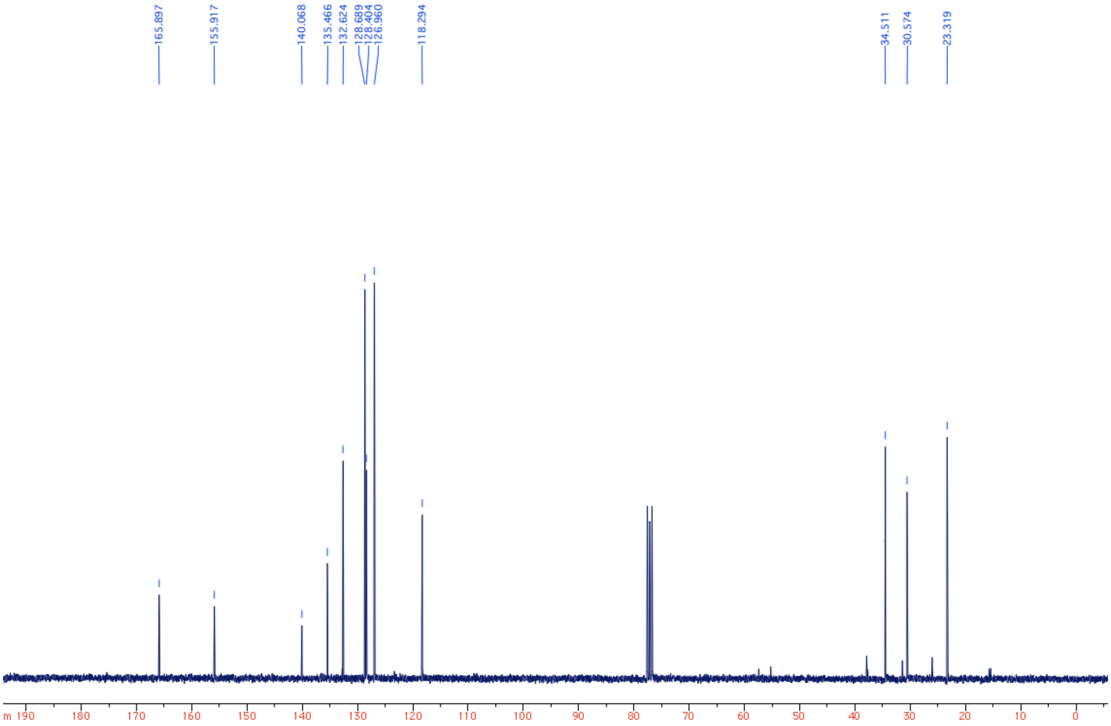
2-(3-Oxo-3-phenylpropyl)cyclopentanone



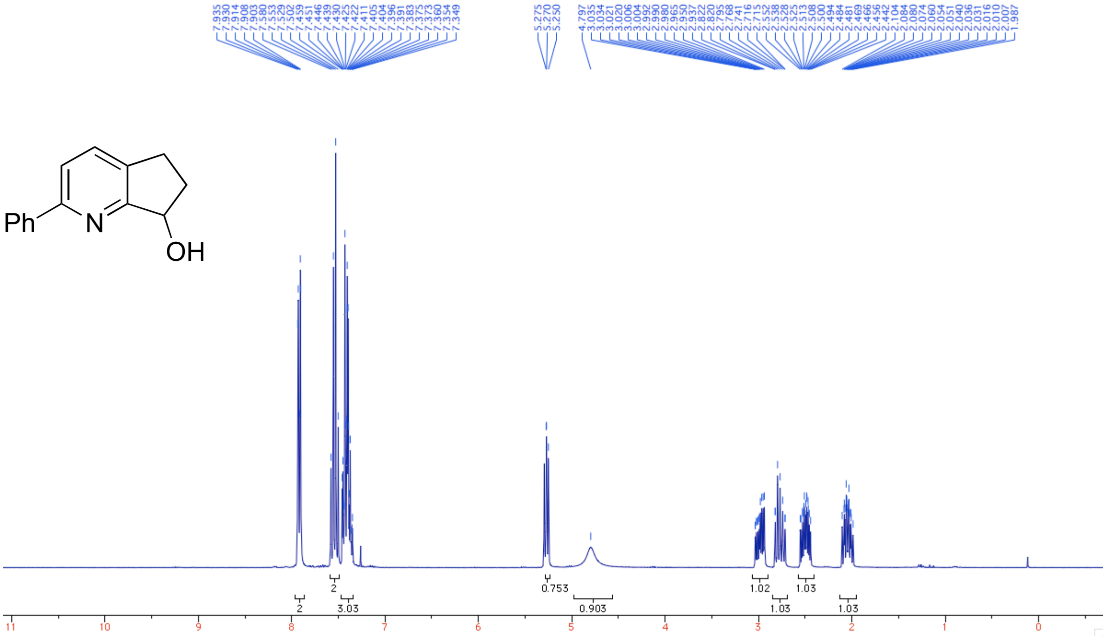


