Asymmetric Nucleophilic Catalysis with Planar-Chiral DMAP Derivatives and Chiral Phosphines: Synthetic and Mechanistic Studies

by

Sarah Yunmi Lee

B.S., Chemistry

Korea Advanced Institute of Science and Technology, 2009

Submitted to the Department of Chemistry
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Massachusetts Institute of Technology
[September 2014]
August 2014

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Department of Chemistry
August 18, 2014

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Abstract

Chapter 1 describes the development and detailed mechanistic investigation of the first non-enzymatic method for the dynamic kinetic resolution of secondary alcohols via enantioselective acylation, with acetyl isopropyl carbonate, through the use of a planar-chiral DMAP derivative (an acylation catalyst) in combination with a ruthenium complex (an alcohol-racemization catalyst).

Chapter 2 describes the development and detailed mechanistic investigation of the enantioselective synthesis of tertiary alkyl fluorides via the α-fluorination of ketenes catalyzed by a planar-chiral nucleophile with *N*-fluorodibenzenesulfonimide in the presence of sodium pentafluorophenoxide.

Chapter 3 describes the development and preliminary mechanistic study of the first asymmetric, phosphine-catalyzed intramolecular [3 + 2] cycloadditions of allenes with alkenes that furnish an array of diastereomerically pure bicyclic compounds bearing two or three contiguous tertiary / quaternary stereocenters.

Thesis Supervisor: Professor Gregory C. Fu
Title: Altair Professor of Chemistry, California Institute of Technology

Preface

Portions of this thesis have appeared in the following publications:

Enantioselective Nucleophile-Catalyzed Synthesis of Tertiary Alkyl Fluorides via the α-Fluorination of Ketenes: Synthetic and Mechanistic Studies
J. Am. Chem. Soc. **2014**, *136*, 8899–8902.
Lee, S. Y.; Neufeind, S.; Fu, G. C.

Nonenzymatic Dynamic Kinetic Resolution of Secondary Alcohols via Enantioselective Acylation: Synthetic and Mechanistic Studies
J. Am. Chem. Soc. **2012**, *134*, 15149–15153.
Lee, S. Y.; Murphy, J.; Ukai, A.; Fu, G. C.

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Finally, this thesis is dedicated to the memory of my beloved father Dr. In-Soo Lee. I have yet to fill my father's shoes but here I am taking another step.

Table of Contents

Chapter 1.

Non-Enzymatic Dynamic Kinetic Resolution of Secondary Alcohols via Enantioselective Acylation

1.1 Introduction

Due to the ubiquity of the secondary carbinol subunit,[1] the development of efficient methods for its enantioselective synthesis has been the target of substantial effort.[2] One of the more widely used approaches to access enantioenriched secondary carbinols, especially in industry, is via a kinetic resolution wherein two enantiomers of a racemic substrate react at different rates to form a product that may or may not be chiral, thereby creating an excess of the slower-reacting enantiomer (Figure 1.1).[3,4] As a result, the ee of starting material and product (if the product is chiral) changes as a function of conversion. A key parameter to express the efficiency of the kinetic resolution is the selectivity factor (s), which is the ratio of the rate constants for the two enantiomers. Under most circumstances, a selectivity factor greater than 10 is required in order for a kinetic resolution to be syntheticaully useful; with the selectivity factor of 10, one can achieve 98% ee of the substrate at 70% conversion.

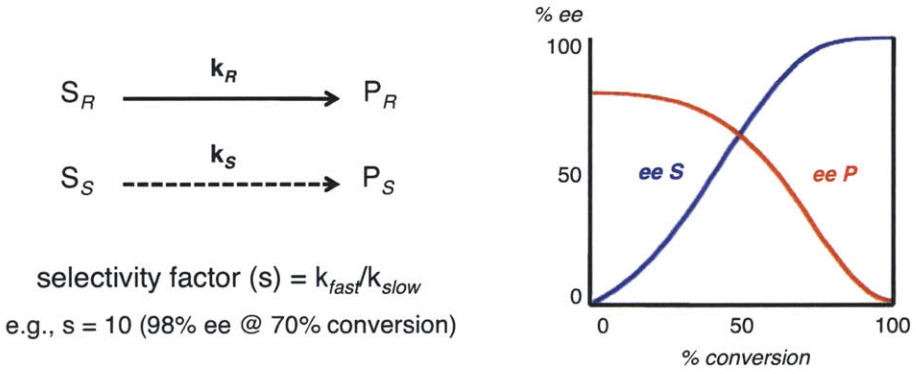

Figure 1.1. Kinetic resolution

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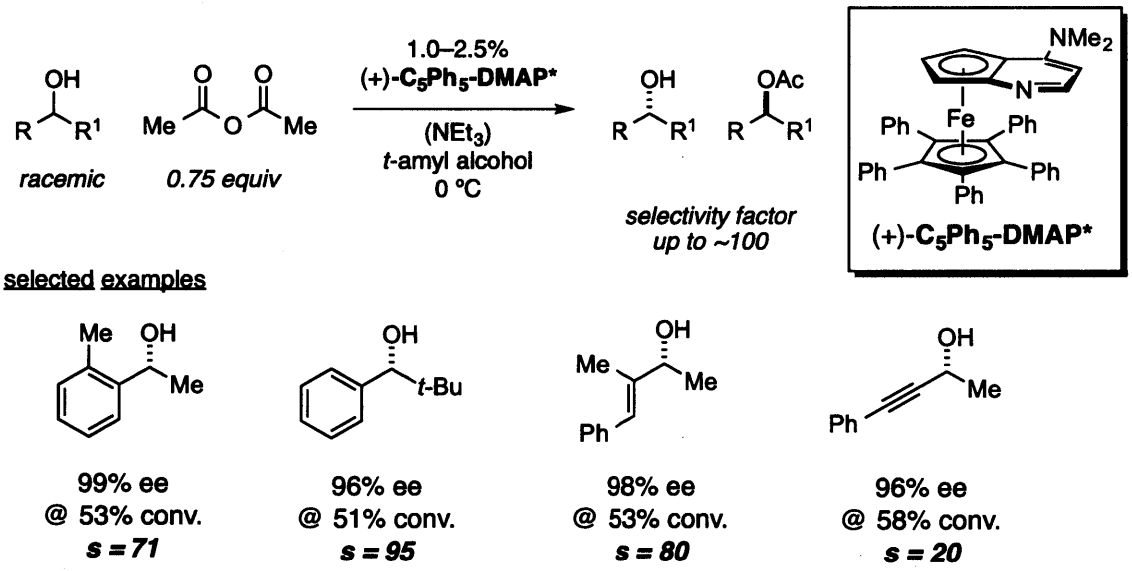
[1] For example, see: *Atorvastatin in the Management of Cardiovascular Risk: From Pharmacology to Clinical Evidence*; Grundy, S., Ed.; Kluwer: Auckland, New Zealand, 2007.

[2] For example, see: *Science of Synthesis, Stereoselective Synthesis*; Molander, G. A., Ed.; Thieme: New York, 2011; Vol. 2.

[3] For leading references on enzymatic resolution, see: (a) Fischer, T.; Pietruszka, J. *Top. Curr. Chem.* **2010**, *297*, 1–43. (b) *Asymmetric Catalysis on Industrial Scale*; Blaser, H.-U., Federsel, H.-J., Eds.; Wiley–VCH: New York, 2010. (c) Pollard, D.; Kosjek, B. In *Organic Synthesis with Enzymes in Non-Aqueous Media*; Carrea, G., Riva, S., Eds.; Wiley–VCH: New York, 2008; pp 169–188.

[4] For reviews on kinetic resolution, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *1*, 5–26.

In early studies, our group established that a planar-chiral derivative of 4-(dimethylamino)pyridine (**C_5Ph_5-DMAP***)[5] serves as an efficient acylation catalyst for the kinetic resolution of a variety of aryl alkyl carbinols,[6] propargylic alcohols,[7] and allylic alcohols[8] via acylation with acetic anhydride, providing selectivity factors up to ~100 (eq 1.1.1).[9] The enantioselectivity of our kinetic resolution turns out to be highly dependent on solvent,[6b] and the optimal solvent for this process is the tertiary alcohol, *tert*-amyl alcohol. Additionally, this process achieves high selectivity at 0 °C. A key intermediate in this kinetic resolution is believed to be the N-acylated catalyst (**1.1**) generated by the reaction of **C_5Ph_5-DMAP*** and acetic anhydride, which serves as an electrophilic chiral acylating agent (Figure 1.2).[10]



(1.1.1)

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[5] Both enantiomers of **C_5Ph_5-DMAP*** are commercially available.

[6] (a) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492–1493. (b) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794–2795. (c) For an application of this method, see: Chen, Y.-H.; McDonald, F. E. *J. Am. Chem. Soc.* **2006**, *128*, 4568–4569.

[7] Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091–5092.

[8] Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009–1010. For a recent application of this method, see: Francais, A.; Leyva, A.; Etxebarria-Jardi, G.; Ley, S. V. *Org. Lett.* **2010**, *12*, 340–343.

[9] For a rewiew on non-enzymatic kinetic resolutions of alcohols, see: Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613–1666.

[10] For X-ray structural analysis of N-acylated **C_5Ph_5-DMAP***, see ref 7.

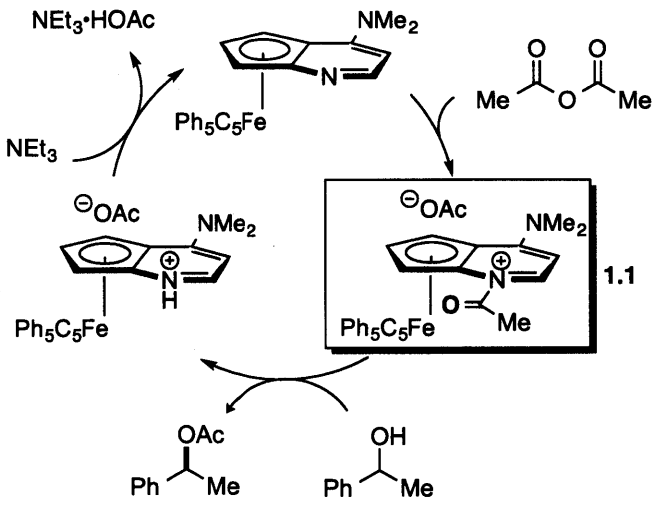

Figure 1.2. Outline of the mechanism for the kinetic resolution of 1-phenylethanol catalyzed by **C_5Ph_5-DMAP***

Although kinetic resolution is a useful method for the preparation of enantiomerically enriched compounds, it has the intrinsic limitation that the maximum theoretical yield is 50%. A powerful strategy to overcome this limitation is dynamic kinetic resolution (DKR), in which kinetic resolution is combined with racemization of the substrate (Figure 1.3).[11] DKR is an example of a Curtin-Hammett system in which the composition of products is controlled by the free energies of the transition states if reactants interconvert rapidly relative to the rate of product formation. This approach allows for the stereoconvergent transformation of both enantiomers of a racemic substrate into a single enantiomer of product. For a successful and efficient DKR, the reaction conditions for kinetic resolution must be compatible with the racemization process, and the racemization must be rapid relative to conversion of the slower-reacting enantiomer to product.

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[11] (a) Pellissier, H. *Chirality from Dynamic Kinetic Resolution;* Royal Society of Chemistry: Cambridge, 2011. (b) Pellissier, H. *Tetrahedron* **2011**, *67*, 3769–3802.

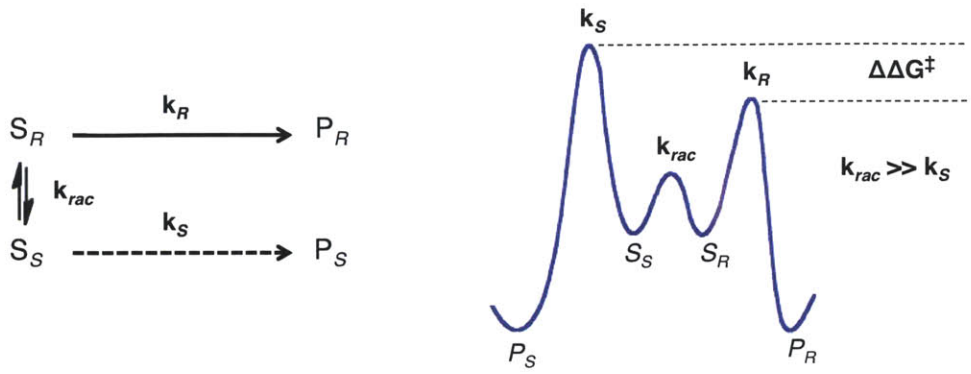

Figure 1.3. Dynamic kinetic resolution

Chemoenzymatic DKR of secondary alcohols, consisting of enzyme-catalyzed kinetic resolution and metal-catalyzed racemization, is one of the most popular approaches for achieving DKR.[12] Enzymes, especially lipases, have long been utilized to catalyze either the hydrolysis of esters or the acylation of alcohols with high selectivity.[12] In 1996, Williams reported the first example of chemoenzymatic DKR, via enantioselective acylation, employing vinyl acetate as an acylating agent.[13] A lipase (an acylation catalyst) and $Rh_2(OAc)_4$ (a racemization catalyst) cooperated to catalyze the DKR of 1-phenylethanol. Following this study, a variety of transition-metal complexes have been combined with enzymes for the DKR of secondary alcohols; ruthenium complexes are most commonly applied as alcohol-racemization catalysts (Figure 1.4).[12,14]

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[12] For reviews and leading references, see: (a) Martín-Matute, B.; Bäckvall, J. E. *Asymmetric Organic Synthesis with Enzymes*; Gotor, B., Alfonso, I., Garcia-Urdiales, E., Eds.; Wiley–VCH: New York, 2008; pp 89–113. (b) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999–1015.

[13] Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1996**, *37*, 7623–7626.

[14] For a review of racemization catalysts for the DKR of alcohols and amines, see: Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. *Coord. Chem. Rev.* **2008**, *252*, 647–658.

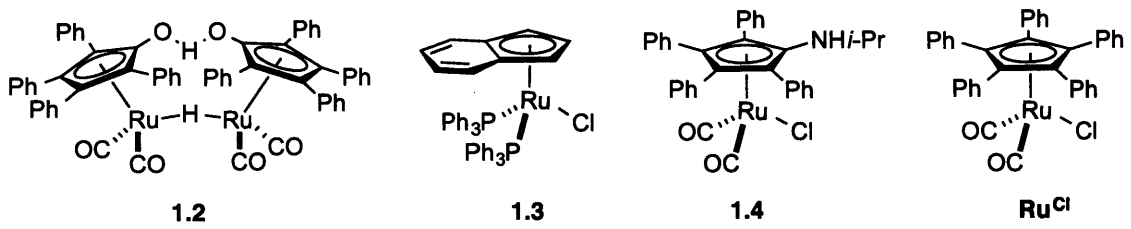
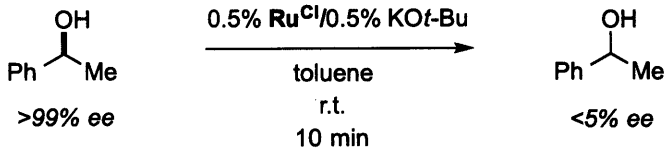


Figure 1.4. Examples of ruthenium complexes for alcohol racemization

While ruthenium complexes **1.2** (Shvo's catalyst) and **1.3** require elevated temperature (60–70 °C) for activation, ruthenium complex **1.4** and $\mathbf{Ru}^{Cl}$ can catalyze rapid alcohol racemization at *room temperature* after being activated by KO*t*-Bu.[14] For example, Bäckvall demonstrated that the racemization of enantiopure 1-phenylethanol in toluene was complete within 10 min at room temperature in the presence of 0.5% of $\mathbf{Ru}^{Cl}$ and KO*t*-Bu (eq 1.1.2).[15] Subsequently, Bäckvall established that this racemization process is compatible with enantioselective enzyme-catalyzed acylation of a wide range of secondary alcohols, including aryl alkyl carbinols, allylic alcohols, aliphatic alcohols, and diols, with excellent functional-group tolerance (eq 1.1.3).[16] Despite the wide substrate scope, chemoenzymatic DKR's, including DKR's with other racemization catalysts, are only effective for substrates featuring non-branched alkyl substituents in the case of aryl alkyl carbinols.[12]



(1.1.2)

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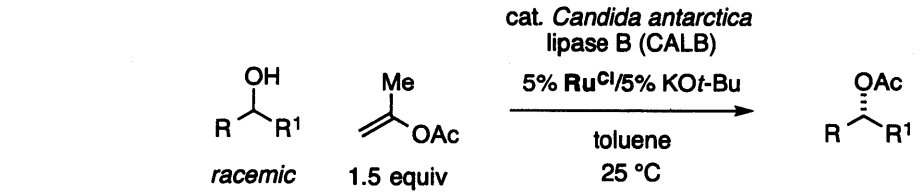
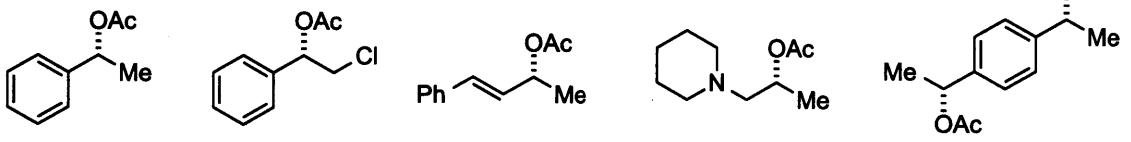
[15] Csjernyik, G.; Bogár, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2004**, *45*, 6799–6802.

[16] (a) Martín-Matute, B.; Edin, M; Bogár, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 6535–6539. (b) Martín-Matute, B.; Edin, M; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825.



(1.1.3)

selected examples



>99% ee
98% yield

>99% ee
83% yield

99% ee
89% yield

>99% ee
99% yield

>99% ee
94% yield
(with 3 equiv of
isopropenyl acetate)

A proposed pathway for alcohol racemization catalyzed by $\mathbf{Ru^{Cl}}$/KO*t*-Bu that accommodates the available mechanistic data is illustrated in Figure 1.5.[17] Initially, ruthienium *tert*-butoxide **1a**, an active racemization catalyst, is generated in situ from $\mathbf{Ru^{Cl}}$ and KO*t*-Bu through an acyl intermediate. This active complex (**1a**) then reacts with 1-phenylethanol in a ligand exchange to form another ruthenium alkoxide (**1b**). Subsequent CO dissociation, followed by β-hydride elimination, produces the ketone-hydride complex (**1c**), in which the ketone remains coordinated until it is reduced by the hydride from either face to give the racemic alkoxide (**1d**) with concomitant CO association. 1-Phenylethanol is then released by another alcohol-alkoxide exchange.

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[17] For mechanistic details of racemization by $\mathbf{Ru^{Cl}}$/KO*t*-Bu, see: (a) ref 16. (b) Nyhlén, J.; Privalov , T.; Bäckvall, J.-E. *Chem. Eur. J.* **2009**, *15*, 5220–5229. (c) Åberg, J. B.; Nyhlén, J.; Martín-Matute, B.; Privalov , T.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2009**, *131*, 9500–9501. (d) Warner, M. C.; Verho, O.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2011**, *133*, 2820–2823.

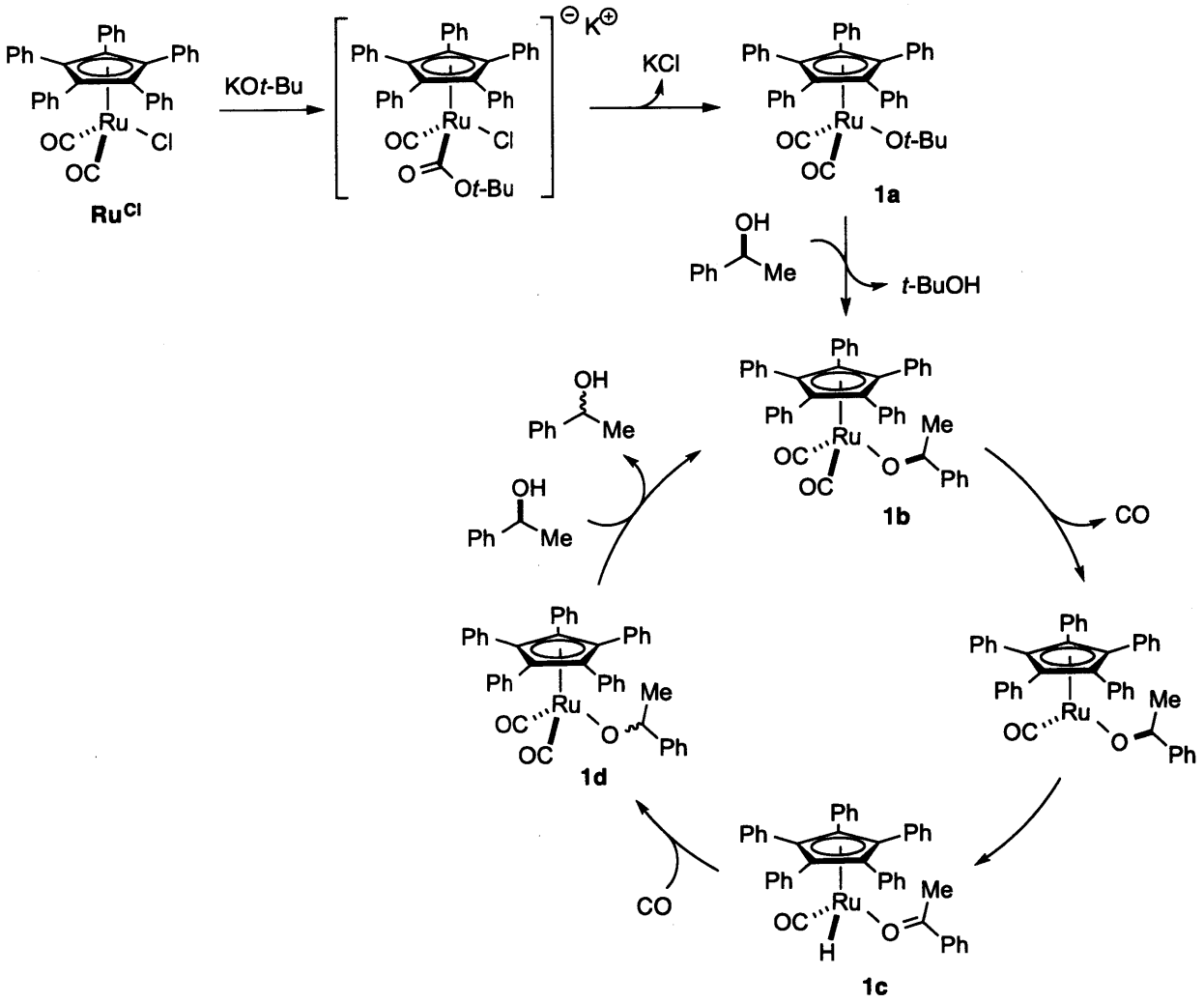

Figure 1.5. A proposed mechanism for the racemization of 1-phenylethanol catalyzed by **Ru^{Cl}**/KO*t*-Bu

Although impressive progress has been described for DKR's that involve enzyme-catalyzed acylations,[12] there was no precedent for non-enzymatic methods. Inspired by Bäckvall's discovery of a ruthenium catalyst that rapidly racemizes secondary alcohols at room temperature,[15,16] we sought to develop a non-enzymatic DKR of secondary alcohols by combining this alcohol-racemization process with our

planar-chiral DMAP derivative (**C_5Ph_5-DMAP***)-catalyzed kinetic resolution of secondary alcohols through acylation, which is most efficient at 0 °C (eq 1.1.1).[18]

1.2 Results and Discussion

We first set out to determine whether the racemization of 1-phenylethanol catalyzed by **Ru^{Cl}**/KO*t*-Bu is compatible with the reaction conditions for our kinetic resolution processes. In general, toluene was used as the solvent for **Ru^{Cl}**/KO*t*-Bu-catalyzed alcohol racemization (eq 1.1.3 and 1.1.4), whereas *tert*-amyl alcohol was the optimal solvent for kinetic resolutions catalyzed by **C_5Ph_5-DMAP*** (eq 1.1.1). In fact, ruthenium *tert*-butoxide **1a** (generated in situ from **Ru^{Cl}** and KO*t*-Bu) in toluene-d_8 reacts with 1 equivalent of *tert*-amyl alcohol in an alkoxide-ligand exchange at room temperature to create a mixture of **1a** and **1e** (~1:1) (eq 1.2.1).[19] When *tert*-amyl alcohol/toluene-d_8 (1:1) was used as the solvent for the reaction of **Ru^{Cl}** with KO*t*-Bu, a mixture of **Ru^{Cl}** and ruthenium alkoxides (**1a** and **1e**) was observed; the higher solubility of KCl in *tert*-amyl alcohol compared to toluene likely changes the equilibrium between ruthenium *tert*-butoxide **1a** and **Ru^{Cl}**/KO*t*-Bu. Therefore, one could envision that utilizing *tert*-amyl alcohol as the solvent might inhibit the ruthenium *tert*-butoxide **1a**-catalyzed racemization of secondary alcohols. We have, however, determined that racemization of 1-phenylethanol proceeds smoothly in *tert*-amyl alcohol even at 0 °C (eq 1.2.2) and that planar-chiral DMAP derivative **C_5Ph_5-**

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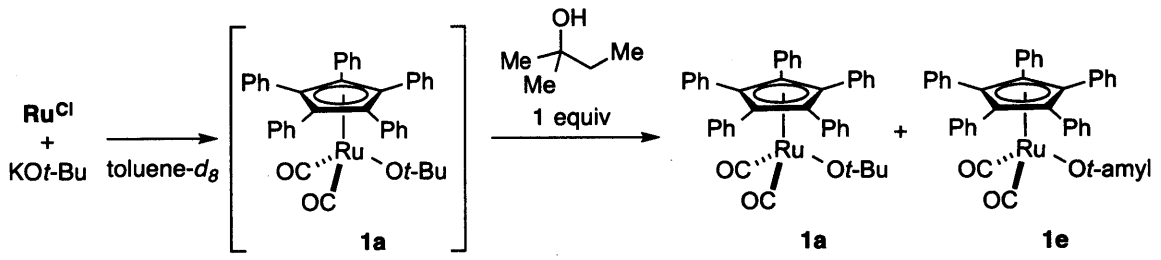
[18] This work is a collaborative effort between Dr. Jaclyn Murphy, Dr. Atsushi Ukai, Dr. Gerald Rowland, and the author. Dr. Ukai initiated the project, and Dr. Murphy made a significant contribution to the optimization of the reaction conditions. The author identified the final reaction conditions and performed all the mechanistic investigations. The author carried out all the experiments presented in this chapter.

[19] In ref 16b, Bäckvall also mentioned that ruthenium *tert*-butoxide **1a** reacts rapidly with 1 equiv of *tert*-amyl alcohol in the alkoxide-ligand exchange to form a mixture of **1a** and **1e** (at either –40 °C or 10 °C).

DMAP* is compatible with the racemization process.[20] Additionally, there was no detectable interaction between the planar-chiral DMAP complex and ruthenium complexes[21] in the ^{1}H NMR spectrum of a mixture of **Ru^{Cl}**, KO*t*-Bu, 1-phenylethanol, and **C_5Ph_5-DMAP*** in *tert*-amyl alcohol / toluene-d_8 (1:1).



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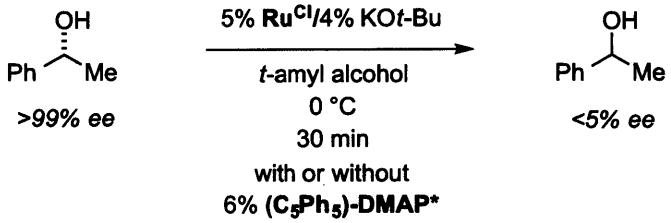

(1.2.2)

Unfortunately, when we applied the conditions that we had found to be optimal for the kinetic resolution of secondary alcohols (eq 1.1.1) to the DKR of 1-phenylethanol in the presence of **Ru^{Cl}**/KO*t*-Bu,[22] it became clear that the ruthenium racemization catalyst is not compatible with our acylation process (eq 1.2.3); at partial conversion, the

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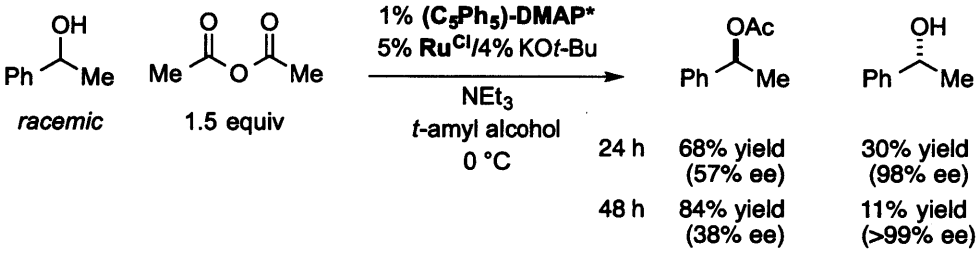
[20] We employ a small excess of **Ru^{Cl}** in order to decrease the likelihood that adventitious KO*t*-Bu will have a deleterious impact on our DKR's by facilitating a Brønsted base-mediated non-enantioselective acylation.

[21] **Ru^{Cl}**, KO*t*-Bu, and 1-phenylethanol in *tert*-amyl alcohol/toluene-d_8 (1:1) generate a mixture of **Ru^{Cl}** (trace), **1a**, **1e**, and another ruthenium alkoxide derived from 1-phenylethanol (major) at room temperature.

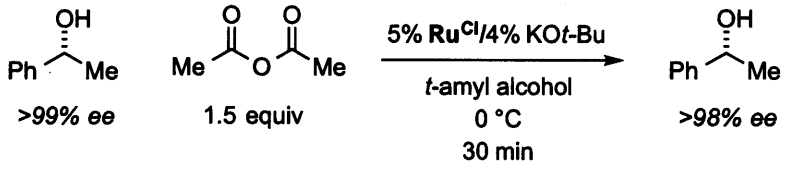
[22] The selectivity factor for the kinetic resolution of 1-phenylethanol under the conditions described in eq 1.1.1 is 43 (99% ee at 55% conversion, after 23.5 hours; see ref 6b).

unreacted 1-phenylethanol was highly enantioenriched (98% ee after 24 h; >99% ee after 48 h), indicating the racemization of 1-phenylethanol was not effective.

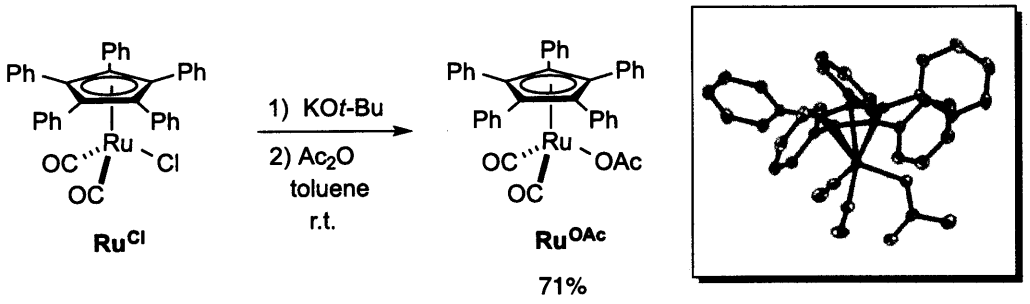


(1.2.3)

An additional control experiment revealed that the racemization by $\mathbf{Ru}^{Cl}$/KO*t*-Bu was inhibited in the presence of acetic anhydride, which was employed as the alcohol-acylating agent in our kinetic resolution processes (eq 1.2.4 vs. eq 1.2.2). On the basis of this observation, we hypothesized that the ruthenium alkoxide might react with acetic anhydride to form a new ruthenium complex that is not capable of catalyzing alcohol racemization. Indeed, we isolated a new ruthenium–acetate complex ($\mathbf{Ru}^{OAc}$) by mixing $\mathbf{Ru}^{Cl}$, KO*t*-Bu, and acetic anhydride in toluene (eq 1.2.5). Ruthenium acetate $\mathbf{Ru}^{OAc}$ is sufficiently stable that it can be purified by column chromatography, and the structure was confirmed by X-ray crystallography, which reveals an h^1-acetate ligand as part of an 18-electron ruthenium complex. Furthermore, using ^{13}C NMR analysis in *tert*-amyl alcohol/toluene-d_8 (1:1), we have confirmed that $\mathbf{Ru}^{OAc}$ forms rapidly under the conditions that we had originally explored for the DKR of 1-phenylethanol.

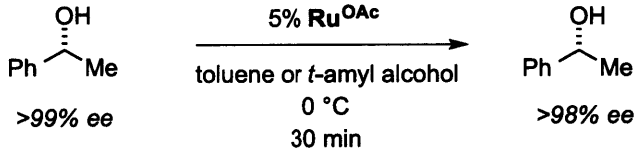


(1.2.4)

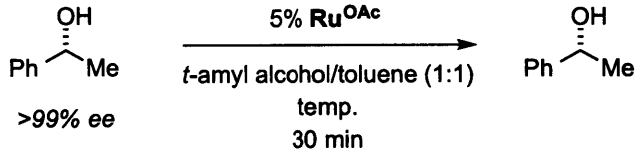


(1.2.5)

As we conjectured, ruthenium acetate $\mathbf{Ru}^{OAc}$ is not an efficient racemization catalyst for 1-phenylethanol under our kinetic resolution conditions (eq 1.2.6); treatment of enantiopure 1-phenyethanol with $\mathbf{Ru}^{OAc}$ did not lead to rapid racemization at 0 °C (>98% ee after 30 min).[23] Additional control experiments revealed that the racemization of 1-phenylethanol by $\mathbf{Ru}^{OAc}$ is faster at higher temperatures, and that the presence of acetic acid leads to slower racemization (eq 1.2.7). [24]



(1.2.6)



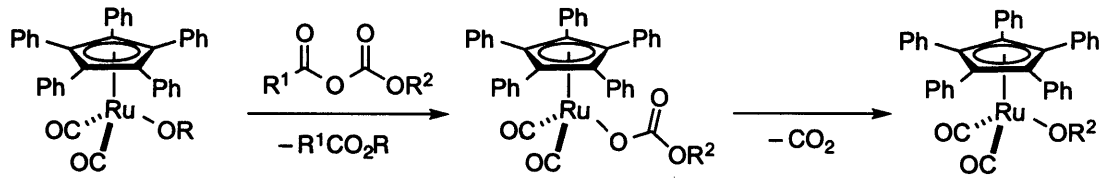
(1.2.7)

additive	temp.	ee (%)
none	60 °C	79
none	80 °C	20
5% HOAc	80 °C	85

[23] No interaction between $\mathbf{Ru}^{OAc}$ and 1-phenylethanol was observed by ^{1}H NMR spectroscopy using *tert*-amyl alcohol/toluene-d_8 (1:1) as the solvent at room temperature.

[24] Notes: (a) Ruthenium **1a** reacts with AcOH within 10 minutes at room temperature (in *tert*-amyl alcohol/toluene (1:1)) to generate $\mathbf{Ru}^{OAc}$ and *t*-BuOH. (b) In the presence of propionic acid and 1-phenylethanol, $\mathbf{Ru}^{OAc}$ does not react to form a ruthenium-propionate adduct after 20 hours at room temperature (in *tert*-amyl alcohol/toluene (1:1)).

In order to develop an effective DKR, we needed to identify an alternative acylating agent that is compatible with our acylation catalyst **C_5Ph_5-DMAP*** and that does not interfere with the ruthenium racemization catalyst. Among various acyl donors, we were particularly drawn to acyl carbonates[25] since they are less electrophilic than anhydrides, and, if acylation of the ruthenium alkoxide were to occur, the resulting ruthenium carbonate might decarboxylate to generate a ruthenium alkoxide, which can serve as a racemization catalyst for alcohols (eq 1.2.8).



(1.2.8)

Indeed, we were pleased to determine that acetyl isopropyl carbonate[26] is a suitable acylating agent in the non-enzymatic DKR catalyzed by **C_5Ph_5-DMAP*** and **Ru^{Cl}**/KO*t*-Bu, using a mixture of the preferred solvent for the kinetic resolution (*tert*-amyl alcohol) and the racemization (toluene) at 10 °C (eq 1.2.9). Under these conditions, the acetate is furnished in 95% yield with 87% ee. During this process, the product ee was constant, and the unreacted 1-phenylethanol was less than 15% ee. Additionally, under these conditions without the use of the ruthenium racemization catalyst

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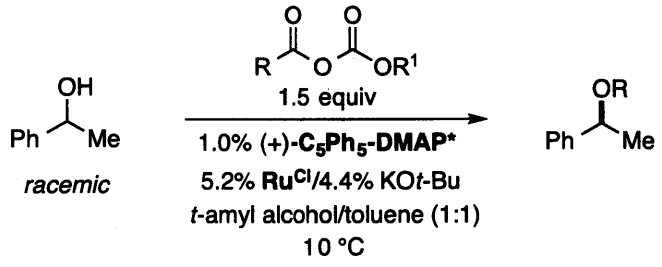
[25] For an example of the use of an acyl carbonate in an enzymatic kinetic resolution of an alcohol, see: Guibe-Jampel, E.; Chalecki, Z.; Bassir, M.; Gelo-Pujic, M. *Tetrahedron* **1996**, *52*, 4397–4402.

[26] Notes: (a) Acetyl isopropyl carbonate can be synthesized in one step from acetic acid and isopropyl chloroformate. After five days at room temperature under nitrogen, there is no detectable decomposition. (b) We are not aware of previous reports of the use of this acyl carbonate as an acylating agent for alcohols. (c) Whereas acylations of alcohols by Ac_2O generally include a stoichiometric Brønsted base as an additive (to capture AcOH), when acetyl isopropyl carbonate is used as the acylating agent, isopropanol is produced, and no added base is required.

(**Ru**^{Cl}/KO*t*-Bu), a simple kinetic resolution proceeded with a selectivity factor of 14, a value consistent with the 87% ee that we observe for the DKR of 1-phenylethanol. Other acyl carbonates provided lower enantioselectivity and yield.



(1.2.9)

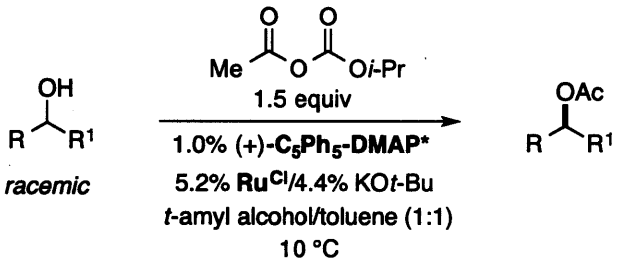
R	R^1	ee (%)	yield (%)
Me	***i*-Pr**	**87**	**95**
Et	*i*-Pr	76	78
Me	Et	78	67

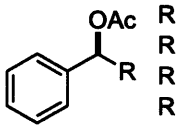
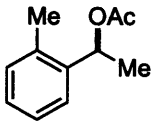
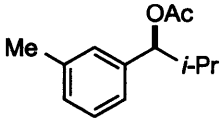
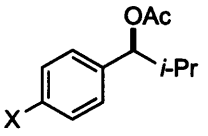
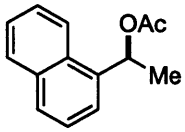
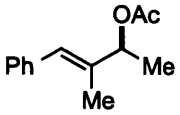
Given that acetyl isopropyl carbonate is compatible with the racemization process by **Ru**^{Cl}/KO*t*-Bu, we were interested in determining whether acetyl isopropyl carbonate does not interact with the ruthenium complex, or if it reacts with the ruthenium alkoxide in a sequential acylation and decarboxylation as we hypothesized (eq 1.2.8). When the mixture of **Ru**^{Cl} and KO*t*-Bu was treated with acetyl isopropyl carbonate in *tert*-amyl alcohol/toluene-d_8 (1:1) at room temperature in the presence or in the absence of 1-phenylethanol, we did not observe any detectable interactions between the acyl carbonate and ruthenium complexes[21] by ^{1}H NMR analysis.

The combination of planar-chiral DMAP derivative **C$_5$Ph$_5$-DMAP*** and a ruthenium racemization catalyst can be applied to the stereoconvergent acylation of an array of secondary alcohols with good ee and in high yield (Table 1.1). For example, our non-enzymatic DKR method is effective for various aryl alkyl carbinols (entries 1–9). The alkyl substituents can range in size from Me to isopropyl (entries 1–4); this method complements chemoenzymatic DKR's, which are not useful when the alkyl substituent is branched (in the α, β, or even the γ position).[12] Additionally, the aromatic ring of aryl alkyl carbinols can be ortho-, meta-, or para-substituted with either electron-poor or

electron-rich groups (entries 5–8) or it can be an extended π system (entry 9). Furthermore, the non-enzymatic DKR of an allylic alcohol proceeds in good enantioselectivity and yield (entry 10). On a gram scale, the DKR described in entry 5 of Table 1.1 proceeded in 92% ee and >99% yield (1.25 g of product; catalyst recovery for **C_5Ph_5-DMAP***: 74%).

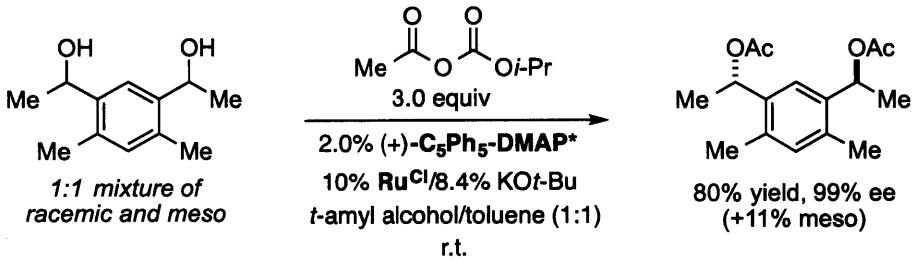
Table *1.1.* Non-Enzymatic DKR of Secondary Alcohols[a]



entry	acetate	ee (%)	yield (%)[b]
1	 R = Me	87	95 (87)
2	R = Et	90	96 (95)
3	R = *i*-Pr	91	98 (95)
4	R = cyclopentyl	82	90 (86)
5		93	97 (92)
6		91	97 (96)
7	 X = Cl	85	89 (88)
8	X = OMe	88	93 (92)
9		90	99 (94)
10		88	97 (90)

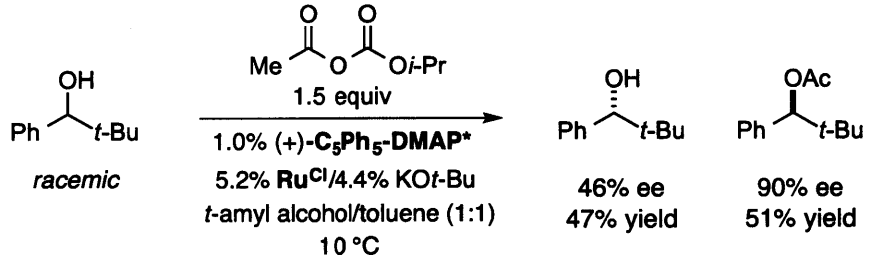
[a]All data are the average of two experiments. [b]The yield was determined by GC analysis with the aid of a calibrated internal standard. The yield of purified product is provided in parentheses.

The non-enzymatic DKR of a diol can also be achieved via enantioselective acylation catalyzed by **C_5Ph_5-DMAP*** and **Ru^{Cl}**/KO*t*-Bu. When three isomers of a diol are subjected to our standard conditions, the C_2-symmetric bis(acetate) can be obtained in excellent ee (eq 1.2.10).



(1.2.10)

Although our non-enzymatic DKR efficiently resolves a relatively broad range of aryl alkyl carbinols, we obtained a disappointing result for the DKR of phenyl *tert*-butyl carbinol (eq 1.2.11).[27] The unreacted alcohol was enantioenriched (46% ee), indicating ineffective racemization of this alcohol during the resolution.[28]



(1.2.11)

Phenyl chloromethyl carbinol was also not successfully resolved by our DKR process (eq 1.2.12).[29] The racemization of this alcohol substrate by ruthenium **1a** was rapid and continuous. The low product ee suggested that the kinetic resolution process under our standard DKR condition was not selective.

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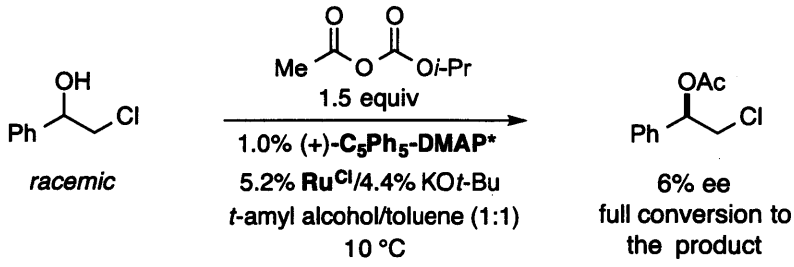
[27] The selectivity factor for the kinetic resolution of phenyl *tert*-butyl carbinol under the condition described in eq 1.1.1 is 95 (96% ee at 51% conversion; see ref 6b).

[28] A control experiment for the racemization of phenyl *tert*-butyl alcohol established that ruthenium **1a** can racemize this alcohol.

[29] The selectivity factor for the kinetic resolution of phenyl chloromethyl carbinol under the condition described in eq 1.1.1 is 32 (98% ee at 56% conversion; see ref 6b).



(1.2.12)

A proposed mechanism for our non-enzymatic DKR of 1-phenylethanol is illustrated in Figure 1.6. A key intermediate is N-acylated catalyst **1.5**, a chiral acylating agent, which is generated by the reaction of **C_5Ph_5-DMAP*** and acetyl isopropyl carbonate; the carbonate anion of intermediate **1.5** potentially decarboxylates to form another acylpyridinium salt with an isoproxide anion (**1.6**). Acyl transfer from N-acylated catalyst **1.5** to 1-phenylethanol, which is rapidly and continuously racemized by ruthenium alkoxide **1a**, produces the acetate product and regenerates the acylation catalyst.

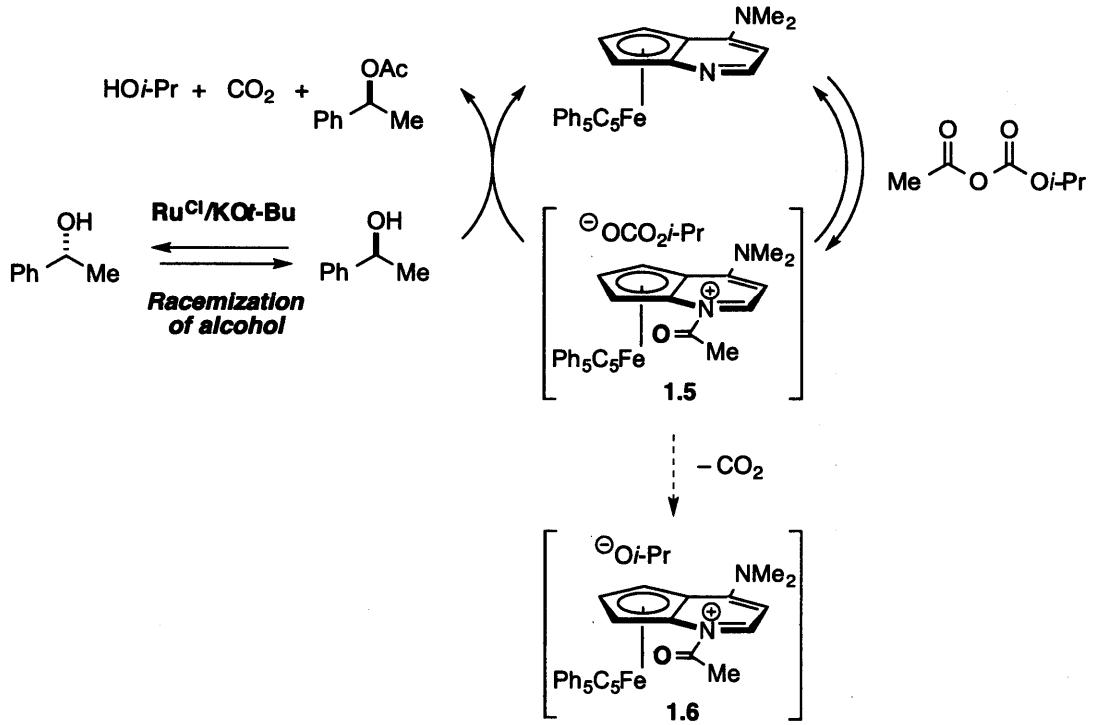
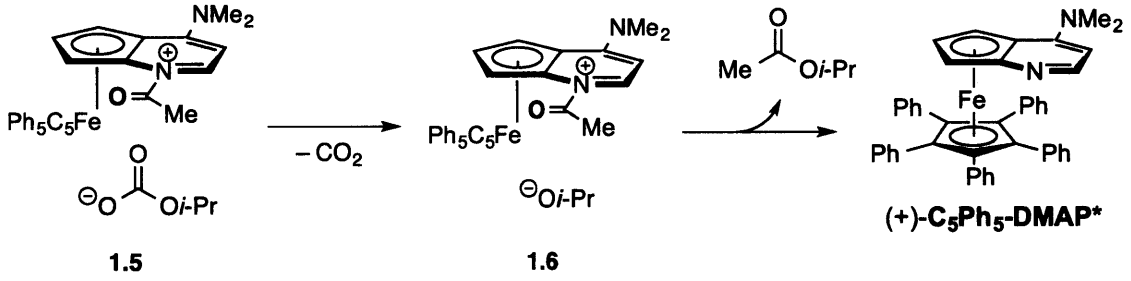


Figure 1.6. Outline of a mechanism for the non-enzymatic DKR of 1-phenylethanol

A kinetic study of the DKR of 1-phenylethanol revealed that the rate law is first order in 1-phenylethanol, first order in **C_5Ph_5-DMAP*** (acylation catalyst), "fractional" (first order at low concentration, approaching zeroth order at higher concentration) order in acetyl isopropyl carbonate, and zeroth order in the racemization catalyst (**Ru**^{Cl}/KO*t*-Bu).[30] According to a ^{1}H NMR spectroscopic study at 10 °C, the resting state of the planar-chiral DMAP derivative during a DKR is a mixture of the free catalyst and the N-acylated catalyst (**1.5**),[31] which explains the fractional order dependence of rate on the concentration of acetyl isopropyl carbonate. The acylation of 1-phenylethanol with a chiral acylating agent (**1.5**) is likely the rate-determining step.

Treatment of **C_5Ph_5-DMAP*** with 1 equivalent of acetyl isopropyl carbonate at 10 °C in *tert*-amyl alcohol/toluene-d_8 (1:1) led to the formation of a mixture of the free catalyst and the N-acylated catalyst (**1.5**) (7:3 mixture after 10 min), observed by ^{1}H NMR spectroscopy. At this temperature, N-acylated catalyst **1.5** slowly converts into the free catalyst and isopropyl acetate (8:2 mixture after 1 h; mostly the free catalyst after 2 h), likely through decarboxylation and deacylation pathway via intermediate **1.6** (eq 1.2.13).[32]



(1.2.13)

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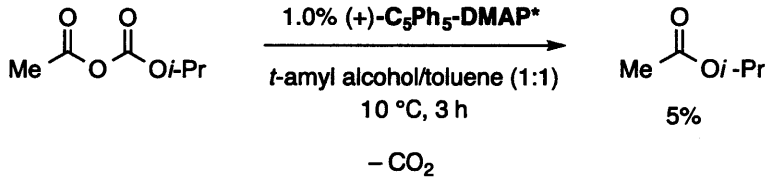
[30] The rate law for the simple kinetic resolution of 1-phenylethanol (for the reaction conditions: see, eq 1.1.1) is first order in 1-phenylethanol, first order in **C_5Ph_5-DMAP***, "fractional order" in acetic anhydride, and zeroth order in triethylamine.

[31] This DKR was conducted with 3.6% **C_5Ph_5-DMAP***, in order to facilitate analysis by ^{1}H NMR spectroscopy.

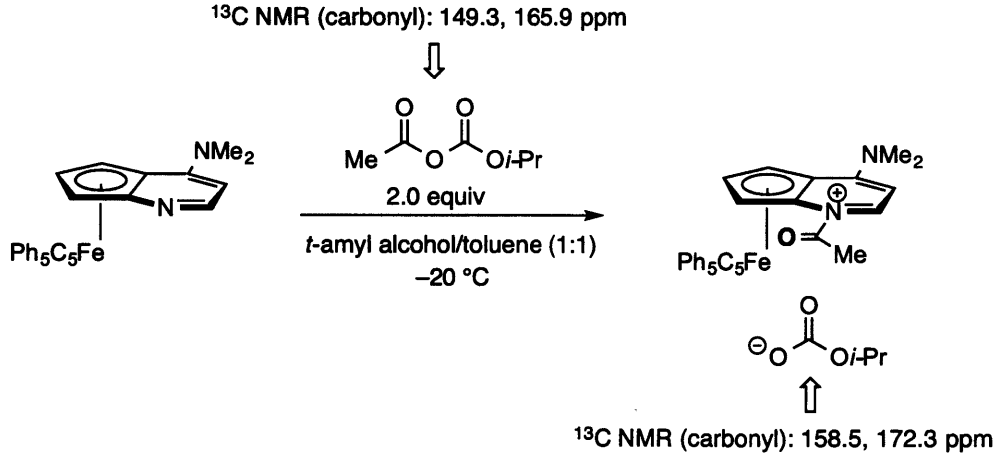
[32] Kim has reported that DMAP catalyzes the decarboxylation of acyl carbonates to form esters: Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560–565.

In view of our observation that C_5Ph_5-DMAP* promotes the formation of isopropyl acetate from acetyl isopropyl carbonate under our DKR conditions, which indicates the acylpyridinium salt (**1.6**) can be generated, we sought insight into which ion pair (**1.5** or **1.6**) is the species that reacts with 1-phenylethanol in the rate-determining acyl-transfer step. In fact, the decarboxylation of acetyl isopropyl carbonate in the presence of C_5Ph_5-DMAP* proceeds significantly more slowly (eq 1.2.14; 5% isopropyl acetate after 3 h) than the non-enzymatic DKR of 1-phenylethanol (37% acetate product after 3 h), suggesting that a carbonate anion of ion pair **1.5** serves as the Brønsted base in the acyl-transfer step (consistent with the proposed mechanism in Figure 1.6).



(1.2.14)

Finally, we have determined that for the reaction of C_5Ph_5-DMAP* and acetyl isopropyl carbonate, lower temperature favors the acylation, leading to almost quantitative generation of the salt **1.5** at – 20 °C, and that this salt is stable for at least 6 h at this temperature (eq 1.2.15; through $^1H/^{13}C$ NMR analysis).



(1.2.15)

1.3 Conclusion

Dynamic kinetic resolution is a powerful strategy for the asymmetric synthesis of secondary alcohols, a common subunit in bioactive compounds. We have developed the first non-enzymatic method for the DKR of secondary alcohols via enantioselective acylation, through the use of a planar-chiral DMAP derivative (acylation catalyst) in combination with a ruthenium complex (racemization catalyst). Our DKR is effective for a variety of secondary alcohols, including aryl alkyl carbinols, an allylic alcohol, and a diol. Simply combining an effective method for the kinetic resolution of alcohols with an active catalyst for the racemization of alcohols did not lead to an efficient DKR. The two processes were incompatible; specifically, the ruthenium racemization catalyst was deactivated by acetic anhydride, the acylating agent typically employed in the kinetic resolution, forming a stable ruthenium–acetate complex. The use of acetyl isopropyl carbonate as an acylating agent was critical to the successful development of this process, as it is compatible with both the kinetic resolution and the racemization processes. Mechanistic studies (reactivity, kinetics, and spectroscopic studies) of this process point to reversible N-acylation of the nucleophilic catalyst, acyl transfer from the catalyst to the alcohol as the rate-determining step, and the carbonate anion serving as the Brønsted base in that acyl-transfer step.

1.4 Experimental Section

I. General Information

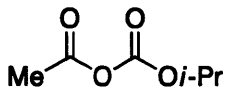
The following reagents were purchased from Aldrich and used as received: KO*t*-Bu, *t*-amyl alcohol (anhydrous), toluene (anhydrous), and NEt_3 (anhydrous). **C_5Ph_5-DMAP*** [33] and **Ru^{Cl}** [34] were synthesized as previously described. 1-Phenylethanol, 1-phenyl-1-propanol, 2-methyl-1-phenyl-1-propanol, 1-(2-methylphenyl)ethanol, and Ac_2O were purchased (Aldrich or Alfa Aesar) and purified by vacuum distillation prior to use. 1-(1-Naphthyl)ethanol was purchased from Aldrich and purified by column chromatography prior to use. The other secondary alcohols have been reported previously and were synthesized either by the addition of a Grignard reagent to an aldehyde or by the reduction of a ketone (purification: column chromatography).

Unless otherwise specified, reactions were conducted with stirring in oven-dried glassware under an atmosphere of nitrogen.

HPLC analyses were carried out on an Agilent 1100 series system equipped with a Daicel CHIRALCEL OD column (internal diameter 4.6 mm, column length 250 mm, particle size 5 μ). GC analyses were obtained on an Agilent 6850 system equipped with a Varian CP-Chirasil-DEX CB column (internal diameter 0.25 mm, column length 25 m).

II. Preparation of Acyl Carbonates

The procedures and yields have not been optimized.



Acetyl isopropyl carbonate [60059-18-9]. Acetic acid (1.7 mL, 30 mmol) was added via syringe to a 250-mL round-bottom flask that contained anhydrous Et_2O (60 mL) and NEt_3 (4.2 mL, 30 mmol) at 0 °C. The reaction mixture was stirred for 5 min, and then isopropyl chloroformate (30 mL, 30 mmol; 1.0 M in toluene; Aldrich) was

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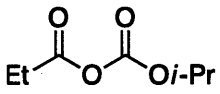
[33] Wurz, R. P.; Lee, E. C.; Ruble, J. C.; Fu, G. C. *Adv. Synth. Catal.* **2007**, *349*, 2345–2352.

[34] Martín-Matute, B.; Edin, M; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825.

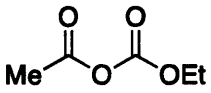
added dropwise via syringe over 10 min. The reaction mixture was stirred at 0 °C for 45 min. Next, an aqueous 10% citric acid solution (30 mL) was added. The organic layer was decanted and then washed with additional citric acid solution (20 mL), a saturated $NaHCO_3$ solution (30 mL), and brine (30 mL). The organic solvent was evaporated under reduced pressure, and the acyl carbonate was purified by vacuum distillation (30 °C at 500 mtorr), which provided a clear, colorless liquid (2.2 g, 50% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (septet, 1H, J = 6.4 Hz), 2.19 (s, 3H), 1.33 (d, 6H, J = 6.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 148.5, 74.5, 21.6, 21.2.



Propionyl isopropyl carbonate [176438-88-3]. Propionic acid (1.2 mL, 15 mmol) was added via syringe to a 250-mL round-bottom flask that contained anhydrous Et_2O (30 mL) and NEt_3 (2.1 mL, 15 mmol) at 0 °C. The reaction mixture was stirred for 5 min, and then isopropyl chloroformate (15 mL, 15 mmol; 1.0 M in toluene; Aldrich) was added dropwise via syringe over 10 min. The reaction mixture was stirred at 0 °C for 45 min. Next, an aqueous 10% citric acid solution (15 mL) was added. The organic layer was decanted and then washed with additional citric acid solution (10 mL), a saturated $NaHCO_3$ solution (15 mL), and brine (15 mL). The organic solvent was evaporated under reduced pressure, and the acyl carbonate was purified by vacuum distillation (27 °C at 450 mtorr), which provided a clear, colorless liquid (1.1 g, 46% yield).



Acetyl ethyl carbonate [15890-77-4]. Acetic acid (0.85 mL, 15 mmol) was added via syringe to a 250-mL round-bottom flask that contained anhydrous Et_2O (30 mL) and NEt_3 (2.1 mL, 15 mmol) at 0 °C. The reaction mixture was stirred for 5 min, and then ethyl chloroformate (1.4 mL, 15 mmol) was added dropwise via syringe over 10 min.

The reaction mixture was stirred at 0 °C for 45 min. Next, an aqueous 10% citric acid solution (15 mL) was added. The organic layer was decanted and then washed with additional citric acid solution (10 mL), a saturated $NaHCO_3$ solution (15 mL), and brine (15 mL). The organic solvent was evaporated under reduced pressure, which provided a clear, colorless liquid (1.3 g, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (quartet, 2H, J = 6.9 Hz), 2.19 (s, 3H), 1.34 (t, 3H, J = 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 148.9, 65.6, 21.0, 13.9.

III. Dynamic Kinetic Resolutions of Secondary Alcohols

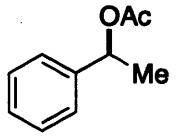
General procedure. In a nitrogen-filled glovebox (for a glovebox-free procedure, see below), **Ru^{Cl}** (16.6 mg, 0.026 mmol), KO*t*-Bu (2.5 mg, 0.022 mmol), toluene (100 μL), and *t*-amyl alcohol (150 μL) were combined in an oven-dried 4-mL vial equipped with a stir bar. The resulting mixture was stirred at r.t. for 6 min, and then the alcohol (0.50 mmol) and (+)-**C_5Ph_5-DMAP*** (3.3 mg in 50 μL toluene, 0.0050 mmol) were added to the vial. The vial was then capped with a septum-lined cap, removed from the glovebox, and cooled to 10 °C. After cooling the solution for 10 min, acetyl isopropyl carbonate (108 μL, 0.750 mmol) was added dropwise to the vial via syringe pump over 20 h (Notes: For optimal results, the tip of the needle should be aligned such that the acetyl isopropyl carbonate drips down the wall of the vial. Some grease was applied to the septum around the needle, to discourage moisture/air from entering the vial during the addition.). The reaction mixture was stirred at 10 °C for an additional 28 h. To remove the (+)-**C_5Ph_5-DMAP***, the mixture was then filtered through a plug of silica gel using Et_2O (10 mL) as the eluant, and the volatiles were removed under reduced pressure with minimal heat (to minimize evaporation of the products, since some are volatile). To remove a trace of a colored impurity, the residue was dissolved in CH_2Cl_2 (20 mL), H_2O (20 mL), and a 70% aqueous solution of *t*-BuOOH (2 mL). This mixture was stirred at r.t. for 2 h, and the product was isolated by extraction into CH_2Cl_2 (3 x 50 mL). The CH_2Cl_2 layers were combined and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by column chromatography (hexanes → 20% Et_2O in hexanes).

Notes: For the sake of convenience, the DKRs were set up in a glovebox. However, this method does *not* require the use of a glovebox (see the next procedure).

For the alcohol illustrated in entry 1 of Table 1.1, the DKR proceeded in 81% ee and 88% yield when the acetyl isopropyl carbonate was added dropwise over 1 min, rather than by syringe pump over 20 h.

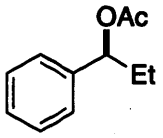
Glovebox-free procedure. $\mathbf{Ru^{Cl}}$ (16.6 mg, 0.026 mmol) and KO*t*-Bu (2.5 mg, 0.022 mmol) were added to an oven-dried 4-mL vial. The vial was capped, and then it was evacuated and backfilled with nitrogen (three cycles). Toluene (100 μL) and *t*-amyl alcohol (150 μL) were added via syringe, and the resulting solution was stirred at r.t. for 6 min. (+)-$\mathbf{C_5Ph_5}$**-DMAP*** (3.3 mg, 0.0050 mmol) was added to another oven-dried 4-mL vial, and this vial was capped, and then it was evacuated and backfilled with nitrogen (three cycles); next, toluene (50 μL) was added. The alcohol (0.50 mmol) and the solution of (+)-$\mathbf{C_5Ph_5}$**-DMAP*** were added in turn by syringe to the vial containing $\mathbf{Ru^{Cl}}$. The resulting mixture was cooled to 10 °C. The remainder of the procedure (addition of acetyl isopropyl carbonate onward) follows the general procedure.

This procedure provided 86% ee and 95% yield for the DKR illustrated in entry 1 of Table 1.1, and it furnished 90% ee and 97% yield for the DKR depicted in entry 2 of Table 1.1.



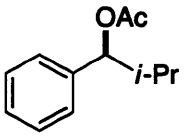
(*S*)-1-Phenylethyl acetate (Table 1.1, entry 1) [16197-93-6]. The title compound was prepared according to the general procedure, using 1-phenylethanol (61 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a clear, colorless oil (70 mg, 85% yield; 95% calibrated GC yield) with 86% ee (GC analysis of the product: CP-Chirasil-DEX CB; heating program: 105 °C → 115 °C @ 1 °C/min, followed by 115 → 175 °C @ 5 °C/min; He flow rate: 1.0 ml/min; retention times: 6.5 min (major), 7.2 min (minor)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a clear, colorless oil (69 mg, 84% yield; 95% calibrated GC yield) with 87% ee.



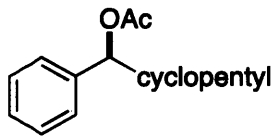
(*S*)-1-Phenylpropyl acetate (Table 1.1, entry 2) [83860-48-4]. The title compound was prepared according to the general procedure, using 1-phenylpropanol (68 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a clear, colorless oil (82 mg, 92% yield; 95% calibrated GC yield) with 90% ee (GC analysis of the product: CP-Chirasil-DEX CB; heating program: 105 °C → 115 °C @ 0.5 °C/min, followed by 115 → 175 °C @ 5 °C/min; He flow rate: 1.0 ml/min; retention times: 9.3 min (major), 9.9 min (minor)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a clear, colorless oil (86 mg, 97% yield; 97% calibrated GC yield) with 90% ee.



(*S*)-2-Methyl-1-phenylpropyl acetate (Table 1.1, entry 3) [84194-67-2]. The title compound was prepared according to the general procedure, using 2-methyl-1-phenylpropanol (75 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a clear, colorless oil (91 mg, 95% yield; 98% calibrated GC yield) with 90% ee (GC analysis of the product: CP-Chirasil-DEX CB; heating program: 105 °C → 115 °C @ 0.5 °C/min, followed by 115 → 175 °C @ 5 °C/min; He flow rate: 1.0 ml/min; retention times: 10.7 min (major), 11.3 min (minor)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a clear, colorless oil (90 mg, 94% yield; 97% calibrated GC yield) with 91% ee.



(*S*)-Cyclopentyl(phenyl) acetate (Table 1.1, entry 4). The title compound was prepared according to the general procedure, using cyclopentyl(phenyl)methanol (88 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a clear, colorless oil (94 mg, 86% yield; 91% calibrated GC yield) with 82% ee (HPLC analysis of the product: Daicel CHIRALCEL OD-H column; solvent system: hexanes; 1.0 mL/min; retention times: 20.2 min (minor), 41.2 min (major)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a clear, colorless oil (94 mg, 86% yield; 88% calibrated GC yield) with 81% ee.

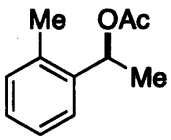
^{1}H NMR (400 MHz, CDCl3) δ 7.33–7.29 (m, 4H), 7.29–7.25 (m, 1H), 5.52 (d, 1H, J = 9.2 Hz), 2.34 (sextet, 1H, J = 8.4 Hz), 2.03 (s, 3H), 1.84–1.77 (m, 1H), 1.67–1.52 (m, 3H), 1.50–1.44 (m, 1H), 1.42–1.36 (m, 2H), 1.18–1.09 (m, 1H).

^{13}C NMR (100 MHz, CDCl3) δ 170.6, 140.8, 128.4, 127.9, 127.2, 80.1, 45.6, 29.8, 29.3, 25.37, 25.35, 21.5.

IR (film) 3033, 2956, 2870, 1739, 1496, 1454, 1371, 1237, 1022, 965, 903, 761 cm^{-1}.

MS (EI) m/z (M^+) calcd for $C_{14}H_{18}O_2$: 218, found: 218.

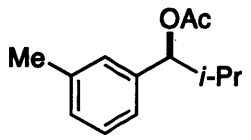
$[a]^{24}_D$ = –43° (c = 1.0, CH_2Cl_2; obtained with (+)-**C_5Ph_5-DMAP***).



(*S*)-1-(2-Methylphenyl)ethyl acetate (Table 1.1, entry 5) [501659-37-6]. The title compound was prepared according to the general procedure, using 1-(2-

methyl)phenylethanol (68 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a clear, colorless oil (86 mg, 96% yield; 99% calibrated GC yield) with 93% ee (GC analysis of the product: CP-Chirasil-DEX CB; heating program: 90 °C → 115 °C @ 0.5 °C/min, followed by 115 → 175 °C @ 5 °C/min; He flow rate: 0.7 ml/min; retention times: 20.7 min (major), 21.5 min (minor)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a clear, colorless oil (78 mg, 87% yield; 94% calibrated GC yield) with 92% ee.



(*S*)-2-Methyl-1-(3-Methylphenyl)propyl acetate (Table 1.1, entry 6). The title compound was prepared according to the general procedure, using 2-methyl-1-(3-methyl)phenylpropanol (82 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a clear, colorless oil (99 mg, 96% yield; 96% calibrated GC yield) with 90% ee (GC analysis of the product: CP-Chirasil-DEX CB; heating program: 105 °C → 115 °C @ 0.5 °C/min, followed by 115 → 175 °C @ 5 °C/min; He flow rate: 1.0 ml/min; retention times: 14.9 min (major), 15.8 min (minor)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a clear, colorless oil (99 mg, 96% yield; 97% calibrated GC yield) with 91% ee.

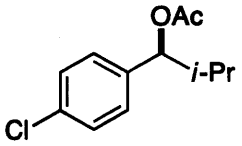
^{1}H NMR (400 MHz, CDCl3) δ 7.24–7.20 (m, 1H), 7.10–7.08 (m, 3H), 5.43 (d, 1H, J = 7.6 Hz), 2.35 (s, 3H), 2.13–2.05 (m, 4H), 0.97 (d, 3H, J = 6.8 Hz), 0.80 (d, 3H, J = 6.8 Hz).

^{13}C NMR (100 MHz, CDCl3) δ 170.5, 139.8, 137.8, 128.5, 128.1, 127.9, 124.2, 81.1, 33.6, 21.6, 21.3, 18.9, 18.6.

IR (film) 2964, 2875, 1736, 1686, 1610, 1450, 1371, 1237, 1160, 1023, 980, 908 cm^{-1}.

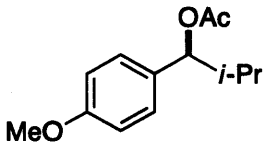
MS (EI) m/z (M^+) calcd for $C_{13}H_{18}O_2$: 206, found: 206.

$[a]^{24}_D$ = –47° (c = 1.0, CH_2Cl_2; obtained with (+)-**C_5Ph_5-DMAP***).



(*S*)-2-Methyl-1-(4-chlorophenyl)propyl acetate (Table 1.1, entry 7) [137408-30-1]. The title compound was prepared according to the general procedure, using 2-methyl-1-(4-chlorophenyl)propanol (92 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a clear, colorless oil (100 mg, 88% yield; 87% calibrated GC yield) with 85% ee (GC analysis of the product: CP-Chirasil-DEX CB; heating program: 105 °C → 115 °C @ 1 °C/min, followed by 115 → 175 °C @ 5 °C/min; He flow rate: 1.0 ml/min; retention times: 17.2 min (major), 17.5 min (minor)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a clear, colorless oil (100 mg, 88% yield; 90% calibrated GC yield) with 85% ee.



(*S*)-2-Methyl-1-(4-methoxyphenyl)propyl acetate (Table 1.1, entry 8). The title compound was prepared according to the general procedure, using 2-methyl-1-(4-methoxyphenyl)propanol (90 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a white solid (103 mg, 93% yield; 95% calibrated GC yield) with 86% ee (GC analysis of the product: CP-Chirasil-DEX CB; heating program: 105 °C → 115 °C @ 0.5 °C/min, followed by 115 → 175 °C @ 5 °C/min; He flow rate: 1.0 ml/min; retention times: 27.5 min (major), 27.8 min (minor)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a white solid (100 mg, 90% yield; 90% calibrated GC yield) with 89% ee.

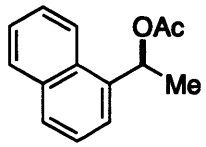
^{1}H NMR (400 MHz, CDCl3) δ 7.22 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.4 Hz), 5.39 (d, 1H, J = 8.0 Hz), 3.79 (s, 3H), 2.09–2.02 (m, 4H), 0.96 (d, 3H, J = 6.8 Hz), 0.76 (d, 3H, J = 6.8 Hz).

^{13}C NMR (100 MHz, CDCl3) δ 170.5, 159.2, 132.0, 128.5, 113.7, 80.9, 55.3, 33.5, 21.4, 19.4, 18.8.

IR (film) 2965, 2873, 1724, 1676, 1606, 1515, 1474, 1456, 1377, 1298, 1244, 1177, 1104, 1032, 1016, 975, 903, 832, 812 cm^{-1}.

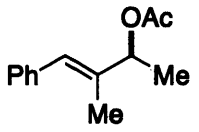
MS (EI) m/z (M^+) calcd for $C_{13}H_{18}O_3$: 222, found: 222.

$[a]^{24}_D$ = –43° (c = 1.0, CH_2Cl_2; obtained with (+)-**C_5Ph_5-DMAP***).



(*S*)-1-(1-naphthyl)ethyl acetate (Table 1.1, entry 9) [16197-95-8]. The title compound was prepared according to the general procedure, using 1-(1-naphthyl)ethanol (86 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a clear, colorless oil (103 mg, 96% yield; 99% calibrated GC yield) with 89% ee (HPLC analysis of the product: Daicel CHIRALCEL OD-H column; solvent system: 1.0% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 9.4 min (minor), 14.4 min (major)).

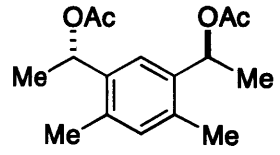
The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a clear, colorless oil (98 mg, 91% yield; 99% calibrated GC yield) with 91% ee.



(*S*,*E*)-3-Methyl-4-phenylbut-3-en-2-yl acetate (Table 1.1, entry 10) [187736-05-6]. The title compound was prepared according to the general procedure, using (*E*)-3-methyl-4-phenylbut-3-en-2-ol (81 mg, 0.50 mmol). After purification by column chromatography (hexanes → 20% Et_2O in hexanes), the title compound was isolated as a clear, colorless oil (98 mg, 96% yield; 95% calibrated GC yield) with 89% ee (HPLC

analysis of the product: Daicel CHIRALCEL OD-H column; solvent system: 1.0% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 5.9 min (major), 7.5 min (minor)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The product was isolated as a clear, colorless oil (85 mg, 83% yield; 99% calibrated GC yield) with 88% ee.



(1*S*,1'*S*)-1,1'-(4,6-Dimethyl-1,3-phenylene)bis(ethane-1,1-diyl) diacetate (1.2.10) [205104-01-4 for the (1*R*,1'*R*) enantiomer]. In a nitrogen-filled glovebox, **Ru^{Cl}** (33.2 mg, 0.052 mmol), KO*t*-Bu (4.9 mg, 0.044 mmol), toluene (200 μL), and *t*-amyl alcohol (300 μL) were combined in an oven-dried 4-mL vial equipped with a stir bar. The resulting mixture was stirred at r.t. for 6 min, and then the alcohol (0.50 mmol) and (+)-**C_5Ph_5-DMAP*** (6.6 mg in 100 μL toluene, 0.010 mmol) were added to the vial. The vial was then capped with a septum-lined cap, removed from the glovebox, and cooled to 10 °C. After cooling the solution for 10 min, acetyl isopropyl carbonate (216 μL, 1.50 mmol) was added dropwise to the vial via syringe pump over 20 h (Notes: For optimal results, the tip of the needle should be aligned such that the acetyl isopropyl carbonate drips down the wall of the vial. Some grease was applied to the septum around the needle, to discourage moisture/air from entering the vial during the addition.). The reaction mixture was stirred at 10 °C for an additional 28 h. To remove the (+)-**C_5Ph_5-DMAP***, the mixture was then filtered through a plug of silica gel using Et_2O (15 mL) as the eluant, and the volatiles were removed under reduced pressure. To remove a trace of a colored impurity, the residue was dissolved in CH_2Cl_2 (40 mL), H_2O (40 mL), and a 70% aqueous solution of *t*-BuOOH (4 mL). This mixture was stirred at r.t. for 2 h, and the product was isolated by extraction into CH_2Cl_2 (3 x 50 mL). The CH_2Cl_2 layers were combined and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by column chromatography (hexanes → 20% Et_2O in hexanes), which furnished a mixture of the d,l and the meso diacetates (126 mg, 91% yield; dr: 7:1) as a clear, colorless oil. The diastereomers were separated by column

chromatography (hexanes → 10% Et_2O in hexanes), which afforded the pure d,l diacetate (111 mg, 80% yield) with 99% ee.

The ee of the product was determined after deacetylation to the diol (HPLC analysis of the diol: Daicel CHIRALCEL OD-H column; solvent system: 5.0% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 17.0 min (major), 28.0 min (minor)).

The second run was performed with (–)-**C_5Ph_5-DMAP***. The mixture of the d,l and the meso diacetates was isolated as a clear, colorless oil (128 mg, 92% yield; dr: 7:1). An additional column chromatography afforded the pure d,l diacetate (110 mg, 79% yield) with 99% ee.

The spectral data match those described in the literature.[35]

$[a]^{24}_D = -94°$ (c = 1.0, CH_2Cl_2; obtained with (+)-**C_5Ph_5-DMAP***).

IV. Preparation of Ru^{OAc}

Synthesis of Ru^{OAc}. In a nitrogen-filled glovebox, **Ru^{Cl}** (100 mg, 0.157 mmol), KO*t*-Bu (17.6 mg, 0.157 mmol), and toluene (2.5 mL) were combined in an oven-dried 20-mL vial equipped with a stir bar. The mixture was stirred at r.t. for 6 min, and then Ac_2O (151 μL, 1.60 mmol) was added to the vial via syringe. The resulting solution was stirred at r.t. for 12 h. Next, the volatiles were removed under reduced pressure, and the residue was purified by column chromatography (20% Et_2O in hexanes → 50% Et_2O in hexanes), which furnished the title compound as a yellow solid (74 mg, 71% yield; not optimized).

^{1}H NMR (400 MHz, CDCl3) δ 7.21–7.17 (m, 5H), 7.10–7.06 (m, 10H), 6.99–6.97 (m, 10H), 2.00 (s, 3H).

^{13}C NMR (100 MHz, CDCl3) δ 198.2, 177.5, 132.2, 130.0, 128.3, 127.9, 106.0, 23.1.

IR (film) 3060, 2039, 1989, 1623, 1601, 1503, 1445, 1361, 1309, 1183, 1075, 1028, 803, 785, 743, 699, 675, 561 cm^{-1}.

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[35] Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794–2795.

Structure determination of Ru^{OAc} by X-ray crystallography. X-ray quality crystals were obtained by slowly evaporating CH_2Cl_2 from a saturated solution of **Ru^{OAc}**.

The crystal contained ca. 5% $(\eta^5\text{-}C_5Ph_5)Ru(CO)_2Cl$, which is omitted for clarity.

Table 1. Crystal data and structure refinement for X11159.

Identification code	x11159	
Empirical formula	C38.91 H27.86 Cl0.05 O3.91 Ru	
Formula weight	660.56	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 19.5003(10) Å	a= 90°.
	b = 10.5810(5) Å	b= 104.8110(10)°.
	c = 14.9192(8) Å	g = 90°.
Volume	2976.0(3) $Å^3$	
Z	4	
Density (calculated)	1.474 Mg/m^3	
Absorption coefficient	0.573 mm^{-1}	
F(000)	1349	

Crystal size	0.45 x 0.20 x 0.08 mm^3
Theta range for data collection	2.16 to 29.94°.
Index ranges	-27<=h<=27, -14<=k<=14, -20<=l<=20
Reflections collected	116985
Independent reflections	8640 [R(int) = 0.0289]
Completeness to theta = 29.94°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9556 and 0.7825
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8640 / 110 / 426
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0212, wR2 = 0.0548
R indices (all data)	R1 = 0.0234, wR2 = 0.0564
Largest diff. peak and hole	0.455 and -0.642 e. $Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for X11159. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Ru(1)	2599(1)	6419(1)	4071(1)	12(1)
C(1)	2032(1)	6959(1)	5182(1)	13(1)
C(11)	1295(1)	6702(1)	5227(1)	14(1)
C(12)	1184(1)	6442(1)	6096(1)	18(1)
C(13)	498(1)	6319(1)	6203(1)	23(1)
C(14)	-79(1)	6446(1)	5441(1)	24(1)
C(15)	27(1)	6702(1)	4574(1)	22(1)
C(16)	711(1)	6835(1)	4462(1)	18(1)

C(2)	2637(1)	6192(1)	5573(1)	12(1)
C(21)	2624(1)	4928(1)	5997(1)	13(1)
C(22)	3065(1)	4642(1)	6872(1)	16(1)
C(23)	3045(1)	3444(1)	7254(1)	18(1)
C(24)	2590(1)	2525(1)	6774(1)	19(1)
C(25)	2148(1)	2801(1)	5904(1)	19(1)
C(26)	2166(1)	3992(1)	5520(1)	16(1)
C(3)	3266(1)	6879(1)	5477(1)	13(1)
C(31)	4013(1)	6568(1)	5960(1)	14(1)
C(32)	4391(1)	7425(1)	6614(1)	18(1)
C(33)	5066(1)	7131(1)	7154(1)	23(1)
C(34)	5375(1)	5981(2)	7044(1)	25(1)
C(35)	5013(1)	5133(1)	6382(1)	25(1)
C(36)	4333(1)	5422(1)	5845(1)	20(1)
C(4)	3026(1)	8042(1)	5007(1)	13(1)
C(41)	3462(1)	9143(1)	4874(1)	14(1)
C(42)	3363(1)	10269(1)	5316(1)	18(1)
C(43)	3737(1)	11353(1)	5205(1)	22(1)
C(44)	4208(1)	11324(1)	4646(1)	22(1)
C(45)	4311(1)	10208(1)	4210(1)	20(1)
C(46)	3944(1)	9115(1)	4328(1)	17(1)
C(5)	2260(1)	8081(1)	4794(1)	13(1)
C(51)	1809(1)	9156(1)	4354(1)	14(1)
C(52)	1898(1)	9718(1)	3544(1)	18(1)
C(53)	1474(1)	10728(1)	3139(1)	22(1)
C(54)	954(1)	11184(1)	3538(1)	22(1)
C(55)868(1)	10645(1)	4352(1)	20(1)	
C(56)1296(1)	9642(1)	4763(1)	16(1)	
C(8) 3019(1)	4851(1)	3902(1)	19(1)	

O(3)	3271(1)	3900(1)	3830(1)	29(1)
O(1)	1638(1)	5699(1)	3315(1)	22(1)
C(6)	1556(1)	5270(1)	2481(1)	20(1)
O(2)	2007(1)	5300(1)	2041(1)	23(1)
C(7)	839(1)	4676(2)	2083(1)	40(1)
C(9A)		1735(14)	6050(30)	3110(20)	22(5)
O(4A)		1230(11)	5740(30)	2537(16)	42(6)
C(9)	2849(1)	7030(1)	3004(1)	18(1)
O(4)	3046(1)	7430(1)	2409(1)	27(1)
Cl(1A)		3017(5)	7011(10)	2694(7)	26(2)

Table 3. Bond lengths [Å] and angles [°] for X11159.

Ru(1)-C(9)	1.894(2)
Ru(1)-C(8)	1.8955(13)
Ru(1)-C(9A)	1.953(14)
Ru(1)-O(1)	2.0689(11)
Ru(1)-C(3)	2.2213(11)
Ru(1)-C(4)	2.2360(11)
Ru(1)-C(2)	2.2363(11)
Ru(1)-C(5)	2.2487(11)
Ru(1)-C(1)	2.2880(11)
Ru(1)-Cl(1A)	2.477(11)
C(1)-C(2)	1.4290(15)
C(1)-C(5)	1.4403(16)
C(1)-C(11)	1.4802(15)
C(11)-C(12)	1.3950(17)
C(11)-C(16)	1.3984(16)
C(12)-C(13)	1.3932(17)

C(12)-H(12)	0.9500
C(13)-C(14)	1.387(2)
C(13)-H(13)	0.9500
C(14)-C(15)	1.387(2)
C(14)-H(14)	0.9500
C(15)-C(16)	1.3919(17)
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
C(2)-C(3)	1.4630(15)
C(2)-C(21)	1.4830(16)
C(21)-C(22)	1.3992(16)
C(21)-C(26)	1.4002(16)
C(22)-C(23)	1.3945(16)
C(22)-H(22)	0.9500
C(23)-C(24)	1.3864(18)
C(23)-H(23)	0.9500
C(24)-C(25)	1.3925(17)
C(24)-H(24)	0.9500
C(25)-C(26)	1.3882(17)
C(25)-H(25)	0.9500
C(26)-H(26)	0.9500
C(3)-C(4)	1.4342(16)
C(3)-C(31)	1.4882(16)
C(31)-C(36)	1.3941(17)
C(31)-C(32)	1.3968(17)
C(32)-C(33)	1.3922(17)
C(32)-H(32)	0.9500
C(33)-C(34)	1.387(2)
C(33)-H(33)	0.9500

C(34)-C(35)	1.387(2)
C(34)-H(34)	0.9500
C(35)-C(36)	1.3965(18)
C(35)-H(35)	0.9500
C(36)-H(36)	0.9500
C(4)-C(5)	1.4459(15)
C(4)-C(41)	1.4841(16)
C(41)-C(46)	1.3939(16)
C(41)-C(42)	1.3984(17)
C(42)-C(43)	1.3912(17)
C(42)-H(42)	0.9500
C(43)-C(44)	1.389(2)
C(43)-H(43)	0.9500
C(44)-C(45)	1.387(2)
C(44)-H(44)	0.9500
C(45)-C(46)	1.3936(17)
C(45)-H(45)	0.9500
C(46)-H(46)	0.9500
C(5)-C(51)	1.4839(16)
C(51)-C(52)	1.3953(16)
C(51)-C(56)	1.3977(16)
C(52)-C(53)	1.3910(17)
C(52)-H(52)	0.9500
C(53)-C(54)	1.3871(19)
C(53)-H(53)	0.9500
C(54)-C(55)	1.3900(19)
C(54)-H(54)	0.9500
C(55)-C(56)	1.3913(17)
C(55)-H(55)	0.9500

C(56)-H(56)	0.9500
C(8)-O(3)	1.1362(16)
O(1)-C(6)	1.2951(17)
C(6)-O(2)	1.2237(18)
C(6)-C(7)	1.510(2)
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
C(9A)-O(4A)	1.171(15)
C(9)-O(4)	1.134(3)

C(9)-Ru(1)-C(8)	88.49(6)
C(9)-Ru(1)-C(9A)	79.0(12)
C(8)-Ru(1)-C(9A)	92.8(12)
C(9)-Ru(1)-O(1)	93.43(6)
C(8)-Ru(1)-O(1)	88.15(5)
C(9A)-Ru(1)-O(1)	15.3(11)
C(9)-Ru(1)-C(3)	120.25(5)
C(8)-Ru(1)-C(3)	98.56(5)
C(9A)-Ru(1)-C(3)	157.6(13)
O(1)-Ru(1)-C(3)	145.65(5)
C(9)-Ru(1)-C(4)	97.30(5)
C(8)-Ru(1)-C(4)	130.58(5)
C(9A)-Ru(1)-C(4)	136.5(11)
O(1)-Ru(1)-C(4)	139.83(5)
C(3)-Ru(1)-C(4)	37.54(4)
C(9)-Ru(1)-C(2)	158.26(5)
C(8)-Ru(1)-C(2)	97.74(5)
C(9A)-Ru(1)-C(2)	121.2(12)

O(1)-Ru(1)-C(2)	107.52(5)
C(3)-Ru(1)-C(2)	38.32(4)
C(4)-Ru(1)-C(2)	62.92(4)
C(9)-Ru(1)-C(5)	107.84(5)
C(8)-Ru(1)-C(5)	159.77(5)
C(9A)-Ru(1)-C(5)	101.8(12)
O(1)-Ru(1)-C(5)	102.32(5)
C(3)-Ru(1)-C(5)	63.15(4)
C(4)-Ru(1)-C(5)	37.61(4)
C(2)-Ru(1)-C(5)	62.74(4)
C(9)-Ru(1)-C(1)	143.10(5)
C(8)-Ru(1)-C(1)	128.38(5)
C(9A)-Ru(1)-C(1)	95.6(13)
O(1)-Ru(1)-C(1)	87.10(4)
C(3)-Ru(1)-C(1)	62.33(4)
C(4)-Ru(1)-C(1)	61.80(4)
C(2)-Ru(1)-C(1)	36.80(4)
C(5)-Ru(1)-C(1)	37.01(4)
C(9)-Ru(1)-Cl(1A)	6.4(3)
C(8)-Ru(1)-Cl(1A)	82.3(3)
C(9A)-Ru(1)-Cl(1A)	81.1(12)
O(1)-Ru(1)-Cl(1A)	94.9(2)
C(3)-Ru(1)-Cl(1A)	119.4(2)
C(4)-Ru(1)-Cl(1A)	100.0(2)
C(2)-Ru(1)-Cl(1A)	157.6(2)
C(5)-Ru(1)-Cl(1A)	113.5(3)
C(1)-Ru(1)-Cl(1A)	149.4(3)
C(2)-C(1)-C(5)	108.92(10)
C(2)-C(1)-C(11)	125.99(10)

C(5)-C(1)-C(11)	124.95(10)
C(2)-C(1)-Ru(1)	69.63(6)
C(5)-C(1)-Ru(1)	70.01(6)
C(11)-C(1)-Ru(1)	129.88(8)
C(12)-C(11)-C(16)	119.35(11)
C(12)-C(11)-C(1)	117.45(11)
C(16)-C(11)-C(1)	122.88(11)
C(13)-C(12)-C(11)	120.40(12)
C(13)-C(12)-H(12)	119.8
C(11)-C(12)-H(12)	119.8
C(14)-C(13)-C(12)	119.93(13)
C(14)-C(13)-H(13)	120.0
C(12)-C(13)-H(13)	120.0
C(13)-C(14)-C(15)	120.03(12)
C(13)-C(14)-H(14)	120.0
C(15)-C(14)-H(14)	120.0
C(14)-C(15)-C(16)	120.42(12)
C(14)-C(15)-H(15)	119.8
C(16)-C(15)-H(15)	119.8
C(15)-C(16)-C(11)	119.88(12)
C(15)-C(16)-H(16)	120.1
C(11)-C(16)-H(16)	120.1
C(1)-C(2)-C(3)	107.63(10)
C(1)-C(2)-C(21)	125.73(10)
C(3)-C(2)-C(21)	126.64(10)
C(1)-C(2)-Ru(1)	73.57(6)
C(3)-C(2)-Ru(1)	70.28(6)
C(21)-C(2)-Ru(1)	121.64(8)
C(22)-C(21)-C(26)	118.79(11)

C(22)-C(21)-C(2)	121.26(10)
C(26)-C(21)-C(2)	119.95(10)
C(23)-C(22)-C(21)	120.18(11)
C(23)-C(22)-H(22)	119.9
C(21)-C(22)-H(22)	119.9
C(24)-C(23)-C(22)	120.52(11)
C(24)-C(23)-H(23)	119.7
C(22)-C(23)-H(23)	119.7
C(23)-C(24)-C(25)	119.68(11)
C(23)-C(24)-H(24)	120.2
C(25)-C(24)-H(24)	120.2
C(26)-C(25)-C(24)	120.08(11)
C(26)-C(25)-H(25)	120.0
C(24)-C(25)-H(25)	120.0
C(25)-C(26)-C(21)	120.75(11)
C(25)-C(26)-H(26)	119.6
C(21)-C(26)-H(26)	119.6
C(4)-C(3)-C(2)	107.35(9)
C(4)-C(3)-C(31)	125.67(10)
C(2)-C(3)-C(31)	125.69(10)
C(4)-C(3)-Ru(1)	71.79(6)
C(2)-C(3)-Ru(1)	71.40(6)
C(31)-C(3)-Ru(1)	132.30(8)
C(36)-C(31)-C(32)	118.56(11)
C(36)-C(31)-C(3)	123.13(11)
C(32)-C(31)-C(3)	118.10(11)
C(33)-C(32)-C(31)	120.80(12)
C(33)-C(32)-H(32)	119.6
C(31)-C(32)-H(32)	119.6

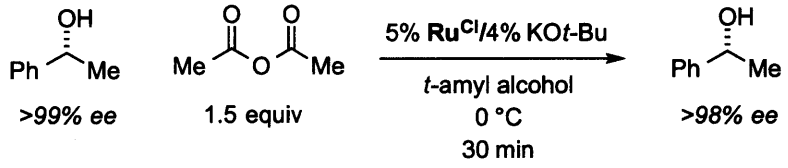
C(34)-C(33)-C(32)	120.17(13)
C(34)-C(33)-H(33)	119.9
C(32)-C(33)-H(33)	119.9
C(33)-C(34)-C(35)	119.63(12)
C(33)-C(34)-H(34)	120.2
C(35)-C(34)-H(34)	120.2
C(34)-C(35)-C(36)	120.26(13)
C(34)-C(35)-H(35)	119.9
C(36)-C(35)-H(35)	119.9
C(31)-C(36)-C(35)	120.56(12)
C(31)-C(36)-H(36)	119.7
C(35)-C(36)-H(36)	119.7
C(3)-C(4)-C(5)	108.72(10)
C(3)-C(4)-C(41)	127.75(10)
C(5)-C(4)-C(41)	122.87(10)
C(3)-C(4)-Ru(1)	70.67(6)
C(5)-C(4)-Ru(1)	71.67(6)
C(41)-C(4)-Ru(1)	130.88(8)
C(46)-C(41)-C(42)	119.20(11)
C(46)-C(41)-C(4)	123.78(11)
C(42)-C(41)-C(4)	117.00(10)
C(43)-C(42)-C(41)	120.46(12)
C(43)-C(42)-H(42)	119.8
C(41)-C(42)-H(42)	119.8
C(44)-C(43)-C(42)	120.01(12)
C(44)-C(43)-H(43)	120.0
C(42)-C(43)-H(43)	120.0
C(45)-C(44)-C(43)	119.83(12)
C(45)-C(44)-H(44)	120.1

C(43)-C(44)-H(44)	120.1
C(44)-C(45)-C(46)	120.43(12)
C(44)-C(45)-H(45)	119.8
C(46)-C(45)-H(45)	119.8
C(45)-C(46)-C(41)	120.06(12)
C(45)-C(46)-H(46)	120.0
C(41)-C(46)-H(46)	120.0
C(1)-C(5)-C(4)	107.24(10)
C(1)-C(5)-C(51)	126.91(10)
C(4)-C(5)-C(51)	125.50(10)
C(1)-C(5)-Ru(1)	72.98(6)
C(4)-C(5)-Ru(1)	70.72(6)
C(51)-C(5)-Ru(1)	126.90(8)
C(52)-C(51)-C(56)	118.79(11)
C(52)-C(51)-C(5)	121.30(10)
C(56)-C(51)-C(5)	119.90(10)
C(53)-C(52)-C(51)	120.86(12)
C(53)-C(52)-H(52)	119.6
C(51)-C(52)-H(52)	119.6
C(54)-C(53)-C(52)	119.89(12)
C(54)-C(53)-H(53)	120.1
C(52)-C(53)-H(53)	120.1
C(53)-C(54)-C(55)	119.83(12)
C(53)-C(54)-H(54)	120.1
C(55)-C(54)-H(54)	120.1
C(54)-C(55)-C(56)	120.31(12)
C(54)-C(55)-H(55)	119.8
C(56)-C(55)-H(55)	119.8
C(55)-C(56)-C(51)	120.30(11)

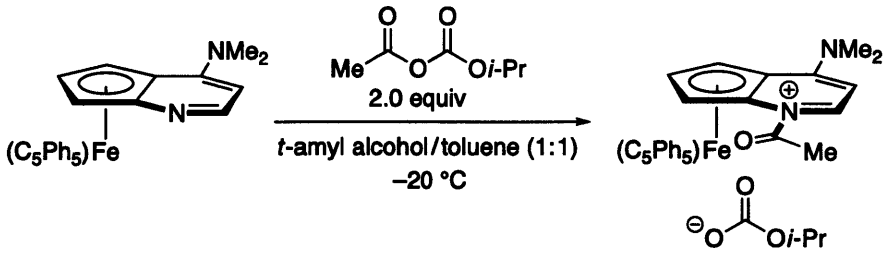
C(55)-C(56)-H(56)	119.8
C(51)-C(56)-H(56)	119.8
O(3)-C(8)-Ru(1)	177.64(11)
C(6)-O(1)-Ru(1)	121.65(10)
O(2)-C(6)-O(1)	125.23(14)
O(2)-C(6)-C(7)	121.31(13)
O(1)-C(6)-C(7)	113.45(14)
O(4A)-C(9A)-Ru(1)	175(3)
O(4)-C(9)-Ru(1)	174.81(14)

Symmetry transformations used to generate equivalent atoms:

V. Mechanistic/Reactivity Studies



Eq 1.2.4. In a nitrogen-filled glovebox, a solution of **Ru**^{Cl} (6.4 mg, 0.010 mmol) and KO*t*-Bu (0.90 mg, 0.0080 mmol) in *t*-amyl alcohol (400 μL) in an oven-dried 5-mL vial equipped with a stir bar was stirred at room temperature for 6 min. The vial was then capped with a septum-lined cap, removed from the glovebox, and cooled to 0 °C. Next, Ac_2O (28 μL, 0.30 mmol) was added dropwise to the reaction vial over 1 min. Then, (*R*)-1-phenylethanol (24 μL, 0.20 mmol) was added, and the reaction mixture was stirred at 0 °C. After 30 min, an aliquot (40 μL) of the reaction mixture was removed and diluted with Et_2O (1.0 mL). The ee of 1-phenylethanol was determined by chiral GC analysis.