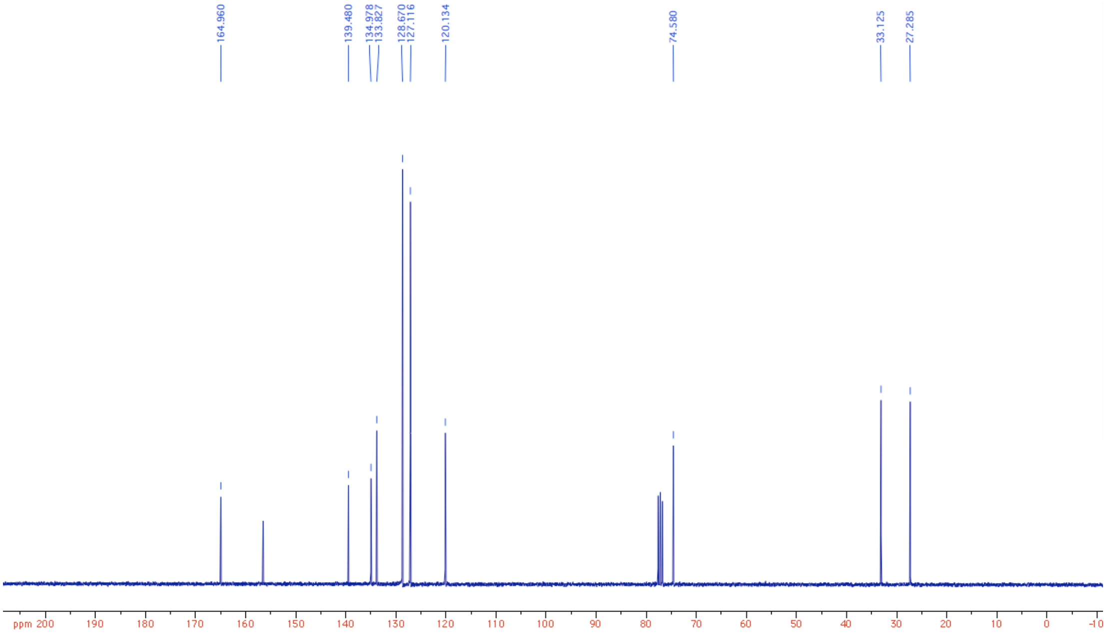
2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine



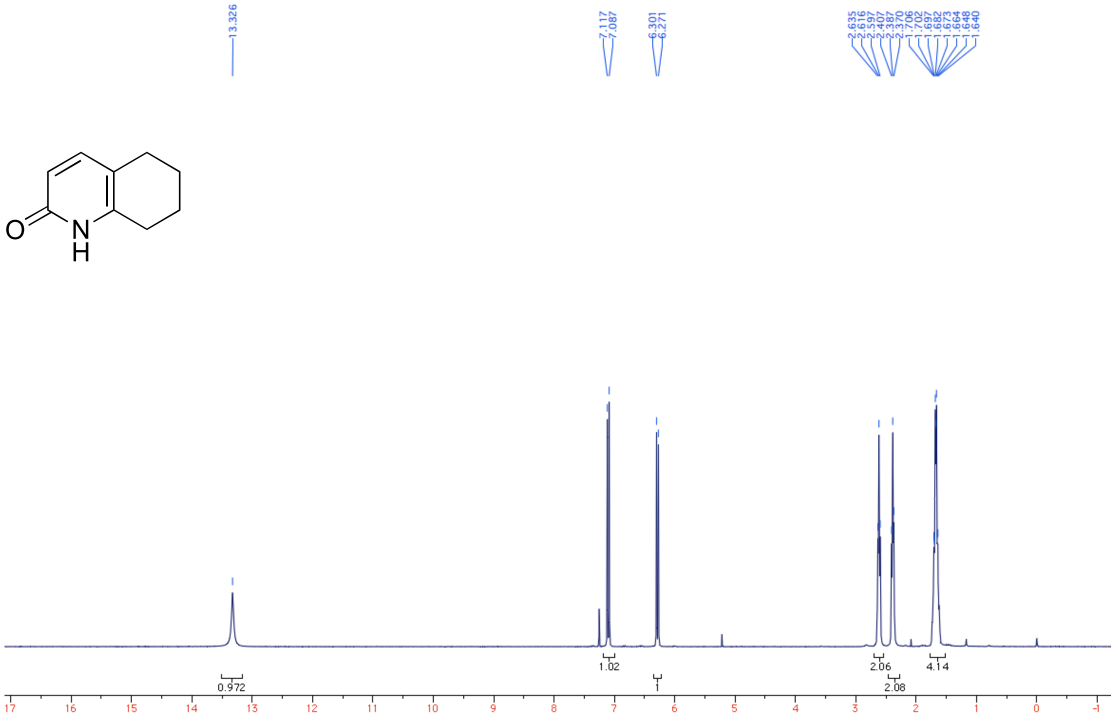


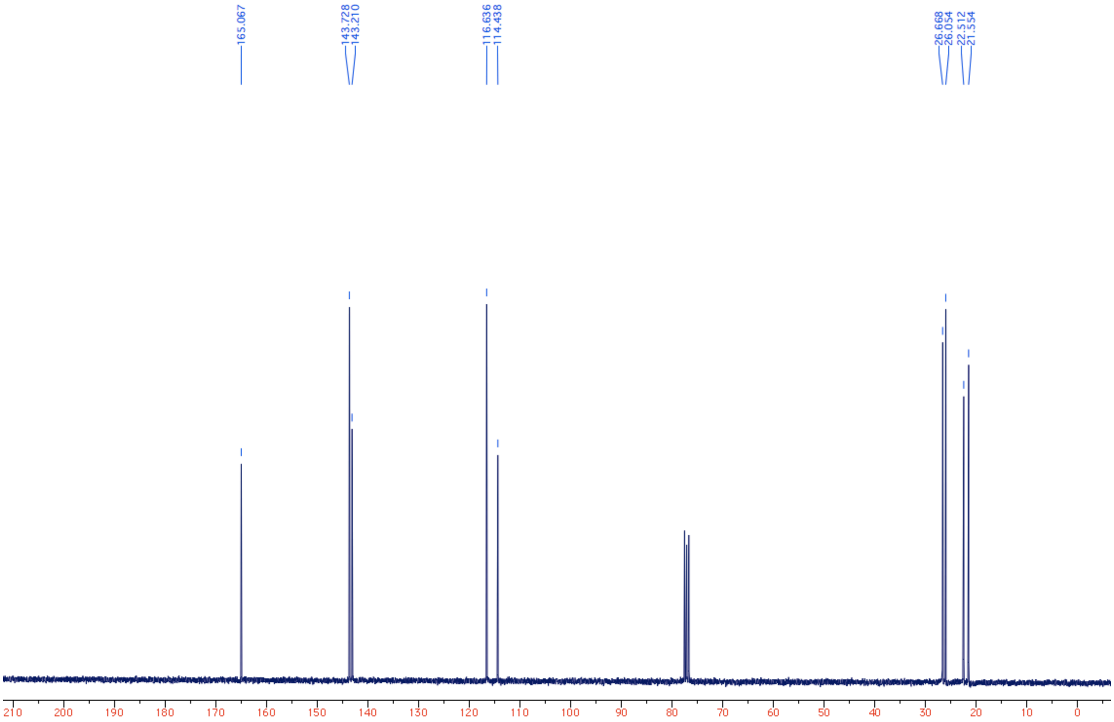
2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (103d)