Eq 1.2.15. In a nitrogen-filled glovebox, **C_5Ph_5-DMAP*** (20 mg, 0.030 mmol), toluene-d_8 (0.25 mL), and *t*-amyl alcohol (0.25 mL) were combined in a dry NMR tube. The NMR tube was then capped with a screw-cap and removed from the glovebox. The NMR tube was cooled to –20 °C, and then acetyl isopropyl carbonate (8.6 μL, 0.60 mmol) was added to the NMR tube via syringe. The reaction was monitored by ^{1}H NMR as a function of time. After 1.5 h at –20 °C, the acylpyridinium salt had formed almost quantitatively. The ^{1}H and ^{13}C NMR spectra of the acylpyridinium salt are included in Section VI.

Determination of the rate law: DKR of 1-phenylethanol. In a nitrogen-filled glovebox, **Ru^{Cl}**, KO*t*-Bu, tetradecane, toluene (250 μL), and *t*-amyl alcohol (250 μL) were combined in an oven-dried 4-mL vial equipped with a stir bar. The mixture was stirred at room temperature for 6 min, and then 1-phenylethanol and **C_5Ph_5-DMAP*** were added to the vial. The vial was then capped with a septum-lined cap, removed from the glovebox, and cooled to 10 °C. After cooling the solution for 10 min, acetyl isopropyl carbonate was added dropwise to the vial via syringe over 1 min. An aliquot (40 μL) of the reaction mixture was removed after 10 min, 30 min, 50 min, 80 min, and 120 min, and then filtered through a short pad of silica. The amount of the product was determined by GC analysis (calibrated with tetradecane as the internal standard).

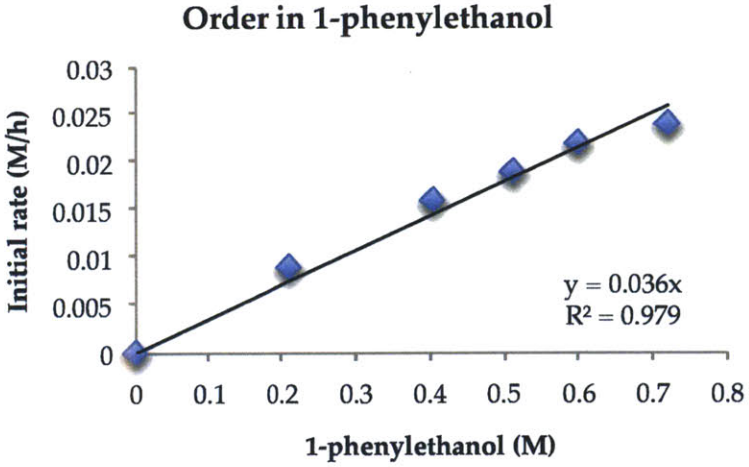
Order in 1-phenylethanol:

Table S1. Observed Initial Rates

$[1\text{-phenylethanol}]_{initial}$ (M)[a]	k_{obs} (M/h)
0.00	0.00
0.21	0.0092
0.40	0.016
0.51	0.019
0.60	0.022
0.72	0.024

[a] Reaction conditions: $[\text{acetyl isopropyl carbonate}]_{initial} = 0.75$ M, $[\mathbf{C_5Ph_5\text{-}DMAP^*}]_{initial} = 5.0$ mM, $[\mathbf{Ru^{Cl}}]_{initial} = 0.026$ M, and $[\text{KO}t\text{-Bu}]_{initial} = 0.022$ M.

Figure S1.



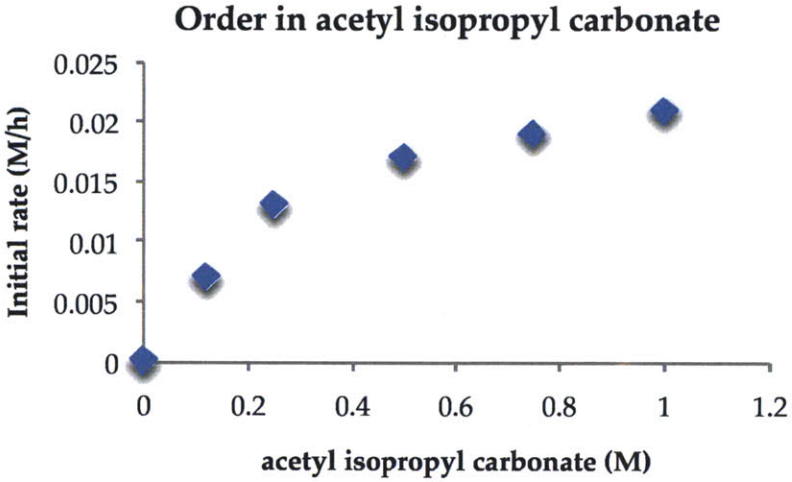
Order in acetyl isopropyl carbonate:

Table S2. Observed Initial Rates

[acetyl isopropyl carbonate]$_{initial}$ (M)[a]	k_{obs} (M/h)
0.00	0.00
0.12	0.0071
0.25	0.013
0.50	0.017
0.75	0.019
1.00	0.021

[a] Reaction conditions: [1-phenylethanol]$_{initial}$ = 0.50 M, [**C$_5$Ph$_5$-DMAP***]$_{initial}$ = 5.0 mM, [**Ru^{Cl}**]$_{initial}$ = 0.026 M, and [KO*t*-Bu] $_{initial}$ = 0.022 M.

Figure S2.



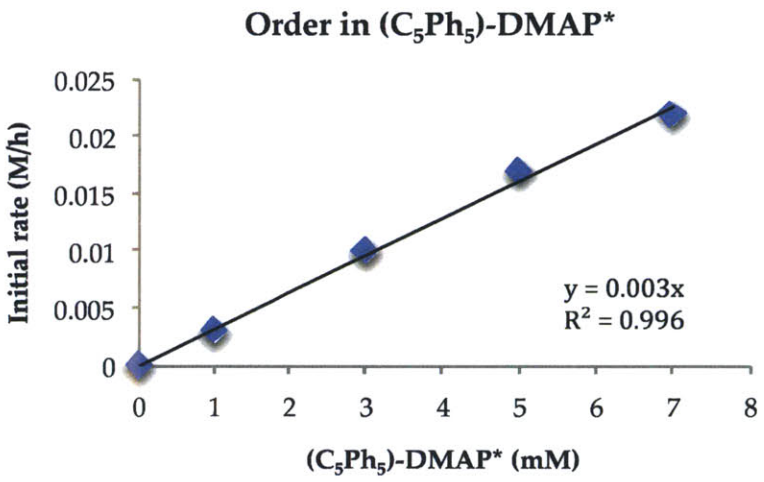
Order in C_5Ph_5-DMAP*:

Table S3. Observed Initial Rates

$[C_5Ph_5\text{-DMAP*}]_{initial}$ (mM)[a]	k_{obs} (M/h)
0.0	0.00
1.0	0.0034
3.0	0.010
5.0	0.017
7.0	0.022

[a] Reaction conditions: $[\text{1-phenylethanol}]_{initial} = 0.50$ M, [acetyl isopropyl carbonate]$_{initial} = 0.75$ M, $[\mathbf{Ru}^{Cl}]_{initial} = 0.026$ M, and $[KO\textit{t}\text{-Bu}]_{initial} = 0.022$ M.

Figure S3.



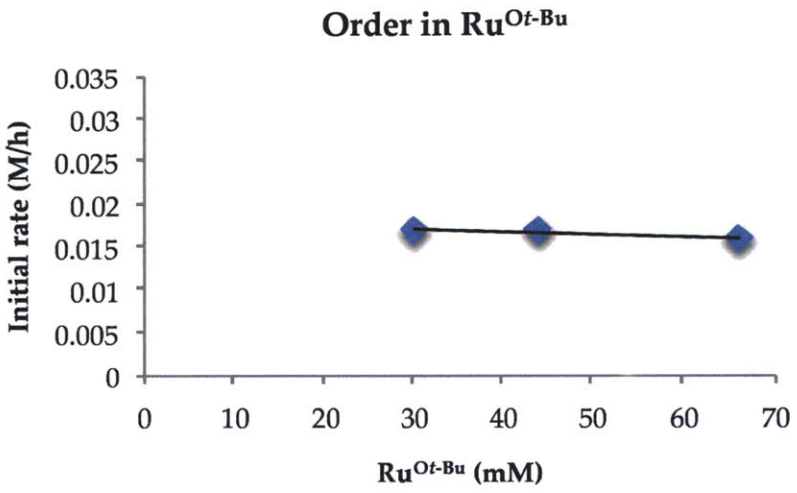
Order in ruthenium 1a:

Table S4. Observed Initial Rates

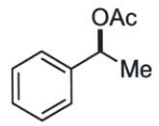
$[\mathbf{Ru}^{\mathbf{O\text{-}t\text{Bu}}}]_{initial}$ (M)[a]	k_{obs} (M/h)
0.030	0.017
0.044	0.017
0.066	0.016

[a] Reaction conditions: $[\text{1-phenylethanol}]_{initial} = 0.50$ M, $[\text{acetyl isopropyl carbonate}]_{initial} = 0.75$ M, and $[\mathbf{C_5Ph_5\text{-}DMAP^*}]_{initial} = 5.0$ mM.

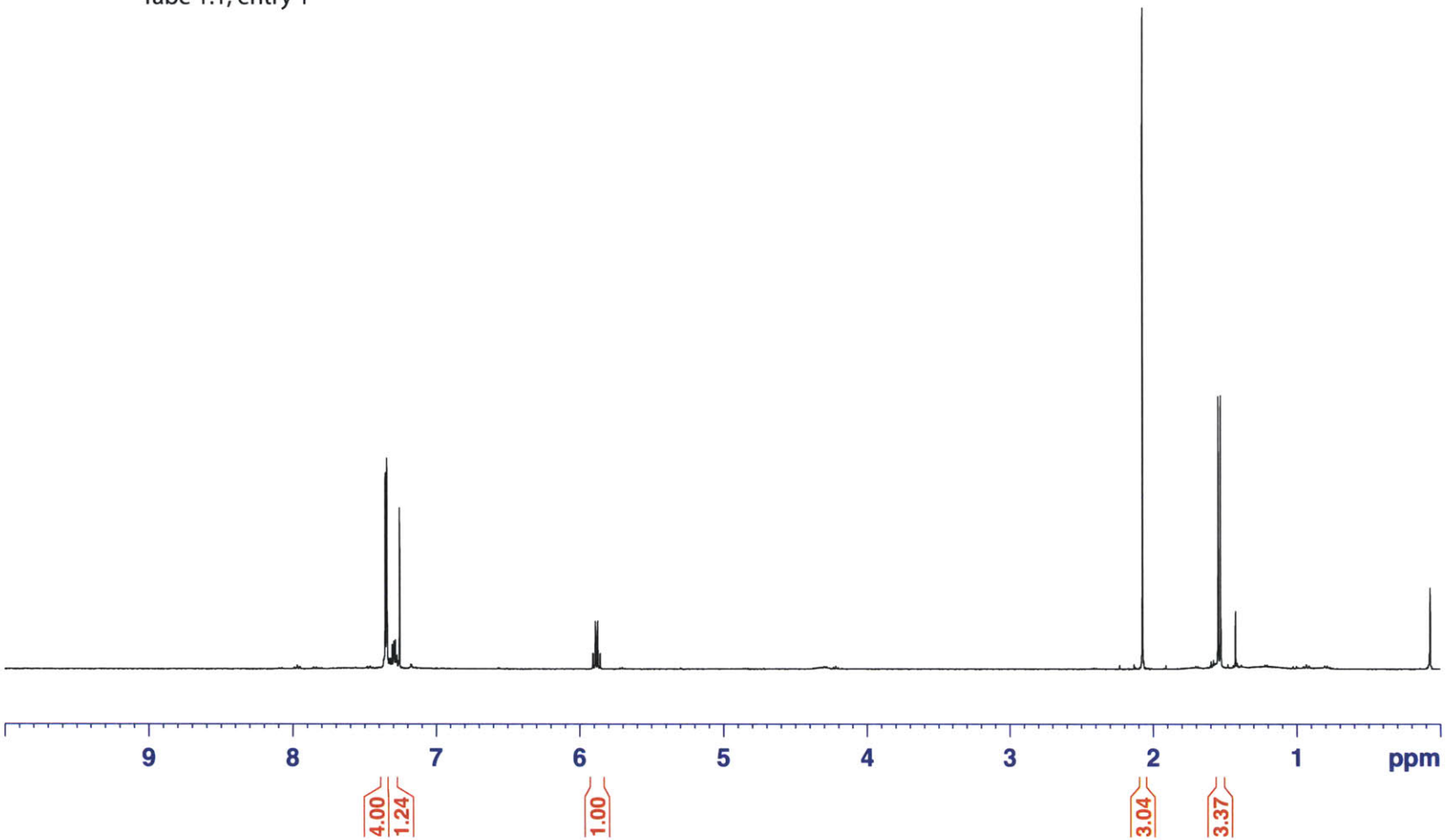
Figure S4.

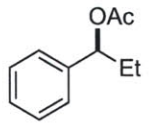


1.5. ^{1}H NMR Spectra of Selected Compounds



Tabe 1.1, entry 1





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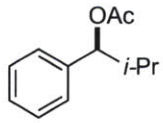

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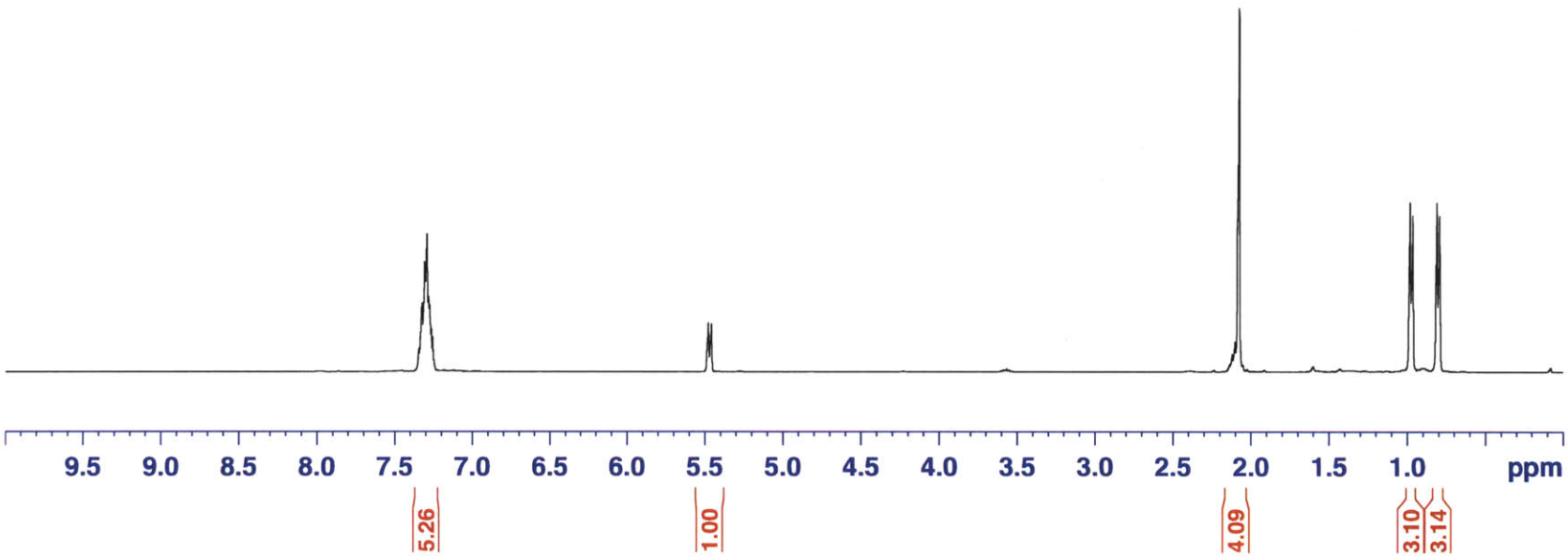

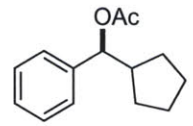

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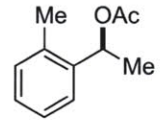

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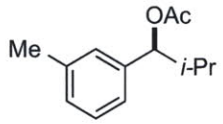

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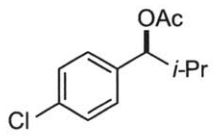

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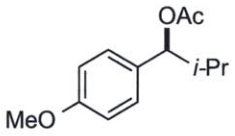

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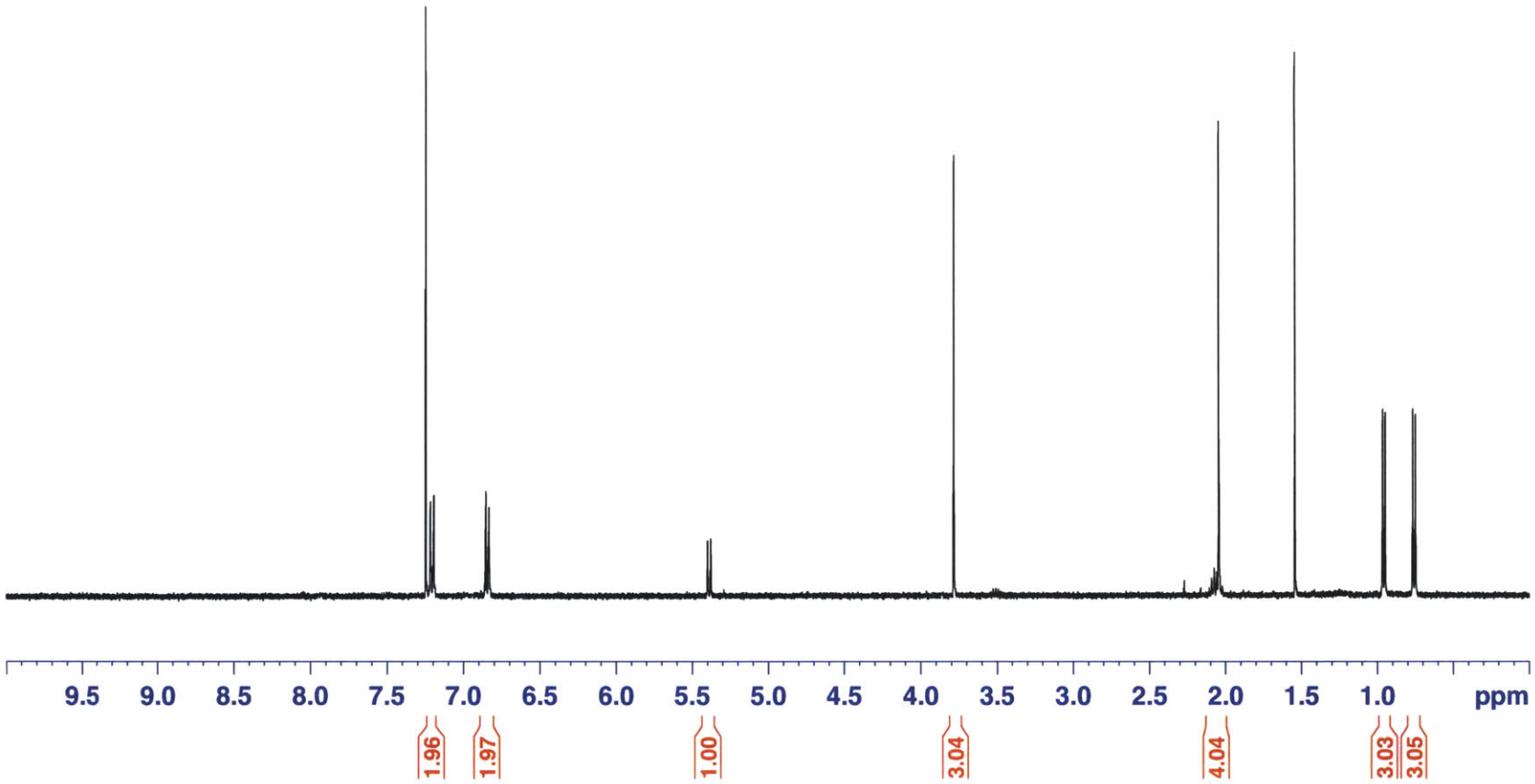

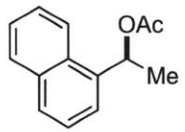

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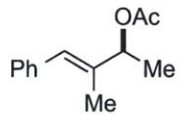

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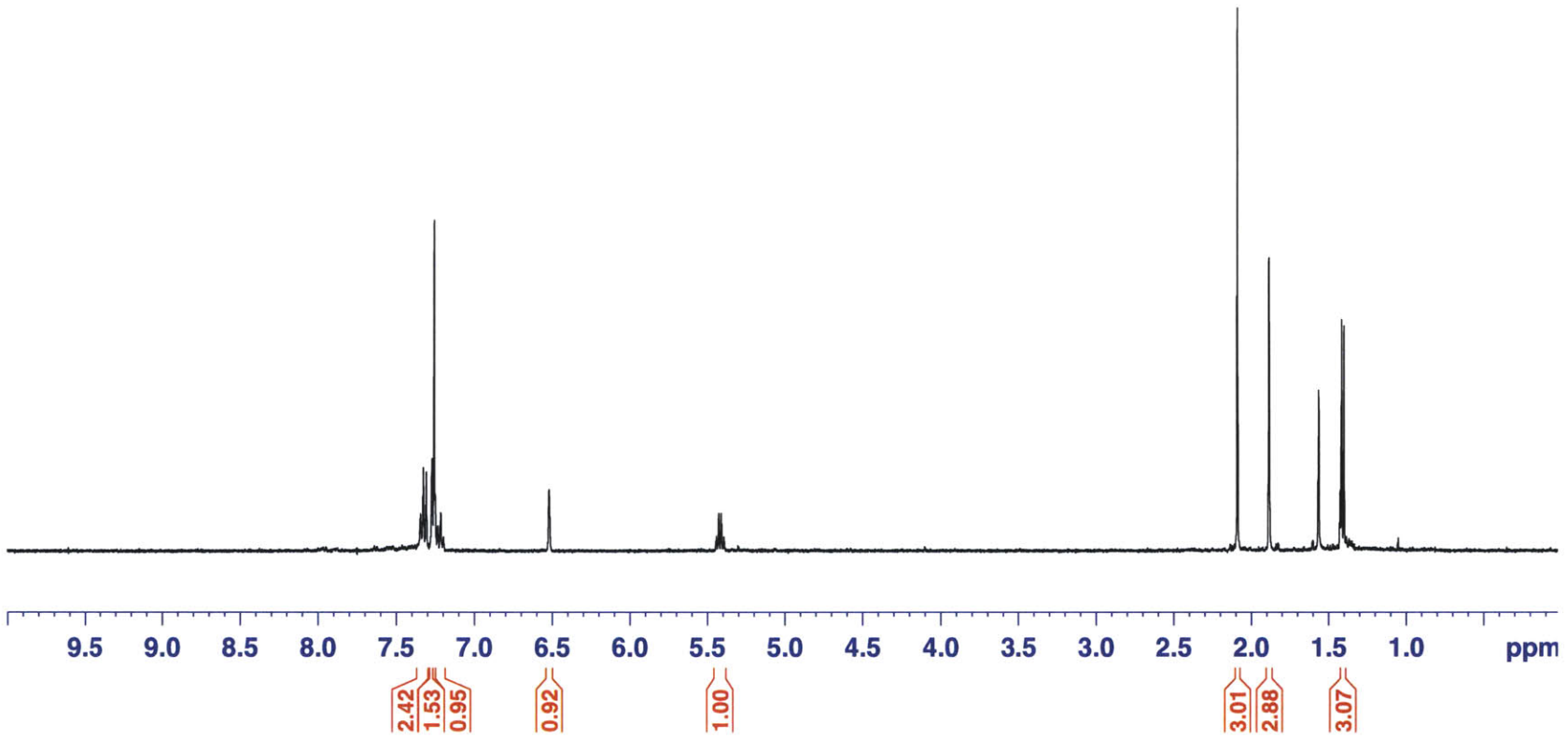
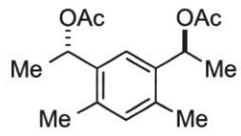
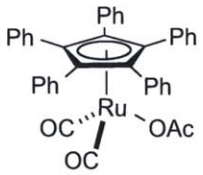


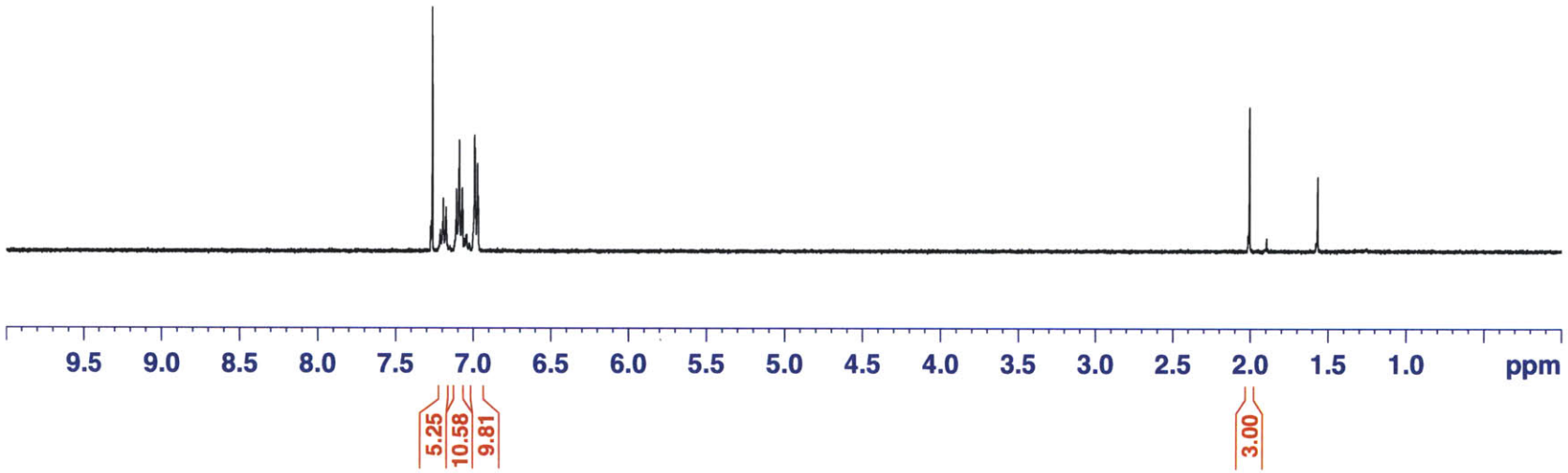

OAc
OAc
Me
Me
Me
Me

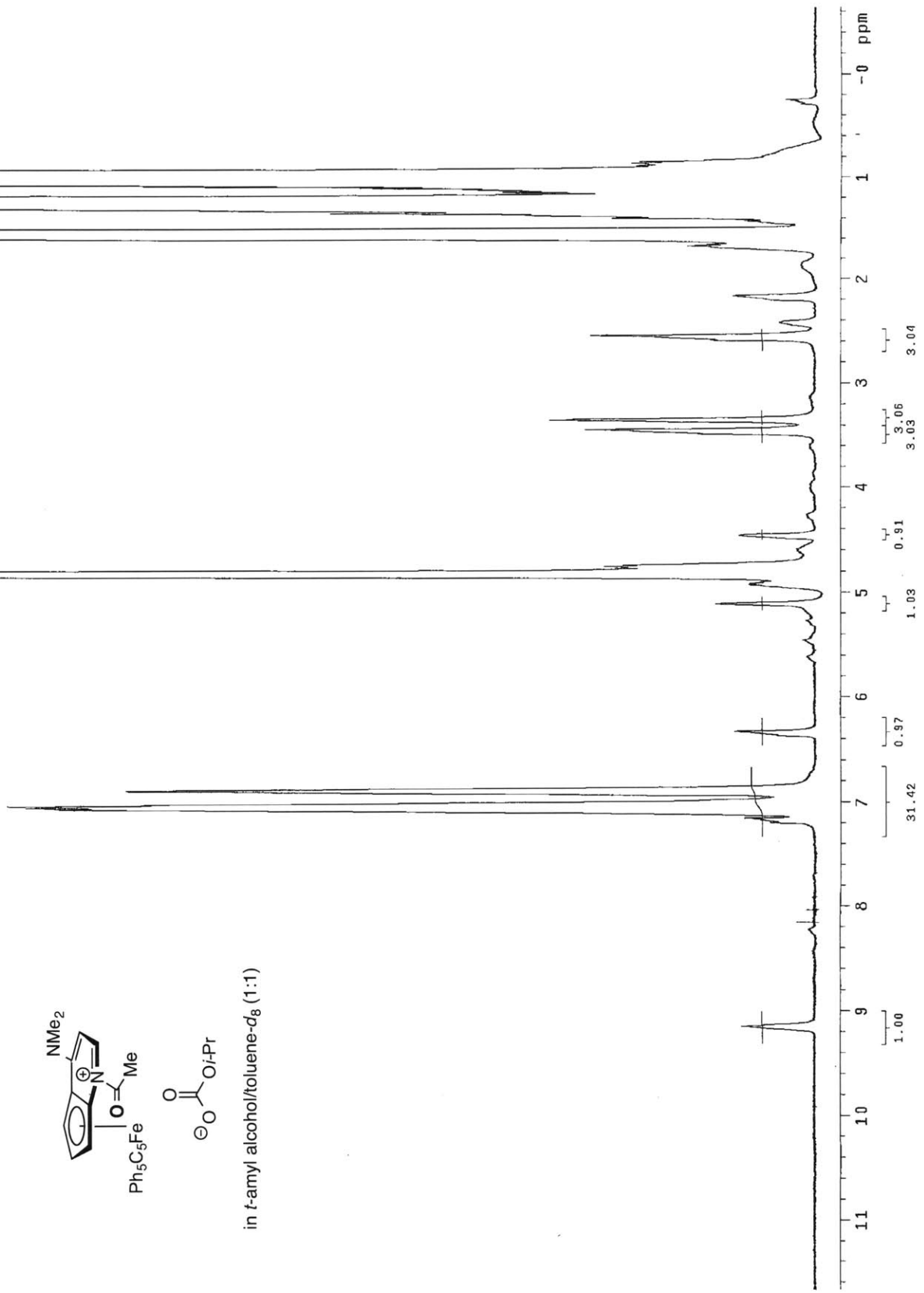
eq 1.2.10

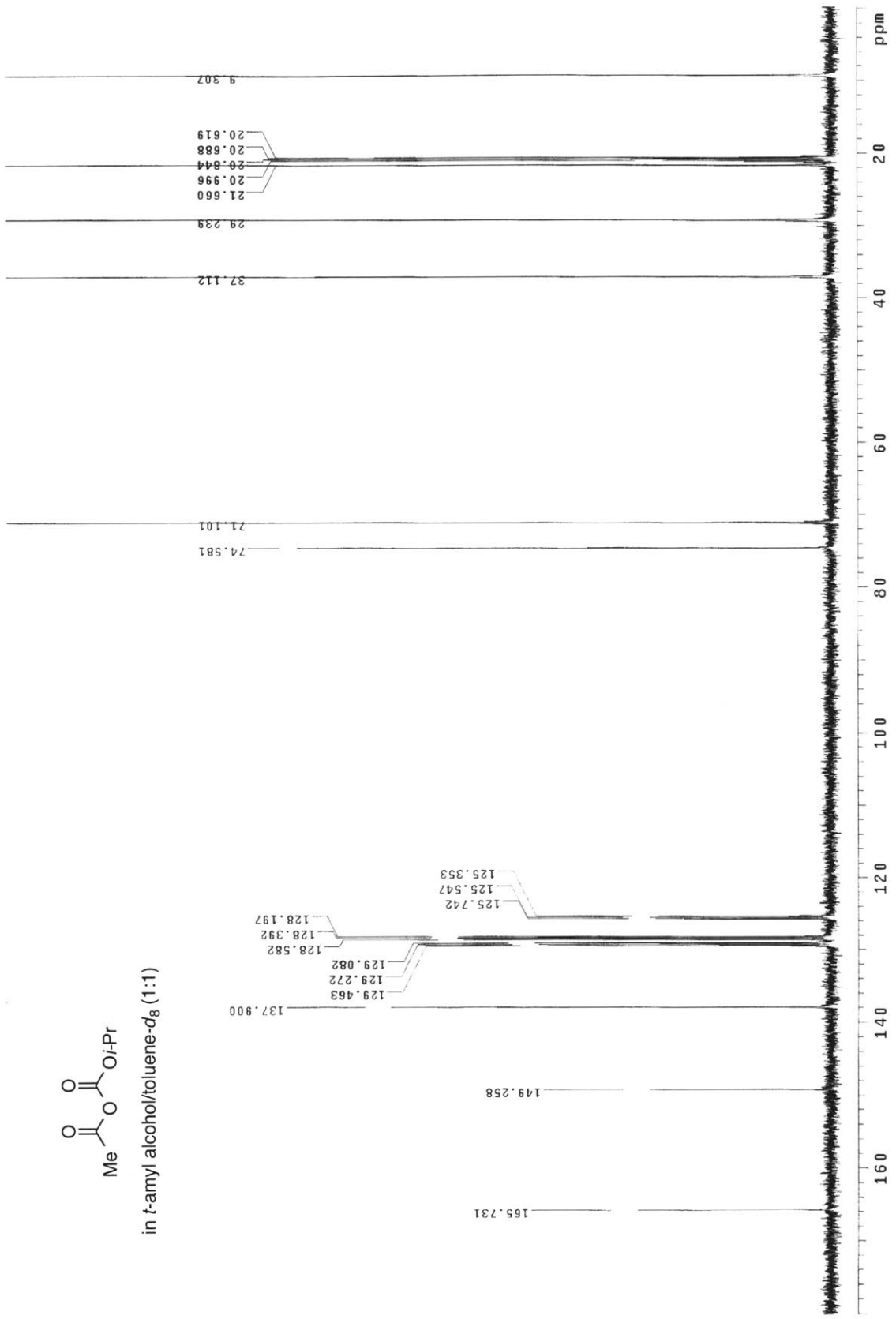
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
0.98
2.00
5.90
6.01
6.05


Ph
Ph
Ph
Ph
Ph
Ru
OC
OAc
OC

Ru^{OAc}


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
5.25
10.58
9.81
3.00


NMe2
Me
Ph5C5Fe
O
O
O
O-i-Pr
in t-amyl alcohol/toluene-d8 (1:1)
11
10
9
8
7
6
5
4
3
2
1
-0 ppm
1.00
31.42
0.97
1.03
0.91
3.06
3.03
3.04


Me
O
O
O
O
O
O-i-Pr
in t-amyl alcohol/toluene-d8 (1:1)
9.307
20.619
20.688
20.844
20.996
21.660
29.239
37.112
71.101
74.581
125.353
125.547
125.742
128.197
128.392
128.582
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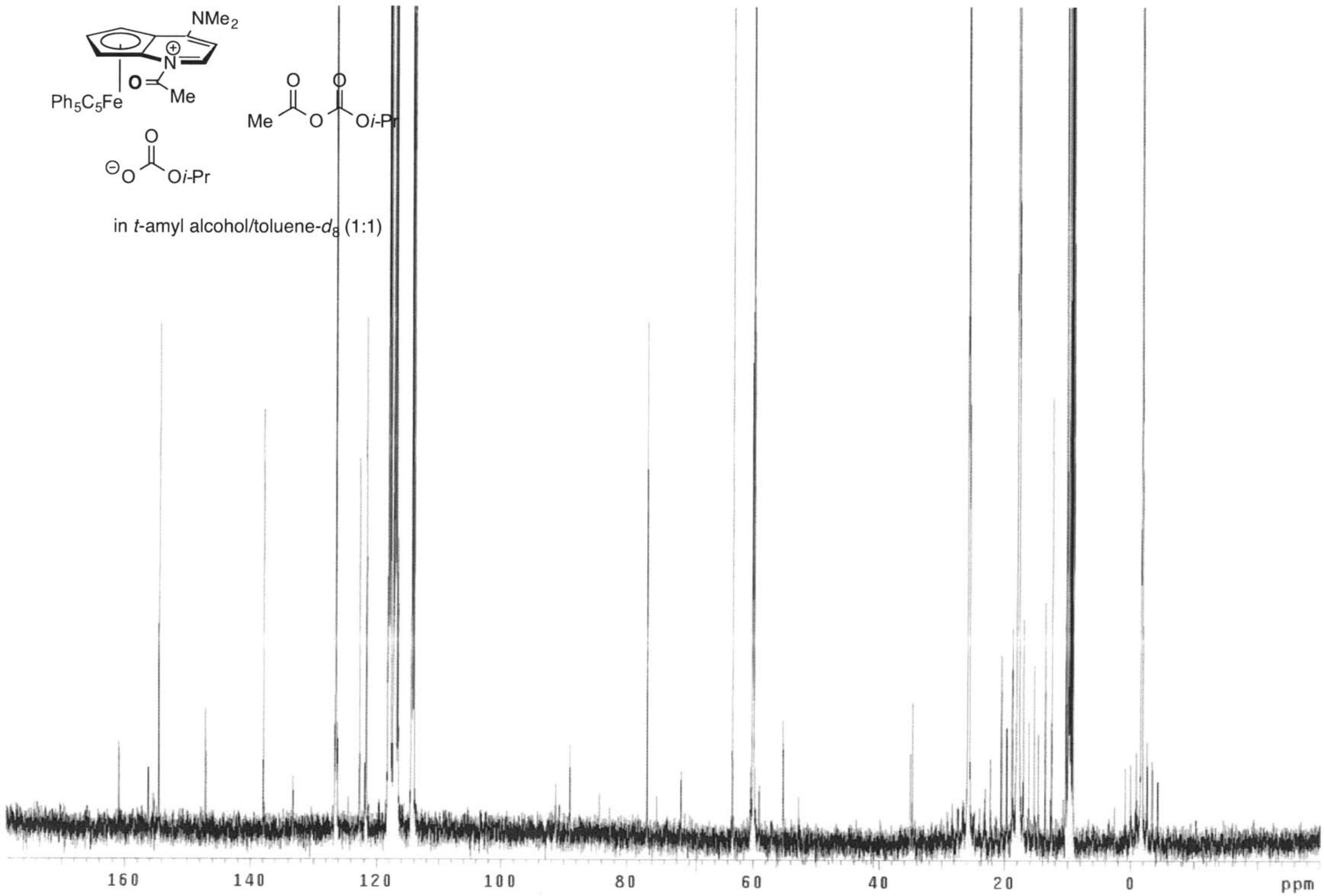
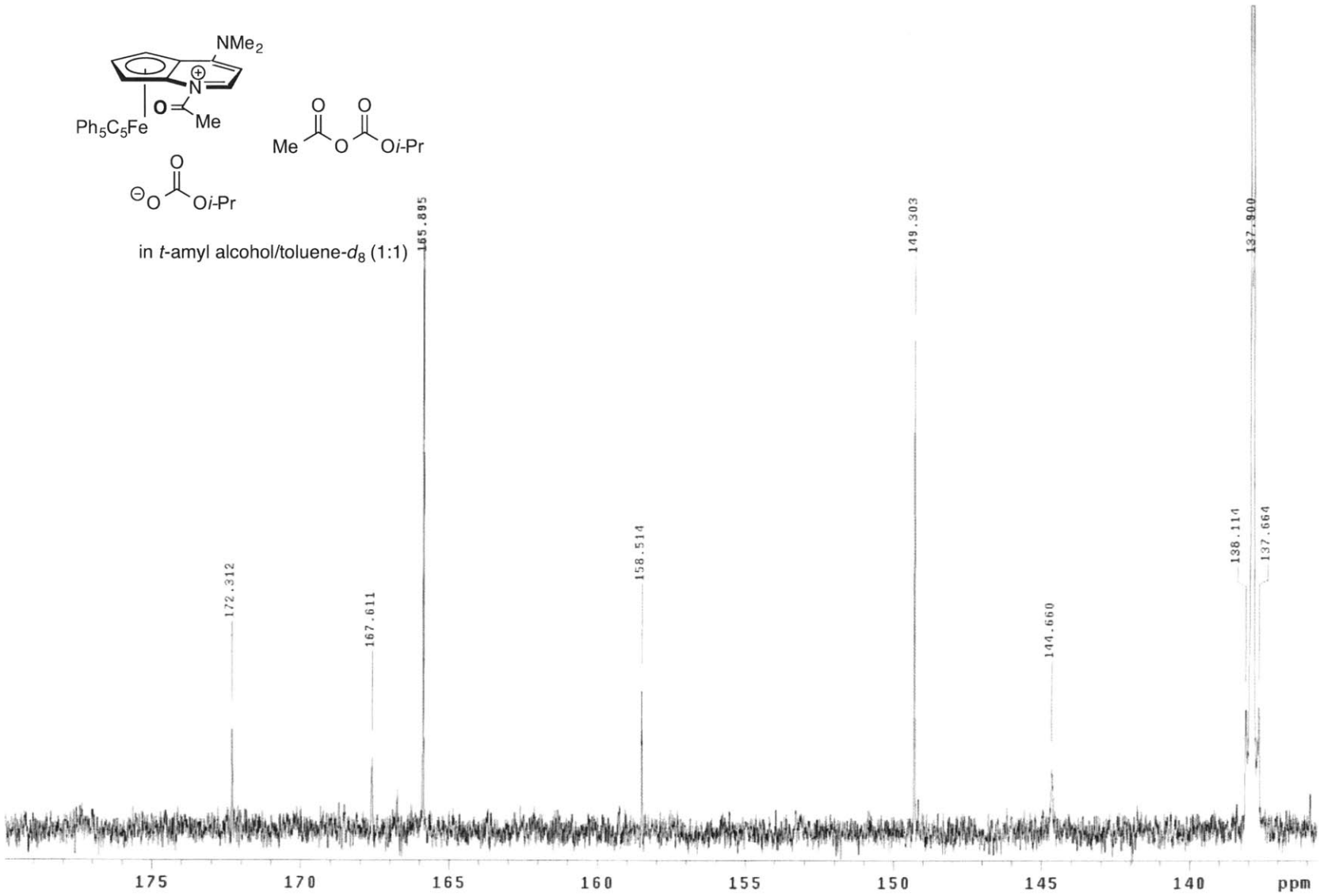
ppm
20
40
60
80
100
120
140
160


NMe2
Ph5C5Fe
Me
O
Oi-Pr
in t-amyl alcohol/toluene-d8 (1:1)
160
140
120
100
80
60
40
20
0
ppm


NMe2
Ph5C5Fe
Me
Me
O
O
O
Oi-Pr
O
O
Oi-Pr
in t-amyl alcohol/toluene-d8 (1:1)
165.895
149.303
137.900
158.514
172.312
167.611
144.660
138.114
137.664
175
170
165
160
155
150
145
140
ppm

Chapter 2.

Enantioselective Nucleophile-Catalyzed Synthesis of Tertiary Alkyl Fluorides via the α-Fluorination of Ketenes

2.1 Introduction

Owing to the properties of fluorine, such as high electronegativity, small size, and relative stability of the C–F bond, the incorporation of fluorine into organic molecules, including stereoselective processes, has become an effective tool in medicinal and pharmaceutical chemistry.[36] Therefore, a great deal of effort has been dedicated to the development of catalytic enantioselective fluorination methods, and, in particular, the α-fluorination of carbonyl compounds has received significant attention.[37]

With respect to the generation of secondary α-fluorocarbonyl compounds, asymmetric catalysis has been well established for achieving high levels of enantioselectivity and high yields for a wide range of substrates, including α-fluoroaldehydes, esters, and amides.[38, 39] For example, Lectka established the asymmetric α-fluorination of acid chlorides with *N*-fluorodibenzenesulfonimide (NFSI) as an electrophilic fluorinating agent[40], catalyzed by a cinchona alkaloid in combination with a transition-metal complex, furnishing an array of secondary alkyl fluorides (eq

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[36] For example, see: (a) *Fluorine in Pharmaceutical and Medicinal Chemistry*; Gouverneur, V., Müller, K., Eds.; Imperial College Press: London, 2012. (b) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; John Wiley & Sons: Chichester, United Kingdom, 2009.

[37] For reviews that include catalytic asymmetric fluorination, see: (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264. (b) Gouverneur, V.; Lozano, O. In *Science of Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Georg Thieme: Stuttgart, Germany, 2011; Volume 3, pp 851–930. (c) Valero, G.; Companyó, X.; Rios, R. *Chem. Eur. J.* **2011**, *17*, 2018–2037. (d) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558–568. (e) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708–2732.

[38] For pioneering examples of catalytic, asymmetric α-fluorinations of aldehydes, see: (a) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703–3706. (b) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem. Int. Ed.* **2005**, *44*, 3706–3710. (c) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828.

[39] (a) Paull, D. H.; Scerba, M. T.; Alden-Danforth, E.; Widger, L. R.; Lectka, T. *J. Am. Chem. Soc.* **2008**, *130*, 17260–17261. (b) Erb, J.; Paull, D. H.; Dudding, T.; Belding, L.; Lectka, T. *J. Am. Chem. Soc.* **2011**, *133*, 7536–7546.

[40] For a review of electrophilic N–F fluorinating agents, see: Baudoux, J.; Cahard, D. *Org. React.* **2007**, *69*, 347–672.

2.1.1.).[39a] A proposed mechanism by Lectka (Figure 2.1) involves in situ generation of mono-substituted ketene **2.1**, which is then activated by cinchona alkaloid **BQd** and a transition metal catalyst to form chiral enolate **2.2**. Fluorine transfer from NFSI to enolate **2.2** leads to an acyl ammonium salt (**2.3**), which subsequently furnishes bis(sulfonimide) intermediate **2.4** by the nucleophilic attack of the $N(SO_2Ph)_2$ anion. Finally, the added nucleophile reacts with intermediate **2.4** in a transacylation process to create the final fluorinated product; depending on the added nucleophile, a variety of enantioenriched, secondary α-fluorinated carbonyl compounds, including esters, carboxylic acids, and amides, can be generated.