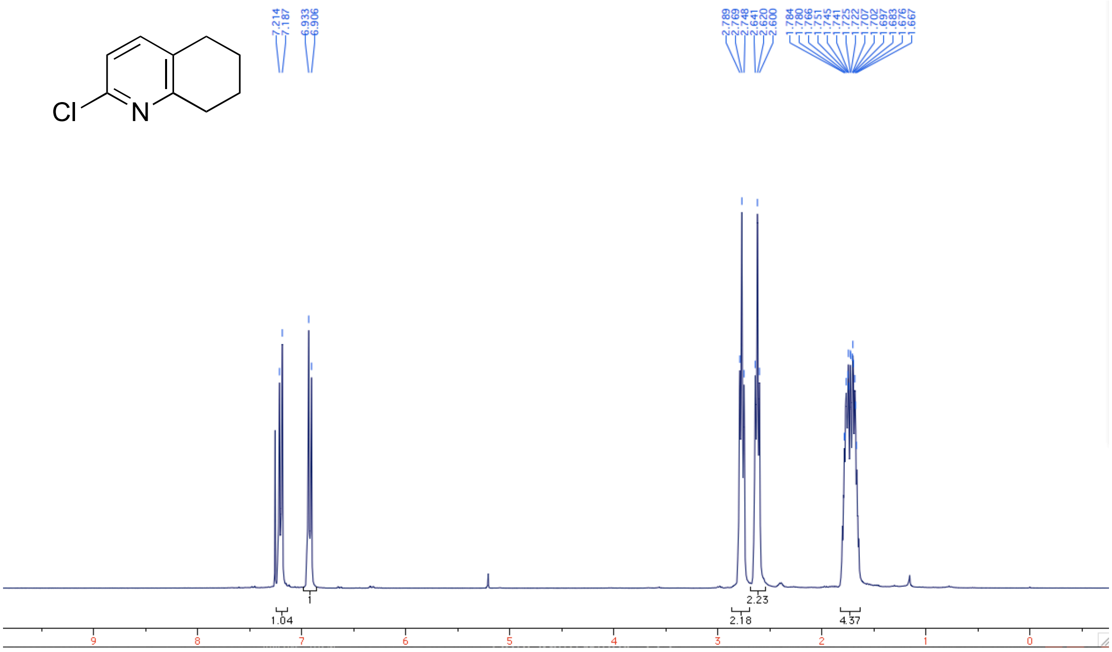


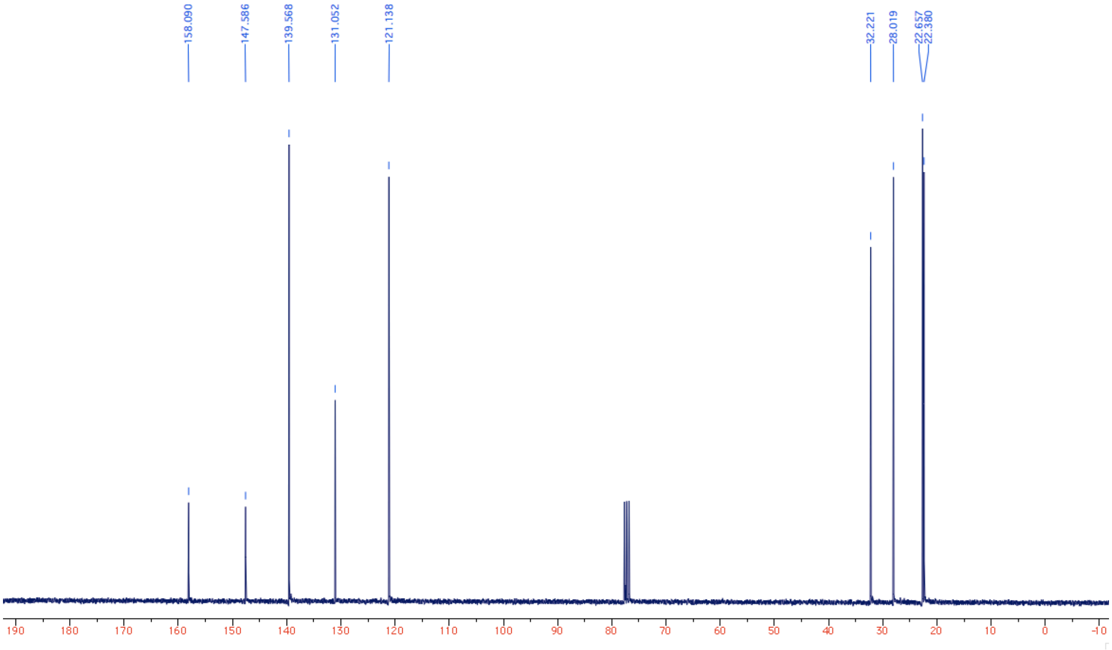
5,6,7,8-tetrahydroquinolin-2(1H)-one



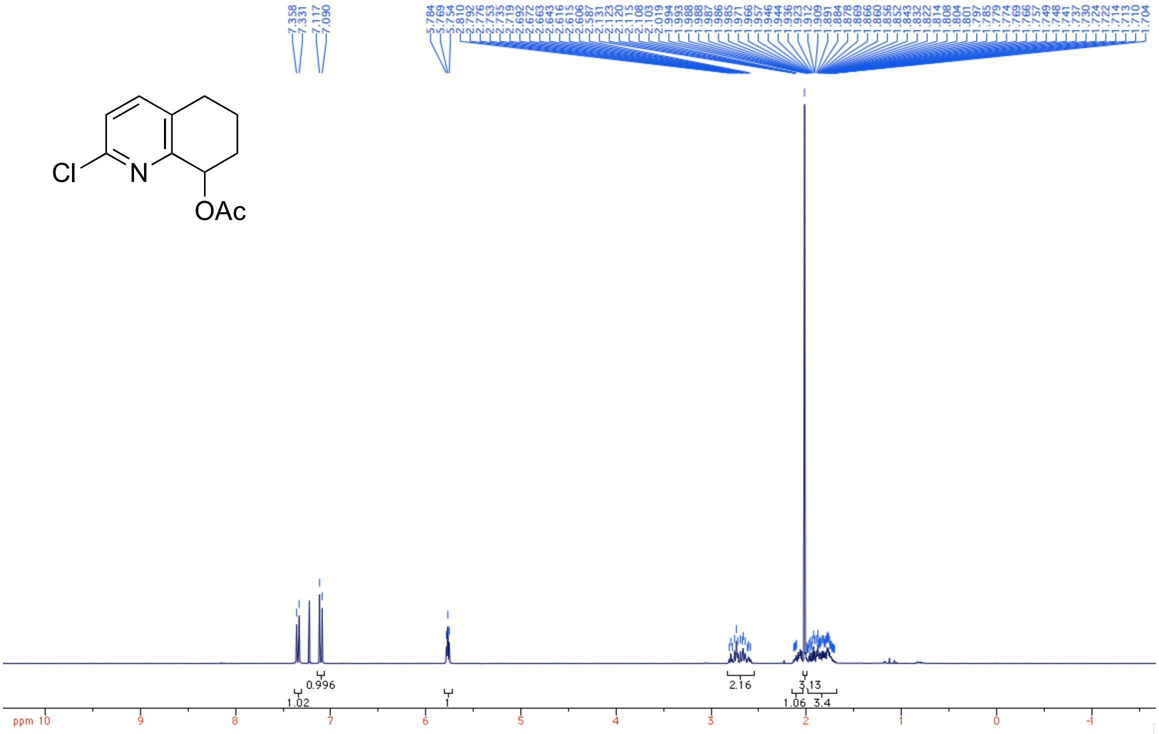


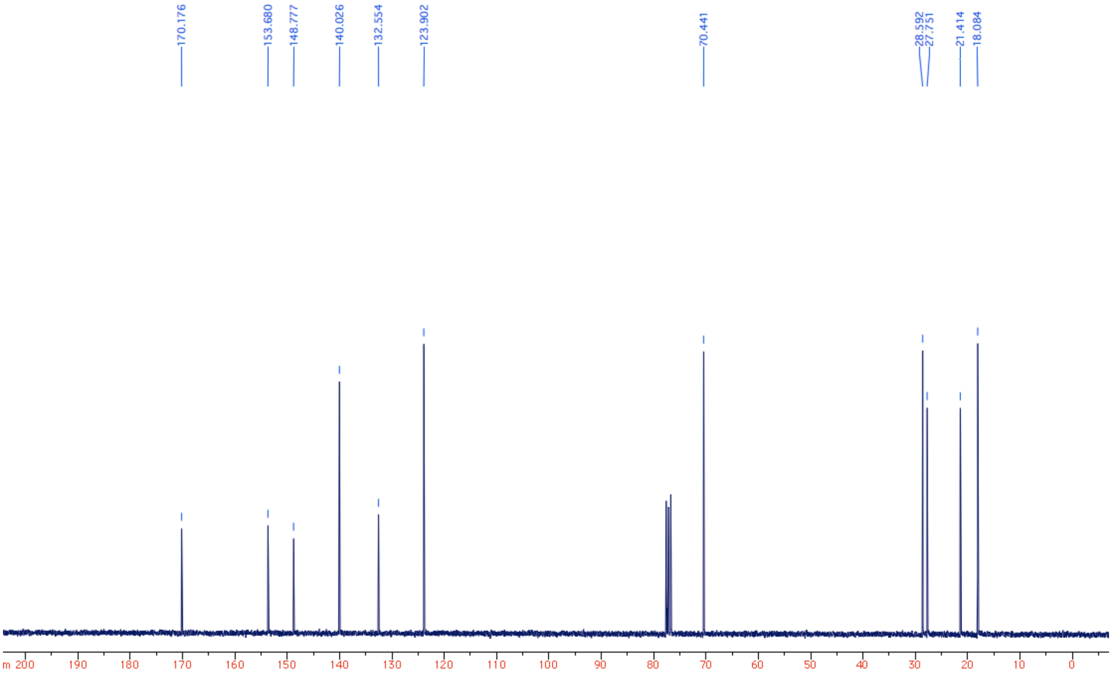
2-Chloro-5,6,7,8-tetrahydroquinoline