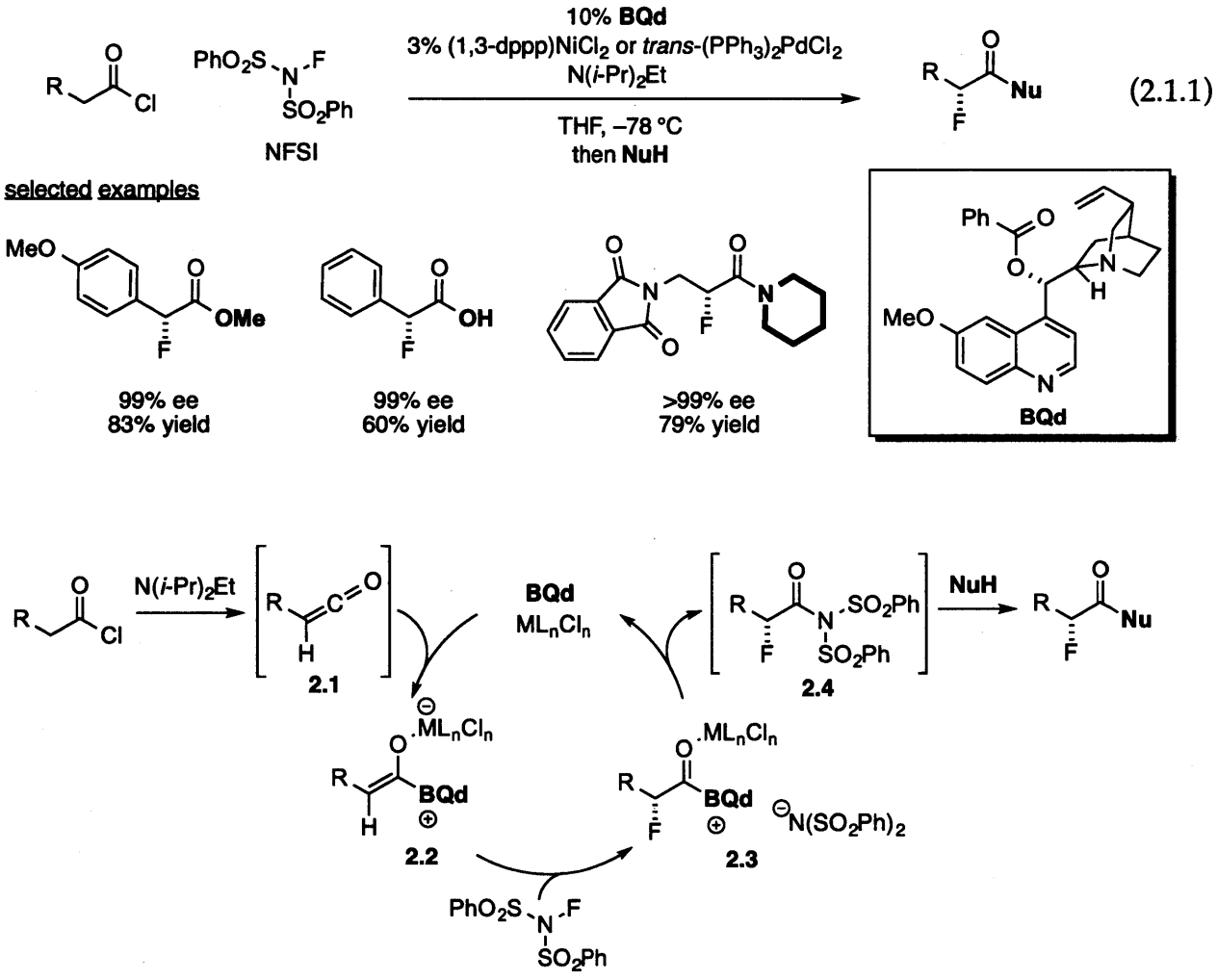

Figure 2.1. A proposed mechanism for the **BQd**/ML_nCl_n-catalyzed asymmetric α-fluorination of an acid chloride

In contrast, there has been limited progress in the development of catalytic asymmetric fluorination methods for the synthesis of tertiary alkyl fluorides.[41,42,43] Specifically, successful methods have focused largely on doubly activated α-fluorocarbonyl compounds, such as β-ketoesters and α-cyanoesters.[37] A pioneering example of the catalytic asymmetric synthesis of such compounds is Togni' electrophilic fluorination of branched β-ketoesters with Selectfluor catalyzed by a titanium TADDOL[44] complex (**2.5**) (eq 2.1.2).[45] This process is believed to proceed through the formation of a metal enolate, and the steric bulk of the titanium complex is responsible for the discrimination of two enantiotopic faces of the p system by the electrophilic fluorine source. Despite advances with respect to doubly activated molecules, we are not aware of any fluorination approaches that afford simple tertiary α-fluoroesters in enantioenriched form.[46]

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[41] For examples of oxindoles, see: (a) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 4204–4207. (b) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165. (c) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4157–4161. (d) Wu, L.; Falivene, L.; Drinkel, E.; Grant, S.; Linden, A.; Cavallo, L.; Dorta, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 2870–2873.

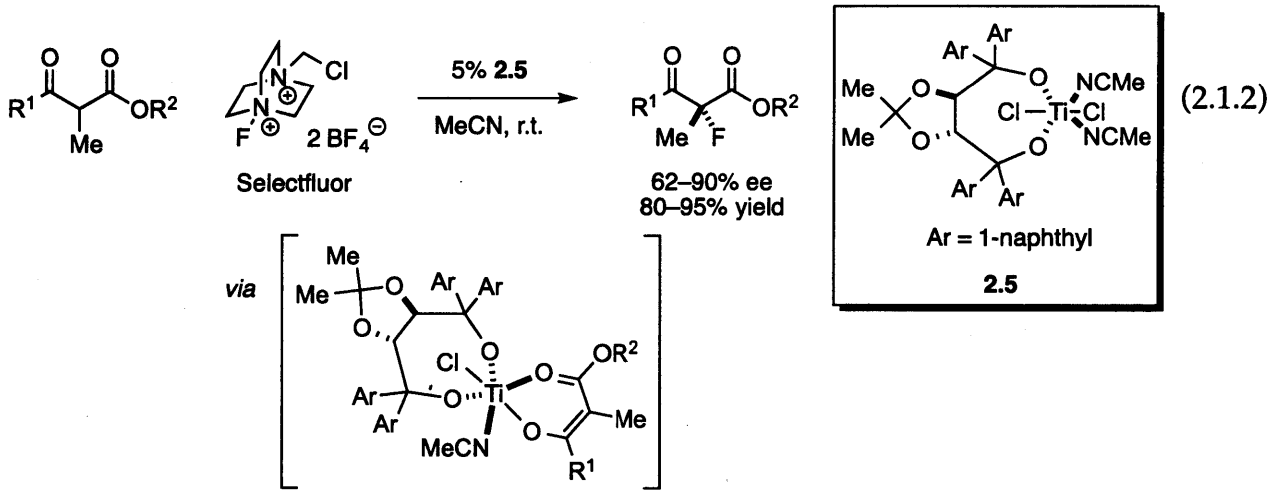
[42] For examples of ketones, see: (a) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035. (b) Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 1268–1271. (c) Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225–5228.

[43] For a few examples of the catalytic enantioselective synthesis of other families of tertiary alkyl fluorides, see: (a) Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376–8379. (b) Shunatona, H. P.; Früh, N.; Wang, Y.-M.; Rauniyar, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 7724–7727. (c) Wu, J.; Wang, Y.-M.; Drljevic, A.; Rauniyar, V.; Phipps, R. J.; Toste, F. D. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 13729–13733.

[44] TADDOL = α,α,α′,α′-tetraaryl-2,2,-dimethyl-1,3-dioxolan-4,5-dimethanol

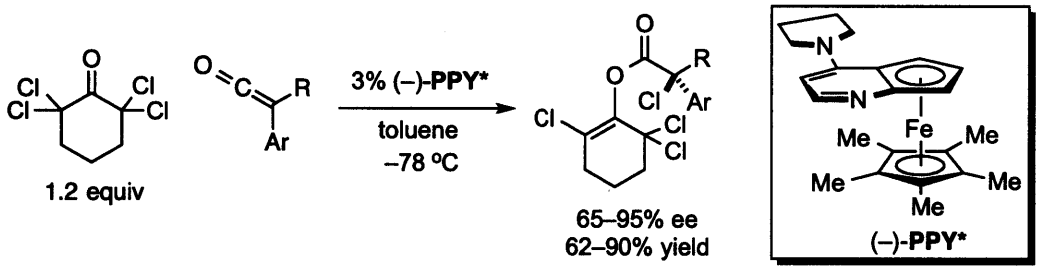
[45] Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4359–4362.

[46] For an example of a bioactive tertiary α-fluoroester, see: Yasuhara, A.; Nakamura, M.; Sakagami, K.; Shimazaki, T.; Yoshikawa, R.; Chaki, S.; Ohta, H.; Nakazato, A. *Bioorg. Med. Chem.* **2006**, *14*, 4193–4207.



(2.1.2)

In an earlier study, our group established that a planar-chiral catalyst, **PPY***,[47] can catalyze the enantioselective chlorination of aryl alkyl ketenes to produce tertiary α-chloroesters in good enantioselectivity and yield when 2,2,6,6-tetrachlorocyclohexanone is employed as the electrophilic chlorinating agent (eq 2.1.3).[48]



(2.1.3)

Two possible mechanisms were proposed for this **PPY***-catalyzed chlorination process (Figure 2.2; A and B).[49] In one mechanism, a key intermediate is chiral enolate **2.6**, which is formed by the nucleophilic addition of **PPY*** to the ketene. In an alternative

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[47] Both enantiomers of **PPY*** are commercially available.

[48] Lee, E. C.; McCauley, K. M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 977–979.

[49] We have hypothesized that planar-chiral DMAP derivatives can serve both as asymmetric nucleophilic catalysts (e.g., Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542–547) and, in protonated form, as enantioselective Brønsted-acid catalysts (e.g., Dai, X.; Nakai, T.; Romero, J. A. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 4367–4369). The catalytic cycle for the Brønsted-acid mode of reactivity parallels the chiral fluorinating agent pathway (substitution of Cl–catalyst* with H–catalyst* in Figure 2.2).

mechanism, **PPY*** reacts with 2,2,6,6-tetrachlorocyclohexanone, rather than the ketene, to generate the N-chlorinated catalyst which serves as a chiral chlorinating agent (**2.7**). The following observations were made: (1) The resting state of the catalyst during the reaction is **PPY*** itself. (2) No reaction is observed between **PPY*** and 2,2,6,6-tetrachlorocyclohexanone at –78 °C or room temperature. (3) The ee value of the product correlates with the ee of **PPY***. However, these observations did not rule out either pathway.

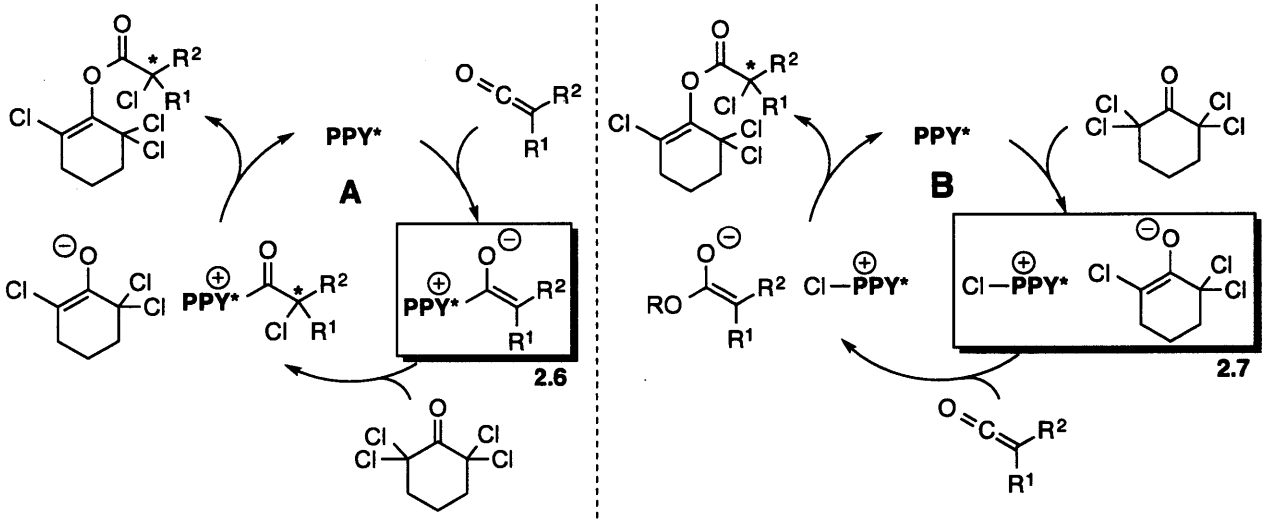

Figure 2.2. Two possible mechanisms for **PPY***-catalyzed asymmetric chlorinations: A) by means of a chiral enolate; B) by means of a chiral chlorinating agent

Cognizant of the paucity of general fluorination methods for the catalytic asymmetric synthesis of tertiary alkyl fluorides, and the synthetic potential of the target method in medicinal chemistry, we decided to pursue the development of **PPY***-catalyzed α-fluorination processes with the use of disubstituted ketenes and an appropriate fluorinating agent, building on our chlorination method for the synthesis of tertiary alkyl chlorides (2.1.3).[50]

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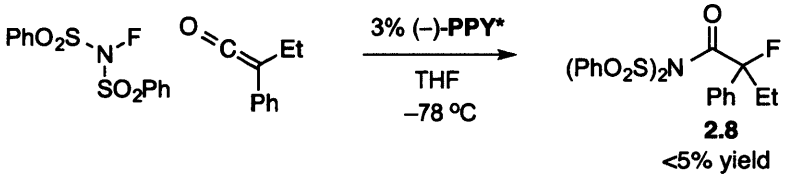
[50] This work is a collaborative effort between Dr. Stefan Neufeind and the author. Dr. Neufeind initiated this project and made a critical contribution to the optimization of the reaction conditions. The author identified the final reaction conditions and conducted all the mechanistic investigations. The author carried out all the experiments presented in this chapter.

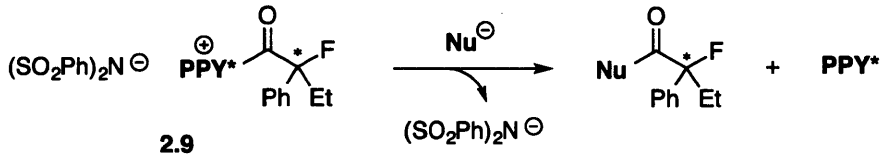
2.2 Results and Discussion

A considerable number of electrophilic fluorinating agents have been reported and employed in electrophilic fluorinations.[40] We were particularly interested in the use of NFSI as a fluorine source, as it is stable, easy-to-handle, and commercially available. We hypothesized that bis(sulfonimide) compound **2.8** might be formed through a similar mechanism to our chlorination example (eq 2.1.3); unfortunately, we obtained discouraging results (<5% yield) (eq 2.2.1).



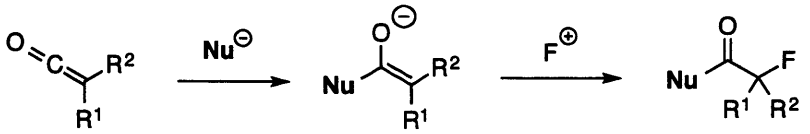
(2.2.1)

We considered the possibility that our failure might be due to the stability of a potential *N*-acylpyridinium intermediate containing an $N(SO_2Ph)_2$ anion (**2.9**). Therefore, we decided to investigate the addition of more reactive nucleophiles, which might be able to attack at the electrophilic carbonyl carbon of **2.9** to generate the corresponding tertiary α-fluorocarbonyl compound and regenerate the catalyst (eq 2.2.2).



(2.2.2)

Of course, we were aware that the added nucleophile could potentially react with the ketene, thereby generating the racemic fluorinated product via the electrophilic fluorination of an achiral enolate (eq 2.2.3). Thus, it was assumed that in order to achieve both high selectivity and yield of the asymmetric fluorination, we needed to identify a nucleophile that reacts preferentially with intermediate **2.9**, rather than the ketene, under the fluorination conditions.



(2.2.3)

Whereas the addition of MeOH or $PhNH_2$ did not lead to the formation of a significant amount of the desired tertiary alkyl fluoride (Table 2.1,[51] entries 1 and 2), employing metal alkoxides provided a substantial quantity of the corresponding tertiary α-fluoroesters (entries 3–7). When sodium *tert*-butoxide was used, racemic product was obtained (entry 3); on the other hand, sodium phenoxide furnished promising yield and enantioselectivity (entry 4). Encouraged by this result, we explored other metal phenoxides, and we determined that a less nucleophilic phenoxide, sodium pentafluorophenoxide, afforded the product with 99% ee and in 98% yield (entry 6).[52] It is noteworthy that only 1% of the undesired non-fluorinated pentafluorophenyl ester was observed by GC analysis of the unpurified reaction mixture, since it is difficult to separate from the desired fluorinated product by simple column chromatography.[53] Potassium pentafluorophenoxide provided a comparable result to the sodium salt (entry 7), and sodium 4-methoxyphenoxide, which is more nucleophilic compared to simple phenoxide, resulted in lower yield and ee of the product (entry 5).

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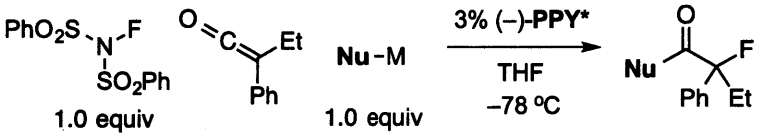
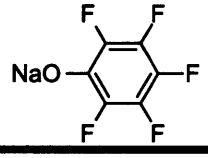
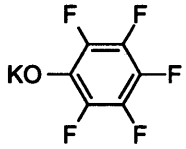
[51] Notes on Table 2.1: (a) Phenyl ethyl ketene (solution in THF) and **Nu**–M (solution in THF) were added dropwise over 2 h via syringe pump simultaneously to the reaction mixture. (b) NFSI was purchased and recrystallized from dichloromethane/*n*-hexanes prior to use.

[52] Notes: (a) When we employed NFSI that was used as received from Alfa Aesar or Oakwood Chemicals (clean by $^1H/^{19}F$ NMR spectroscopy), the fluorination of phenyl ethyl ketene described in entry 6 of Table 2.1 proceeded in 88% yield and 97% ee (with 7% of the corresponding non-fluorinated pentafluorophenyl ester). (b) When Selectfluor is employed in place of NFSI, the fluorination of phenyl ethyl ketene illustrated in entry 6 of Table 2.1 proceeded in <5% yield.

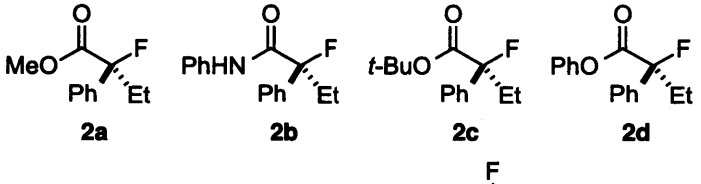
[53] The non-fluorinated and the fluorinated esters can be separated by using preparative HPLC on a C18-column (reverse phase; 20% water in acetonitrile as the eluent).

Table 2.1. Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides: Effect of Added Nucleophile[a]

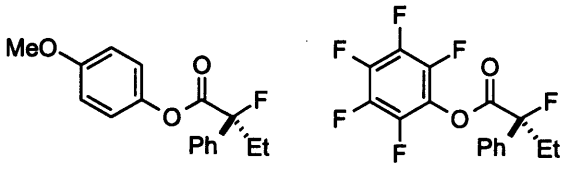


entry	Nu–M	product	ee (%)	yield (%)[b]
1	MeOH	**2a**	–	–
2	$PhNH_2$	**2b**	33	<5
3	NaO*t*-Bu	**2c**	<2	54
4	NaOPh	**2d**	88	79
5		**2e**	59	58
6		**2f**	99	98[c]
7		**2f**	99	98

[a]All data are the average of two experiments. [b]Determined through GC analysis with the aid of an internal standard. [c]Yield of purified product.



2a **2b** **2c** **2d**



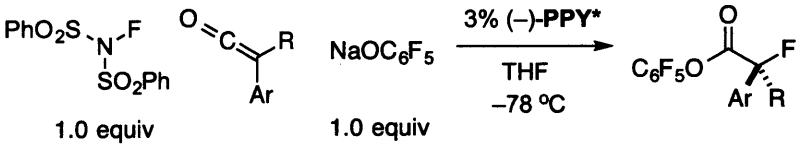
2e **2f**

When phenyl ethyl ketene was treated with 1 equivalent of $NaOC_6F_5$ at –78 °C in THF-d_8, no interaction was observed by $^1H/^{19}F$ NMR spectroscopy, presumably due to the relatively low nucleophilicity of $NaOC_6F_5$. This observation is consistent with the stereochemical outcome when employing $NaOC_6F_5$ in our fluorination of phenyl ethyl ketene (Table 2.1, entry 6). In contrast, phenyl ethyl ketene rapidly reacted with NaO*t*-

Bu to generate the corresponding achiral enolate at –78 °C in THF-d_8, accounting for the low product ee with the use of NaO*t*-Bu in the **PPY***-catalyzed fluorination (Table 2.1, entry 3).

We can achieve the catalytic asymmetric α-fluorination of an array of aryl alkyl ketenes for the synthesis of tertiary alkyl fluorides (Table 2.2). Reactions of phenyl alkyl ketenes in which the alkyl group ranges in size from methyl to cyclopentyl proceed with good to excellent enantiomeric excess (entries 1–5; lower ee is observed with larger alkyl groups). Furthermore, the aromatic ring can be meta- or para-substituted (entries 6–9), or an extended π system (entry 10). Finally, a heteroaryl-substituted ketene proved to be a suitable substrate (entry 11). On a gram scale, the fluorination illustrated in entry 2 of Table 2.2 proceeded in 99% ee and 90% yield.

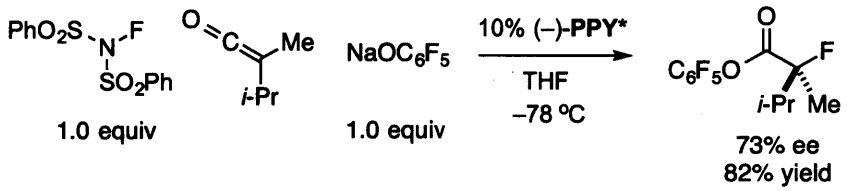
***Table* 2.2.** Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides[a]



entry	Ar	R	ee (%)	yield (%)[b]
1	Ph	Et	99	98
2	Ph	Me	98	92
3	Ph	*i*-Bu	95	95
4	Ph	Bn	78	96
5[c]	Ph	cyclopentyl	80	84
6	4-ClC_6H_4	Et	97	86
7	4-MeC_6H_4	Et	97	92
8	4-(OMe)C_6H_4	Et	97	91
9	3-MeC_6H_4	Et	97	97
10	2-naphthyl	Et	94	89
11	3-thiophenyl	*i*-Bu	98	94

[a]All data are the average of two experiments. [b]Yield of purified product (contains ≤5% of the non-fluorinated pentafluorophenyl ester). [c]Catalyst loading: 10%.

In addition, **PPY*** can be applied to the asymmetric α-fluorination of a dialkyl ketene. When methyl isopropyl ketene is subjected to our fluorination conditions, the corresponding tertiary α-fluoroester can be isolated with promising ee (eq 2.2.4); it is interesting to note that our **PPY***-catalyzed reactions of ketenes have generally not been effective for dialkyl ketenes,[54] including our α-chlorination method (2.1.3).[48]



(2.2.4)

Although successful in many instances, we have found some limitations of this new fluorination method (Figure 2.3). For example, *o*-tolyl ethyl ketene provided the corresponding tertiary alkyl fluoride with only 50% ee under our standard fluorination conditions. Additionally, when employing phenyl isopropyl ketene or *tert*-butyl ketene, none of the desired fluorination product was observed. Surveying various reaction parameters did not improve these results.

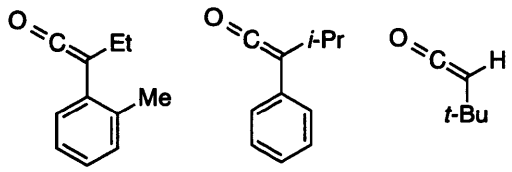


Figure* 2.3.** Unsuccessful substrates in **PPY-catalyzed enantioselective α-fluorinations of ketenes

The enantioenriched α-fluoro pentafluorophenyl esters that are generated in this catalytic asymmetric C–F bond-forming process can be derivatized through reactions with nucleophiles to a methyl ester, an acid, an amide, and an alcohol (Figure 2.4).

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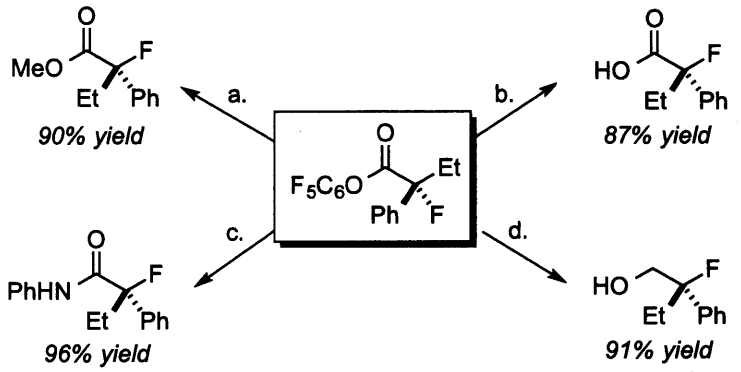
[54] For the exception, see: Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6358–6360.

These functionalizations proceed under mild conditions in good yield with no erosion in enantiomeric excess.



Conditions: (a) 5 equiv Et_3N, MeOH/THF, r.t.; (b) 5 equiv Et_3N, H_2O/THF, r.t.; (c) 1.5 equiv $PhNH_2$, 1.5 equiv Et_3N, THF, 65 °C; (d) 1.5 equiv $NaBH_4$, THF, r.t.

Figure 2.4. Transformations of an enantioenriched tertiary α-fluoroester

Like our **PPY***-catalyzed chlorination method (Figure 2.2),[48] two possible pathways can be envisioned for the **PPY***-catalyzed enantioselective fluorination of ketenes that furnishes enantioenriched tertiary α-fluoroesters (Figure 2.5).[49] In one mechanism, a key intermediate is a **PPY***-derived chiral enolate (**2.10**) (Figure 2.5; pathway A). In the other mechanism, a **PPY***-derived chiral fluorinating agent (**2.11**) is afforded by the reaction of **PPY*** with NFSI; the $N(SO_2Ph)_2$ anion then reacts with the ketene to generate another ion pair (**2.12**), which undergoes the C–F bond-forming step (Figure 2.5; pathway B). The added nucleophile, $NaOC_6F_5$, participates in the final step of both mechanisms to produce tertiary α-fluoroesters.

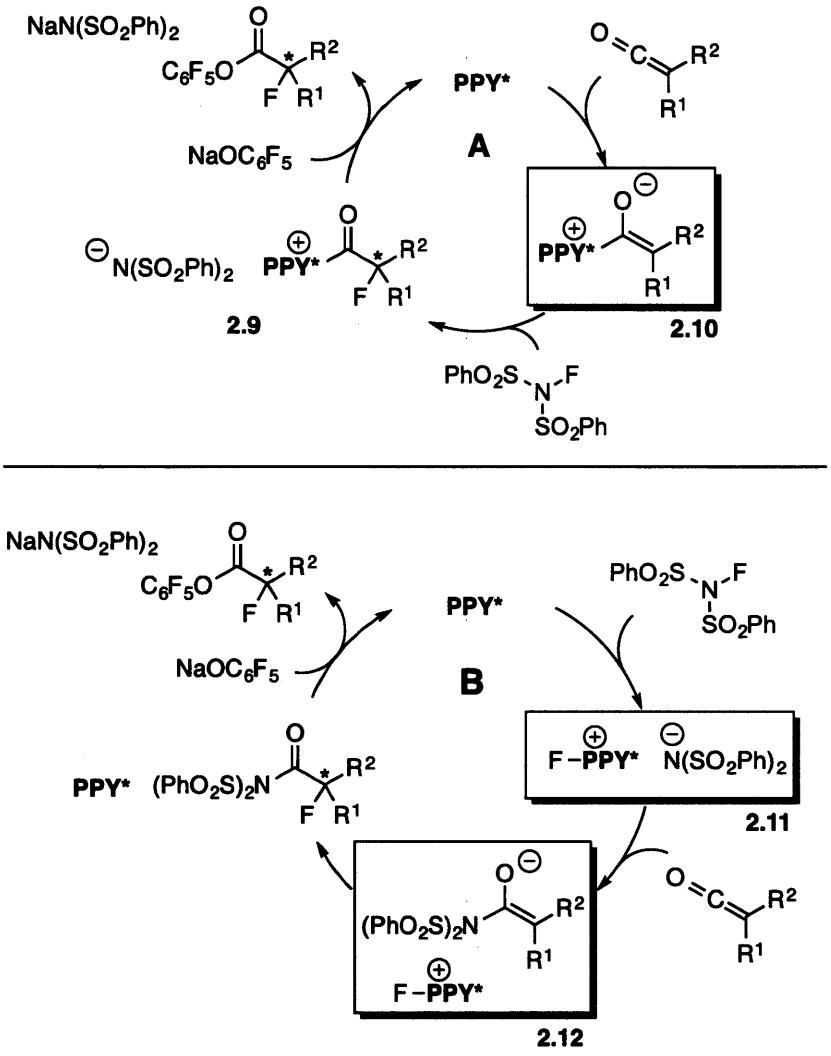


Figure 2.5. An outline of two possible mechanisms for the **PPY***-catalyzed enantioselective α-fluorination of ketenes: A) by means of a chiral enolate (top); B) by means of a chiral fluorinating agent (bottom)

To gain insight into the operative pathway, we determined the rate law for the fluorination of phenyl ethyl ketene, which is first order in **PPY***, first order in NFSI, and zeroth order in both phenyl ethyl ketene and $NaOC_6F_5$. Furthermore, the catalytic reaction rate does vary upon the choice of ketene (Figure 2.6), suggesting that the ketene is involved in the rate-determining step.

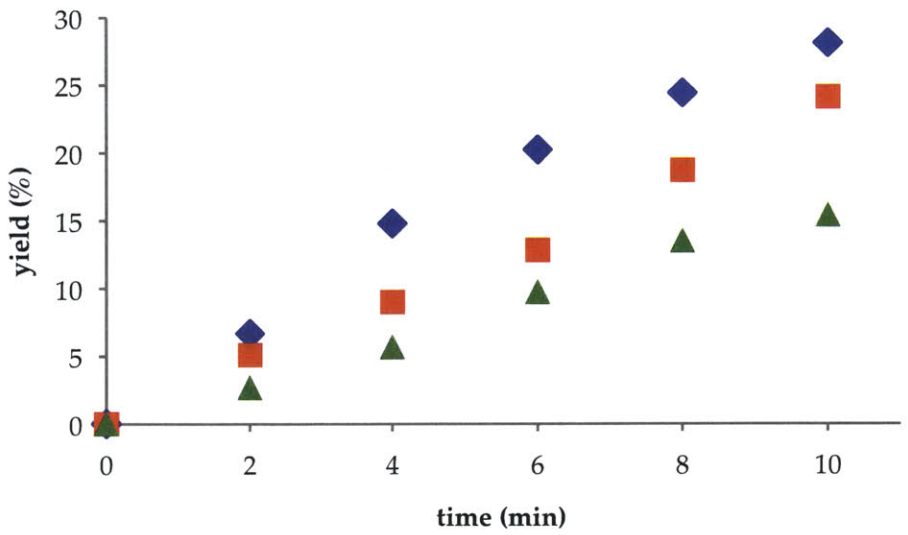


Figure 2.6. Comparison of reaction rates: fluorination of phenyl methyl ketene (◆), phenyl ethyl ketene (■), and phenyl isobutyl ketene (▲) catalyzed by **PPY***

A "chiral enolate" pathway accommodates these kinetic data (Figure 2.5; pathway A). The nucleophilic addition of **PPY*** to the ketene affords chiral enolate **2.10**, which is the resting state of the catalytic cycle,[55] and in the turnover-limiting step, this enolate is fluorinated by NFSI, generating the enantioenriched α-fluorinated acylpyridinium salt (**2.9**). Acyl transfer with $NaOC_6F_5$ then produces the tertiary α-fluoroester and regenerates the catalyst, **PPY***.

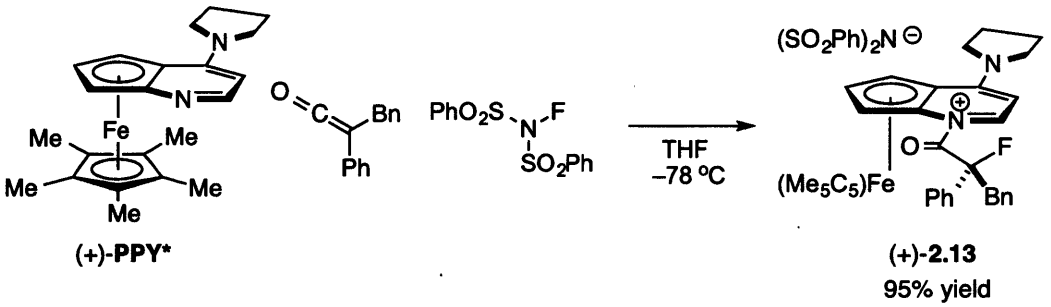
On the other hand, our kinetic data cannot be explained by a "chiral fluorinating agent" pathway (Figure 2.5; pathway B);[56] specifically, in this mechanism, the reaction rate should be independent of the identity of the ketene, since the turnover-limiting step is likely N-fluorination of **PPY***, according to the rate law.

---

[55] Notes: (a) In THF-d_8 at –78 °C, **PPY*** rapidly reacts with phenyl ethyl ketene to provide a somewhat complicated mixture, and we were not able to identify products in the ^{1}H NMR spectrum. (b) We were not able to determine the resting state of the catalyst under our standard fluorination conditions.

[56] In THF-d_8 at –78 °C, no reaction is observed when **PPY*** is mixed with NFSI by ^{19}F NMR spectroscopy.

On the basis of our earlier inability to achieve **PPY***-catalyzed asymmetric fluorination of ketenes with NFSI in the absence of an added nucleophile (eq 2.2.1), we hypothesized that N-acylpyridinium salt **2.9** might be isolable. Indeed, reaction of **PPY***, phenyl benzyl ketene, and NFSI (1:1:1) provided α-fluorinated acylpyridinium salt **2.13** as a blue solid (eq 2.2.5).[57,58] This salt is stable at room temperature under nitrogen for at least 6 months.



(2.2.5)

Unfortunately, structural characterization by X-ray crystallography was hampered by the tendency of salt **2.13** to form oils under recrystallization conditions, even with other common non-coordinating anions obtained by anion exchange.[59] However, anion exchange of $N(SO_2Ph)_2$ for a carborane,[60] $CB_{11}H_{12}$, through treatment with $CsCB_{11}H_{12}$ furnished a new acylpyridinium salt (eq 2.2.6) that proved to be amenable to crystallization (Figure 2.7).

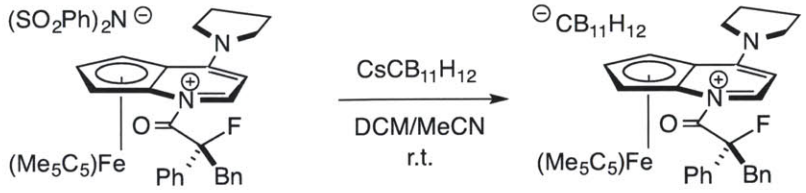
---

[57] The yield was determined by ^1H NMR spectroscopy with the aid of an internal standard.

[58] We were also able to prepare the corresponding *N*-acylpyridinium salts derived from other ketenes, including phenyl ethyl ketene, but they were more difficult to purify than salt **2.13**.

[59] Anions tried: Cl, SbF_6, PF_6, BPh_4, BArF (through treatment with the corresponding sodium salts).

[60] For a review on carboranes, see: Reed, C. A. *Acc. Chem. Res.* **1998**, *31*, 133–139.



(2.2.6)

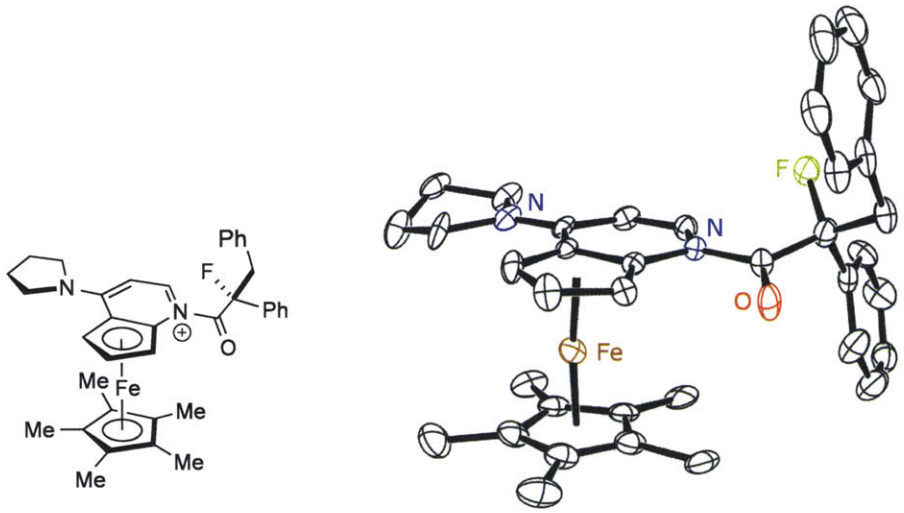
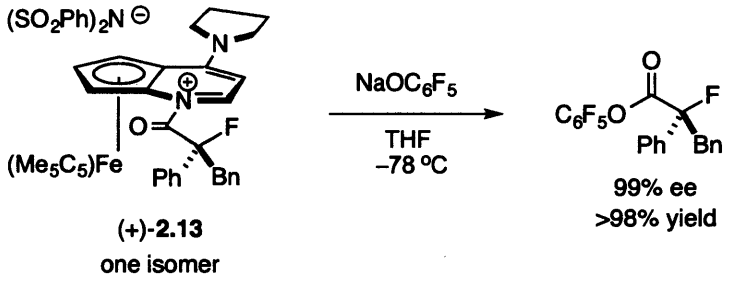


Figure 2.7. ORTEP diagram of N-acylated (+)-**PPY*** (thermal ellipsoids illustrated at the 35% probability level; for the sake of clarity, the carborane counteranion, the hydrogen atoms, the solvent, and the second molecule in the asymmetric unit have been omitted, and only the major component of the disorder in the Cp* group is shown)

The pyrrolidino group, the pyridine ring, and the carbonyl group of the *N*-acylpyridinium cation lie approximately in a single plane, allowing overlap between the π systems, which decreases the electrophilicity of the carbonyl group. With regard to the orientation around the N–C (acyl) bond, the carbonyl oxygen is positioned on the same side as the fused cyclopentadienyl ring, presumably in order to minimize unfavorable steric interactions. Finally, the stereochemistry of the fluorine-bearing carbon of the *N*-acylpyridnium cation is consistent with the fluorination product that is

generated by (+)-**PPY***. The fluorination of chiral enolate **2.10** with NFSI is likely the stereochemistry-determining step of this asymmetric fluorination.

We have confirmed that *N*-acylpyridnium salt **2.13** is a chemically and kinetically competent intermediate in our proposed catalytic cycle (Figure 2.5; pathway A); upon treatment of this salt with $NaOC_6F_5$ in THF at –78 °C, the enantioenriched tertiary α-fluoroester is furnished with the retention of stereochemistry (eq 2.2.7). It is interesting to note that this catalyst-regeneration issue from an N-acylated catalyst is not encountered in "related" processes such as our **PPY***-catalyzed chlorination of ketenes (eq 2.1.3)[48] or Lectka's fluorination of acid chlorides via formation of mono-substituted ketenes (eq 2.1.1)[39].



(2.2.7)

2.3 Conclusion

The development of new approaches to produce tertiary alkyl fluorides is an important objective, due to the significance of organofluorine compounds in medicinal chemistry. We have developed a method for the catalytic asymmetric synthesis of tertiary α-fluoroesters via the **PPY***-catalyzed α-fluorination of ketenes with NFSI in the presence of $NaOC_6F_5$, and we have established that this process is effective for a variety of aryl alkyl ketenes and a dialkyl ketene. The addition of $NaOC_6F_5$ was the key to enabling catalyst turnover, as it releases the catalyst (**PPY***) from a relatively stable N-acylated intermediate. A mechanistic investigation indicates that this new process likely proceeds through the formation of a chiral enolate by the nucleophilic addition of **PPY*** to a ketene. In the rate- and stereochemistry-determining step, this chiral enolate is fluorinated by NFSI, furnishing an enantioenriched α-fluoro-*N*-acylpyridinium salt, which has been isolated, structurally characterized, and determined to be a chemically competent intermediate in the **PPY***-catalyzed fluorination process.

2.4 Experimental Section

I. General Information

Unless otherwise noted, all materials were purchased from commercial suppliers. *N*-fluorobenzenesulfonimide (NFSI) was purchased from either Alfa Aesar or Oakwood Chemicals and purified by recrystallization from dichloromethane/hexanes prior to use. Both enantiomers of **PPY*** are commercially available from Strem Chemicals (catalog numbers 26-3700 and 26-3701).

Aryl alkyl ketenes were synthesized by the dehydrohalogenation of the corresponding acid chlorides.[61] Isopropyl methyl ketene was prepared from the corresponding a-bromo acid bromide.[54] THF was purified prior to use by passage through a column of neutral alumina under argon.

HPLC analyses were carried out on an Agilent 1100 series system with Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μ). Chiral GC data were obtained on an Agilent 6850 series system equipped with a Varian CP-Chirasil-DEX CB column.

II. Preparation of C_6F_5ONa

Sodium pentafluorophenoxide. In a nitrogen-filled glovebox, a solution of pentafluorophenol (4.60 g, 25.0 mmol) in THF (7.50 mL) was added dropwise over 60 seconds to a round-bottom flask that contained NaH (0.60 g, 25.0 mmol) in THF (7.5 mL). The reaction mixture was stirred at r.t. for 30 min, and then it was concentrated under reduced pressure, furnishing the desired product as a white powder. The powder was dried under high vacuum (250 mtorr) overnight and used without further purification.

^{19}F NMR (282 MHz, acetone-d_6) δ –173.2 (m), –173.6 (m), –192.3 (m).

FT-IR (neat) 3659, 3233, 2360, 1616, 1502, 1460, 1377, 1274, 1247, 1164, 994 cm^{-1}.

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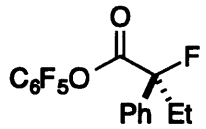
[61] (a) Zuhl, A. M.; Mohr, J. T.; Bachovchin, D. A.; Niessen, S.; Hsu, K.-L.; Berlin, J. M.; Dochnahl, M.; López-Alberca, M. P.; Fu, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2012**, *134*, 5068–5071. (b) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006–10007. (c) Allen, A. D.; Baigrie, L. M.; Gong, L.; Tidwell, T. T. *Can. J. Chem.* **1991**, *69*, 138–145.

III. Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides

General Procedure 1 (glovebox-free). NFSI (126 mg, 0.400 mmol; note: NFSI should be recrystallized from dichloromethane/*n*-hexanes before use) was added to an oven-dried 100-mL round-bottom flask equipped with a stir bar. The flask was capped with a rubber septum, and then it was evacuated and backfilled with nitrogen (three cycles); next, THF (32 mL) was added via syringe. (–)-**PPY*** (4.5 mg, 0.012 mmol) was added to an oven-dried 4-mL vial, and this vial was capped, and then it was evacuated and backfilled with nitrogen (three cycles); next, THF (0.40 mL) was added via syringe. C_6F_5ONa (82.4 mg, 0.400 mmol) was added to an oven-dried 20-mL vial, and this vial was capped, and then it was evacuated and backfilled with nitrogen (three cycles); next, THF (8.0 mL) was added via syringe. Another 20-mL vial was evacuated and backfilled with nitrogen (three cycles); next, ketene (0.400 mmol) and THF (8.0 mL) were added in turn via syringe. A nitrogen-filled balloon was attached to the flask that contained the NFSI solution, which was then cooled to –78 °C, and the solution of (–)-**PPY*** was added to the flask via syringe. Then, the ketene (8.0 mL of a 0.050 M solution in THF; 0.40 mmol) and C_6F_5ONa (8.0 mL of a 0.050 M solution in THF; 0.40 mmol) were added to the 100-mL round-bottom flask dropwise simultaneously via syringe pump over 2 h (Note: the needles should be aligned such that the C_6F_5ONa and ketene solutions do not mix prior to reaching the reaction mixture). The reaction mixture was stirred at –78 °C for an additional 2 h, and then it was concentrated under reduced pressure. To remove the (–)-**PPY*** and $NaN(SO_2Ph)_2$, the residue was dissolved in CH_2Cl_2 (5.0 mL) and filtered through a pad of silica (eluted with CH_2Cl_2 (20 mL)). The solution was concentrated, and the product was purified by column chromatography (hexanes → 10% Et_2O in hexanes; $KMnO_4$ stain).

Notes: (a) The ee of the product was determined after transesterification to the corresponding phenyl ester (conditions: 1.5 equiv PhOH, 2.0 equiv Et_3N; THF (0.1 M in ester); 12 h at r.t.). (b) For the ketene illustrated in Entry 1 of Table 2.2, the fluorination proceeded in 86% ee and 98% yield when the ketene and C_6F_5ONa solutions were added dropwise over 1 min, rather than by syringe pump over 2 h. (c) The amount of hydrodefluorination product was determined by GC analysis.

General Procedure 2 (with a glovebox; the yields and ee's are essentially identical to General Procedure 1 (vide infra). In a nitrogen-filled glovebox, NFSI (126 mg, 0.400 mmol; NFSI should be recrystallized from dichloromethane/*n*-hexanes before use) and THF (32 mL) were combined in an oven-dried 100-mL round-bottom flask equipped with a stir bar. The flask was fitted with a rubber septum and then removed from the glovebox. A nitrogen-filled balloon was attached to the flask, which was then cooled to –78 °C, and then a solution of (–)-**PPY*** (4.5 mg in THF (0.40 mL); 0.012 mmol) was added to the flask via syringe. Then, the ketene (8.0 mL of a 0.050 M solution in THF; 0.40 mmol) and C_6F_5ONa (8.0 mL of a 0.050 M solution in THF; 0.40 mmol) were added dropwise to the flask simultaneously via syringe pump over 2 h (Note: the needles should be aligned such that the C_6F_5ONa and ketene solutions do not mix prior to reaching the reaction mixture). The reaction mixture was stirred at –78 °C for an additional 2 h, and then it was concentrated under reduced pressure. To remove the (–)-**PPY*** and $NaN(SO_2Ph)_2$, the residue was dissolved in CH_2Cl_2 (5.0 mL) and filtered through a pad of silica (eluted with CH_2Cl_2 (10 mL)). The solution was concentrated, and the product was purified by column chromatography (hexanes → 10% Et_2O in hexanes; $KMnO_4$ stain).



(*S*)-Perfluorophenyl 2-fluoro-2-phenylbutanoate (Table 2.2, entry 1). The title compound was prepared according to General Procedure 2, using phenyl ethyl ketene (58.5 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a colorless oil (135 mg, 97% yield; contained 1% perfluorophenyl 2-phenylbutanoate) with 99% ee.

The ee of the product was determined after transesterification to phenyl 2-fluoro-2-phenylbutanoate (HPLC analysis of the product: Daicel CHIRALCEL OJ-H column; solvent system: hexanes; 1.0 mL/min; retention times: 34.5 min (major), 51.2 min (minor)).

The second run was performed with (+)-**PPY*** according to General Procedure 1. The product was isolated as a colorless oil (137 mg, 99% yield; contained 1% perfluorophenyl 2-phenylbutanoate) with 98% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.59–7.56 (m, 2H), 7.47–7.40 (m, 3H), 2.63–2.53 (m, 1H), 2.37–2.29 (m, 1H), 1.12 (t, 3H, J = 7.5 Hz).

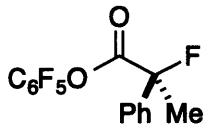
^{13}C NMR (125 MHz, CDCl3) δ 167.0, 141.1 (dm, J_{CF} = 253 Hz), 139.8 (dm, J_{CF} = 250 Hz), 137.9 (dm, J_{CF} = 246 Hz), 136.6, 129.2, 128.7, 124.8, 124.5, 97.5 (d, J_{CF} = 193 Hz), 31.2, 7.3.

^{19}F NMR (282 MHz, CDCl3) δ –152.3 (m), –157.0 (t, J = 22 Hz), –161.8 (m), –164.7 (dd, J = 19 Hz, J = 28 Hz).

FT-IR (neat) 2929, 2855, 1801, 1783, 1653, 1521, 1496, 1464, 1451, 1387, 1344, 1299, 1208, 1149, 1110, 1087, 998, 911, 843, 765, 722, 714 cm^{-1}.

MS (FAB) m/z (M+Na$^+$) calcd for $C_{16}H_{10}F_6NaO_2$: 371, found: 371.

$[a]^{25}_D$ = +11 (c = 1.0, $CHCl_3$; obtained with (+)-**PPY***).



(*S*)-Perfluorophenyl 2-fluoro-2-phenylpropanoate (Table 2.2, entry 2). The title compound was prepared according to General Procedure 1, using phenyl methyl ketene (52.9 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a light-yellow oil (124 mg, 93% yield; contained 2% perfluorophenyl 2-phenylpropanoate) with 98% ee.

The ee of the product was determined after transesterification to phenyl 2-fluoro-2-phenylpropanoate (HPLC analysis of the product: Daicel CHIRALCEL OJ-H column; solvent system: hexanes; 1.0 mL/min; retention times: 57.0 min (major), 70.1 min (minor)).

The second run was performed with (+)-**PPY*** according to General Procedure 1. The product was isolated as a light-yellow oil (122 mg, 91% yield; contained 2% perfluorophenyl 2-phenylpropanoate) with 97% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.60–7.58 (m, 2H), 7.48–7.43 (m, 3H), 2.13 (d, 3H, J = 22.0 Hz).

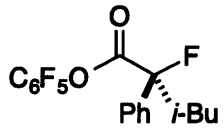
^{13}C NMR (125 MHz, CDCl3) δ 167.2, 140.9 (dm, J_{CF} = 251 Hz), 139.8 (dm, J_{CF} = 250 Hz), 137.8 (dm, J_{CF} = 247 Hz), 137.4, 129.4, 128.8, 124.7, 124.6, 94.6 (d, J_{CF} = 188 Hz), 24.3.

^{19}F NMR (282 MHz, CDCl3) δ –149.5 (q, J = 23 Hz), –152.6 (m), –157.0 (t, J = 22 Hz), –161.9 (m).

FT-IR (neat) 2995, 1787, 1724, 1521, 1497, 1472, 1449, 1378, 1228, 1148, 1090, 1068, 1029, 994, 914, 773, 726 cm^{-1}.

MS (EI) m/z ($M-F^+$) calcd for $C_{15}H_8F_5O_2$: 315, found: 315.

$[a]^{25}_D$ = +74 (c = 1.0, $CHCl_3$; obtained with (+)-**PPY***).



(*S*)-Perfluorophenyl 2-fluoro-4-methyl-2-phenylpentanoate (Table 2.2, entry 3). The title compound was prepared according to General Procedure 1, using phenyl isobutyl ketene (69.7 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a colorless oil (143 mg, 95% yield; contained 1% perfluorophenyl 4-methyl-2-phenylpentanoate) with 94% ee.

The ee of the product was determined after transesterification to phenyl 2-fluoro-4-methyl-2-phenylpentanoate (HPLC analysis of the product: Daicel CHIRALCEL OJ-H column; solvent system: hexanes; 1.0 mL/min; retention times: 15.2 min (minor), 28.7 min (major)).

The second run was performed with (+)-**PPY*** according to General Procedure 2. The product was isolated as a colorless oil (143 mg, 95% yield; contained 1% perfluorophenyl 4-methyl-2-phenylpentanoate) with 96% ee.

^1H NMR (500 MHz, CDCl3) δ 7.60–7.58 (m, 2H), 7.45–7.42 (m, 3H), 2.53–2.43 (m, 1H), 2.29–2.21 (m, 1H), 1.97 (septet, 1H, J = 5.0 Hz), 1.06–1.02 (m, 6H).

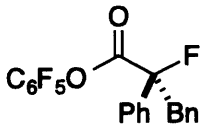
^{13}C NMR (125 MHz, CDCl3) δ 167.2, 141.0 (dm, J_{CF} = 254 Hz), 139.8 (dm, J_{CF} = 248 Hz), 137.8 (dm, J_{CF} = 243 Hz), 137.3, 129.1, 128.7, 124.6, 124.5, 97.4 (d, J_{CF} = 193 Hz), 46.1, 24.7, 23.7.

^{19}F NMR (282 MHz, CDCl3) δ –152.3 (m), –157.1 (t, J = 22 Hz), –161.9 (m), –162.9 (dd, J = 20 Hz, J = 31 Hz).

FT-IR (neat) 2961, 1785, 1718, 1653, 1559, 1520, 1472, 1450, 1199, 1100, 1073, 1010, 997, 725 cm^{-1}.

MS (EI) m/z ($M-F^+$) calcd for $C_{18}H_{14}F_5O_2$: 357, found: 357.

$[a]^{25}_D$ = +14 (c = 1.0, $CHCl_3$; obtained with (+)-**PPY***).



(*S*)-Perfluorophenyl 2-fluoro-2,3-diphenylpropanoate (Table 2.2, entry 4). The title compound was prepared according to General Procedure 1, using phenyl benzyl ketene (83.3 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a white solid (159 mg, 97% yield; contained 3% perfluorophenyl 2,3-diphenylpropanoate) with 78% ee.

The ee of the product was determined after transesterification to phenyl 2-fluoro-2,3-diphenylpropanoate (HPLC analysis of the product: Daicel CHIRALCEL OJ-H column; solvent system: hexanes; 1.0 mL/min; retention times: 53.6 min (major), 70.6 min (minor)).

The second run was performed with (+)-**PPY*** according to General Procedure 1. The product was isolated as a white solid (156 mg, 95% yield; contained 2% perfluorophenyl 2,3-diphenylpropanoate) with 77% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.62–7.60 (m, 2H), 7.47–7.42 (m, 3H), 7.31–7.26 (m, 5H), 3.82 (dd, 1H, J = 14.8 Hz, J = 30 Hz), 3.57 (dd, 1H, J = 14.8 Hz, J = 19.6 Hz).

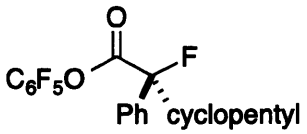
^{13}C NMR (125 MHz, CDCl3) δ 166.3, 140.9 (dm, J_{CF} = 251 Hz), 139.8 (dm, J_{CF} = 250 Hz), 137.8 (dm, J_{CF} = 247 Hz), 136.5, 133.1, 130.5, 129.3, 128.8, 128.4, 127.5, 124.7, 124.4, 97.0 (d, J_{CF} = 195 Hz), 44.2.

^{19}F NMR (282 MHz, CDCl3) δ –151.8 (m), –157.0 (t, J = 21 Hz), –161.3 (dd, J = 20 Hz, J = 31 Hz), –161.9 (m).

FT-IR (neat) 2360, 1782, 1653, 1521, 1496, 1469, 1456, 1449, 1427, 1257, 1174, 1142, 1118, 1101, 1080, 1029, 995, 985, 916, 849, 769, 726 cm^{-1}.

MS (EI) m/z (M–F$^+$) calcd for $C_{21}H_{12}F_6O_2$: 391, found: 391.

$[a]^{25}_D$ = +17 (c = 1.0, $CHCl_3$; obtained with (+)-**PPY***).



(*S*)-Perfluorophenyl 2-cyclopentyl-2-fluoro-2-phenylacetate (Table 2.2, entry 5). The title compound was prepared according to General Procedure 1, using phenyl

cyclopentyl ketene (74.5 mg, 0.400 mmol) and 10% (–)-**PPY*** (15.1 mg, 0.0400 mmol). Reaction time: 12 h. After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a colorless oil (130 mg, 84% yield; contained 1% perfluorophenyl 2-cyclopentyl-2-phenylacetate) with 79% ee.

The ee of the product was determined after transesterification to phenyl 2-cyclopentyl-2-fluoro-2-phenylacetate (HPLC analysis of the product: Daicel CHIRALCEL OJ-H column; solvent system: hexanes; 1.0 mL/min; retention times: 23.4 min (major), 36.1 min (minor)).

The second run was performed with (+)-**PPY*** according to General Procedure 1. The product was isolated as a colorless oil (130 mg, 84% yield; contained 1% perfluorophenyl 2-cyclopentyl-2-phenylacetate) with 80% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.62–7.60 (m, 2H), 7.45–7.38 (m, 3H), 3.15 (doublet of quintets, 1H, J = 34.0 Hz, J = 8.5 Hz), 1.99–1.92 (m, 1H), 1.86–1.74 (m, 2H), 1.71–1.63 (m, 2H), 1.60–1.51 (m, 2H), 1.50–1.41 (m, 1H).

^{13}C NMR (125 MHz, CDCl3) δ 167.0, 141.0 (dm, J_{CF} = 254 Hz), 139.8 (dm, J_{CF} = 247 Hz), 137.8 (dm, J_{CF} = 245 Hz), 136.7, 128.9, 128.6, 124.9, 124.4, 98.3 (d, J_{CF} = 195 Hz), 46.0, 26.7, 26.2.

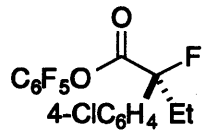
^{19}F NMR (282 MHz, CDCl3) δ –152.3 (m), –157.2 (t, J = 22 Hz), –162.0 (m), –177.9 (d, J = 34 Hz).

FT-IR (neat) 2962, 2874, 2670, 2463, 1799, 1784, 1654, 1520, 1472, 1450, 1359, 1318, 1207, 1159, 1075, 1011, 998, 957, 910, 879, 840, 754, 715 cm^{-1}.

MS (EI) m/z (M–F$^+$) calcd for $C_{19}H_{14}F_5O_2$: 369, found: 369.

$[a]^{25}_D$ = –46 (c = 1.0, $CHCl_3$; obtained with (+)-**PPY***).

$[a]^{25}_D$ = +41 (c = 1.0, $CHCl_3$; obtained with (–)-**PPY***).



(*S*)-Perfluorophenyl 2-(4-chlorophenyl)-2-fluorobutanoate (Table 2.2, entry 6). The title compound was prepared according to General Procedure 1, using 4-chlorophenyl ethyl ketene (72.2 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was

isolated as a colorless oil (134 mg, 88% yield; contained 3% perfluorophenyl 2-(4-chlorophenyl)butanoate) with 96% ee.

The ee of the product was determined after transesterification to phenyl 2-(4-chlorophenyl)-2-fluorobutanoate (HPLC analysis of the product: Daicel CHIRALCEL OJ-H column; solvent system: hexanes; 1.0 mL/min; retention times: 44.5 min (minor), 63.1 min (major)).

The second run was performed with (+)-**PPY*** according to General Procedure 1. The product was isolated as a colorless oil (129 mg, 84% yield; contained 3% perfluorophenyl 2-(4-chlorophenyl)butanoate) with 98% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.54–7.50 (m, 2H), 7.45–7.40 (m, 2H), 2.66–2.45 (m, 1H), 2.39–2.20 (m, 1H), 1.11 (t, 3H, J = 7.5 Hz).

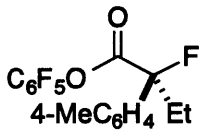
^{13}C NMR (125 MHz, CDCl3) δ 166.5, 140.9 (dm, J_{CF} = 250 Hz), 139.9 (dm, J_{CF} = 252 Hz), 137.9 (dm, J_{CF} = 252 Hz), 135.4, 135.1, 129.0, 126.3, 124.4, 97.1 (d, J_{CF} = 193 Hz), 31.3, 7.3.

^{19}F NMR (282 MHz, CDCl3) δ –152.4 (m), –156.8 (t, J = 20 Hz), –161.7 (m), –165.0 (dd, J = 20 Hz, J = 28 Hz).

FT-IR (neat) 2983, 2944, 2360, 1802, 1785, 1653, 1598, 1521, 1493, 1462, 1403, 1360, 1299, 1207, 1150, 1095, 998, 909, 825, 747, 714 cm^{-1}.

MS (EI) m/z (M–F$^+$) calcd for $C_{16}H_9ClF_5O_2$: 363, found: 363.

[a]$^{25}_D$ = –5.3 (c = 2.0, $CHCl_3$; obtained with (–)-**PPY***).



(*S*)-Perfluorophenyl 2-fluoro-2-(*p*-tolyl)butanoate (Table 2.2, entry 7). The title compound was prepared according to General Procedure 1, using *p*-tolyl ethyl ketene (64.1 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a colorless oil (135 mg, 93% yield; contained 5% perfluorophenyl 2-(*p*-tolyl)butanoate) with 97% ee.

The ee of the product was determined after transesterification to phenyl 2-fluoro-2-(*p*-tolyl)butanoate (HPLC analysis of the product: Daicel CHIRALCEL OJ-H column;

solvent system: hexanes; 1.0 mL/min; retention times: 39.7 min (minor), 48.7 min (major)).

The second run was performed with (+)-**PPY*** according to General Procedure 2. The product was isolated as a colorless oil (132 mg, 91% yield; contained 5% perfluorophenyl 2-(p-tolyl)butanoate) with 97% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.38–7.36 (m, 2H), 7.17–7.15 (m, 2H), 2.54–2.41 (m, 1H), 2.29 (s, 3H), 2.27–2.17 (m, 1H), 1.03 (t, 3H, J = 7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 167.0, 141.0 (dm, J_{CF} = 255 Hz), 139.7 (dm, J_{CF} = 251 Hz), 139.2, 137.8 (dm, J_{CF} = 244 Hz), 133.6, 129.4, 124.7, 124.5, 97.5 (d, J_{CF} = 192 Hz), 31.1, 21.1, 7.4.

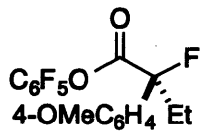
^{19}F NMR (282 MHz, CDCl3) δ –152.3 (m), –157.1 (t, J = 22 Hz), –162.0 (m), –163.6 (dd, J = 19 Hz, J = 29 Hz).

FT-IR (neat) 2982, 2944, 2360, 1800, 1783, 1654, 1462, 1300, 1205, 1150, 1107, 1085, 1023, 998, 907, 814, 736 cm^{-1}.

MS (EI) m/z (M–F$^+$) calcd for $C_{17}H_{12}F_5O_2$: 343, found: 343.

[a]$^{25}_D$ = –13 (c = 1.0, $CHCl_3$; obtained with (+)-**PPY***).

[a]$^{25}_D$ = +11 (c = 1.0, $CHCl_3$; obtained with (–)-**PPY***).



(*S*)-Perfluorophenyl 2-fluoro-2-(4-methoxyphenyl)butanoate (Table 2.2, entry 8). The title compound was prepared according to General Procedure 1, using 4-methoxyphenyl ethyl ketene (70.5 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes→ 10% Et_2O in hexanes), the title compound was isolated as a colorless oil (134 mg, 89% yield; contained 1% perfluorophenyl 2-(4-methoxyphenyl)butanoate) with 97% ee.

The ee of the product was determined after transesterification to phenyl 2-fluoro-2-(4-methoxyphenyl)butanoate (HPLC analysis of the product: Daicel CHIRALCEL AD-H column; solvent system: hexanes; 1.0 mL/min; retention times: 12.0 min (major), 13.6 min (minor)).

The second run was performed with (+)-**PPY*** according to General Procedure 2. The product was isolated as a colorless oil (140 mg, 93% yield; contained 1% perfluorophenyl 2-(4-methoxyphenyl)butanoate) with 97% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.52–7.49 (m, 2H), 6.98–6.94 (m, 2H), 3.84 (s, 3H), 2.62–2.52 (m, 1H), 2.37–2.29 (m, 1H), 1.13 (t, 3H, J = 7.5 Hz).

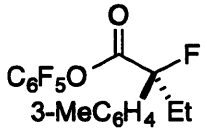
^{13}C NMR (126 MHz, CDCl3) δ 167.0, 160.2, 141.0 (dm, J_{CF} = 253 Hz), 139.7 (dm, J_{CF} = 249 Hz), 137.8 (dm, J_{CF} = 244 Hz), 128.5, 126.3, 124.6, 114.0, 97.3 (d, J_{CF} = 192 Hz), 55.3, 30.9, 7.4.

^{19}F NMR (282 MHz, CDCl3) δ –152.4 (m), –157.2 (t, J = 21 Hz), –161.8 to –162.1 (m).

FT-IR (neat) 2943, 2842, 1799, 1783, 1611, 1584, 1521, 1465, 1307, 1257, 1199, 1182, 1149, 1086, 1033, 997, 907, 829 cm^{-1}.

MS (FAB) m/z (M^+) calcd for $C_{17}H_{12}F_6O_3$: 378, found: 378.

$[a]^{25}_D$ = +31 (c = 2.0, $CHCl_3$; obtained with (–)-**PPY***).



(*S*)-Perfluorophenyl 2-fluoro-2-(*m*-tolyl)butanoate (Table 2.2, entry 9). The title compound was prepared according to General Procedure 1, using *m*-tolyl ethyl ketene (64.1 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a colorless oil (140 mg, 97% yield; contained 2% perfluorophenyl 2-(*m*-tolyl)butanoate) with 96% ee.

The ee of the product was determined after transesterification to phenyl 2-fluoro-2-(*m*-tolyl)butanoate (HPLC analysis of the product: Daicel CHIRALCEL OJ-H column; solvent system: hexanes; 1.0 mL/min; retention times: 24.0 min (minor), 43.0 min (major)).

The second run was performed with (+)-**PPY*** according to General Procedure 2. The product was isolated as a colorless oil (141 mg, 97% yield; contained 3% perfluorophenyl 2-(*m*-tolyl)butanoate) with 98% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.40–7.32 (m, 3H), 7.24–7.22 (m, 1H), 2.64–2.51 (m, 1H), 2.41 (s, 3H), 2.39–2.28 (m, 1H), 1.13 (t, 3H, J = 7.5 Hz).

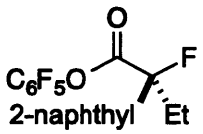
^{13}C NMR (125 MHz, CDCl3) δ 166.9, 141.0 (dm, J_{CF} = 253 Hz), 139.8 (dm, J_{CF} = 253 Hz), 138.6, 137.9 (dm, J_{CF} = 244 Hz), 136.5, 129.9, 128.6, 125.4, 124.5, 121.8, 97.5 (d, J_{CF} = 192 Hz), 31.2, 21.5, 7.4.

^{19}F NMR (282 MHz, CDCl3) δ –152.3 (m), –157.1 (t, J = 22 Hz), –161.9 (m), –164.1 (dd, J = 19 Hz, J = 28 Hz).

IR (neat) 2983, 2945, 1801, 1785, 1653, 1609, 1521, 1464, 1384, 1358, 1299, 1255, 1212, 1181, 1149, 1109, 1087, 997, 937, 906, 856, 821, 788, 729, 713 cm^{-1}.

MS (EI) m/z (M–F$^+$) calcd for $C_{17}H_{12}F_5O_2$: 343, found: 343.

[a]$^{25}_D$ = +33 (c = 3.0, $CHCl_3$; obtained with (+)-**PPY***).



(*S*)-Perfluorophenyl 2-fluoro-2-(naphthalen-2-yl)butanoate (Table 2.2, entry 10). The title compound was prepared according to General Procedure 1, using 2-naphthyl ethyl ketene (78.5 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a colorless oil (143 mg, 90% yield; contained 2% perfluorophenyl 2-(naphthalen-2-yl)butanoate) with 94% ee.

The ee of the product was determined after transesterification to phenyl 2-fluoro-2-(naphthalen-2-yl)butanoate (HPLC analysis of the product: Daicel CHIRALCEL OD-H column; solvent system: hexanes; 1.0 mL/min; retention times: 7.44 min (major), 8.93 min (minor)).

The second run was performed with (+)-**PPY*** according to General Procedure 1. The product was isolated as a colorless oil (140 mg, 88% yield; contained 3% perfluorophenyl 2-(naphthalen-2-yl)butanoate) with 93% ee.

^{1}H NMR (500 MHz, CDCl3) δ 8.11 (s, 1H), 7.95–7.88 (m, 3H), 7.69 (m, 1H), 7.58–7.54 (m, 2H), 2.77–2.64 (m, 1H), 2.53–2.41 (m, 1H), 1.19 (t, 3H, J = 7.5 Hz).

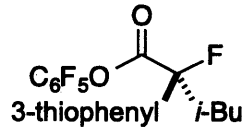
^{13}C NMR (125 MHz, CDCl3) δ 166.9, 141.0 (dm, J_{CF} = 253 Hz), 139.8 (dm, J_{CF} = 245 Hz), 137.8 (dm, J_{CF} = 250 Hz), 133.8, 133.4, 132.9, 128.7, 128.5, 127.7, 127.0, 126.7, 124.5, 124.3, 122.1, 97.7 (d, J_{CF} = 192 Hz), 31.3, 7.4.

^{19}F NMR (282 MHz, CDCl3) δ –152.2 (m), –157.0 (t, J = 22 Hz), –161.8 (m), –163.9 (dd, J = 20 Hz, J = 28 Hz).

FT-IR (neat) 3063, 2981, 2944, 1800, 1784, 1653, 1601, 1559, 1521, 1472, 1437, 1358, 1296, 1273, 1203, 1147, 1108, 1087, 997, 921, 897, 860, 817, 750, 724, 709 cm^{-1}.

MS (EI) m/z (M^+) calcd for $C_{20}H_{12}F_6O_2$: 398, found: 398.

$[a]^{25}_D$ = +23 (c = 1.0, $CHCl_3$; obtained with (+)-**PPY***).



(*S*)-Perfluorophenyl 2-fluoro-4-methyl-2-(thiophen-3-yl)pentanoate (Table 2.2, entry 11). The title compound was prepared according to General Procedure 1, using 3-thiophenyl isobutyl ketene (72.1 mg, 0.400 mmol). After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a light-yellow oil (143 mg, 93% yield; contained 3% perfluorophenyl 4-methyl-2-(thiophen-3-yl)pentanoate) with 96% ee.

The ee of the product was determined after transesterification to phenyl 2-fluoro-4-methyl-2-(thiophen-3-yl)pentanoate (HPLC analysis of the product: Daicel CHIRALCEL OJ-H column; solvent system: hexanes; 1.0 mL/min; retention times: 21.5 min (minor), 38.0 min (major)).

The second run was performed with (+)-**PPY*** according to General Procedure 2. The product was isolated as a light-yellow oil (144 mg, 94% yield; contained 3% perfluorophenyl 4-methyl-2-(thiophen-3-yl)pentanoate) with 99% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.49 (dd, 1H, J = 3.3 Hz, J = 1.3 Hz), 7.40–7.38 (m, 1H), 7.21 (dd, 1H, J = 5.3 Hz, J = 1.3 Hz), 2.50–2.39 (m, 1H), 2.28–2.20 (m, 1H), 1.97 (septet, 1H, J = 6.5 Hz), 1.04 (d, 6H, J = 6.5 Hz).

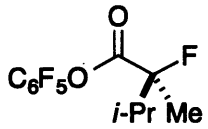
^{13}C NMR (125 MHz, CDCl3) δ 166.7, 141.0 (dm, J_{CF} = 255 Hz), 139.8 (dm, J_{CF} = 252 Hz), 138.4, 137.8 (dm, J_{CF} = 245 Hz), 126.8, 124.8, 124.5, 122.7, 96.2 (d, J_{CF} = 192 Hz), 46.3, 24.8, 23.4.

^{19}F NMR (282 MHz, CDCl3) δ –152.2 (m), –155.6 (dd, J = 18 Hz, J = 32 Hz), –156.9 (t, J = 22 Hz), –161.8 (m).

FT-IR (neat) 3118, 2962, 2875, 2671, 2464, 2360, 1800, 1785, 1653, 1520, 1370, 1276, 1203, 1181, 1146, 1117, 1099, 999, 967, 861, 840, 797, 782, 729, 708 cm^{-1}.

MS (EI) m/z ($M-F^+$) calcd for $C_{16}H_{12}F_5O_2S$: 363, found: 363.

$[a]^{25}_D$ = +12 (c = 1.0, $CHCl_3$; obtained with (+)-**PPY***).



(*S*)-Perfluorophenyl 2-fluoro-2,3-dimethylbutanoate (eq 2.2.4). The title compound was prepared according to General Procedure 1, using isopropyl methyl ketene (39.3 mg, 0.400 mmol) and 10% (–)-**PPY*** (15.1 mg, 0.0400 mmol). Reaction time: 12 h. After purification by flash chromatography (eluted with hexanes → 10% Et_2O in hexanes), the title compound was isolated as a light-yellow oil (97 mg, 81% yield; contained 1% perfluorophenyl 2,3-dimethylbutanoate) with 73% ee.

The ee of the product was determined by chiral GC analysis (CP-Chirasil-DEX CB; heating program: 105 °C → 115 °C @ 1 °C/min, followed by 115 → 175 °C @ 5 °C/min; He flow rate: 1.0 mL/min; retention times: 22.4 min (minor), 23.0 min (major)).

The second run was performed with (+)-**PPY*** according to General Procedure 1. The product was isolated as a light-yellow oil (99 mg, 83% yield; contained 1% perfluorophenyl 2,3-dimethylbutanoate) with 74% ee.

^1H NMR (500 MHz, CDCl3) δ 2.33–2.23 (m, 1H), 1.71 (d, 3H, J = 22.0 Hz), 1.10 (d, 6H, J = 7.0 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 168.4, 141.0 (dm, J_{CF} = 254 Hz), 139.8 (dm, J_{CF} = 246 Hz), 137.8 (dm, J_{CF} = 243 Hz), 124.5, 97.6 (d, J_{CF} = 189 Hz), 35.0, 21.3, 16.2.

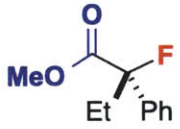
^{19}F NMR (282 MHz, CDCl3) δ –152.7 (m), –157.2 (t, J = 22 Hz), –162.0 (m), –164.9 (quintet, J = 22 Hz).

FT-IR (neat) 2980, 2887, 2671, 2463, 1804, 1787, 1655, 1524, 1471, 1394, 1379, 1360, 1247, 1211, 1169, 1148, 1110, 1064, 1008, 995, 941, 910, 868, 809, 744, 714 cm^{-1}.

MS (FAB) m/z ($M+Na^+$) calcd for $C_{12}H_{10}F_6NaO_2$: 323, found: 323.

$[a]^{25}_D$ = +12 (c = 1.0, $CHCl_3$; obtained with (+)-**PPY***).

IV. Derivatizations of the Products



Transesterification: Methyl (*R*)-2-fluoro-2-phenylbutanoate. (*R*)-Perfluorophenyl 2-fluoro-2-phenylbutanoate (104 mg, 0.30 mmol; 98% ee), Et_3N (209 mL, 1.50 mmol), MeOH (1.5 mL), and THF (1.5 mL) were added to a 20-mL vial. The mixture was stirred at r.t. for 12 h, and then it was concentrated under reduced pressure. The residue was purified by column chromatography (hexanes → 10% Et_2O in hexanes), which furnished the product as a colorless oil. First run: 52 mg (88%, 98% ee). Second run: 54 mg (92%, 98% ee).

The ee of the product was determined by HPLC (Daicel CHIRALCEL AS-H column; solvent system: 1.0% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 6.38 min (minor), 7.77 min (major)).

^{1}H NMR (500 MHz, CDCl3) δ 7.52–7.50 (m, 2H), 7.40–7.32 (m, 3H), 3.77 (s, 3H), 2.46–2.33 (m, 1H), 2.24–2.12 (m, 1H), 0.96 (t, 3H, J = 7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 171.0, 138.1, 128.4, 124.7, 124.6, 97.5 (d, J_{CF} = 189 Hz), 52.8, 31.5, 7.5.

^{19}F NMR (282 MHz, CDCl3) δ –167.2 (dd, J = 21 Hz, J = 28 Hz).

FT-IR (neat) 2979, 2954, 2884, 1761, 1740, 1496, 1449, 1437, 1383, 1256, 1221, 1138, 1094, 1072, 1017, 1003, 919, 809, 770, 732 cm^{-1}.

MS (EI) m/z (M^+) calcd for $C_{11}H_{13}FO_2$: 196, found: 196.

$[a]^{25}_D$ = +17 (c = 1.0, $CHCl_3$).

Hydrolysis: (*R*)-2-Fluoro-2-phenylbutanoic acid. (*R*)-Perfluorophenyl 2-fluoro-2-phenylbutanoate (104 mg, 0.30 mmol; 98% ee), Et_3N (209 mL, 1.50 mmol), H_2O (1.5 mL), and THF (1.5 mL) were added to a 20-mL vial. The mixture was stirred at r.t. for 12 h, and then it was concentrated under reduced pressure. H_2O (5 mL) and EtOAc (5

mL) were added. The aqueous phase was brought to pH 2 by the addition of 1 N HCl. The mixture was transferred to a separatory funnel, to which EtOAc (5 mL) was added. The layers were separated, and the aqueous layer was washed with EtOAc (5 mL x2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (2.0% MeOH in CH_2Cl_2), which furnished the product as a white solid. First run: 47 mg (86%, 98% ee). Second run: 48 mg (88%, 98% ee).

The ee of the product was determined by HPLC (Daicel CHIRALCEL OJ-H column; solvent system: 5.0% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 19.8 min (minor), 26.7 min (major)).

^{1}H NMR (500 MHz, CDCl3) δ 10.0 (br s, 1H), 7.53–7.51 (m, 2H), 7.41–7.34 (m, 3H), 2.47–2.34 (m, 1H), 2.25–2.14 (m, 1H), 0.99 (t, 3H, J = 7.5 Hz).

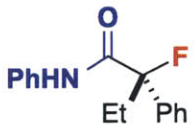
^{13}C NMR (125 MHz, CDCl3) δ 175.6, 137.2, 128.7, 128.5, 124.8, 97.1 (d, J_{CF} = 188 Hz), 31.2, 7.4.

^{19}F NMR (282 MHz, CDCl3) δ –167.2 (dd, J = 21 Hz, J = 27 Hz).

FT-IR (neat) 2925, 1728, 1497, 1450, 1220, 1142, 1071, 990, 727 cm^{-1}.

MS (EI) m/z (M^+) calcd for $C_{10}H_{11}FO_2$: 182, found: 182.

$[a]^{25}_D$ = –11 (c = 0.40, MeOH).[62]



Amidation: (*R*)-2-Fluoro-*N*,2-diphenylbutanamide. (*R*)-Perfluorophenyl 2-fluoro-2-phenylbutanoate (104 mg, 0.30 mmol; 98% ee), aniline (41.9 mg, 0.45 mmol), Et_3N (63 mL, 0.45 mmol), and THF (3.0 mL) were added to a 20-mL vial, which was then sealed with a septum cap and heated to 65 °C for 12 h. The mixture was allowed to cool to r.t., and then it was concentrated under reduced pressure. The residue was purified by column chromatography (hexanes → 10% Et_2O in hexanes), which furnished the product as a white solid. First run: 77 mg (95%, 98% ee). Second run: 75 mg (97%, 98% ee).

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[62] Hamman, S.; Michals, D. R.; Pickard, S. T.; Smith, H. E. *J. Fluorine Chem.* **1993**, *62*, 131–137.

The ee of the product was determined by HPLC (Daicel CHIRALCEL OJ-H column; solvent system: 2.0% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 33.3 min (minor), 35.0 min (major)).

^{1}H NMR (500 MHz, CDCl3) δ 8.17 (br s, 1H), 7.62–7.60 (m, 2H), 7.58–7.55 (m, 2H), 7.41–7.37 (m, 2H), 7.36–7.31 (m, 3H), 7.14–7.11 (m, 1H), 2.55–2.41 (m, 1H), 2.29–2.17 (m, 1H), 1.00 (t, 3H, J = 7.5 Hz).

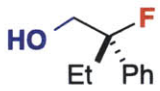
^{13}C NMR (125 MHz, CDCl3) δ 168.6, 138.4, 136.9, 129.0, 128.4, 124.8, 124.53, 124.45, 119.9, 100.4 (d, J_{CF} = 191 Hz), 31.9, 7.6.

^{19}F NMR (282 MHz, CDCl3) δ –164.9 (ddd, J = 20 Hz, J = 8.5 Hz, J = 30 Hz).

FT-IR (neat) 3400, 2918, 2360, 1497, 1448, 1061, 913, 878, 759 cm^{-1}.

MS (EI) m/z (M^+) calcd for $C_{16}H_{16}FNO$: 257, found: 257.

$[a]^{25}_D$ = +54 (c = 1.0, $CHCl_3$).



Reduction: (*R*)-2-Fluoro-2-phenylbutan-1-ol [188359-07-1]. $NaBH_4$ (17.0 mg, 1.45 mmol) was added to a 20-mL vial that contained (*R*)-perfluorophenyl 2-fluoro-2-phenylbutanoate (104 mg, 0.30 mmol; 98% ee) and THF (3.0 mL). The mixture was stirred at r.t. for 4 h, and then H_2O (0.2 mL) was added. The mixture was transferred to a separatory funnel, to which Et_2O (5 mL) and H_2O (1 mL) were added. The layers were separated, and the aqueous layer was washed with Et_2O (5 mL x2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (10% Et_2O in hexanes), which furnished the product as a clear, colorless oil. First run: 46 mg (92%, 98% ee). Second run: 45 mg (90%, 98% ee).

The ee of the product was determined by chiral GC (CP-Chirasil-DEX CB; heating program: 105 °C → 115 °C @ 1 °C/min, followed by 115 → 175 °C @ 5 °C/min; He flow rate: 1.0 mL/min; retention times: 29.8 min (minor), 30.2 min (major)).

^{1}H NMR (500 MHz, CDCl3) δ 7.41–7.38 (m, 2H), 7.33–7.30 (m, 3H), 3.91–3.80 (m, 2H), 2.22–2.11 (m, 1H), 1.98–1.80 (m, 1H), 0.82 (t, 3H, J = 7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 139.7, 128.4, 127.6, 124.8, 100.4 (d, J_{CF} = 176 Hz), 68.8, 28.9, 7.1.

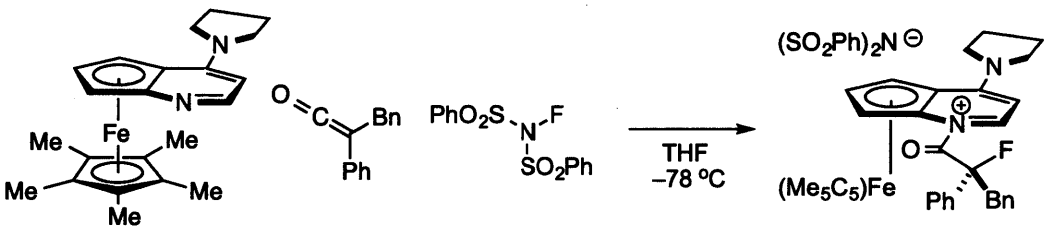
^{19}F NMR (282 MHz, CDCl3) δ –170.5 (ddt, J = 22 Hz, J = 21 Hz, J = 45 Hz).

FT-IR (neat) 3400, 2918, 2360, 1497, 1448, 1061, 913, 878, 759 cm^{-1}.

$[a]^{25}_{D}$ = –4.0 (c = 1.0, $CHCl_3$).

$[a]^{25}_{D}$ = –2.2 (c = 1.0, MeOH).[63]

V. Synthesis of the Acylpyridinium Salt



(+)-**PPY***

(+)-**2.13**
95% yield

Eq 2.2.5. NFSI (67.3 mg, 0.213 mmol; NFSI should be recrystallized from dichloromethane/*n*-hexanes before use) was added to an oven-dried 100-mL round-bottom flask equipped with a stir bar. The flask was capped with a rubber septum, and then it was evacuated and backfilled with nitrogen (three cycles); next, THF (47 mL) was added via syringe. (+)-**PPY*** (80.3 mg, 0.213 mmol) was added to an oven-dried 4-mL vial, and this vial was capped, and then it was evacuated and backfilled with nitrogen (three cycles); next, THF (1.0 mL) was added. Another 4-mL vial was evacuated and backfilled with nitrogen (three cycles); next, phenyl benzyl ketene (44.4 mg, 0.213 mmol) and THF (2.0 mL) were added in turn via syringe. A nitrogen balloon was attached to the flask that contained the NFSI solution, which was then cooled to –78 °C, and the solution of (+)-**PPY*** was added to the vial via syringe. Then, the solution of ketene was added dropwise to the vial via syringe pump over 20 min (color change: purple → violet → blue). The reaction mixture was stirred at –78 °C for an additional 30 min, and then it was concentrated under high vacuum (250 mtorr; the mixture was not exposed to the air) at r.t., furnishing acylpyridinium salt **2.13** as a blue solid (190 mg;

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[63] Goj, O.; Burchardt, A.; Haufe, G. *Tetrahedron: Asymmetry* **1997**, *8*, 399–408.

~90% pure by ^{1}H NMR spectroscopy; 95% yield by ^{1}H NMR spectroscopy vs. an internal standard). This salt is stable at r.t. for at least six months under N_2 atmosphere.

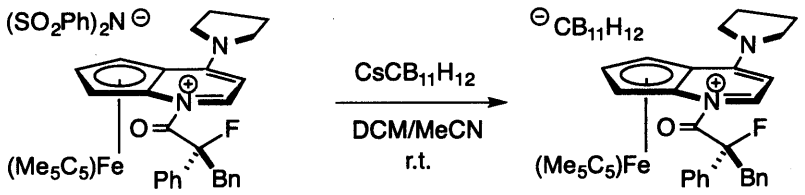
^{1}H NMR (500 MHz, CD_2Cl2) δ 8.07–8.00 (m, 1H), 7.80–7.74 (m, 5H), 7.60–7.40 (m, 5H), 7.34–7.16 (m, 10H), 6.13 (s, 1H), 5.83–5.73 (m, 1H), 4.63–4.51 (m, 1H), 4.43–4.34 (m, 1H), 3.90–3.78 (m, 4H), 3.75–3.51 (m, 2H), 2.25–2.04 (m, 4H), 1.54 (s, 15H).

^{19}F NMR (282 MHz, CD_2Cl_2) δ –159.6 (t, J = 26 Hz).

FT-IR (neat) 3063, 2916, 1717, 1684, 1653, 1611, 1498, 1478, 1445, 1383, 1347, 1327, 1280, 1237, 1154, 1133, 1086, 1052, 998, 921, 790, 753, 720 cm^{-1}.

MS (FAB) m/z (M^+) calcd for $C_{37}H_{40}FFeN_2O$: 603, found: 603.

$[a]^{25}_D$ = +1904 (c = 0.010, $CHCl_3$).



(+)-**2.13**

Eq 2.2.6. In a nitrogen-filled glovebox, acylpyridinium salt **2.13** (59.4 mg, 0.066 mmol) was dissolved in CH_2Cl_2 (1.5 mL). To this solution was added $Cs(CB_{11}H_{12})$ in CH_3CN (0.3 mL) at r.t., resulting in the formation of a white precipitate. After 30 min, the solution was filtered through an acrodisc to remove the precipitated $CsN(SO_2Ph)_2$, and then the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (1.0 mL), and this solution was then filtered through an acrodisc to remove the remaining cesium salt. The solvent was removed, furnishing a blue solid. Crystals suitable for X-ray crystallography were grown from CH_2Cl_2/pentane at –20 °C.

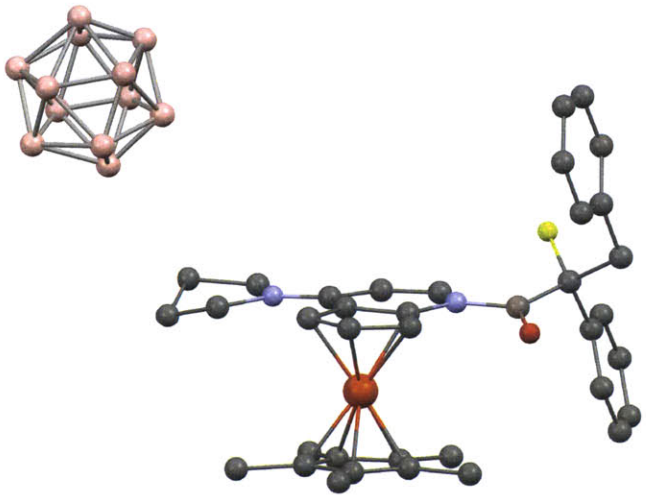
^{1}H NMR (500 MHz, CD_2Cl2) δ 8.05–8.00 (m, 1H), 7.56–7.49 (m, 5H), 7.23–7.20 (m, 3H), 7.12–7.09 (m, 2H), 6.00 (d, 1H, J = 3.5 Hz), 5.85–5.84 (m, 1H), 5.36 (s, 1H), 4.57–4.56 (m, 1H), 4.47–4.46 (m, 1H), 3.87–3.75 (m, 5H), 3.62 (dd, 1H, J = 14.5 Hz, J = 27.5 Hz), 2.37 (br s, 2H), 2.33–2.08 (m, 5H), 2.06–1.63 (m, 2H), 1.57 (s, 15H), 1.38–1.02 (m, 4H), 0.90 (m, 2H).

^{19}F NMR (282 MHz, CD_2Cl_2) δ –160.0 (t, J = 26 Hz).

^{11}B NMR (160 MHz, CD_2Cl_2) δ –7.13 (s), –13.2 (s), –16.0 (s).

FT-IR (neat) 3336, 3061, 2920, 2544, 1723, 1609, 1559, 1498, 1477, 1416, 1382, 1346, 1325, 1256, 1231, 1212, 1172, 1086, 1067, 1022, 999, 954, 921, 857, 786, 771 cm^{-1}.

MS (FAB) m/z (M^+) calcd for $C_{37}H_{40}FFeN_2O$: 603, found: 603.



Low-temperature diffraction data (ϕ-and ω-scans) were collected on a Bruker Kappa diffractometer coupled to a Apex II CCD detector with graphite monochromated Mo K_α radiation (λ = 0.71073 Å) for the structure of compound syl004. The structure was solved by direct methods using SHELXS [1] and refined against F^2 on all data by full-matrix least squares with SHELXL-2013 [2] using established refinement techniques [3]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups). Unless otherwise noted, all disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3- distances and displacement parameters (standard uncertainty 0.01 $Å^2$) as well as rigid bond restraints (standard uncertainty 0.002 $Å^2$) for anisotropic displacement parameters.

Compound syl004 crystallizes in the orthorhombic space group $P2_12_12_1$ with two molecules in the asymmetric unit along with two $CB_{11}H_{12}$ cages, 1.3 molecules of pentane, and 0.7 molecules of dichloromethane. In both iron complexes, the pentamethylcyclopentadienyl ligand was disordered over two positions. The occupancies for the major component refined to 0.541(11) and 0.69(3) for the first and second molecule, respectively. For the second moleculen the iron

was also disordered over two positions and was refined with the pentamethylcyclopentadienyl disorder. The carbonyl group in the second iron molecule was also modeled as a two part disorder where the occupancies for the two components refined to 0.508(10) and 0.492(10). The asymmetric unit contains two solvent accessible voids, one of which was modeled as a pentane molecule disordered over two positions and the second as a mixture of pentane and dichloromethane. The proximity of the two solvent positions was sufficiently close to treat them as a single disorder. The occupancy of the dichloromethane and one of the pentane molecules refined to 0.705(7) and the other two pentane positions refined to 0.295(7). The anisotropic displacement parameters for the carbon atoms (C1T, C2T, C3T, C4T, C5T) in the pentane molecule sharing a site with dichloromethane did not refine well and were constrained to be equivalent. The C-Cl distances in the dichloromethane were restrained to be equivalent. The 1,2- and 1,3- carbon-carbon distances in all pentane molecules were restrained to 1.54(2) Å and 2.52(4) Å, respectively. One of the $CB_{11}H_{12}$ cages was disordered over two positions with occupancies, 0.708(6) and 0.291(7) for the major and minor components, respectively. The position of the carbon atom in the both carborane cages is uncertain, and the position of the carbon atoms was determined by the shortest bond length, which is significantly longer than the typical C-B bond length. The carbon atom in the carborane cage is most likely disordered over multiple positions leading to the distorted bond lengths, which was not modeled.

[1] Sheldrick, G. M. *Acta Cryst.* **1990**, A46, 467–473.

[2] Sheldrick, G. M. *Acta Cryst.* **2008**, A64, 112–122.

[3] Müller, P. *Crystallography Reviews* **2009**, *15*, 57–83.

Table 1. Crystal data and structure refinement for syl004.