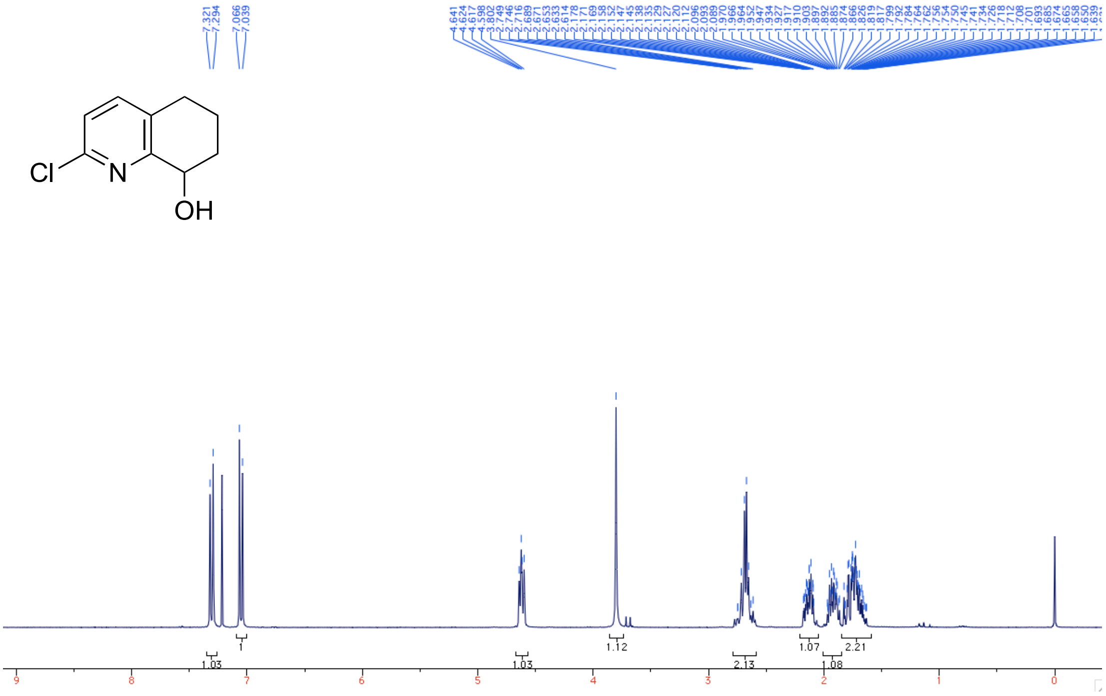


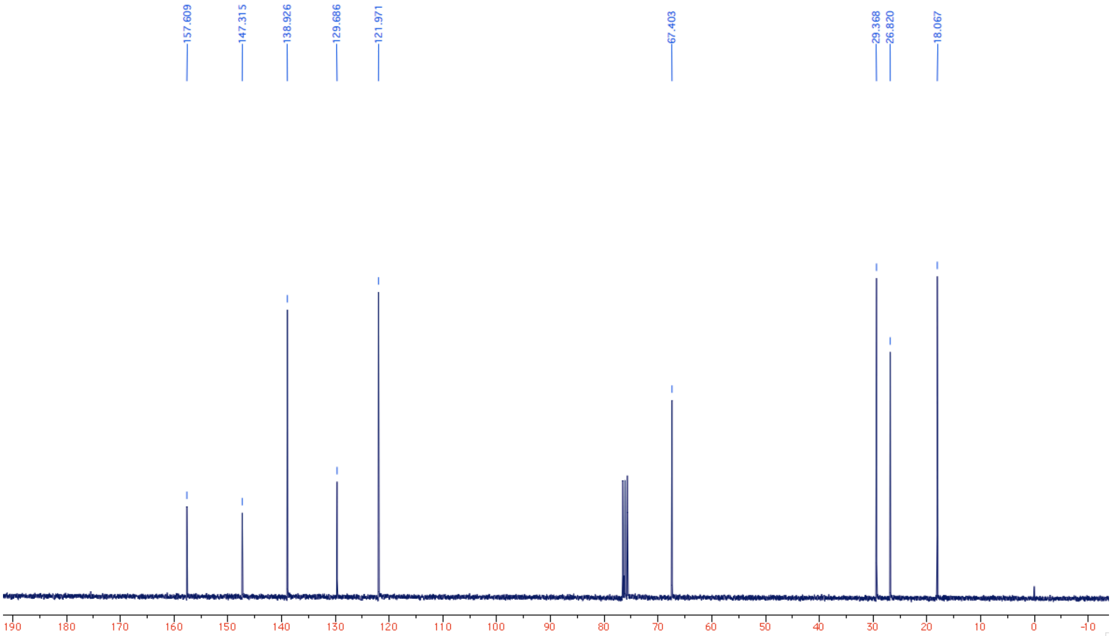
2-chloro-5,6,7,8-tetrahydroquinolin-8-yl acetate





2-Chloro-5,6,7,8-tetrahydroquinolin-8-ol (103f)





Acknowledgement

It gives me immense pleasure to express my deepfelt gratitude to my research supervisor Prof. Dr. Oliver Reiser for his constructive guidance, suggestions, support and freedom made me to inspire and move further in research carrier.

I would like to thank Prof. Dr. T. Palanivelu, Prof. M. Dhandapani and Prof. C. Rangasamy, Prof. Dr. V. Raghunathan, Kandhaswami Kander's College, for their excellent teaching during my bachelors and for being my inspiration of chemistry.

I deeply acknowledge Prof. Dr. P. C. Srinivasan, University of Madras. I am thankful to him for the opportunities he provided to learn research and excellent teaching during my masters. I am grateful to Prof. A. K. Mohanakrishnan, University of Madras, for his excellent teaching and personal guidance during my masters.

I warmly thank Prof. Dr. Burkhard König and Prof. Dr. Arno Pfitzner being the doctoral committee member for my thesis. I thank Prof. Dr. Armin Buschauer for being chairman in my thesis defense.

I am happy to express my sincere thanks to Dr. Peter Kreitmeier for his great support in ordering chemicals, technical supports, etc. I thank Dr. Petra Hilgers and Dr. Kirsten Zeitler for their valuable suggestions during my research.

I am thankful to Ms. Andrea Roithmeier for measuring my HPLC samples. I thank Mr. Georg Adolin, Mr. Klaus Dörig and Mr. Robert Tomahogh for their technical support. I would like to thank Mr. Hirtreiter, Mrs. Rotermund and Ms. Ohli for helping me in official work.

I thank my labmates Alexander Schätz, Ananta Karmakar and Olbrich Tobias for providing me an amicable atmosphere in the lab. My sincere and heartfelt thanks to all my friends, whose care, affection, sharing of knowledge and the funny times we had, I never forget. To name a few of them, Tapan, Ananta da, Senthil, Srinivas, Anu, Mouchumi, Sudipta, Woraluk, Chinna, Amilan, Muruganantham, Sushma, Arpita, Pritha, Deepak, Balakrishna

and Suva. I would like to thank Dr. Raja and his family, Laxmi and Rajeswari family, Prof. Latha and her family, Dr. Savitha and her family, Dr. Kumaran, Dr. Prabha, Akilandeswari, Parimala and Chandralekha has always been there for any personal and professional help.

I thank Dr. Burgermeister, Mr. Kastner, Ms. Schramm and Ms. Stühler for recording NMR spectra; Dr. Mayer, Mr. Keirmeier, Mr. Söllner and Mr. Wandinger for recording mass-spectra and elemental analysis.

None of this work would have been possible without the strong support of my mother (C. Palaniammal) and my late father (S. Chinnusamy) and brother (C. Chandrasekaran). I can't imagine a better environment in which to grow up. My parents have made so many sacrifices to get me where I am today, and I can't thank them enough for that. I thank my parents in law (Rasappan-Krishnaveni) and sister in law (Sasikala) for their love, encouragement and support.

I am grateful to Evonik-degussa for the financial support throughout my Ph.D period. I thank Prof. Dr. Leuchtenberger for his valuable suggestions and fellowship carrier.

Finally my heartfelt thanks to my dear husband Ramesh for his love, support, criticism and careful mentoring on every aspect of my work.