Identification code	syl004
Empirical formula	C41.59 H60.47 B11 Cl0.70 F Fe N2 O
Formula weight	823.22
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic

Space group	P 21 21 21	
Unit cell dimensions	a = 14.8695(15) Å	α= 90°.
	b = 15.973(2) Å	β= 90°.
	c = 37.274(4) Å	γ = 90°.
Volume	8853.2(17) $Å^3$	
Z	8	
Density (calculated)	1.235 Mg/m^3	
Absorption coefficient	0.423 mm^{-1}	
F(000)	3472	
Crystal size	0.400 x 0.250 x 0.200 mm^3	
Theta range for data collection	1.679 to 25.027°.	
Index ranges	-17<=h<=17, -19<=k<=14, -43<=l<=44	
Reflections collected	65941	
Independent reflections	15615 [R(int) = 0.0679]	
Completeness to theta = 25.242°	97.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7458 and 0.6284	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15615 / 3857 / 1586	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2sigma(I)]	R1 = 0.0610, wR2 = 0.1396	
R indices (all data)	R1 = 0.0960, wR2 = 0.1563	
Absolute structure parameter	-0.006(7)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.511 and -0.403 $e/Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for syl004. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Fe(1)	7238(1)	4901(1)	3584(1)	35(1)
C(1)	6922(8)	6144(8)	3519(4)	47(2)
C(2)	6989(9)	5771(8)	3181(3)	46(2)
C(3)	7871(8)	5445(9)	3143(3)	41(2)
C(4)	8352(8)	5606(13)	3467(4)	41(2)
C(5)	7770(9)	6062(9)	3701(4)	46(2)
C(6)	6119(9)	6586(10)	3670(5)	64(4)
C(7)	6271(10)	5761(11)	2887(5)	60(4)
C(8)	8246(12)	5058(11)	2805(3)	57(4)
C(9)	9337(9)	5420(20)	3524(6)	53(4)
C(10)	8014(13)	6397(13)	4064(4)	69(5)
C(1A)	6956(9)	6116(9)	3703(4)	48(2)
C(2A)	6817(9)	5959(11)	3332(4)	47(2)
C(3A)	7637(10)	5647(11)	3180(4)	42(2)
C(4A)	8306(9)	5652(15)	3459(5)	41(2)
C(5A)	7882(10)	5936(11)	3780(4)	44(2)
C(6A)	6284(11)	6487(12)	3958(6)	64(4)
C(7A)	5928(10)	6026(13)	3143(6)	61(4)
C(8A)	7788(13)	5333(12)	2810(4)	50(4)
C(9A)	9273(11)	5390(30)	3411(7)	51(5)
C(10A)	8329(15)	6097(15)	4139(5)	61(5)
C(11)	6964(4)	3695(4)	3437(1)	27(1)

C(12)	6160(4)	4102(4)	3543(2)	31(2)
C(13)	6276(4)	4362(5)	3901(2)	44(2)
C(14)	7141(4)	4149(5)	4020(2)	42(2)
C(15)	7597(4)	3714(4)	3729(2)	26(1)
C(16)	8488(4)	3395(4)	3683(2)	30(2)
N(2)	9119(3)	3446(4)	3932(1)	38(1)
C(19)	9016(4)	3871(6)	4280(2)	52(2)
C(20)	9962(4)	3948(6)	4426(2)	60(2)
C(21)	10436(5)	3221(5)	4261(2)	52(2)
C(22)	10043(4)	3107(5)	3882(2)	47(2)
C(17)	8668(4)	3028(4)	3340(2)	36(2)
C(18)	8044(4)	2978(4)	3081(2)	34(2)
N(1)	7181(3)	3280(3)	3114(1)	27(1)
C(23)	6546(4)	3257(5)	2835(2)	35(2)
O(1)	5919(3)	3739(3)	2834(1)	49(1)
C(24)	6662(4)	2650(5)	2523(2)	41(2)
F(1)	7106(2)	1932(2)	2651(1)	44(1)
C(25)	5730(5)	2345(5)	2393(2)	48(2)
C(26)	5230(5)	1851(6)	2669(2)	49(2)
C(27)	5407(6)	999(6)	2712(2)	56(2)
C(28)	4974(6)	524(7)	2969(2)	72(3)
C(29)	4327(6)	920(8)	3187(2)	72(3)
C(30)	4142(5)	1746(7)	3152(2)	63(3)
C(31)	4586(4)	2224(6)	2895(2)	51(2)
C(32)	7227(4)	3052(5)	2232(2)	40(2)
C(33)	7058(5)	3862(6)	2118(2)	58(2)
C(34)	7558(6)	4236(6)	1862(2)	66(2)

C(35)	8274(5)	3799(6)	1704(2)	57(2)
C(36)	8432(5)	2989(6)	1808(2)	60(2)
C(37)	7910(5)	2615(5)	2068(2)	50(2)
Fe(2)	3011(6)	4380(5)	5569(2)	31(1)
C(201)	1900(7)	5090(10)	5435(4)	38(2)
C(202)	2380(8)	4848(10)	5121(3)	40(2)
C(203)	3273(8)	5172(10)	5150(3)	41(2)
C(204)	3342(9)	5603(9)	5479(4)	41(2)
C(205)	2501(9)	5562(9)	5660(4)	38(2)
C(206)	937(8)	4896(14)	5516(5)	44(4)
C(207)	2038(10)	4342(12)	4809(3)	47(4)
C(208)	3981(10)	5083(14)	4865(4)	53(4)
C(209)	4171(11)	6049(12)	5608(6)	52(4)
C(210)	2265(13)	5956(11)	6015(4)	47(3)
C(211)	3312(4)	3833(4)	6039(2)	33(1)
C(212)	4085(4)	3913(5)	5827(2)	42(1)
C(213)	3908(4)	3482(5)	5504(2)	47(1)
C(214)	3038(5)	3145(5)	5505(2)	42(1)
C(215)	2636(4)	3366(4)	5846(2)	33(1)
C(216)	1769(4)	3233(4)	5996(2)	28(1)
N(202)	1099(4)	2852(4)	5834(1)	36(1)
C(219)	1122(5)	2520(5)	5463(2)	49(2)
C(220)	170(5)	2294(6)	5383(2)	64(2)
C(221)	-245(5)	2102(5)	5739(2)	54(2)
C(222)	213(4)	2704(5)	5994(2)	43(2)
C(217)	1644(4)	3569(4)	6352(2)	30(1)
C(218)	2298(4)	3976(4)	6530(2)	33(1)

N(201)	3146(3)	4114(3)	6396(1)	33(1)
C(223)	3893(17)	4512(16)	6569(6)	41(3)
O(201)	4570(11)	4695(10)	6417(5)	52(4)
C(224)	3749(17)	4786(16)	6946(6)	44(2)
F(201)	3210(30)	4222(17)	7141(12)	36(3)
C(225)	4532(14)	4941(17)	7174(7)	50(2)
C(226)	5090(20)	4121(16)	7146(8)	50(3)
C(227)	5685(15)	3961(14)	6869(6)	52(3)
C(228)	6129(14)	3204(14)	6866(5)	53(3)
C(229)	6013(14)	2612(15)	7121(6)	54(3)
C(230)	5385(16)	2755(17)	7396(6)	56(3)
C(231)	4920(30)	3500(20)	7407(10)	52(3)
C(232)	3386(14)	5644(12)	6956(5)	53(2)
C(233)	3805(14)	6313(11)	6785(4)	56(3)
C(234)	3429(15)	7121(12)	6791(5)	61(3)
C(235)	2612(18)	7219(16)	6986(7)	68(3)
C(236)	2218(17)	6619(13)	7134(5)	66(3)
C(237)	2621(16)	5805(12)	7142(5)	57(3)
Fe(2B)	2938(13)	4531(12)	5581(5)	38(2)
C(01B)	1806(15)	5215(19)	5508(7)	37(3)
C(02B)	2240(16)	5080(20)	5172(6)	40(3)
C(03B)	3138(17)	5399(19)	5195(6)	42(3)
C(04B)	3225(18)	5765(17)	5544(7)	40(3)
C(05B)	2409(17)	5673(17)	5735(7)	36(3)
C(06B)	836(16)	5060(30)	5597(10)	40(6)
C(07B)	1810(20)	4680(30)	4851(7)	51(6)
C(08B)	3840(20)	5450(30)	4902(8)	55(6)

C(09B)	4010(20)	6270(30)	5675(11)	44(6)
C(10B)	2190(30)	5960(30)	6111(8)	46(5)
C(23B)	3759(16)	4679(14)	6591(6)	40(3)
O(01B)	4322(10)	5023(10)	6415(5)	44(3)
C(24B)	3668(15)	4868(14)	6994(5)	44(2)
F(01B)	3250(30)	4166(19)	7151(13)	43(4)
C(25B)	4693(12)	4798(14)	7134(6)	48(2)
C(26B)	5082(19)	3934(15)	7173(8)	49(3)
C(27B)	5760(14)	3658(13)	6938(6)	54(3)
C(28B)	6166(13)	2896(13)	6976(6)	58(3)
C(29B)	5880(13)	2367(13)	7249(5)	56(3)
C(30B)	5226(16)	2602(15)	7484(6)	57(3)
C(31B)	4850(30)	3390(20)	7452(10)	51(3)
C(32B)	3044(12)	5622(10)	7030(5)	51(2)
C(33B)	3331(13)	6399(9)	6911(5)	59(3)
C(34B)	2869(15)	7125(13)	6919(6)	66(3)
C(35B)	1988(14)	7060(12)	7086(5)	70(3)
C(36B)	1672(13)	6307(10)	7209(4)	63(3)
C(37B)	2192(11)	5580(10)	7181(4)	50(2)
C(101)	2969(5)	4453(5)	3881(2)	53(2)
B(1)	2368(5)	3867(5)	3568(2)	40(2)
B(2)	1903(5)	4793(6)	3760(2)	46(2)
B(3)	2767(5)	5502(5)	3820(2)	42(2)
B(4)	3788(5)	5049(6)	3673(2)	45(2)
B(5)	3538(4)	4043(5)	3516(2)	34(2)
B(6)	2807(5)	4145(5)	3153(2)	39(2)
B(7)	1789(5)	4601(5)	3299(2)	44(2)

B(8)	2040(5)	5606(5)	3454(2)	40(2)
B(9)	3211(5)	5786(5)	3402(2)	41(2)
B(10)	3675(5)	4864(6)	3209(2)	43(2)
B(11)	2605(5)	5212(5)	3080(2)	41(2)
C(102)	2651(8)	9757(8)	4296(3)	73(2)
B(12)	1918(8)	9796(9)	4663(3)	67(2)
B(13)	3094(8)	10068(10)	4696(3)	69(2)
B(14)	3404(8)	10535(10)	4295(4)	72(2)
B(15)	2446(7)	10559(9)	4003(3)	65(2)
B(16)	1553(8)	10106(9)	4238(3)	62(2)
B(17)	1342(8)	10725(9)	4607(3)	62(2)
B(18)	2299(9)	10708(9)	4891(3)	66(2)
B(19)	3175(9)	11162(10)	4666(3)	70(2)
B(20)	2807(8)	11447(9)	4215(3)	66(2)
B(21)	1647(7)	11194(8)	4206(3)	54(2)
B(22)	2128(9)	11565(9)	4610(3)	65(2)
C(02A)	2178(15)	9584(14)	4315(5)	70(2)
B(12A)	2220(16)	9454(14)	4773(6)	70(2)
B(13A)	3209(14)	9651(15)	4520(7)	69(2)
B(14A)	2936(16)	10309(16)	4172(6)	70(2)
B(15A)	1768(15)	10583(17)	4203(6)	68(2)
B(16A)	1346(13)	10042(17)	4566(6)	67(2)
B(17A)	1874(15)	10398(16)	4948(5)	66(2)
B(18A)	3039(15)	10171(16)	4918(6)	68(2)
B(19A)	3459(13)	10723(16)	4554(7)	68(2)
B(20A)	2567(15)	11292(14)	4349(6)	67(2)
B(21A)	1608(15)	11113(16)	4621(6)	64(2)

B(22A)	2671(17)	11173(15)	4822(6)	66(2)
C(1S)	8995(13)	6889(12)	6237(4)	118(4)
Cl(1S)	9847(3)	6476(4)	6467(1)	109(2)
Cl(2S)	9254(5)	7254(6)	5829(2)	166(3)
C(1T)	9600(40)	6610(40)	6353(14)	133(4)
C(2T)	9220(30)	7350(30)	6159(10)	133(4)
C(3T)	9610(30)	7290(50)	5744(10)	133(4)
C(4T)	8710(20)	7470(30)	5548(10)	133(4)
C(5T)	8840(30)	7550(30)	5148(9)	133(4)
C(1U)	7592(15)	7489(12)	4936(5)	147(7)
C(2U)	7043(14)	7906(14)	5218(6)	170(5)
C(3U)	6024(14)	7852(16)	5188(6)	173(5)
C(4U)	5545(15)	8331(13)	5495(6)	158(5)
C(5U)	5715(13)	7863(12)	5861(5)	128(5)
C(1V)	6500(40)	7650(30)	4762(11)	150(8)
C(2V)	6250(50)	8010(30)	5141(11)	167(6)
C(3V)	6050(40)	7200(20)	5370(10)	167(6)
C(4V)	5960(40)	7470(30)	5774(10)	156(6)
C(5V)	5870(40)	8430(30)	5742(15)	155(9)

VI. Mechanistic/Reactivity Studies

Figure 2.6. **Comparison of reaction rates.** In a nitrogen-filled glovebox, NFSI (15.8 mg, 0.050 mmol), tetradecane (13 mL, 0.050 mmol; internal standard), and THF (37.8 mL) were combined in an oven-dried 50-mL round-bottom flask equipped with a stir bar. The flask was fitted with a rubber septum, and then the flask was removed from the glovebox. A nitrogen-filled balloon was attached to the flask, which was cooled to –78 °C. Next a solution of **PPY*** (0.188 mg in 0.050 mL of THF; 0.50 μmol) was added to the flask via syringe. Then, a solution of the ketene (0.050 mmol in 0.10 mL of THF) and a solution of C_6F_5ONa (10.3 mg in 0.10 mL of THF; 0.050 mmol) were added dropwise to the flask simultaneously over 8 seconds. An aliquot (1.00 mL) of the reaction mixture was removed after 2 min, 4 min, 6 min, 8 min, and 10 min and quenched with 1.0 mL of methanol (a syringe with a long metal needle that contained 1.0 mL of MeOH was used to take an aliquot of the reaction mixture). The amount of product was determined by GC analysis.

yield / time (min)	phenyl methyl ketene	phenyl ethyl ketene	phenyl isobutyl ketene
0	0	0	0
2	6.7	5.1	2.7
4	15	9.0	5.7
6	20	13	9.7
8	24	19	14
10	28	24	15

Determination of the rate law: fluorination of phenyl ethyl ketene. In a nitrogen-filled glovebox, NFSI, hexadecane (internal standard), and THF (37.8 mL) were combined in an oven-dried 50-mL round-bottom flask equipped with a stir bar. The flask was fitted with a rubber septum, and then the flask was removed from the glovebox. A nitrogen-filled balloon was attached to the flask, which was cooled to –78

°C. Next a solution of **PPY*** (in 0.050 mL of THF) was added to the flask via syringe. Then, a solution of the ketene (in 0.10 mL of THF) and a solution of C_6F_5ONa (in 0.10 mL of THF) were added dropwise to the flask simultaneously over 8 seconds. An aliquot (1.00 mL) of the reaction mixture was removed after 2 min, 4 min, 6 min, 8 min, and 10 min, and quenched with 1.0 mL of methanol (a syringe with a long metal needle that contained 1.0 mL of MeOH was used to take an aliquot of the reaction mixture). The amount of product was determined by GC analysis.

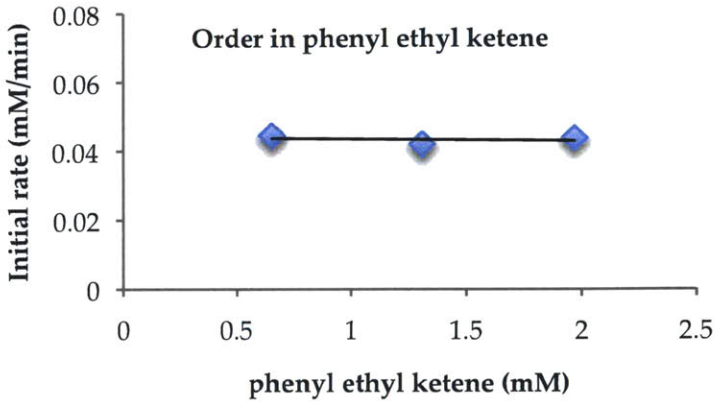
Order in phenyl ethyl ketene:

Table S1. Observed Initial Rates

$[\text{phenyl ethyl ketene}]_{initial}$ (mM)[a]	k_{obs} (mM/min)
0.657	0.044
1.31	0.042
1.97	0.044

[a] Reaction conditions: $[NFSI]_{initial}$ = 1.31 mM, $[C_6F_5ONa]_{initial}$ = 1.31 mM, and $[\textbf{PPY*}]_{initial}$ = 0.0131 mM.

Figure S1.



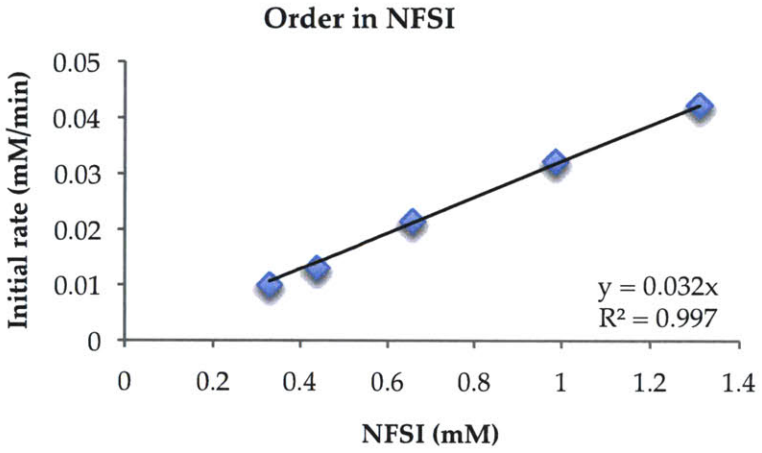
Order in NFSI:

Table S2. Observed Initial Rates

$[NFSI]_{initial}$ (mM)[a]	k_{obs} (mM/min)
0.329	0.010
0.437	0.013
0.657	0.022
0.986	0.032
1.31	0.042

[a] Reaction conditions: $[\text{phenyl ethyl ketene}]_{initial}$ = 1.31 mM, $[C_6F_5ONa]_{initial}$ = 1.31 mM, and $[\mathbf{PPY^*}]_{initial}$ = 0.0131 mM.

Figure S2.



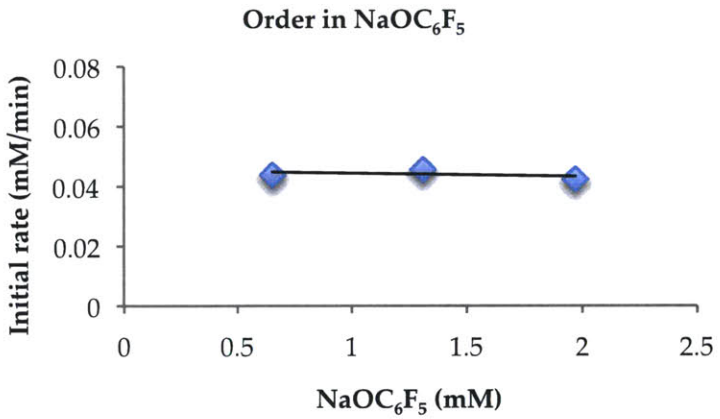
Order in C_6F_5ONa:

Table S3. Observed Initial Rates

$[C_6F_5ONa]_{initial}$ (mM)[a]	k_{obs} (mM/min)
0.657	0.044
0.986	0.046
1.31	0.042

[a] Reaction conditions: $[\text{phenyl ethyl ketene}]_{initial}$ = 1.31 mM, $[NFSI]_{initial}$= 1.31 mM, and $[PPY^*]_{initial}$ = 0.0131 mM.

Figure S3.



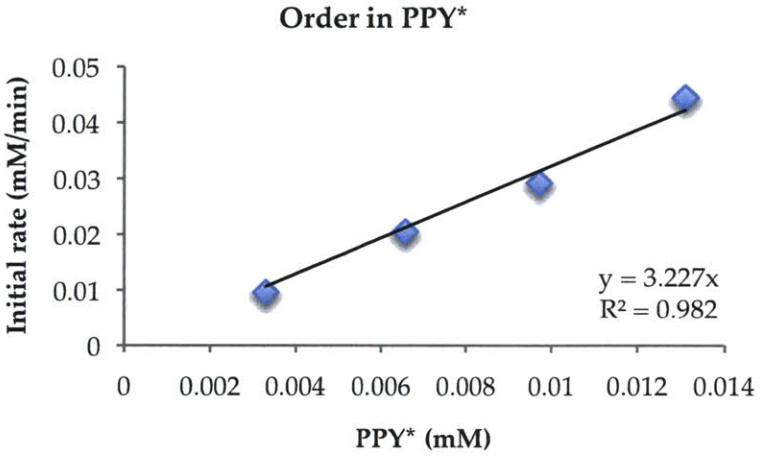
Order in PPY*:

Table S4. Observed Initial Rates

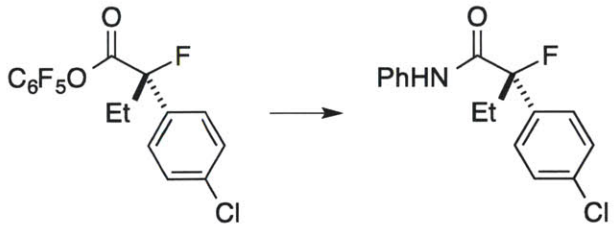
$[PPY^*]_{initial}$ (mM)[a]	k_{obs} (mM/min)
0.00329	0.0096
0.00657	0.020
0.00972	0.029
0.0131	0.044

[a] Reaction conditions: $[\text{phenyl ethyl ketene}]_{initial}$ = 1.31 mM, $[NFSI]_{initial}$= 1.31 mM, and $[C_6F_5ONa]_{initial}$ = 1.31 mM.

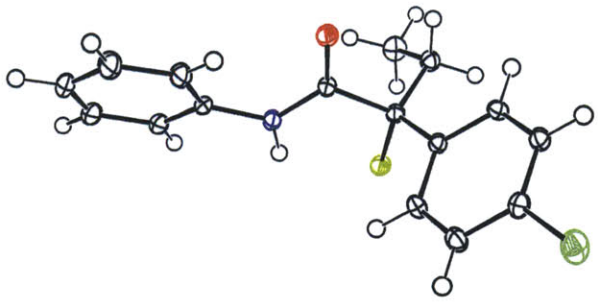
Figure S4.



VII. Determination of Absolute Configuration



(*R*)-2-(4-Chlorophenyl)-2-fluoro-*N*-phenylbutanamide (derived from the product of Table 2, entry 6). (*R*)-Perfluorophenyl 2-(4-chlorophenyl)-2-fluorobutanoate (38.3 mg, 0.10 mmol; 97% ee, obtained with (+)-**PPY***), aniline (14.0 mg, 0.15 mmol), Et_3N (20 mL), and THF (1.0 mL) were added to a 4-mL vial, which was then sealed and heated at 65 °C for 12 h. The mixture was then allowed to cool to r.t., and the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexanes → 10% Et_2O in hexanes), which furnished the product as a white solid (29 mg, 99% yield). X-ray quality crystals were obtained by cooling a saturated solution in ethanol. The absolute stereochemistry was determined to be (*R*) by X-ray crystallography. The absolute configurations of other fluorinated products (from aryl alkyl ketenes) were assigned by analogy.



A crystal of $C_{16}H_{15}ClFNO$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Apex II diffractometer with filtered Mo-Kα radiation at a temperature of 100 K. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using least squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter. Density corresponding to approximately 24 electrons per unit cell could not be modeled in a chemically reasonable manner and was removed using

Platon/Squeeze, leaving voids totaling 166 cubic angstroms. The use of Squeeze does not change the interpretation of the chemical absolute stereochemistry.

[1] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.* (2009). 42, 339-341.

[2] SHELXS, G.M. Sheldrick, *Acta Cryst.* (2008). A64, 112–122.

[3] SHELXL, G.M. Sheldrick, *Acta Cryst.* (2008). A64, 112–122.

Table 1. Crystal data and structure refinement for 002.

Identification code	syl002-sr	
Empirical formula	$C_{16}H_{15}ClFNO$	
Formula weight	291.74	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Hexagonal	
Space group	$P6_1$	
Unit cell dimensions	a = 21.7099(11) Å	$\alpha = 90°$.
	b = 21.7099(11) Å	$\beta = 90°$.
	c = 5.3925(3) Å	$\gamma = 120°$.
Volume	2201.1(3) $Å^3$	
Z	6	
Density (calculated)	1.321 Mg/m^3	
Absorption coefficient	0.266 mm^{-1}	
F(000)	912	
Crystal size	0.38 x 0.12 x 0.03 mm^3	
Theta range for data collection	1.876 to 35.120°.	
Index ranges	-34<=h<=34, -34<=k<=34, -8<=l<=8	

Reflections collected	51350
Independent reflections	6146 [R(int) = 0.0653]
Completeness to theta = 25.242°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.8720
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6146 / 1 / 241
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0407, wR2 = 0.0932
R indices (all data)	R1 = 0.0591, wR2 = 0.0989
Absolute structure parameter (Flack)	0.03(2)
Largest diff. peak and hole	0.376 and -0.234 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for 002. U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	15063(1)	3609(1)	3361(1)	27(1)
F(1)	13136(1)	4755(1)	-2250(2)	17(1)
N(1)	11893(1)	3720(1)	-1195(3)	14(1)
O(1)	12102(1)	3852(1)	2988(2)	19(1)
C(1)	13056(1)	4635(1)	345(3)	13(1)
C(2)	12295(1)	4024(1)	835(3)	13(1)
C(3)	11181(1)	3144(1)	-1228(3)	14(1)

C(4)	10763(1)	3099(1)	-3257(3)	18(1)
C(5)	10072(1)	2536(1)	-3452(4)	25(1)
C(6)	9800(1)	2012(1)	-1649(4)	29(1)
C(7)	10220(1)	2058(1)	366(4)	29(1)
C(8)	10911(1)	2624(1)	598(3)	21(1)
C(9)	13577(1)	4397(1)	1111(3)	13(1)
C(10)	13988(1)	4652(1)	3252(3)	15(1)
C(11)	14448(1)	4413(1)	3933(3)	16(1)
C(12)	14499(1)	3921(1)	2459(3)	16(1)
C(13)	14099(1)	3659(1)	311(4)	18(1)
C(14)	13634(1)	3895(1)	-347(3)	16(1)
C(15)	13170(1)	5316(1)	1562(3)	16(1)
C(16)	12760(1)	5625(1)	274(4)	22(1)

Table 3. Bond lengths [Å] and angles [°] for 002.

Cl(1)-C(12)	1.7386(18)
F(1)-C(1)	1.4180(19)
N(1)-H(1)	0.83(3)
N(1)-C(2)	1.349(2)
N(1)-C(3)	1.421(2)
O(1)-C(2)	1.228(2)
C(1)-C(2)	1.537(2)
C(1)-C(9)	1.518(2)
C(1)-C(15)	1.521(2)
C(3)-C(4)	1.394(2)

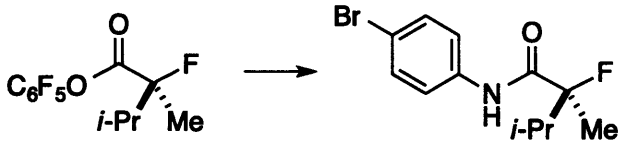
C(3)-C(8)	1.387(2)
C(4)-H(4)	0.91(3)
C(4)-C(5)	1.387(3)
C(5)-H(5)	0.93(3)
C(5)-C(6)	1.385(3)
C(6)-H(6)	0.92(2)
C(6)-C(7)	1.390(3)
C(7)-H(7)	0.83(3)
C(7)-C(8)	1.390(3)
C(8)-H(8)	0.93(3)
C(9)-C(10)	1.393(2)
C(9)-C(14)	1.398(2)
C(10)-H(10)	0.93(3)
C(10)-C(11)	1.385(2)
C(11)-H(11)	0.97(3)
C(11)-C(12)	1.380(3)
C(12)-C(13)	1.388(2)
C(13)-H(13)	0.98(2)
C(13)-C(14)	1.387(3)
C(14)-H(14)	0.94(2)
C(15)-H(15A)	0.94(3)
C(15)-H(15B)	0.94(3)
C(15)-C(16)	1.523(3)
C(16)-H(16A)	1.01(3)
C(16)-H(16B)	1.00(3)
C(16)-H(16C)	1.00(3)

C(2)-N(1)-H(1)	119.0(18)
C(2)-N(1)-C(3)	126.41(15)
C(3)-N(1)-H(1)	114.5(17)
F(1)-C(1)-C(2)	107.97(13)
F(1)-C(1)-C(9)	106.65(13)
F(1)-C(1)-C(15)	107.61(13)
C(9)-C(1)-C(2)	108.76(13)
C(9)-C(1)-C(15)	115.27(14)
C(15)-C(1)-C(2)	110.29(14)
N(1)-C(2)-C(1)	115.81(14)
O(1)-C(2)-N(1)	125.45(16)
O(1)-C(2)-C(1)	118.74(15)
C(4)-C(3)-N(1)	117.07(15)
C(8)-C(3)-N(1)	122.58(15)
C(8)-C(3)-C(4)	120.29(16)
C(3)-C(4)-H(4)	117.9(17)
C(5)-C(4)-C(3)	120.10(18)
C(5)-C(4)-H(4)	121.8(17)
C(4)-C(5)-H(5)	123.2(19)
C(6)-C(5)-C(4)	120.00(19)
C(6)-C(5)-H(5)	116.6(19)
C(5)-C(6)-H(6)	121.6(17)
C(5)-C(6)-C(7)	119.62(18)
C(7)-C(6)-H(6)	118.8(17)
C(6)-C(7)-H(7)	119(2)
C(6)-C(7)-C(8)	120.9(2)
C(8)-C(7)-H(7)	120(2)

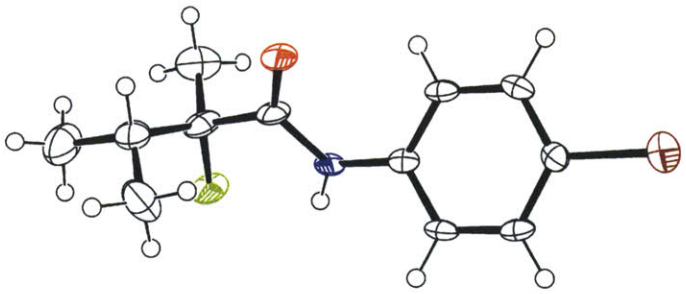
C(3)-C(8)-C(7)	119.04(18)
C(3)-C(8)-H(8)	121.0(16)
C(7)-C(8)-H(8)	119.9(16)
C(10)-C(9)-C(1)	121.91(15)
C(10)-C(9)-C(14)	119.14(15)
C(14)-C(9)-C(1)	118.93(14)
C(9)-C(10)-H(10)	122.7(16)
C(11)-C(10)-C(9)	120.61(16)
C(11)-C(10)-H(10)	116.6(16)
C(10)-C(11)-H(11)	121.0(15)
C(12)-C(11)-C(10)	119.28(16)
C(12)-C(11)-H(11)	119.7(15)
C(11)-C(12)-Cl(1)	119.05(14)
C(11)-C(12)-C(13)	121.46(16)
C(13)-C(12)-Cl(1)	119.48(14)
C(12)-C(13)-H(13)	121.0(14)
C(14)-C(13)-C(12)	118.94(16)
C(14)-C(13)-H(13)	120.1(14)
C(9)-C(14)-H(14)	120.1(14)
C(13)-C(14)-C(9)	120.56(15)
C(13)-C(14)-H(14)	119.4(14)
C(1)-C(15)-H(15A)	107.1(16)
C(1)-C(15)-H(15B)	108.6(15)
C(1)-C(15)-C(16)	112.62(15)
H(15A)-C(15)-H(15B)	108(2)
C(16)-C(15)-H(15A)	111.3(16)
C(16)-C(15)-H(15B)	109.2(16)

C(15)-C(16)-H(16A)	110.6(15)
C(15)-C(16)-H(16B)	109.0(14)
C(15)-C(16)-H(16C)	109.9(17)
H(16A)-C(16)-H(16B)	105(2)
H(16A)-C(16)-H(16C)	111(2)
H(16B)-C(16)-H(16C)	111(2)

Symmetry transformations used to generate equivalent atoms:



(*S*)-*N*-(4-Bromophenyl)-2-fluoro-2,3-dimethylbutanamide (derived from the product of eq 3). (*S*)-Perfluorophenyl 2-fluoro-2,3-dimethylbutanoate (30 mg, 0.10 mmol; 73% ee, obtained with (–)-**PPY***), 4-bromoaniline (34 mg, 0.20 mmol), Et_3N (42 mL, 0.30 mmol), and THF (0.3 mL) were added to a 4-mL vial, which was then sealed and heated at 65 °C for 12 h. The mixture was then allowed to cool to room temperature, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexanes → 10% Et_2O in hexanes), which furnished the product as a white solid. The product was further purified by recrystallization from *n*-hexanes (>90% ee). X-ray quality crystals were obtained by slowly evaporating *n*-hexanes from a saturated solution of the amide in *n*-hexanes. The absolute stereochemistry was determined to be (*S*) by X-ray crystallography.



A crystal of $C_{12}H_{15}BrFNO$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker Apex II diffractometer with filtered Mo-Kα radiation at a temperature of 100 K. The crystal was determined to be a two-component non-merohedral twin. Both components were integrated and the data processed with TWINABS. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

[1] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. (2009). 42, 339–341.

[2] SHELXS, G.M. Sheldrick, Acta Cryst. (2008). A64, 112–122.

[3] SHELXL, G.M. Sheldrick, Acta Cryst. (2008). A64, 112–122.

Table 1. Crystal data and structure refinement for syl003.

Identification code	syl003
Empirical formula	C_{12} H_{15} Br F N O
Formula weight	288.16
Temperature	100 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$

Unit cell dimensions	a = 8.4495(7) Å	$\alpha = 90°$.
	b = 5.1247(4) Å	$\beta = 95.193(4)°$.
	c = 14.4009(12) Å	$\gamma = 90°$.
Volume	621.02(9) $Å^3$	
Z	2	
Density (calculated)	1.541 Mg/m^3	
Absorption coefficient	3.301 mm^{-1}	
F(000)	292	
Crystal size	0.25 x 0.24 x 0.08 mm^3	
Theta range for data collection	2.420 to 26.371°.	
Index ranges	-10<=h<=10, -6<=k<=6, -17<=l<=18	
Reflections collected	23534	
Independent reflections	2470	
Completeness to theta = 25.242°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.862085 and 0.634353	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2470 / 1 / 149	
Goodness-of-fit on F^2	1.092	
Final R indices [I>2sigma(I)]	R1 = 0.0343, wR2 = 0.0842	
R indices (all data)	R1 = 0.0361, wR2 = 0.0856	
Absolute structure parameter (Flack)	0.021(6)	
Largest diff. peak and hole	0.659 and -0.544 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for syl003. U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	6518(1)	6703(2)	7272(1)	39(1)
F(1)	8681(6)	3998(8)	1596(3)	40(1)
O(1)	8051(7)	9638(9)	2920(4)	38(1)
N(1)	8106(7)	5310(11)	3272(4)	25(1)
C(9)	8147(8)	7862(12)	5679(5)	23(1)
C(7)	7805(8)	5592(12)	4220(5)	20(1)
C(8)	8490(8)	7585(12)	4765(5)	24(2)
C(1)	8216(9)	7372(10)	2693(6)	29(2)
C(11)	6450(8)	4068(12)	5525(5)	24(1)
C(12)	6810(8)	3804(12)	4613(5)	24(1)
C(2)	8620(8)	6720(20)	1691(4)	34(2)
C(4)	7261(12)	7717(14)	1007(6)	40(2)
C(5)	5694(9)	6660(40)	1196(5)	49(2)
C(10)	7113(8)	6135(11)	6043(4)	23(2)
C(3)	10267(11)	7688(17)	1567(7)	50(2)
C(6)	7660(14)	7130(30)	4(6)	60(3)

Table 3. Bond lengths [Å] and angles [°] for syl003.

Br(1)-C(10)	1.906(7)
F(1)-C(2)	1.404(11)
O(1)-C(1)	1.218(8)
N(1)-C(7)	1.420(9)
N(1)-C(1)	1.355(8)
C(9)-C(8)	1.381(10)
C(9)-C(10)	1.379(9)
C(7)-C(8)	1.383(9)
C(7)-C(12)	1.396(10)
C(1)-C(2)	1.548(10)
C(11)-C(12)	1.382(10)
C(11)-C(10)	1.385(9)
C(2)-C(4)	1.532(11)
C(2)-C(3)	1.503(11)
C(4)-C(5)	1.479(13)
C(4)-C(6)	1.542(12)

C(1)-N(1)-C(7)	122.8(6)
C(10)-C(9)-C(8)	119.4(6)
C(8)-C(7)-N(1)	121.2(6)
C(8)-C(7)-C(12)	119.4(6)
C(12)-C(7)-N(1)	119.3(6)
C(9)-C(8)-C(7)	120.2(6)
O(1)-C(1)-N(1)	124.2(7)
O(1)-C(1)-C(2)	119.8(7)

N(1)-C(1)-C(2)	116.0(6)
C(12)-C(11)-C(10)	118.3(6)
C(11)-C(12)-C(7)	120.8(6)
F(1)-C(2)-C(1)	108.6(6)
F(1)-C(2)-C(4)	107.5(6)
F(1)-C(2)-C(3)	105.8(6)
C(4)-C(2)-C(1)	108.2(6)
C(3)-C(2)-C(1)	108.9(7)
C(3)-C(2)-C(4)	117.5(7)
C(2)-C(4)-C(6)	108.8(8)
C(5)-C(4)-C(2)	113.0(7)
C(5)-C(4)-C(6)	112.2(8)
C(9)-C(10)-Br(1)	118.9(5)
C(9)-C(10)-C(11)	121.7(6)
C(11)-C(10)-Br(1)	119.3(5)

Symmetry transformations used to generate equivalent atoms:

2.5. ^{1}H NMR Spectra of Selected Compounds

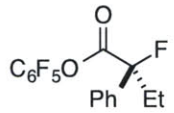


Table 2.2, entry 1

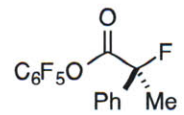


Table 2.2, entry 2

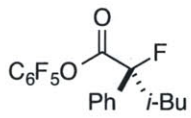


Table 2.2, entry 3

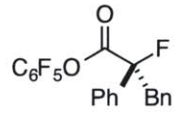
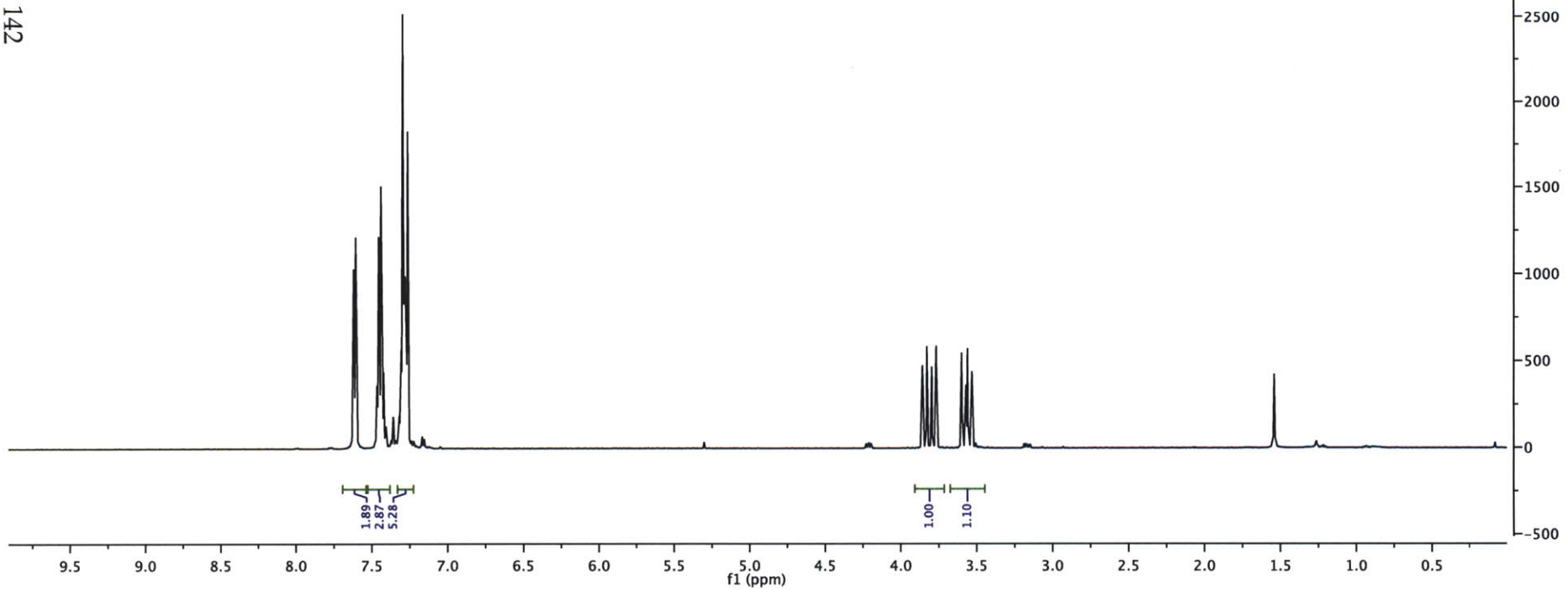


Table 2.2, entry 4



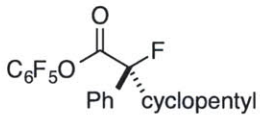


Table 2.2, entry 5

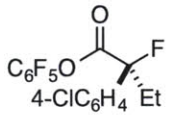


Table 2.2, entry 6

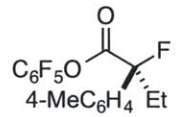
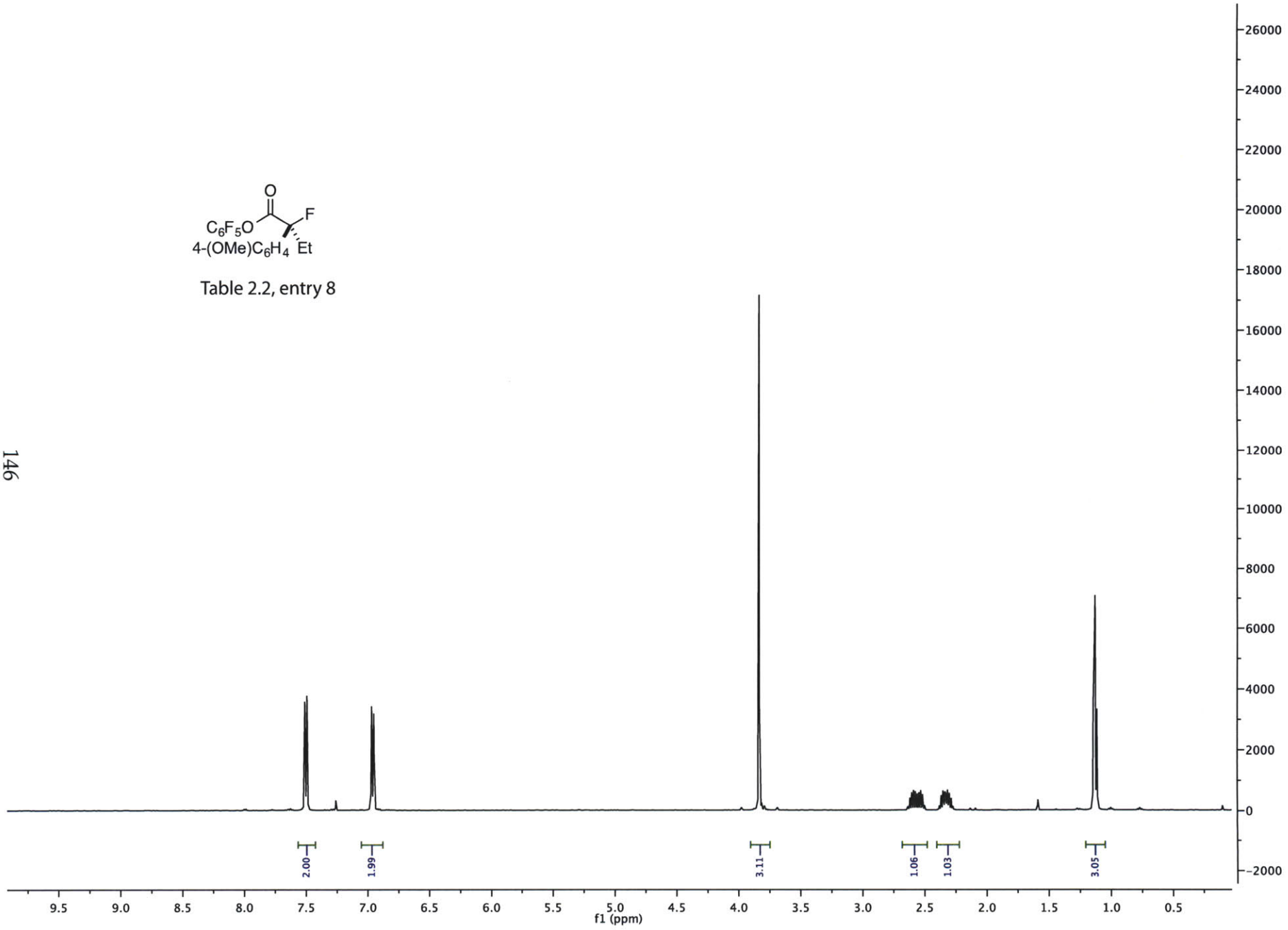
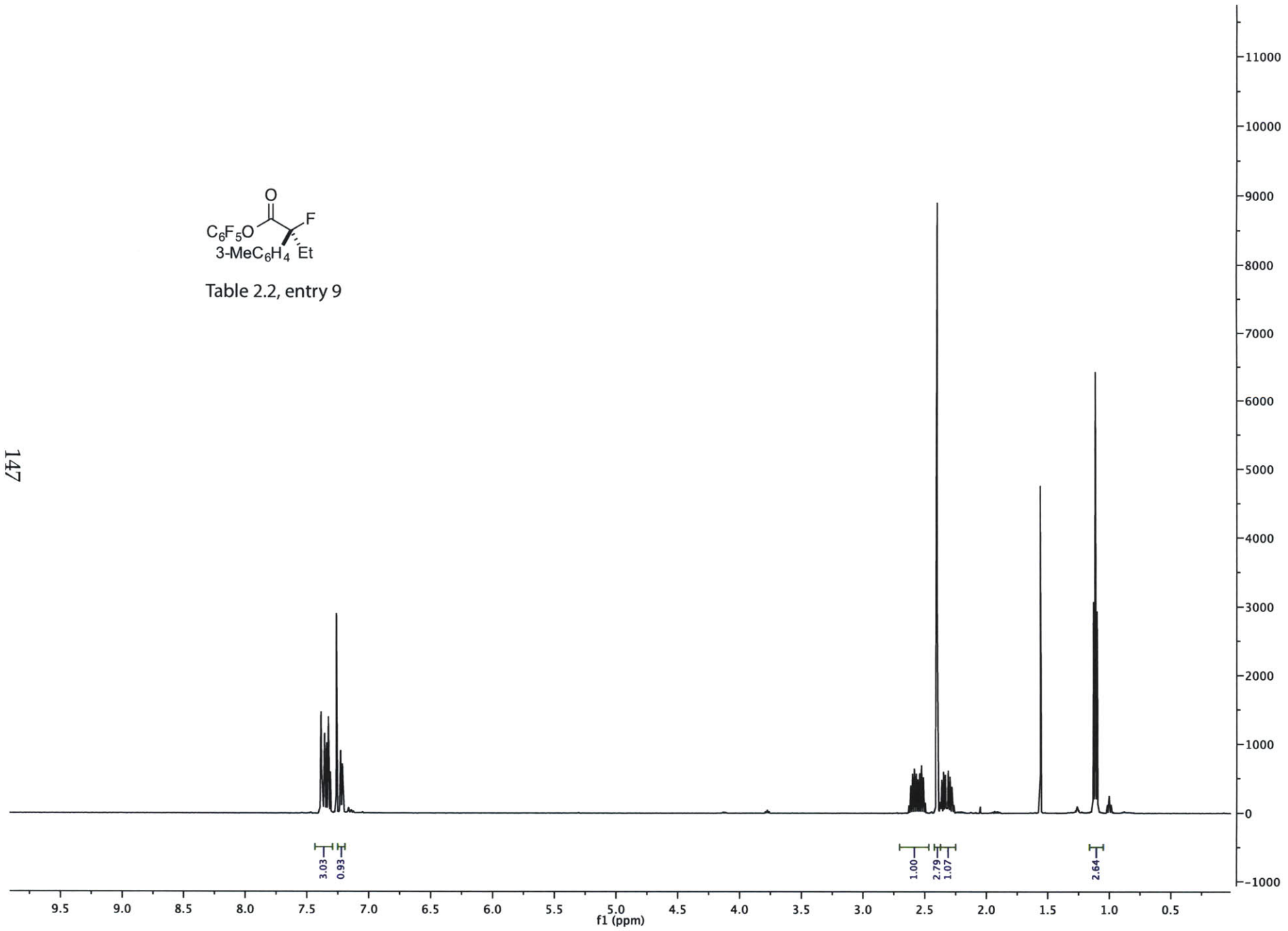


Table 2.2, entry 7


O
F
C6F5O
4-(OMe)C6H4
Et
Table 2.2, entry 8
2.00
1.99
3.11
1.06
1.03
3.05
f1 (ppm)


O
F
C_6F_5O
3-MeC_6H_4 Et
Table 2.2, entry 9
3.03
0.93
1.00
2.79
1.07
2.64
f1 (ppm)

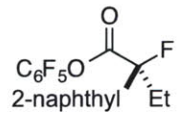


Table 2.2, entry 10

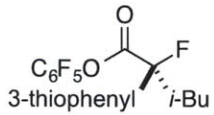
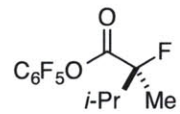


Table 2.2, entry 11


O
F
C_6F_5O
i-Pr
Me

eq 2.2.4

23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
1.00
3.30
6.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

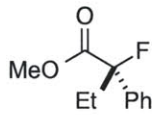


Figure 2.4

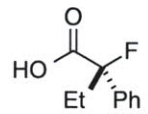


Figure 2.4

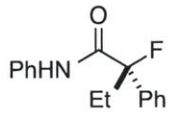


Figure 2.4

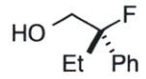
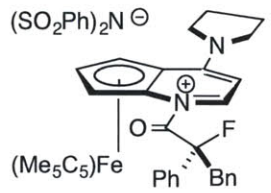
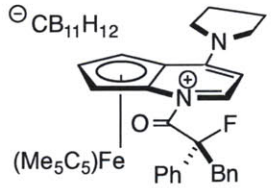


Figure 2.4



(+)-**2.13**

eq 2.2.5



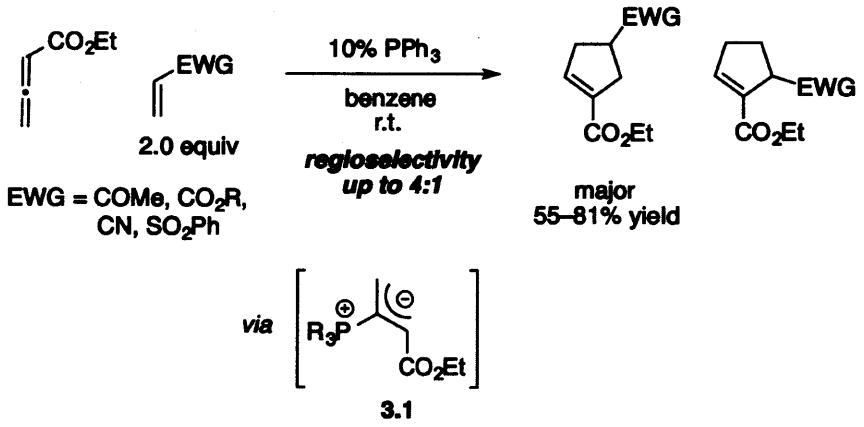
eq 2.2.6

Chapter 3.

Asymmetric Phosphine-Catalyzed Intramolecular [3 + 2] Cycloadditions of Allenes with Alkenes

3.1 Introduction

During the past decade, interest in the use of tertiary phosphines as nucleophilic catalysts has greatly increased.[64] In particular, phosphines have served as efficient catalysts for [3 + 2] cycloadditions of allenes (or alkynes) with olefins to form cyclopentenes. Lu reported the first example of this process, in which a mixture of regiomeric cyclopentenes was generated through the use of triphenylphosphine (eq 3.1.1).[65] A key intermediate in this reaction is believed to be phosphonium zwitterion **3.1**, which is formed by nucleophilic addition of the phosphine to the allene; in this case, the olefin prefers to first react at the α-position, rather than the γ-position, of the carbonyl group of **3.1** to afford the major regioisomer.[66]



(3.1.1)

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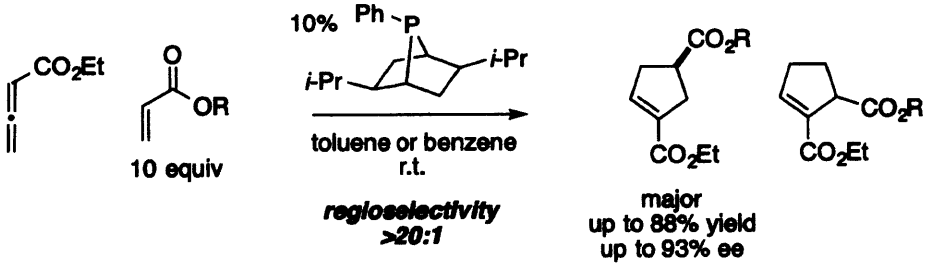
[64] For reviews, see: (a) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140–1152. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050. (c) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588–11619.

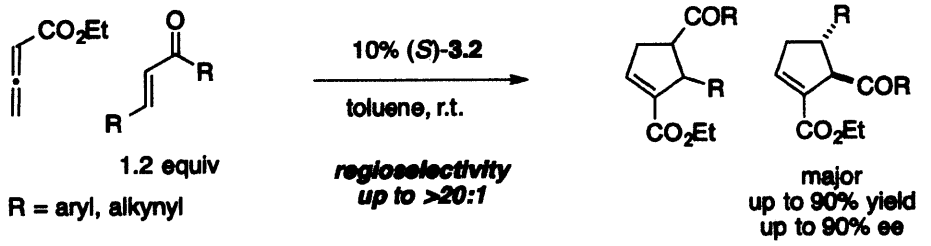
[65] (a) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906–2908. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535–544.

[66] This [3 + 2] cycloaddition process has been suggested to proceed in a stepwise manner. For references, see: (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470–3471. (b) Dudding, T.; Kwon, O.; Mercier, E. *Org. Lett.* **2006**, *8*, 3643–3646.

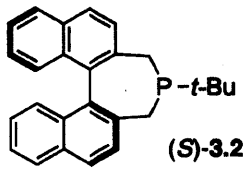
In 1997, Zhang reported a pioneering study of an asymmetric variant of [3 + 2] cycloaddition processes catalyzed by a chiral phosphine (eq 3.1.2);[67] acrylate esters react with a 2,3-butadienoate to form cyclopentenes in high enantiomeric excess with good regioselectivity. Following this example, our group demonstrated that chiral phosphepine **3.2** can catalyze the asymmetric [3 + 2] cycloaddition of 2,3-butadienoates with β-substituted enones, thereby generating cyclopentenes with two adjacent stereocenters (eq 3.1.3).[68] Interestingly, the regiochemical preference of this process was reversed relative to previously described cycloadditions of β-unsubstituted α,β-unsaturated carbonyl compounds.



(3.1.2)



(3.1.3)



Recently, our group further extended the scope of this enantioselective [3 + 2] cycloaddition process to include γ-substituted allenoates (and a γ-substituted allenamide) and heteroatom-substituted olefins, affording cyclopentenes with an array

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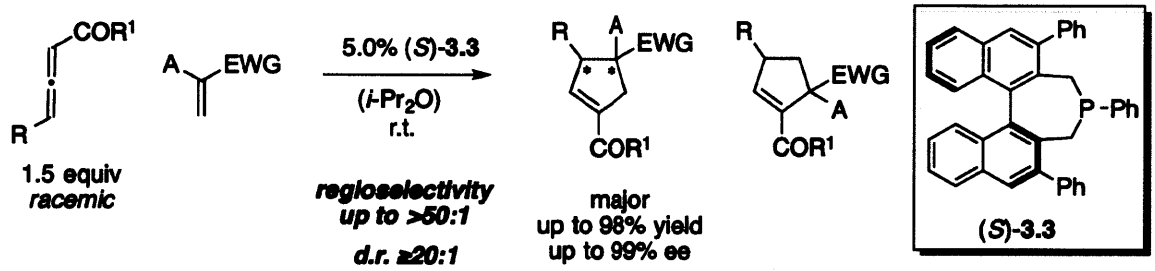
[67] Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837.

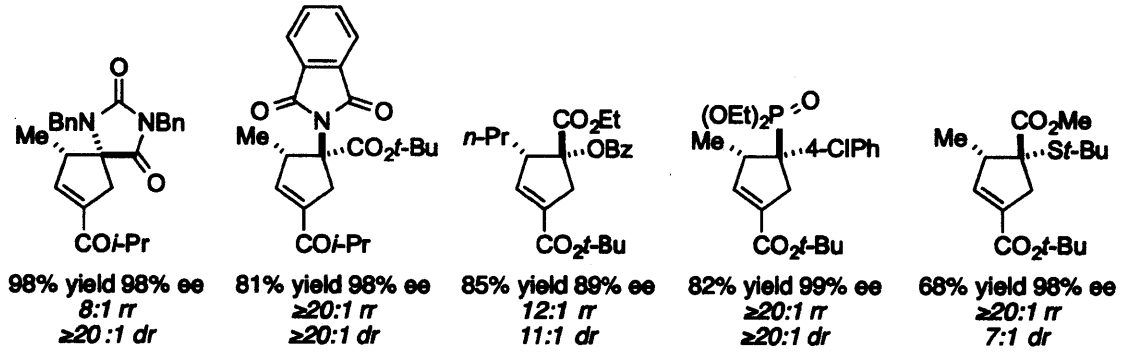
[68] Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426–1429.

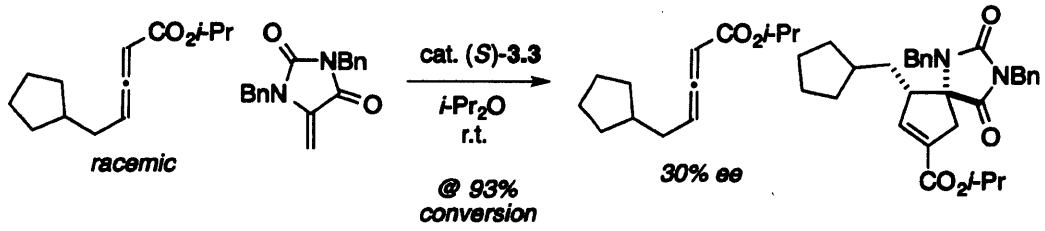
of heteroatom-substituted (N, P, O, and S) quaternary stereocenters in good ee, diastereoselectivity, regioselectivity, and yield (eq 3.1.4).[69] The development and application of new chiral phosphepine **3.3** was the key to achieving high selectivities and yields in this process. Notably, a modest kinetic resolution of the allene was observed during the cycloaddition reaction (eq 3.1.5).



(3.1.4)

selected examples



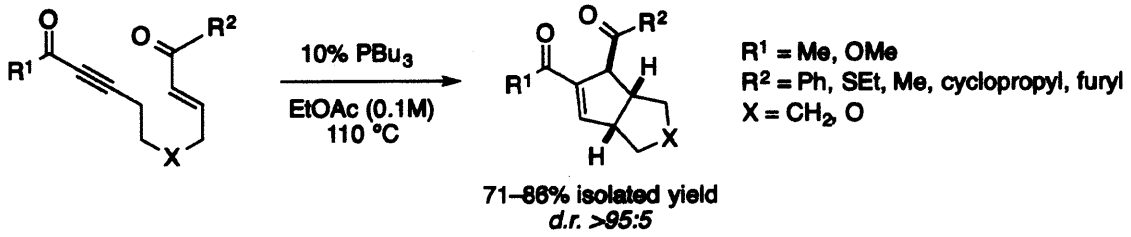


(3.1.5)

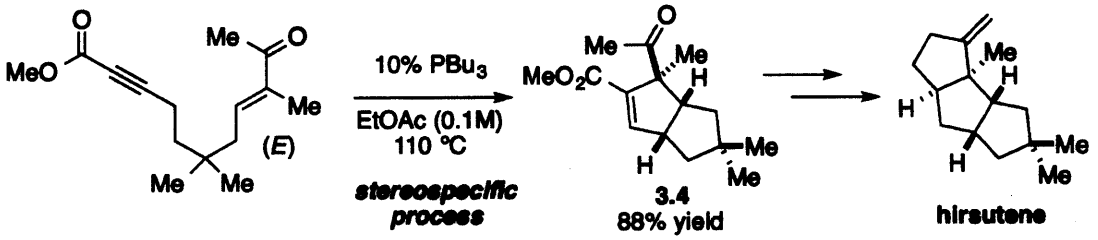
With regard to *intramolecular* phosphine-catalyzed [3 + 2] cycloadditions in which complex molecular frameworks can be constructed in a single operation from

[69] Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293–12297.

simple acyclic precursors, there have been a few reports of *diastereoselective* processes.[70] In contrast to intermolecular reactions that often create cycloadducts as mixtures of regioisomers, the regioselectivity of intramolecular processes can be controlled by conformational restrictions. Krische described the first example of such processes in which tributylphosphine catalyzes the diastereoselective formation of diquinanes bearing three contiguous stereocenters from electron-deficient 1,7-enynes (eq 3.1.6).[70a] Subsequently, this approach was applied to the total synthesis of hirsutene through the use of a 1,7-enyne substrate containing a trisubstituted olefin. Concise access to a single diastereomer of diquinane **3.4** bearing one quaternary and two tertiary stereocenters was achieved (eq 3.1.7).[70b] This study also revealed that this intramolecular cycloaddition process is stereospecific with respect to the olefin geometry; the reaction of a 1,7-enyne substrate with a (*Z*)-olefin provided the epimer of **3.4**. Another powerful method for highly diastereoselective, intramolecular [3 + 2] cycloadditions is the tributylphosphine-catalyzed synthesis of cyclopentene-fused dihydrocoumarins from 2-styrenyl allenoates reported by Kwon (eq 3.1.8).[70c] Despite progress in the development of stereoselective, phosphine-catalyzed intramolecular [3 + 2] cycloaddition reactions, we are not aware of any reports of an asymmetric variant of such processes.



(3.1.6)



(3.1.7)

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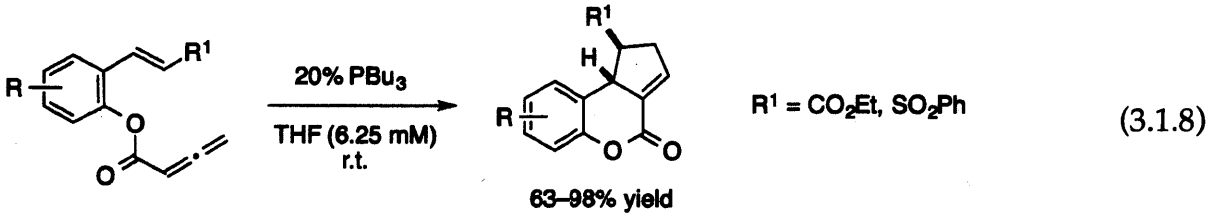
[70] (a) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682–3683. (b) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855–5857. (c) Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069–3072.



(3.1.8)

As described above, the diastereoselective intramolecular cycloaddition reaction is a powerful approach to concise synthesis of bicyclic compounds such as diquinanes and coumarin derivatives, which are common subunits in a wide range of natural products and bioactive compounds.[71,72] The ability to achieve bond constructions of this type in enantioenriched form would markedly enhance the synthetic potential of these processes. Building on our recent development of new chiral phosphines for intermolecular cycloadditions of allenes with olefins,[69] as well as the pioneering work of Krische[70a,b] and Kwon,[70c] we sought to develop diastereo- and enantioselective phosphine-catalyzed intramolecular [3 + 2] cycloaddition reactions of allenes with olefins for the synthesis of bicyclic compounds that bear multiple (two or three) stereocenters.[73]

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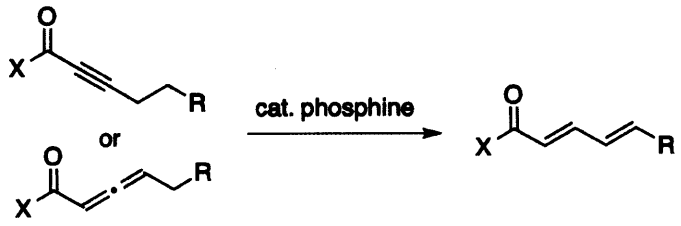
[71] Diquinanes are not only subunits in natural products but also versatile synthetic intermediates. For references, see: (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671–719. (b) Singh. V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647–3692.

[72] Coumarins are a privileged structure in medicinal chemistry. For a review, see: Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

[73] This work is a collaborative effort between Dr. Atsuko Nishiguchi, Dr. Yuji Fujiwara, and the author. Dr. Fujiwara initiated the project and identified the initial reaction conditions. Dr. Nishiguchi explored the substrate scope. Exploring the scope includes the identification of the reaction conditions for the preparation of target ene-allene substrates. The author explored and expanded the substrate scope further to include different classes of substrates, finalized the reaction conditions, and conducted the mechanistic investigation. The author carried out all the experiments presented in this chapter.

3.2 Results and Discussion

One of the challenges associated with the development of this intramolecular [3 + 2] cycloaddition is the potential phosphine-catalyzed isomerization of alkynes (or allenes) to the corresponding 1,3-dienes (eq 3.2.1);[74] yet, Krische demonstrated that this undesired reactivity can be circumvented by the enhanced rate of five-membered-ring formation.[70a,b] Given our previous success in developing an array of asymmetric phosphine-catalyzed transformations of allenes,[75] along with Krische's work on intramolecular cycloadditions of 1,7-enynes to form 5,5-fused ring systems,[70a,b] we decided to explore substrates bearing electron-poor alkene/allene groups (ene-allenes) that would form diquinanes upon cycloaddition.



(3.2.1)

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[74] For phosphine-catalyzed isomerizations of alkynes to 1,3-dienes, see: (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933–7935. (b) Kwong, C. K.-W.; Fu, M. Y.; Lam, C. S.-L.; Toy, P. H. *Synthesis* **2008**, 2307–2317.

[75] For γ-additions of nucleophiles to allenes, see: (a) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231–14233. (b) Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568–4569. (c) Sinisi, R.; Sun, J.; Fu, G. C. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20652–20654. (d) Fujiwara, Y.; Sun, J.; Fu, G. C. *Chem. Sci.* **2011**, *2*, 2196–2198. (e) Lundgren, R. J.; Wilsily, A.; Marion, N.; Ma, C.; Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2525–2528. For [4 + 2] annulations of allenes with imines, see: Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235. For intermolecular [3 + 2] cycloadditions of allenes with olefins, see: ref 68 and ref 69.

As a starting point for our effort to develop an asymmetric intramolecular [3 + 2] cycloaddition process, we surveyed a variety of chiral phosphine catalysts for the reaction of substrate (*E*)-**3.5** (Table 3.1). We were particularly interested in employing binaphthyl-based C_2-symmetric phosphepines, which proved to be exceedingly useful for asymmetric, intermolecular [3 + 2] cycloadditions of allenes with olefins.[68,69,76] Indeed, phosphines **3.6** and **3.2** provided the *cis*-fused diquinane (**A**) bearing three new contiguous stereocenters with promising enantioselectivity and yield, as well as complete diastereoselectivity (Table 3.1, entries 1 and 2); however, the formation of diene **B** was somewhat significant. Employing phosphine **3.3**, which bears 3,3′ phenyl substituents on the 1,1′-binaphthyl framework, enhanced the enantioselectivity of the cycloaddition process (Table 3.1, entry 3). Finally, we were pleased to determine that the 3,5-dimethoxyphenyl-substituted phosphine (**3.7**)[77] generated the bicyclic product as a single diastereomer with excellent enantioselectivity and good yield, while suppressing the formation of diene **B** (Table 3.1, entry 4).

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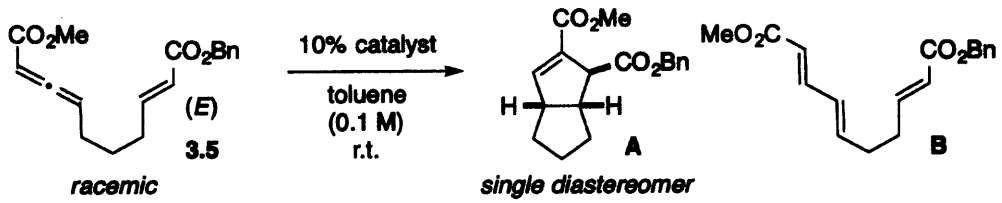
[76] A range of chiral phosphines, including bidentate phosphines, was studied, and they were less effective compared to the binaphthyl-based phosphepines listed in Table 3.1.

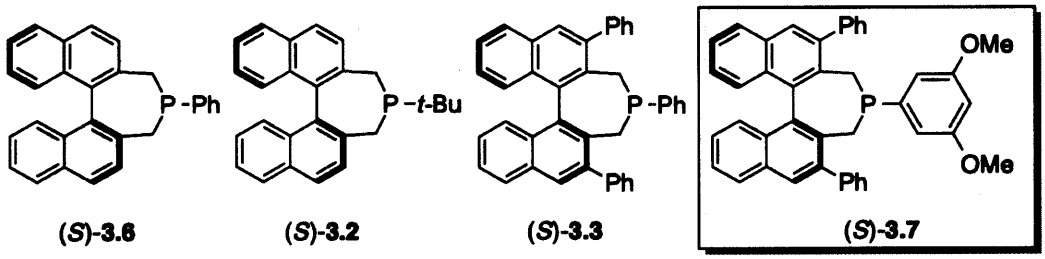
[77] (a) We are not aware of previous reports of phosphine **3.7**. (b) Phosphine **3.7** can be handled conveniently in the air. After exposure of the solid phosphine to air for two months, no phosphine oxide was detected by ^{31}P NMR analysis. (c) This phosphine can be recovered as a phosphine oxide after the reaction is quenched by adding H_2O_2 (aq). The phosphine oxide of phosphine **3.7** does not catalyze the cycloaddition.

Table 3.1. Asymmetric Intramolecular [3 + 2] Cycloadditions: Effect of the Choice of Phosphine Catalyst



entry	catalyst	A ee (%)	A yield (%)[a]	B yield (%)[a]
1	(*S*)-**3.6**	70	73	17
2	(*S*)-**3.2**	–85	67	25
3	(*S*)-**3.3**	90	69	24
4	(*S*)-**3.7**	97	85	7

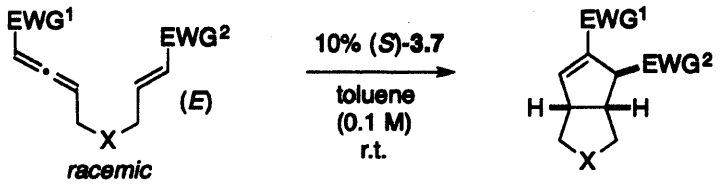
[a]The yield was determined by ^{1}H NMR analysis with the aid of an internal standard.

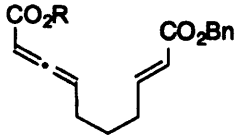
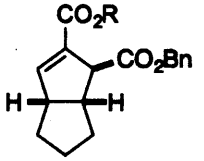
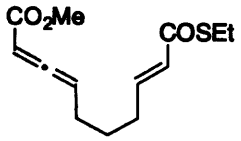
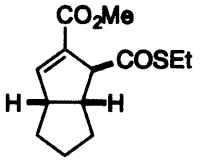
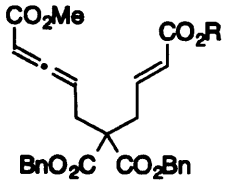
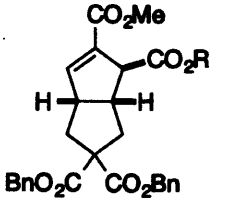
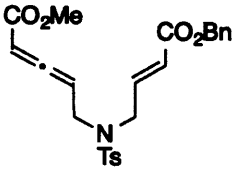
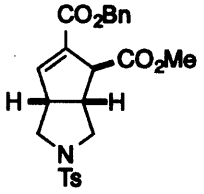


(*S*)-**3.6** (*S*)-**3.2** (*S*)-**3.3** (*S*)-**3.7**

Our method is effective for furnishing, with excellent stereocontrol, an array of diastereomerically pure diquinanes containing three adjacent tertiary stereocenters from simple acyclic, electron-poor ene-allene substrates (Table 3.2). For example, allenoates can be coupled with electron-deficient alkenes bearing a (thio)ester to produce the diquinane products in good yield and ee (Table 3.2, entries 1–5). Additionally, substitution on the tether between the allene and the alkene is tolerated. For example, malonate-tethered substrates as well as a substrate with a tosylamide linkage, afforded the corresponding diquinanes in the presence of phosphine **3.7** (entries 6–8).

Table 3.2. Catalytic Asymmetric Intramolecular [3 + 2] Cycloadditions of Allenoates with Electron-Deficient Alkenes[a]

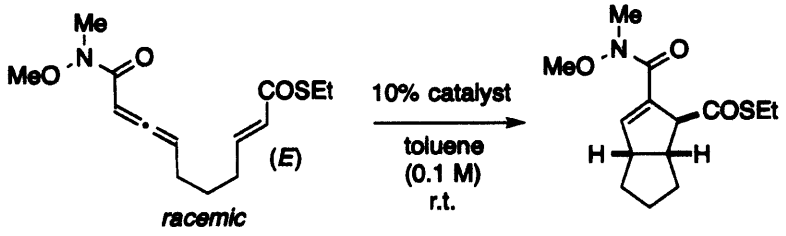


entry	substrate		product	ee (%)	yield (%)[b]
1		R = Me		97	83
2		Et		98	86
3		*t*-Bu		98	84
4		Bn		98	90
5				93	88
6[c]		R = Me		97	88
7		Bn		95	88
8[d]				94	95

[a]All data are the average of two experiments. [b]Yield of purified product; for each cycloaddition, only one product diastereomer was observed by ^{1}H NMR analysis of the unpurified mixture. [c]Reaction temperature: 40 °C. [d]Ts = 4-$CH_3C_6H_4SO_2$.

When we attempted to couple allenamides,[78] in place of allenoates, with electron-deficient olefins through the use of phosphine **3.7**, the intramolecular cycloaddition proceeded with only moderate ee and yield (Table 3.3, entry 1). Thus, other phosphepine catalysts were examined for this allenamide substrate (Table 3.3, entries 2–4). In contrast to the trend observed for cycloadditions of allenoates (Table 3.1), non-3,3'-substituted phosphines (**3.2** and **3.6**) provided improved enantioselectivity (Table 3.3, entries 3 and 4). In particular, the bulky *tert*-butyl-substituted phosphine **3.2** furnished the cycloadduct in 66% isolated yield as a single diastereomer with 89% ee (Table 3.3, entry 3).

Table 3.3. Asymmetric Intramolecular [3 + 2] Cycloadditions of Allenamides with Electron-Deficient Alkenes: Effect of the Choice of Phosphine Catalyst



entry	catalyst	ee (%)[d]	yield (%)[a]
1	(*S*)-**3.7**	30	17
2	(*S*)-**3.3**	40	42
3[b]	(*S*)-**3.2**	−89	66[c]
4	(S)-**3.6**	46	41

[a]The yield was determined by ^{1}H NMR analysis with the aid of an internal standard; only one product diastereomer was observed. [b]Catalyst loading: 20%. The yield and ee are the average of two experiments. [c]Yield of purified product. [d]The absolute stereochemistry of the product has not yet been determined.

[78] For a review of the synthetic utility of Weinreb amides, see: Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707–3738.

Next, we turned our attention to the challenge of achieving asymmetric intramolecular [3 + 2] cycloadditions of substrates that contain an allene and a trisubstituted olefin, thereby creating three contiguous stereocenters, including one all-carbon quaternary center. Studies of phosphine-catalyzed intramolecular cycloadditions of allenes (or alkynes) with olefins to date have primarily focused on the use of substrates containing 1,2-disubstituted alkenes.[70,80] The enantioselective construction of all-carbon quaternary centers is a particularly difficult challenge within the area of asymmetric catalysis, due in part to the inherent steric congestion present in the formation of such stereocenters.[81] In fact, we have established that chiral phosphepines (**3.2** or **3.7**) can couple allenoates with trisubstituted alkenes containing a thioester as an electron-withdrawing group with good enantioselectivity and yield, as well as complete diastereoselectivity, and that the linker between the allenoate and the alkene can bear substituents (Table 3.4, entries 1–3).[82]

Additionally, with the use of phenylsubstituted phosphine **3.6**, a malonate-tethered ene-allene containing a trisubstituted alkene affords the diastereomerically pure diquinane bearing two tertiary stereocenters and one all-carbon quaternary stereocenter at the angular point of the ring fusion (Table 3.4, entry 4). We are not aware of a prior example employing a trisubstituted alkene with this substitution pattern in such intramolecular cycloaddition processes.

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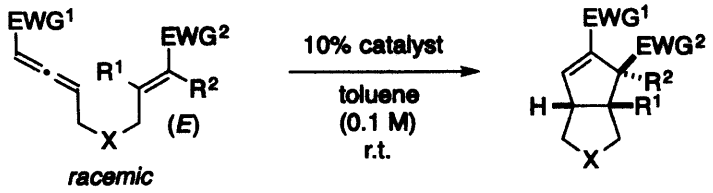
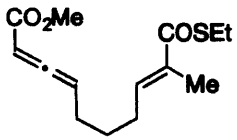
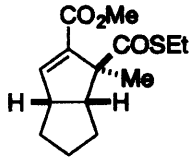
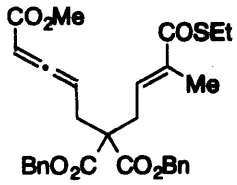
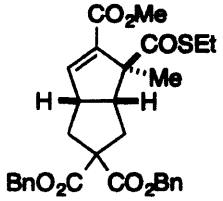
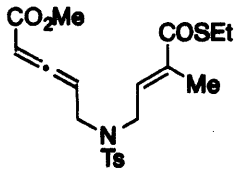
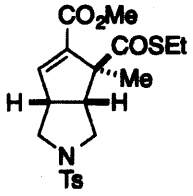
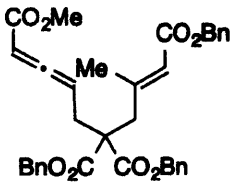
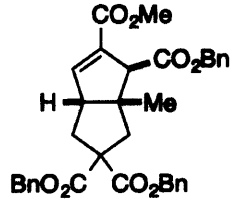
[80] To the best of our knowledge, there is only one example of the use of a substrate that bears a trisubstituted olefin in such diastereoselective processes: see ref 70b (eq 3.1.7).

[81] For a discussion regarding the challenge of the development catalytic asymmetric methods for the construction of quaternary all-carbon centers, see: Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367.

[82] Substrates bearing esters as an electron-withdrawing group attached to the alkene of this type were less reactive toward intramolecular cycloaddition with the allenoate; generally, less than 50% yield of the product was obtained.

Table 3.4. Catalytic Asymmetric Intramolecular [3 + 2] Cycloadditions of Allenoates with Electron-Deficient Trisubstituted Alkenes

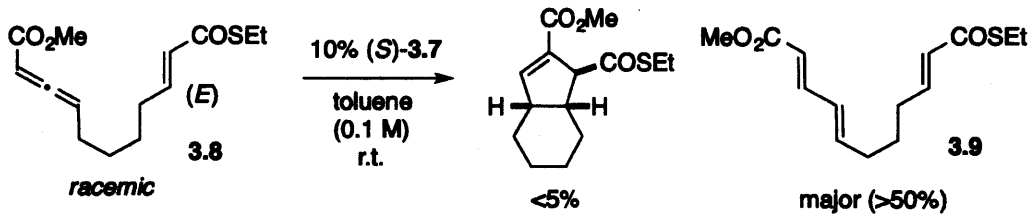


entry	catalyst	substrate	product	ee (%)[d]	yield (%)[b]
1[c]	(*S*)-3.2			97	56
2[a]	(*S*)-3.7			98	93
3[a]	(*S*)-3.2			94	78
4[a]	(*S*)-3.6			90	93

[a]All data are the average of two experiments. [b]Yield of purified product; for each cycloaddition, only one product diastereomer was observed by ^{1}H NMR analysis of the unpurified mixture. [c]Catalyst loading: 20%. [d]The absolute stereochemistry of the product has not yet been determined.

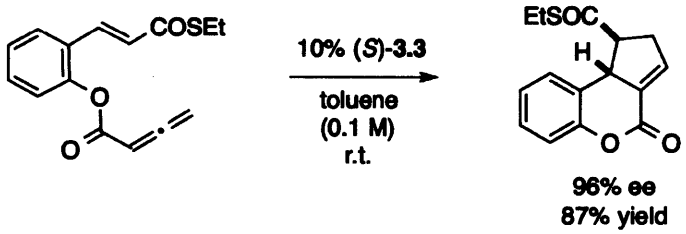
Efforts to extend our intramolecular cycloaddition approach to the asymmetric synthesis of hydrindanes, important target molecules in organic synthesis,[71] were not successful (eq 3.2.2). When substrate **3.8** was subjected to our cycloaddition conditions, the undesired side product **3.9** was formed predominantly by the competitive isomerization of the allene in the presence of the phosphine. A survey of various

reaction parameters, such as catalyst, temperature, and concentration, did not lead to an improved yield of the corresponding hydrindane.



(3.2.2)

Building on Kwon's work on diastereoselective reactions of 2-styrenyl allenoates (eq 3.1.8),[70c] we explored the possibility that chiral phoshepines can catalyze the intramolecular [3 + 2] cycloaddition of these substrates for the asymmetric synthesis of cyclopentene-fused dihydrocoumarins,[83] with the goal of providing a versatile approach. Indeed, an ene-allene of this type with a thioester as the electron-withdrawing group attached to the alkene was a suitable substrate in our intramolecular cycloaddition, providing the corresponding coumarin derivative bearing two adjacent stereocenters as a single diastereomer in good ee and yield (eq 3.2.3).[85]



(3.2.3)

Encouraged by this result, we became interested in the use of 2-styrenyl *allenamides* as substrates in our asymmetric cycloaddition method to produce

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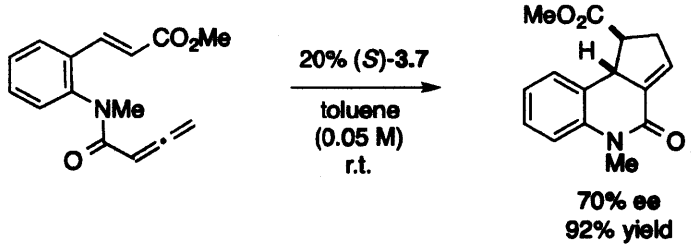
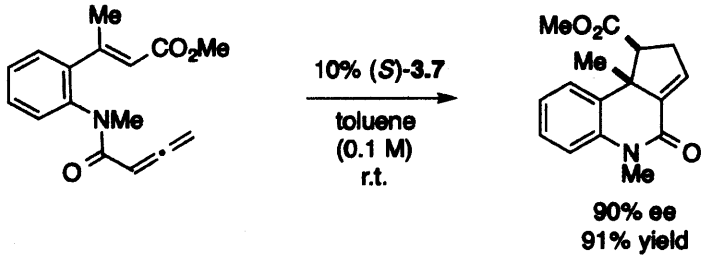
[83] For an intermolecular, phosphine-catalyzed [3 + 2] cycloaddition of allenoates with chromen-2-ones for the asymmetric synthesis of coumarin derivatives (up to 76% ee), see: Neel, M.; Gouin, J.; Voituriez, A.; Marinetti, A. *Synthesis* **2011**, 2003–2009.

[85] The absolute stereochemistry has not yet been assigned.

cyclopentene-fused dihydroquinolin-2-ones,[86] which are important motifs in natural products and medicinally active compounds;[87] to our knowledge, substrates of this type have not yet been explored in the literature. Therefore, we were pleased to establish that phosphine **3.7** can achieve the enantioselective synthesis of dihydroquinolin-2-one derivatives with complete diastereoselectivity, thereby generating two adjacent stereocenters (eq 3.2.4 and eq 3.2.5).[88] In particular, a trisubstituted alkene was compatible with this cycloaddition process, installing one all-carbon quaternary stereocenter at the angular position in addition to an adjacent tertiary stereocenter (eq 3.2.5).



(3.2.4)



(3.2.5)

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[86] For examples of asymmetric syntheses of quinolinone derivatives, see: (a) Guthrie, D. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 15492–15500. (b) Blay, G.; Cardona, L.; Torres, L.; Pedro, J. R. *Synthesis* **2007**, 108–112. (c) Dong, C.; Alper, H. *Tetrahedron: Asymmetry* **2004**, *15*, 35–40. (d) El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264–4270.

[87] For examples, see: (a) Zhou, W.; Zhang, L.; Jiao, N. *Tetrahedron* **2009**, *65*, 1982–1987. (b) Ito, C.; Itoigawa, M.; Otsuka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*,1344–1348. (c) Patel, M.; McHugh, R. J., Jr.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943–1945. (d) Seitz, W.; Geneste, H.; Backfisch, G.; Delzer, J.; Graef, C.; Hornberger, W.; Kling, A.; Subkowskic, T.; Norbert, Z. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 527–531.

[88] The absolute stereochemistry has not yet been determined.

An outline of a possible mechanism for this asymmetric, intramolecular phosphine-catalyzed [3 + 2] cycloaddition of ene-allenes is illustrated in Figure 3.1. Phosphonium zwitterion **3.10** is formed by the nucleophilic attack of phosphine at the β-position of the allene. Then this 1,3-dipole (**3.10**) undergoes an intramolecular [3 + 2] cycloaddition with the electron-poor alkene, furnishing phosphonium ylide **3.11**. Upon proton transfer, the phosphine is eliminated to form the cycloaddition product.

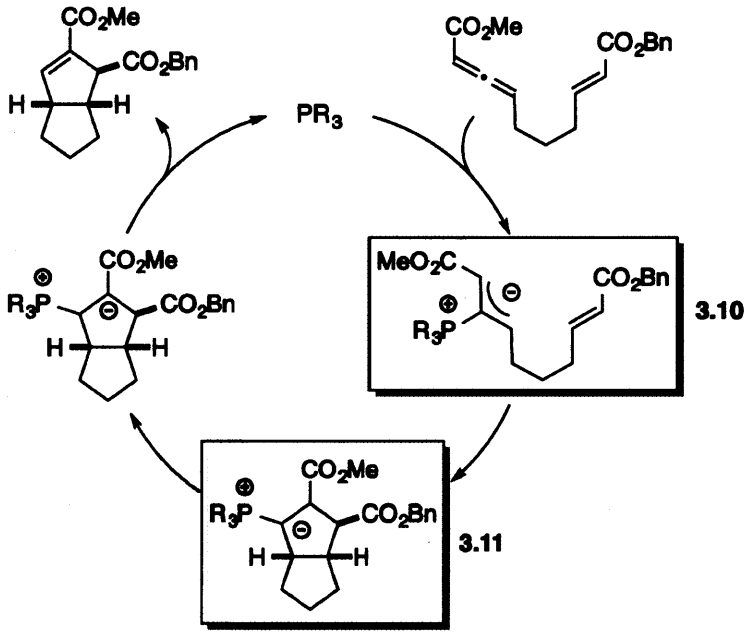

Figure 3.1. Outline of a possible mechanism for asymmetric, intramolecular phosphine-catalyzed [3 + 2] cycloadditions between electron-poor allenes and olefins

Interestingly, at partial conversion of this asymmetric cycloaddition process, we observed modest enantiomeric enrichment of the unreacted starting ene-allene (71% ee at 79% conversion) (eq 3.2.6),[89] suggesting that the two enantiomers of the allene react with different rates in the nucleophilic addition of phosphine **3.7** to form the same intermediate, phosphonium zwitterion **3.10**.

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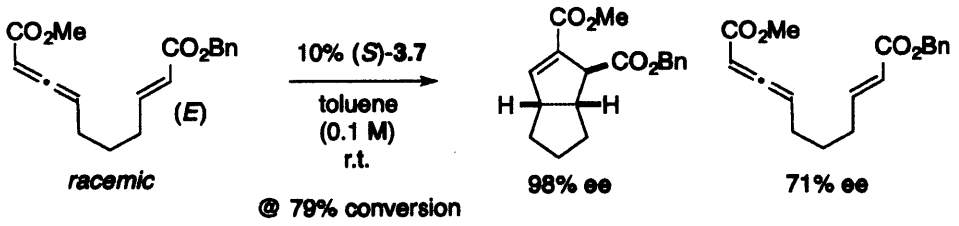
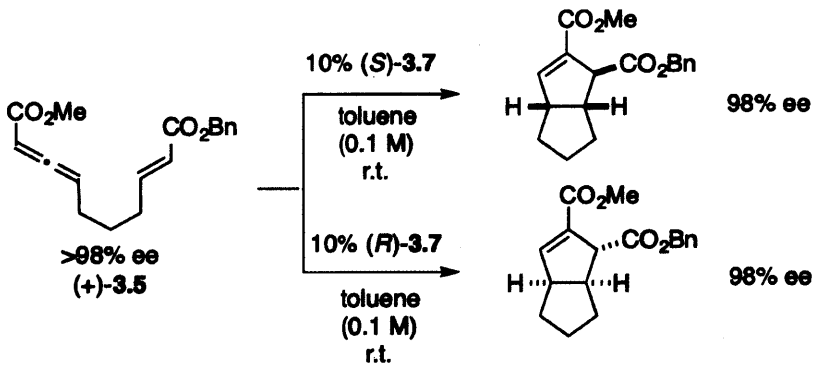
[89] Previously, a modest kinetic resolution of allenes was observed for intermolecular, asymmetric phosphine-catalyzed allene/olefin [3 + 2] cycloadditions (eq 3.1.5; see ref 69).



(3.2.6)

In addition, the ee of the cycloadduct is constant during the reaction, and the intramolecular cycloaddition of an enantiopure allene (**3.5**)[90] with either (*S*)-**3.7** or (*R*)-**3.7** provided the opposite enantiomer (eq 3.2.7), indicating that this asymmetric cycloaddition reaction is a stereoconvergent process wherein both enantiomers of the racemic allene are converted into the same enantiomer of the product by a chiral phosphine.



(3.2.7)

Given that substrates containing (*E*)-olefins all formed cycloaddition products as a single diastereomer, we sought insight into whether our intramolecular cycloaddition process is stereospecific with respect to the olefin geometry. Indeed, when substrate (Z)-**3.5** was exposed to phosphine **3.7**, the epimeric diquinane (**3.12**) was afforded *exclusively*

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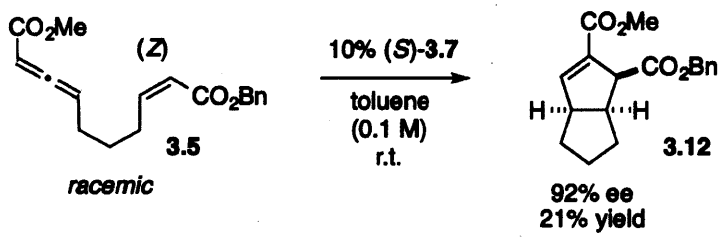
[90] (a) The two enantiomers of racemic **3.5** were separated by preparative HPLC on an IA column. (b) $[\alpha]^{25}_{D} = +102$ (c = 1.0, $CHCl_3$; the fast-eluting enantiomer on an IA column).

with 92% ee (eq 3.2.8),[91] establishing that the diastereoselectivity of this transformation is determined by the olefin geometry of the ene-allene substrates.



(3.2.8)

3.3 Conclusion and Future Work.

Cycloaddition is a powerful approach that allows for the construction of structural complexity in a single manipulation. We have developed the first asymmetric, phosphine-catalyzed intramolecular [3 + 2] cycloaddition reactions of racemic allenes with di- or trisubstitued olefins. This stereoconvergent process furnishes diasteromerically pure bicyclic compounds bearing two or three contiguous tertiary/quaternary stereocenters, from simple acyclic precursors. Specifically, diquinanes as well as cyclopentene-fused dihydrocoumarins and dihydroquinolin-2-ones, which are important families of natural products and bioactive compounds, were produced in good yield and enantioselectivity. A preliminary mechanistic study has established that the diastereoselectivity of this process is determined by the olefin geometry, and a modest kinetic resolution of the allene was observed during the reaction.

Future studies are directed toward further mechanistic investigations, including kinetic studies, to elucidate the reaction pathway, as well as derivatizations of the cycloaddition products to other potentially useful compounds; we anticipate that one or two additional stereocenters can be readily installed through diastereoselective functionalizations of the olefin.

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[91] (a) The relative stereochemistry was determined by NOESY. (b) The absolute stereochemistry has not yet been assigned.

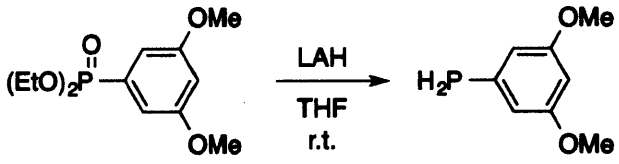
3.4 Experimental Section

I. General Information

Unless otherwise noted, all materials were purchased from commercial suppliers. Toluene, THF, and Et_2O was purified prior to use by passage through a column of neutral alumina under argon.

^{13}C NMR spectroscopic data for all phosphorus-containing compounds were collected on a Varian 600 MHz spectrometer at ambient temperature with ^{1}H and ^{31}P decoupling. HPLC analyses were carried out on an Agilent 1100 series system with Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μ).

II. Preparation of Phosphine 3.7



(3,5-Dimethoxyphenyl)phosphane. In a nitrogen-filled glovebox, $LiAlH_4$ (376 mg, 9.90 mmol), Et_2O (8.5 mL; anhydrous) and a stir bar were added to a 40-mL vial. Next, diethyl (3,5-dimethoxyphenyl)phosphonate[92] (904mg, 3.30 mml) was added dropwise. The vial was then capped and removed from the glovebox, and a nitrogen-filled balloon was attached to this vial. The reaction mixture was stirred at r.t. for 12 h. Et_2O (5 mL) and 15% NaOH (aq) (0.4 mL) was added, and the mixture was stirred for additional 20 min. Next, the mixture was dried over $MgSO_2$, filtered, and concentrated under reduced pressure, which furnished the phosphine as a light yellow oil (^{1}H NMR contains impurities). This phosphine was used in the next step without further purification. Note that this phosphine needs to be stored under inert atmosphere.

^{31}P NMR (162 MHz, CDCl3) δ 130.8.

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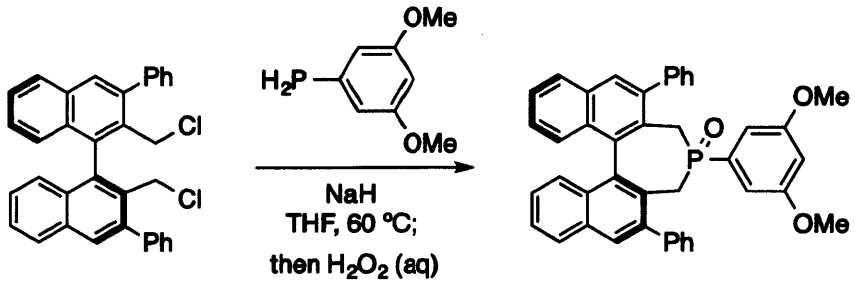
[92] Dvorak, C. A.; Liu, C. ; Shelton, J.; Kuei, C.; Sutton, S. W.; Lovenberg, T. W.; Carruthers, N. I. *ACS Med. Chem. Lett.* **2012**, *3*, 637–639.



Synthesis of a Phosphine Oxide of (*S*)-3.7. In a nitrogen-filled glovebox, 2,2'-bis(chloromethyl)-3,3'-diphenyl-1,1'-binaphthalene[93,94] (790 mg, 1.57 mmol), THF (50 mL; anhydrous) and a stir bar were added to a 100-mL round-bottom flask. Sodium hydride (98 mg, 4.08 mmol) and (3,5-dimethoxyphenyl)phosphane (400mg, 2.35 mmol) in THF (10 mL) were added in turn. The flask was fitted with a rubber septum and then removed from the glovebox. A nitrogen-filled balloon was attached to the flask, which was then heated to 60 °C. After 20 h, the mixture was cooled to room temperature. H_2O (3 mL) was added, and the mixture was concentrated under reduced pressure. CH_2Cl_2 (50 mL), H_2O (10 mL), and 50% H_2O_2 (aq) (1.5 mL) were added in turn, and the mixture was stirred at r.t. After 1 h, it was cooled to 0 °C, and then the saturated solution of $Na_2S_2O_3$ (aq) (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (20 mL x3), and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc in CH_2Cl_2→40% EtOAc in CH_2Cl_2), which afforded the phosphine oxide as a white crystalline solid (780 mg, 81%).

^{1}H NMR (600 MHz, CDCl3) δ 8.0 (s, 1H), 7.96 (d, 1H, J = 7.7 Hz), 7.89 (d, 1H, J = 7.3 Hz), 7.77 (s, 1H), 7.50–7.44 (m, 5H), 7.38–7.34 (m, 1H), 7.29–7.21 (m, 5H), 7.19–7.18 (m, 1H), 7.15–7.14 (m, 2H), 6.51 (t, 1H, J = 2.6 Hz), 6.18 (dd, 2H, J = 11.9 Hz, J = 2.3 Hz), 3.66–3.59 (m, 1H), 3.58 (s, 6H), 3.56–3.46 (m, 1H), 3.33–3.21 (m, 2H).