CURRICULUM VITAE

TAMILSELVI CHINNUSAMY

C/o Prof. Dr. Oliver Reiser
Institute of Organic Chemistry
University of Regensburg
D-93053, Regensburg, Germany
Tel.: +49-9419434647
Fax: +49-9419434121
tamilselvi.chinnusamy@chemie.uni-regensburg.de

B-15, Kallangadu st
Pandamagalam
Paramathi-Velur
Namakkal Dist,
Tamilnadu
India, Pin: 637208
Tel.: +91-4268230709
ctamilselvi@gmail.com

Education

Nov 2006-June 2010	Ph.D (Asymmetric Catalysis)	Institute of Organic Chemistry University of Regensburg D-93053, Regensburg, Germany
July 2004-Oct 2006	Research Associate	Department of Oncology Operation Dr.Reddy's Laboratories Ltd., Hyderabad, India.
June 2002-June 2004	M.Sc (Organic chemistry)	Department of Organic Chemistry University of Madras Chennai-26, India.
June 1999-April 2002	B.Sc (Chemistry)	Department of Chemistry Periyar University Namakkal, India

Awards/Fellowships and Recognitions

- **Ph.D** fellowship awarded by Evonik-Degussa Industries, Essen, Germany
- **GATE** (2004) **– 90.41** Percentiles awarded by IIT's and IISc
- **CSIR** (2004) – **JRF (Junior Research Fellowship)** awarded by Council of Scientific and Industrial Research

Research Experience

10/2006 – 06/2010	Ph.D thesis	Prof. Dr. Oliver Reiser (Chair of Inst.) Institute of Organic Chemistry **University of Regensburg, Germany**
07/2004 - 10/2006	Research Associate	Dr.P.V.Raghu Director, Department of Onology R&D Dr.Reddy's Laboratories Ltd., Hyderabad, India
06/2003- 06/2004	Master thesis	Prof. P. C. Srinivasan (Retired -Head of Dept.) Department of Organic Chemistry **University of Madras, India.**

Research Publications

3. **T**. **Chinnusamy**; Reiser, O., A recyclable TEMPO catalyst for the aerobic oxidation of sulfides to sulfoxides. *ChemSusChem,* **2010**, ***Accepted***.

2. **T**. **Chinnusamy**.; P. Hilgers.; Reiser, O., Recoverable and Recyclable Catalyst. *Chapter 4,* Catalysts Bound to soluble polymers, **2009**, 77-100.

1. A. Gheorghe, **T. Chinnusamy**, E. Cuevas-Yanez, P. Hilgers, O. Reiser, Combination of Perfluoroalkyl and Triazole Moieties: A New Recovery Strategy for TEMPO. *Org. Lett.* **2008**, *10*, 4171-4174.

Conference Posters

4. **T. Chinnusamy**, O. Reiser. "Fluorous Tag Clicked Tridentate Schiff Base V(O)Complex for Asymmetric Oxidation of α-Hydroxy Carbonyl Compounds Using O_2" in Heidelberg Forum of Molecular Catalysis at University of Heidelberg, 22nd June 2009, Germany.

3. **T. Chinnusamy**, O. Reiser. "Fluorous Tag Clicked Tridentate Schiff Base V(O)Complex for Asymmetric Oxidation of α-Hydroxy Carbonyl Compounds Using O_2" -2nd German-Indian Symposium on "*Frontiers of Chemistry"* at university of Leipzig, Sep 16th – 19th , Germany.

2. **T. Chinnusamy**, O. Reiser. "A novel fluorous tag immobilized tridentate Schiff base via Click chemistry for Asymmetric Sulfoxidation" -International 10-th Frühjahrssymposium in 2008 of the GDCh Younger Chemists Forum. March 27th - 29th March, 2008, Rostock, Germany.

1. **T. Chinnusamy**, A. Gheorghe, E. Cuevas-Yanez, O. Reiser. "Expedient Immobilization of TEMPO on Fluorous Tag and Polystyrene *via* Click Reaction and Its Catalytic Activity" in Heidelberg Forum of Molecular Catalysis at University of Heidelberg, 22nd June 2007, Germany.

Personal Details

DOB : 10/07/1982
Sex : Female
Nationality : Indian
Martial status : Married

References

Prof. Dr. Oliver Reiser
Institute of Organic Chemistry
University of Regensburg
D-93053, Regensburg, Germany
Tel.: +49-9419434631 (4630)
Fax: +49-9419434121
oliver.reiser@chemie.uni-regensburg.de

Prof. Dr. A. K. Mohanakrishnan
Department of Organic Chemistry
University of Madras
Chennai-25, India.
Phone: +91-44-2474665
rmohan_67@hotmail.com