^{13}C NMR (151 MHz, CDCl3) δ 172.7, 160.8, 141.2, 140.8, 140.7, 140.3, 135.3, 135.1, 133.8, 132.52, 135.50, 131.9, 130.2, 129.6, 129.4, 128.4, 128.3, 128.14, 128.10, 127.4, 127.0, 126.8, 126.6, 126.5, 126.4, 126.2, 108.4, 104.7, 55.6, 33.4, 31.7, 29.9, 22.8, 14.3.

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[93] OOi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139–5151.

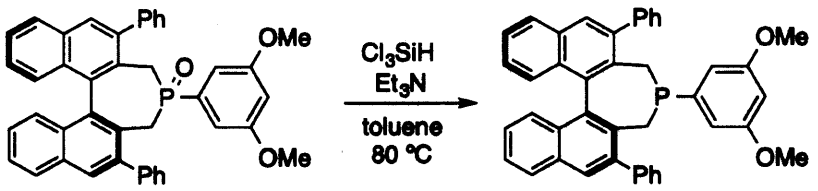
[94] Zhou, Y.-G.; Zhang, X. *Chem. Commun.* **2002**, 1124–1125.

^{31}P NMR (243 MHz, CDCl3) δ 53.7.

FT-IR (film) 3055, 1588, 1416, 1206, 1158, 704 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{42}H_{34}O_3P$: 617, found: 617.

$[\alpha]^{25}_D$ = +12 (c = 1.0, $CHCl_3$).



Synthesis of Phosphine (*S*)-3.7. A phosphine oxide (730 mg, 1.18 mmol) was added to a 100-mL round-bottom flask, which was then evacuated and back-filled with nitrogen (three cycles). Next, toluene (24 mL; anhydrous) and Et_3N (1.15 mL) were added in turn. Cl_3SiH (0.60 mL; Aldrich) was then added dropwise over 3 min, and the mixture was heated at 80 °C for 16 h. The mixture was allowed to cool to r.t., and 10% NaOH (aq) (50 mL) was added. This solution was stirred at r.t. for 30 min, and then the aqueous layer was extracted with toluene (20 mL x 2). The combined organic layer was dried over $MgSO_2$, filtered, and concentrated under reduced pressure. The residue (a light yellow solid) was dissolved in toluene (8.0 mL) and then filtered through a short pad of silica (eluent: toluene 5.0 mL). The solution was concentrated, which furnished the product as a white crystalline solid (700 mg, 99%).

^{1}H NMR (600 MHz, CDCl3) δ 7.93 (d, 1H, *J* = 8.4 Hz), 7.89 (s, 1H), 7.85–7.81 (m, 1H), 7.67 (d, 2H, *J* = 7.5 Hz), 7.65 (s, 1H), 7.48–7.39 (m, 4H), 7.37–7.34 (m, 1H), 7.27–7.16 (m, 9H), 6.31 (t, 1H, *J* = 2.4 Hz), 5.91 (dd, 2H, *J* = 7.2 Hz, *J* = 2.4 Hz), 3.53 (s, 6H), 3.23 (dd, 1H, *J* = 14.7 Hz, *J* = 4.1 Hz), 2.94 (dd, 1H, *J* = 9.8 Hz, *J* = 12.5 Hz), 2.78–2.71 (m, 2H).

^{13}C NMR (151 MHz, CDCl3) δ 172.3, 160.5, 141.6, 141.4, 140.31, 138.6, 134.9, 134.1, 132.3, 132.2, 131.9, 131.8, 131.4, 130.0, 129.7, 129.3, 128.9, 128.31, 128.25, 127.3, 126.8, 126.7, 126.3, 126.08, 126.10, 125.7, 125.4, 108.8, 101.3, 55.3, 28.3, 25.6.

^{31}P NMR (243 MHz, CDCl3) δ 6.18.

FT-IR (film) 2929, 1587, 1410, 1204, 1155, 703 cm^{-1}.

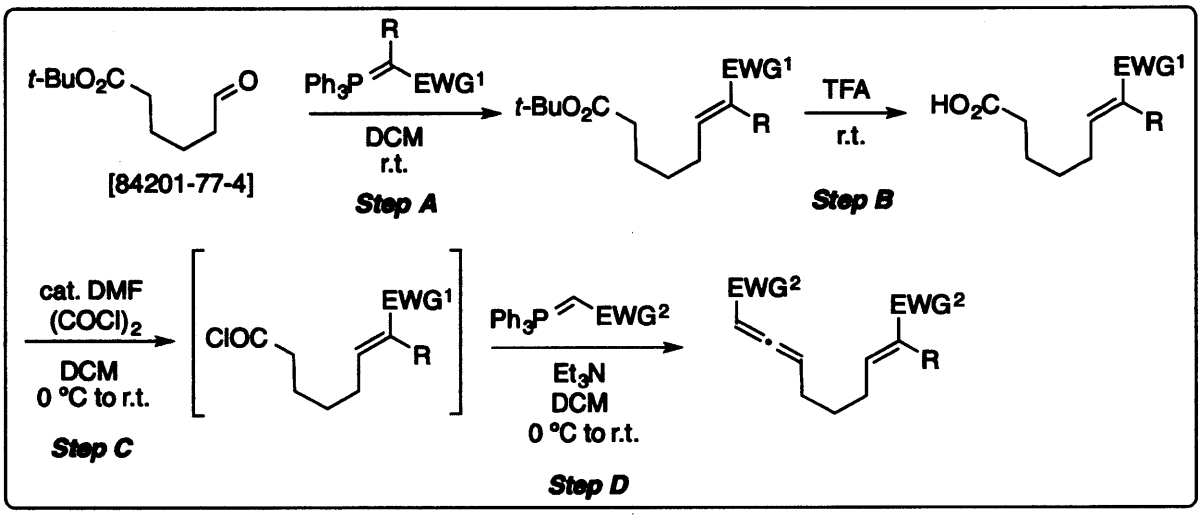
TOF-MS *m*/*z* (M + H)$^+$ calcd for $C_{42}H_{34}O_2P$: 601, found: 601.

$[\alpha]^{25}_D$ = –212 (c = 1.0, $CHCl_3$).

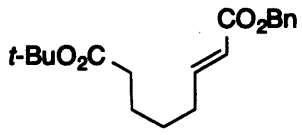
III. Preparation of Substrates

The yields in this section have not been optimized.

1) Substrates for entries 1–5 of Table 3.2, entries 1–4 of Table 3.3, and entry 1 of Table 3.4



General Procedure A (Step A). A phosphorane (1.2 equiv) was added to a round-bottom flask that contained 0.1 M solution of *tert*-butyl 6-oxohexanoate (1.0 equiv) in CH_2Cl_2. The resulting solution was stirred at r.t. for 12 h, and then it was concentrated under reduced pressure. The residue was then purified by column chromatography (hexanes→20% EtOAc in hexanes), which furnished the (*E*)-olefin (yield generally greater than 80%; minor (Z)-isomer needs to be separated at this stage).



1-Benzyl 8-(*tert*-butyl) (*E*)-oct-2-enedioate. The title compound was prepared according to General Procedure A, using benzyl 2-(triphenyl-λ^5-phosphanylidene)acetate. Yellow oil.

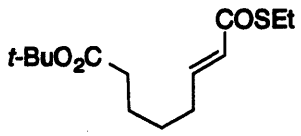
^{1}H NMR (500 MHz, CDCl3) δ 7.40–7.33 (m, 5H), 7.01 (dt, 1H, *J* =15.8 Hz, *J* = 6.8

Hz), 5.89 (dt, 1H, J =15.8 Hz, J = 1.7 Hz), 5.18 (s, 2H), 2.27–2.20 (m, 4H), 1.65–1.59 (m, 2H), 1.52–1.48 (m, 2H), 1.45 (s, 9H).

^{13}C NMR (125 MHz, CDCl3) δ 172.8, 166.5, 149.4, 136.4, 128.7, 128.31, 128.26, 121.5, 80.3, 66.2, 35.4, 32.0, 28.3, 27.6, 24.7.

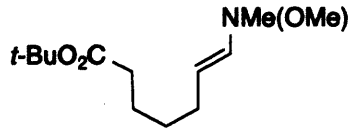
FT-IR (film) 2934, 1726, 1654, 1367, 1261, 1161, 981, 697 cm^{-1}.

TOF-MS m/z $(M + NH_4)^+$ calcd for $C_{19}H_{30}NO_4$: 336, found: 336.



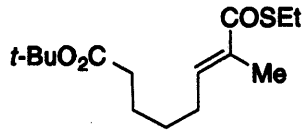
***tert*-Butyl (*E*)-8-(ethylthio)-8-oxooct-6-enoate.** The title compound was prepared according to General Procedure A, using *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 6.87 (dt, 1H, J =15.5 Hz, J = 7.1 Hz), 6.11 (dt, 1H, J =15.4 Hz, J = 1.5 Hz), 2.94 (q, 2H, J = 7.1 Hz), 2.24–2.19 (m, 4H), 1.65–1.59 (m, 2H), 1.52–1.46 (m, 2H), 1.44 (s, 9H), 1.28 (t, 3H, J = 7.1 Hz).



***tert*-Butyl (*E*)-7-(methoxy(methyl)amino)hept-6-enoate.** The title compound was prepared according to General Procedure A, using *N*,*O*-dimethyl-*N*-((triphenyl-λ^5-phosphanylidene)methyl)hydroxylamine. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 6.95 (dt, 1H, J =15.4 Hz, J = 7.0 Hz), 6.40 (d, 1H, J =15.0), 3.69 (s, 3H), 3.23 (s, 3H), 2.27–2.21 (m, 4H), 1.65–1.59 (m, 2H), 1.52–1.46 (m, 2H), 1.43 (s, 9H).

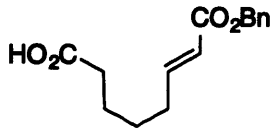


***tert*-Butyl (*E*)-8-(ethylthio)-7-methyl-8-oxooct-6-enoate.** The title compound was

prepared according to General Procedure A, using *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)propanethioate. Yellow oil.

^{1}H NMR (300 MHz, CDCl3) δ 6.71 (td, 1H, *J* =7.6 Hz, *J* = 1.4 Hz), 2.91 (q, 2H, *J* = 7.5 Hz), 2.26–2.18 (m, 4H), 1.87–1.86 (m, 3H), 1.68–1.49 (m, 4H), 1.45 (s, 9H), 1.26 (t, 3H, *J* = 7.1 Hz).

General Procedure B (Step B). A *tert*-butyl ester and TFA (3 vol. to *tert*-butyl ester) were added to a round-bottom flask, and the reaction mixture was stirred at r.t. for 12 h. Toluene was added (3 vol. to TFA) was added which was then concentrated under reduced pressure to remove TFA. This residue was purified by column chromatography (20% EtOAc in hexanes→50% EtOAc in hexanes); generally >70% of the carboxylic acid was afforded.



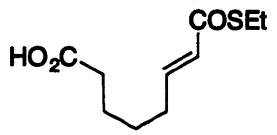
(*E*)-8-(Benzyloxy)-8-oxooct-6-enoic acid. The title compound was prepared according to General Procedure B, using 1-benzyl 8-(*tert*-butyl) (*E*)-oct-2-enedioate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 10.7 (br s, 1H), 7.40–7.33 (m, 5H), 7.01 (dt, 1H, *J* =15.8 Hz, *J* = 7.0 Hz), 5.90 (dt, 1H, *J* =15.3 Hz, *J* = 1.7 Hz), 5.19 (s, 2H), 2.38 (t, 2H, *J* = 7.7 Hz), 2.27–2.20 (m, 2H), 1.71–1.65 (m, 2H), 1.57–1.51 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 179.5, 166.5, 149.2, 136.2, 128.7, 128.30, 128.27, 121.6, 66.2, 33.8, 31.9, 27.5, 24.2.

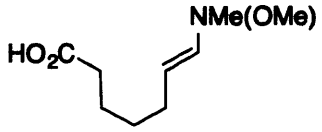
FT-IR (film) 2942, 1716, 1456, 1266, 981, 698 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{15}H_{19}O_4$: 263, found: 263.



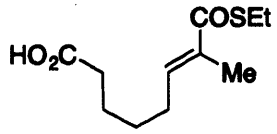
(*E*)-8-(Ethylthio)-8-oxooct-6-enoic acid. The title compound was prepared according to General Procedure B, using *tert*-butyl (*E*)-8-(ethylthio)-8-oxooct-6-enoate. White solid.

^{1}H NMR (500 MHz, CDCl3) δ 10.8 (br s, 1H), 6.88 (dt, 1H, *J* =15.5 Hz, *J* = 6.9 Hz), 6.13 (dt, 1H, *J* =15.5 Hz, *J* = 1.5 Hz), 2.95 (q, 2H, *J* = 7.2 Hz), 2.39 (t, 2H, *J* = 7.6 Hz), 2.26–2.21 (m, 2H), 1.72–1.66 (m, 2H), 1.58–1.53 (m, 2H), 1.29 (t, 3H, *J* = 7.4 Hz).



(*E*)-7-(Methoxy(methyl)amino)hept-6-enoic acid. The title compound was prepared according to General Procedure B, using *tert*-butyl (*E*)-7-(methoxy(methyl)amino)hept-6-enoate. White solid.

^{1}H NMR (500 MHz, CDCl3) δ 6.97 (dt, 1H, *J* =15.8 Hz, *J* = 6.6 Hz), 6.42 (d, 1H, *J* =15.5), 3.71 (s, 3H), 3.25 (s, 3H), 2.38 (t, 2H, *J* =7.1 Hz), 2.30–2.26 (m, 2H), 1.72–1.66 (m, 2H), 1.58–1.52 (m, 2H).



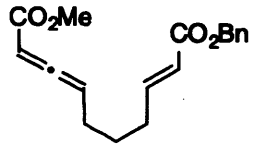
(*E*)-8-(Ethylthio)-7-methyl-8-oxooct-6-enoic acid. The title compound was prepared according to General Procedure B, using *tert*-butyl (*E*)-8-(ethylthio)-7-methyl-8-oxooct-6-enoate. Yellow solid.

^{1}H NMR (300 MHz, CDCl3) δ 6.69 (td, 1H, *J* =7.2 Hz, *J* = 1.5 Hz), 2.91 (q, 2H, *J* = 7.6 Hz), 2.41–2.35 (m, 2H), 2.26–2.19 (m, 2H), 1.87 (d, 3H, *J* = 1.2 Hz), 1.73–1.61 (m, 2H), 1.57–1.38 (m, 2H), 1.26 (t, 3H, *J* = 7.5 Hz).

General Procedure C (Step C). A carboxylic acid (1.0 equiv) and a stir bar were placed in a round-bottom flask, which was then evacuated and back-filled with nitrogen (three cycles). CH_2Cl_2 (10 vol. to the carboxylic acid; anhydrous) and dimethylformadmide (0.1 equiv) were added in turn via syringe, and then the mixture was cooled to 0 °C. Next, oxalyl chloride (1.2 equiv) was added dropwise over 1 min via

syringe. The reaction mixture was slowly warmed up to r.t. over the period of 2 h, which was then concentrated under reduced pressure. The residue was used in the next step without further purification.

General Procedure D (Step D). A phosphorane (1.0 equiv) and a stir bar were added to a round-bottom flask, which was then evacuated and back-filled with nitrogen (three cycles). CH_2Cl_2 (10 vol. to the acid chloride; anhydrous) was added in turn via syringe, and then the mixture was cooled to 0 °C. Next, a 0.1 M solution of the acid chloride (prepared from step C) in CH_2Cl_2 was added dropwise over 3 min via syringe, and then triethylamine (1.2 equiv) was added. The reaction mixture was slowly warmed up to r.t. over the period of 4 h, which was then concentrated under reduced pressure. This residue was purified by column chromatography (hexanes→20% EtOAc in hexanes).



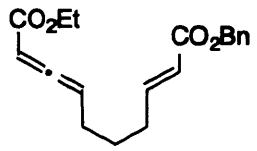
10-Benzyl 1-methyl (*E*)-deca-2,3,8-trienedioate. The title compound was synthesized according to General Procedure C/D from (*E*)-8-(benzyloxy)-8-oxooct-6-enoic acid, using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 68%. The title compound was isolated as a colorless oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.39–7.32 (m, 5H), 7.00 (dt, 1H, *J* =15.9 Hz, *J* = 6.9 Hz), 5.90 (dt, 1H, *J* =15.6 Hz, *J* = 1.6 Hz), 5.63–5.60 (m, 2H), 5.19 (s, 2H), 3.75 (s, 3H), 2.32–2.27 (m, 2H), 2.20–2.15 (m, 2H), 1.68–1.62 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 212.6, 166.6, 166.4, 149.0, 136.3, 128.7, 128.33, 128.30, 121.8, 94.8, 88.5, 66.2, 52.1, 31.4, 27.0, 26.9.

FT-IR (neat) 2949, 1960, 1718, 1653, 1437, 1263, 1165, 1026 cm^{-1}.

LRMS (EI) *m*/*z* $(M + H)^+$ calcd for $C_{18}H_{21}O_4$: 301, found: 301.



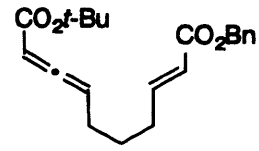
10-Benzyl 1-ethyl (*E*)-deca-2,3,8-trienedioate. The title compound was synthesized according to General Procedure C/D from (*E*)-8-(benzyloxy)-8-oxooct-6-enoic acid, using ethyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 30%. The title compound was isolated as a colorless oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.39–7.33 (m, 5H), 7.01 (dt, 1H, *J* =15.4 Hz, *J* = 5.0 Hz), 5.90 (dt, 1H, *J* =15.6 Hz, *J* = 1.0 Hz), 5.62–5.60 (m, 2H), 5.19 (s, 2H), 4.23–4.17 (m, 2H), 2.33–2.28 (m, 2H), 2.20–2.15 (m, 2H), 1.68–1.62 (m, 2H), 1.28 (t, 3H, *J* =7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 212.5, 166.5, 166.2, 149.1, 136.3, 128.7, 128.33, 128.30, 121.8, 94.7, 88.9, 66.2, 61.0, 31.4, 27.04, 26.95, 14.4.

FT-IR (neat) 2937, 1960, 1718, 1653, 1262, 1173, 1028 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{19}H_{23}O_4$: 315, found: 315.



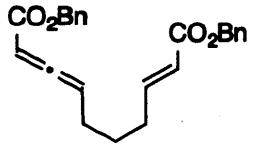
10-Benzyl 1-(*tert*-butyl) (*E*)-deca-2,3,8-trienedioate. The title compound was synthesized according to General Procedure C/D from (*E*)-8-(benzyloxy)-8-oxooct-6-enoic acid, using *tert*-butyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 51%. The title compound was isolated as a colorless oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.38–7.32 (m, 5H), 7.00 (dt, 1H, *J* =15 Hz, *J* = 5.0 Hz), 5.90 (dt, 1H, *J* =15 Hz, *J* = 1.0 Hz), 5.57–5.50 (m, 2H), 5.19 (s, 2H), 2.33–2.28 (m, 2H), 2.18–2.14 (m, 2H), 1.68–1.62 (m, 2H), 1.48 (s, 9H).

^{13}C NMR (125 MHz, CDCl3) δ 212.0, 166.5, 165.5, 149.2, 136.3, 128.7, 128.31, 128.29, 121.7, 94.4, 90.4, 81.0, 66.2, 31.4, 28.3, 27.1, 27.0.

FT-IR (neat) 2929, 1959, 1718, 1654, 1367, 1258, 1144, 1025 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{21}H_{27}O_4$: 343, found: 343.



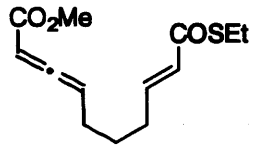
10-Benzyl 1-(*tert*-butyl) (*E*)-deca-2,3,8-trienedioate. The title compound was synthesized according to General Procedure C/D from (*E*)-8-(benzyloxy)-8-oxooct-6-enoic acid, using benzyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 31%. The title compound was isolated as a colorless oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.40–7.27 (m, 10H), 6.97 (dt, 1H, *J* =15.2 Hz, *J* = 6.8 Hz), 5.86 (dt, 1H, *J* =15.9 Hz, *J* = 1.5 Hz), 5.67–5.61 (m, 2H), 5.22–5.15 (m, 4H), 2.28–2.24 (m, 2H), 2.20–2.15 (m, 2H), 1.66–1.59 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 212.8, 166.4, 165.9, 149.0, 136.4, 136.2, (128.69, 128.67, 128.34, 128.30, 128.29), 121.8, 94.9, 88.6, 66.7, 66.2, 31.4, 27.1, 26.9.

FT-IR (neat) 2931, 1959, 1716, 1654, 1454, 1258, 1148, 978 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{25}O_4$: 377, found: 377.



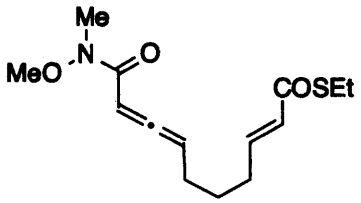
Methyl (*E*)-10-(ethylthio)-10-oxodeca-2,3,8-trienoate. The title compound was synthesized according to General Procedure C/D from (*E*)-8-(ethylthio)-8-oxooct-6-enoic acid, using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 31%. The title compound was isolated as a light yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 6.86 (dt, 1H, *J* =15.6 Hz, *J* = 6.8 Hz), 6.12 (dt, 1H, *J* =15.5 Hz, *J* = 1.6 Hz), 5.64–5.59 (m, 2H), 3.75 (s, 3H), 2.95 (q, 2H, *J* =7.5 Hz), 2.31–2.26 (m, 2H), 2.20–2.15 (m, 2H), 1.69–1.63 (m, 2H), 1.28 (t, 3H, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 212.6, 190.1, 166.5, 144.2, 129.5, 94.8, 88.5, 52.1, 31.3, 27.1, 27.0, 23.2, 14.9.

FT-IR (neat) 2931, 1960, 1719, 1669, 1632, 1437, 1260, 1162, 1031 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{13}H_{19}O_3S$: 255, found: 255.



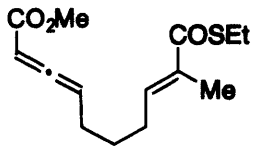
***S*-Ethyl (*E*)-10-(methoxy(methyl)amino)-10-oxodeca-2,7,8-trienethioate.** The title compound was synthesized according to General Procedure C/D from (*E*)-8-(ethylthio)-8-oxooct-6-enoic acid, using *N,O*-dimethyl-*N*-((triphenyl-λ^5-phosphanylidene)methyl)hydroxylamine. The overall yield (2 steps) was 30%. The title compound was isolated as a colorless oil.

^{1}H NMR (500 MHz, CDCl3) δ 6.89–6.83 (m, 1H), 6.19 (t, 1H, *J* = 3.0 Hz), 6.12 (dt, 1H, *J* = 15.6 Hz, *J* = 1.4 Hz), 5.67–5.62 (m, 1H), 3.72 (s, 3H), 3.25 (s, 3H), 2.96–2.91 (m, 2H), 2.31–2.27 (m, 2H), 2.20–2.15 (m, 2H), 1.69–1.63 (m, 2H), 1.29–1.26 (m, 3H).

^{13}C NMR (125 MHz, CDCl3) δ 212.4, 190.1, 166.0, 144.5, 129.4, 94.7, 86.9, 61.8, 32.8, 31.4, 27.2, 27.1, 23.2, 14.9.

FT-IR (neat) 2933, 1958, 1718, 1662, 1631, 1424, 1369, 1174, 997 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{22}NO_3S$: 284, found: 284.



Methyl (*E*)-10-(ethylthio)-9-methyl-10-oxodeca-2,3,8-trienoate. The title compound was synthesized according to General Procedure C/D from (*E*)-8-(Ethylthio)-7-methyl-8-oxooct-6-enoic acid, using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 32%. The title compound was isolated as a light yellow oil.

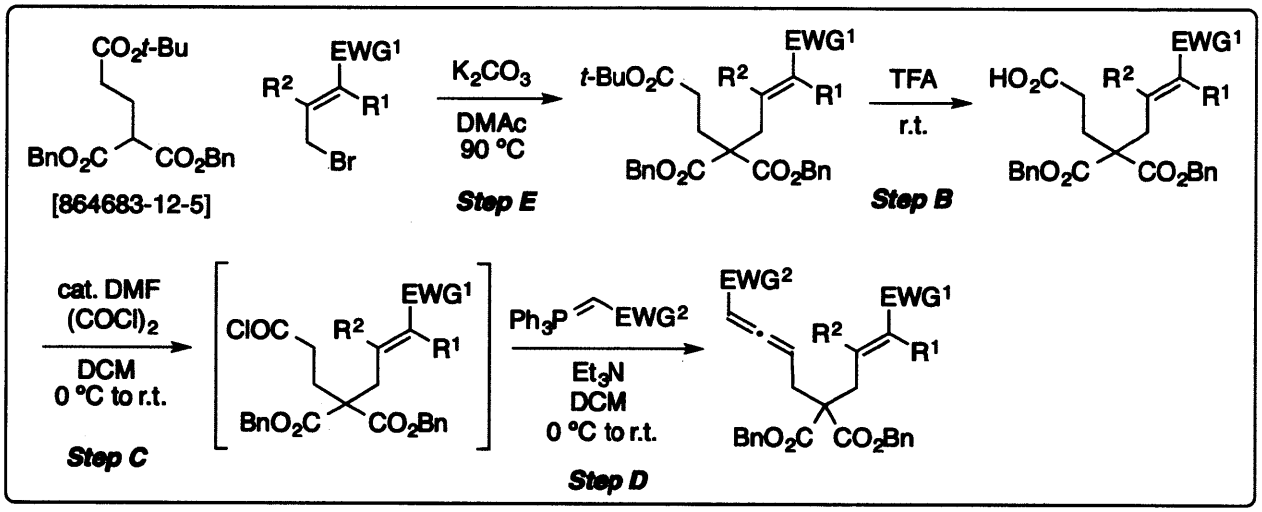
^{1}H NMR (500 MHz, CDCl3) δ 6.72–6.68 (m, 1H), 5.65–5.62 (m, 2H), 3.74 (s, 3H), 2.92 (q, 2H, *J* = 7.2 Hz), 2.31–2.25 (m, 2H), 2.21–2.16 (m, 2H), 1.88 (s, 3H), 1.68–1.61 (m, 2H), 1.27 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 212.5, 193.9, 166.6, 139.7, 136.7, 94.9, 88.5, 52.2, 27.9, 27.5, 27.1, 23.4, 14.9, 12.6.

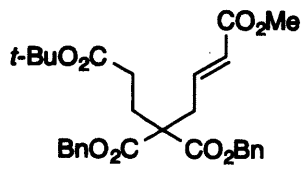
FT-IR (neat) 2924, 1961, 1723, 1654, 1437, 1260, 1161 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{14}H_{21}O_3S$: 269, found: 269.

2) Substrates for entries 6 and 7 of Table 3.2, entries 2 and 4 of Table 3.4



General Procedure E (Step E). K_2CO_3 was added to a round-bottom flask that contained 1.0 M solution of 1,1-dibenzyl 3-(*tert*-butyl) propane-1,1,3-tricarboxylate (1.0 equiv) in DMAc. Next, allyl bromide (1.2 equiv) was added, and the mixture was heated to 90 °C. After 4 h, the mixture was allowed to cool to r.t., and H_2O was added. The aqueous phase was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by column chromatography (10% EtOAc in hexanes→20% EtOAc in hexanes), which furnished the (*E*)-olefin (yield 60–90%).



3,3-Dibenzyl 1-(*tert*-butyl) 6-methyl (*E*)-hex-5-ene-1,3,3,6-tetracarboxylate. The

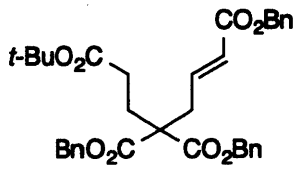
title compound was prepared according to General Procedure E, using methyl (*E*)-4-bromobut-2-enoate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.33–7.31 (m, 6H), 7.27–7.25 (m, 4H), 6.76 (dt, 1H, *J* =15.7 Hz, *J* = 7.9 Hz), 5.80 (dt, 1H, *J* =15.5 Hz, *J* = 1.3 Hz), 5.15–5.10 (m, 4H), 3.70 (s, 3H), 2.78 (dd, 2H, *J* = 7.9 Hz, *J* = 1.5 Hz), 2.24–2.14 (m, 4H), 1.43 (s, 9H).

^{13}C NMR (125 MHz, CDCl3) δ 171.6, 170.1, 166.1, 142.2, 135.3, 128.7, 128.6, 128.4, 125.1, 80.8, 67.6, 57.0, 51.6, 36.2, 30.6, 28.4, 28.2.

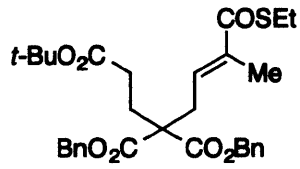
FT-IR (film) 2978, 1729, 1437, 1368, 1272, 1169, 698 cm^{-1}.

TOF-MS *m*/*z* $(M + NH_4)^+$ calcd for $C_{29}H_{38}NO_8$: 528, found: 528.



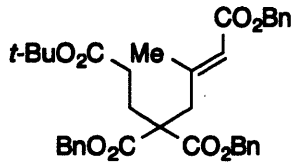
3,3,6-Tribenzyl 1-(*tert*-butyl) (*E*)-hex-5-ene-1,3,3,6-tetracarboxylate. The title compound was prepared according to General Procedure E, using benzyl (*E*)-4-bromobut-2-enoate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.37–7.28 (m, 11H), 7.26–7.24 (m, 4H), 6.81 (dt, 1H, *J* =15.6 Hz, *J* = 7.4 Hz), 5.84 (d, 1H, *J* =15.3 Hz), 5.16–5.09 (m, 6H), 2.78 (dd, 2H, *J* = 8.0 Hz, *J* = 1.8 Hz), 2.24–2.12 (m, 4H), 1.43 (s, 9H).



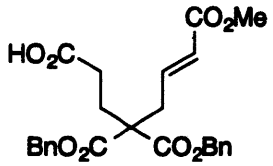
3,3-Dibenzyl 1-(*tert*-butyl) (*E*)-7-(ethylthio)-6-methyl-7-oxohept-5-ene-1,3,3-tricarboxylate. The title compound was prepared according to General Procedure E, using *S*-ethyl (*E*)-4-bromo-2-methylbut-2-enethioate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.35–7.25 (m, 10 H), 6.56 (td, 1H, *J* =7.3 Hz, *J* = 1.5 Hz), 5.13–5.11 (m, 4H), 2.89 (q, 2H, *J* = 7.6 Hz), 2.79 (dd, 2H, *J* =7.1 Hz, *J* = 1.6 Hz), 2.28–2.22 (m, 2H), 2.21–2.12 (m, 2H), 1.79 (s, 3H), 1.43 (s, 9H), 1.27 (t, 3H, *J* =7.6 Hz).



3,3,6-Tribenzyl 1-(*tert*-butyl) (*E*)-5-methylhex-5-ene-1,3,3,6-tetracarboxylate. The title compound was prepared according to General Procedure E, using benzyl (*E*)-4-bromo-3-methylbut-2-enoate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.37–7.34 (m, 5H), 7.32–7.29 (m, 6H), 7.26–7.23 (m, 4H), 5.71 (d, 1H, J = 1.6 Hz), 5.13–5.07 (m, 6H), 2.82 (s, 2H), 2.22–2.18 (m, 2H), 2.15–2.12 (m, 2H), 2.04 (d, 3H, J = 1.3 Hz), 1.41 (s, 9H).



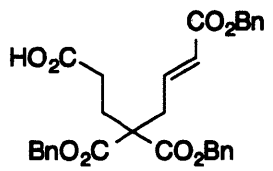
(*E*)-4,4-Bis((benzyloxy)carbonyl)-8-methoxy-8-oxooct-6-enoic acid. The title compound was prepared according to General Procedure B, using 3,3-Dibenzyl 1-(*tert*-butyl) 6-methyl (*E*)-hex-5-ene-1,3,3,6-tetracarboxylate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 11.2 (br s, 1H), 7.33–7.31 (m, 6H), 7.27–7.25 (m, 4H), 6.76 (dt, 1H, J =15.6 Hz, J = 7.8 Hz), 5.82 (d, 1H, J =15.5 Hz), 5.16–5.10 (m, 4H), 3.71 (s, 3H), 2.80 (dd, 2H, J = 7.8 Hz, J = 0.6 Hz), 2.37–2.24 (m, 4H).

^{13}C NMR (125 MHz, CDCl3) δ 178.1, 170.0, 166.1, 142.0, 135.1, 128.7, 128.6, 128.4, 125.2, 67.7, 56.7, 51.6, 36.4, 29.2, 28.1.

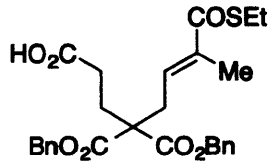
FT-IR (neat) 2952, 1732, 1455, 1271, 1172, 697 cm^{-1}.

TOF-MS m/z $(M + NH_4)^+$ calcd for $C_{25}H_{30}NO_8$: 472, found: 472.



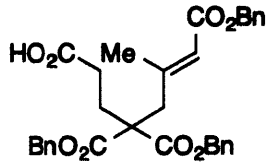
(*E*)-8-(Benzyloxy)-4,4-bis((benzyloxy)carbonyl)-8-oxooct-6-enoic acid. The title compound was prepared according to General Procedure B, using 3,3,6-Tribenzyl 1-(*tert*-butyl) (*E*)-hex-5-ene-1,3,3,6-tetracarboxylate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.40–7.28 (m, 11H), 7.26–7.22 (m, 4H), 6.81 (dt, 1H, *J* =15.2 Hz, *J* = 7.6 Hz), 5.86 (d, 1H, *J* =15.4 Hz), 5.16–5.08 (m, 6H), 2.80 (dd, 2H, *J* = 7.7 Hz, *J* = 1.4 Hz), 2.36–2.31 (m, 2H), 2.30–2.23 (m, 2H).



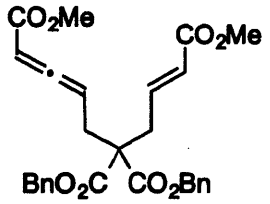
(*E*)-4,4-Bis((benzyloxy)carbonyl)-8-(ethylthio)-7-methyl-8-oxooct-6-enoic acid. The title compound was prepared according to General Procedure B, using 3,3-dibenzyl 1-(*tert*-butyl) (*E*)-7-(ethylthio)-6-methyl-7-oxohept-5-ene-1,3,3-tricarboxylate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.33–7.29 (m, 6 H), 7.27–7.25 (m, 4H), 6.54 (td, 1H, *J* =7.2 Hz, *J* = 1.5 Hz), 5.16–5.11 (m, 4H), 2.90 (q, 2H, *J* = 7.4 Hz), 2.81 (dd, 2H, *J* =7.0 Hz, *J* = 1.5 Hz), 2.36–2.33 (m, 2H), 2.30–2.25 (m, 2H), 1.80 (s, 3H), 1.27 (t, 3H, *J* =7.4 Hz).



(*E*)-8-(Benzyloxy)-4,4-bis((benzyloxy)carbonyl)-6-methyl-8-oxooct-6-enoic acid. The title compound was prepared according to General Procedure B, using 3,3,6-tribenzyl 1-(*tert*-butyl) (*E*)-5-methylhex-5-ene-1,3,3,6-tetracarboxylate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.37–7.34 (m, 5H), 7.33–7.28 (m, 6H), 7.26–7.23 (m, 4H), 5.72 (d, 1H, *J* = 1.5 Hz), 5.13–5.08 (m, 6H), 2.84 (s, 2H), 2.33–2.29 (m, 2H), 2.25–2.21 (m, 2H), 2.04 (d, 3H, *J* = 1.2 Hz).



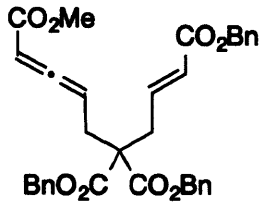
4,4-Dibenzyl 1,8-dimethyl (*E*)-octa-1,6,7-triene-1,4,4,8-tetracarboxylate. The title compound was synthesized according to General Procedure C/D from (*E*)-4,4-bis((benzyloxy)carbonyl)-8-methoxy-8-oxooct-6-enoic acid, using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 54%. The title compound was isolated as a colorless oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.33–7.31 (m, 6H), 7.26–7.23 (m, 4H), 6.73 (dt, 1H, *J* =15.5 Hz, *J* = 7.5 Hz), 5.83 (dt, 1H, *J* =15.5 Hz, *J* = 1.0 Hz), 5.52 (dt, 1H, *J* =6.0 Hz, *J* = 2.5 Hz), 5.39 (td, 1H, *J* =8.3 Hz, *J* = 6.3 Hz), 5.14–5.11 (m, 4H), 3.71 (s, 3H), 3.69 (s, 3H), 2.89 (dd, 2H, *J* =7.5 Hz, *J* = 1.5 Hz), 2.77–2.75 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 213.4, 169.5, 166.2, 165.9, 142.0, 135.2, 128.8, 128.7, 128.5, 125.4, 89.6, 88.4, 67.8, 57.4, 52.1, 51.6, 35.4, 31.7.

FT-IR (neat) 2951, 1964, 1725, 1659, 1436, 1271, 1167, 1029 cm^{-1}.

LRMS (EI) *m*/*z* $(M + H)^+$ calcd for $C_{28}H_{29}O_8$: 493, found: 493.



1,4,4-Tribenzyl 8-methyl (*E*)-octa-1,6,7-triene-1,4,4,8-tetracarboxylate. The title compound was synthesized according to General Procedure C/D from (*E*)-8-(benzyloxy)-4,4-bis((benzyloxy)carbonyl)-8-oxooct-6-enoic acid, using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 28%. The title compound was isolated as a colorless oil.

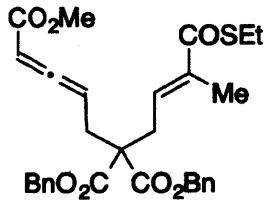
^{1}H NMR (500 MHz, CDCl3) δ 7.38–7.32 (m, 5H), 7.31–7.28 (m, 6H), 7.25–7.22 (m, 4H), 6.78 (dt, 1H, *J* =15.7 Hz, *J* = 7.5 Hz), 5.87 (dt, 1H, *J* =15.5 Hz, *J* = 1.0 Hz), 5.51 (dt, 1H,

J =6.5 Hz, J = 2.0 Hz), 5.39 (td, 1H, J =8.3 Hz, J = 6.3 Hz), 5.14 (s, 2H), 5.12 (dd, 4H, J =5.9 Hz, J = 4.0 Hz), 3.67 (s, 3H), 2.89 (dd, 2H, J =7.8 Hz, J = 1.5 Hz), 2.77–2.75 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 213.4, 169.5, 166.0, 165.7, 142.4, 136.2, 135.2, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 125.5, 89.7, 88.4, 67.8, 66.3, 57.4, 52.1, 35.4, 31.7.

FT-IR (neat) 2951, 1964, 1725, 1653, 1456, 1267, 1166, 1028 cm^{-1}.

LRMS (EI) m/z (M + H)$^+$ calcd for $C_{34}H_{33}O_8$: 569, found: 569.



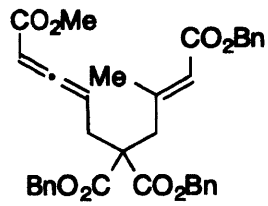
5,5-Dibenzyl 1-methyl (*E*)-9-(ethylthio)-8-methyl-9-oxonona-1,2,7-triene-1,5,5-tricarboxylate. The title compound was synthesized according to General Procedure C/D from (*E*)-4,4-bis((benzyloxy)carbonyl)-8-(ethylthio)-7-methyl-8-oxooct-6-enoic acid, using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 76%. The title compound was isolated as a colorless oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.33–7.31 (m, 6H), 7.27–7.24 (m, 4H), 6.56 (td, 1H, J =7.5 Hz, J = 1.5 Hz), 5.53 (dt, 1H, J =6.2 Hz, J = 2.4 Hz), 5.44 (td, 1H, J =8.3 Hz, J = 6.3 Hz), 5.15–5.13 (m, 4H), 3.70 (s, 3H), 2.95–2.85 (m, 4H), 2.84–2.77 (m, 2H), 1.81 (d, 3H, J =1.2 Hz), 1.27 (t, 3H, J =7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 213.3, 193.7, 169.8, 165.9, 139.3, 135.2, 132.7, 128.7, 128.6, 128.4, 89.8, 88.4, 67.8, 57.4, 52.1, 32.0, 23.5, 14.7, 12.7.

FT-IR (neat) 2952, 1964, 1732, 1656, 1439, 1265, 1166, 1009 cm^{-1}.

TOF-MS m/z (M + Na)$^+$ calcd for $C_{30}H_{32}O_7SNa$: 559, found: 559.



1,4,4-Tribenzyl 8-methyl (*E*)-octa-1,6,7-triene-1,4,4,8-tetracarboxylate. The title compound was synthesized according to General Procedure C/D from (*E*)-8-(benzyloxy)-4,4-bis((benzyloxy)carbonyl)-6-methyl-8-oxooct-6-enoic acid, using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 43%. The title compound was isolated as a colorless oil.

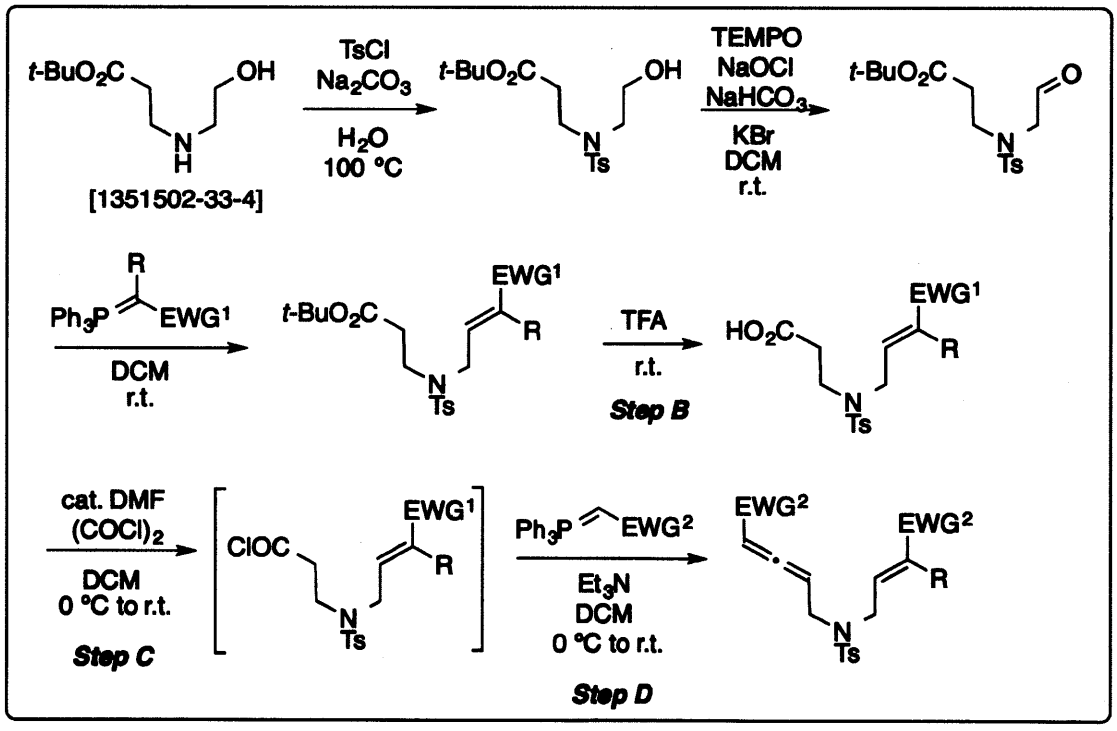
^{1}H NMR (500 MHz, CDCl3) δ 7.39–7.33 (m, 5H), 7.32–7.29 (m, 6H), 7.26–7.22 (m, 4H), 5.78 (d, 1H, *J* =1.1 Hz), 5.51 (dt, 1H, *J* =6.1 Hz, *J* = 2.4 Hz), 5.40 (td, 1H, *J* =7.8 Hz, *J* = 6.2 Hz), 5.13–5.09 (m, 6H), 3.68 (s, 3H), 2.92 (s, 2H), 2.82–2.72 (m, 2H), 2.03 (d, 3H, *J* =1.1 Hz).

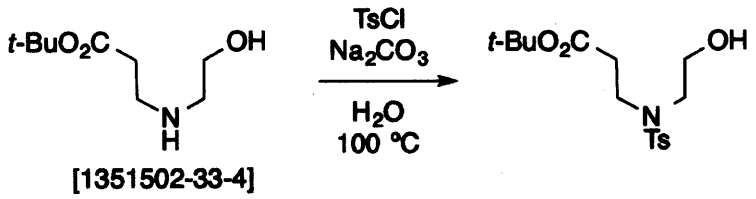
^{13}C NMR (125 MHz, CDCl3) δ 213.3, 169.9, 165.8, 165.4, 154.2, 136.4, 135.1, 128.8, 128.7, 128.6, 128.5, 128.34, 128.26, 120.6, 90.0, 88.5, 67.8, 65.8, 57.4, 52.1, 43.2, 31.4, 19.6.

FT-IR (neat) 2919, 1962, 1718, 1653, 1437, 1261, 1145, 1073, 1027 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{35}H_{35}O_8$: 583, found: 583.

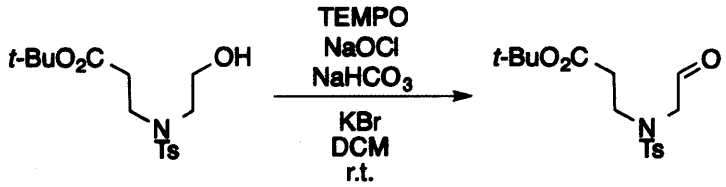
3) Substrates for entry 8 of Table 3.2 and entry 3 of Table 3.4





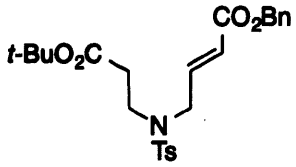
[1351502-33-4]

***tert*-Butyl 3-((*N*-(2-hydroxyethyl)-4-methylphenyl)sulfonamido)propanoate.** *tert*-Butyl 3-((2-hydroxyethyl)amino)propanoate (3.80 g, 20 mmol), tosyl chloride (4.19 g, 22 mmol), sodium carbonate (2.33 g, 22 mmol), H_2O (80 mL), and a stir bar were combined in a 300-mL round-bottom flask. The mixture was heated to 100 °C for 1 h. Then, it was allowed to cool to r.t., and EtOAc (100 mL) was added. The aqueous layer was extracted with EtOAc (100 mL x 2), and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was used in the next step without further purification.



***tert*-Butyl 3-((4-methyl-*N*-(2-oxoethyl)phenyl)sulfonamido)propanoate.** *tert*-Butyl 3-((*N*-(2-hydroxyethyl)-4-methylphenyl)sulfonamido)propanoate (5.15 g, 15 mmol), TEMPO (234 mg, 1.5 mmol), sodium bicarbonate (1.93 g, 23 mmol), potassium bromide (180 mg, 1.5 mmol), CH_2Cl_2 (100 mL), and a stir bar were combined in a 500-mL round-bottom flask. Sodium hypochlorite (10.0 mL; 14.5% aqueous solution) was added dropwise over 15 min. This mixture was stirred at r.t. for 16 h. Next, the saturated solution of $Na_2S_2O_3$ (aq) (150 mL) was added, and the mixture was stirred at r.t. for addition 30 min. The saturated solution of NaCl (100 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (100 mL x2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by column chromatography (20% EtOAc in hexanes→50% EtOAc in hexanes), which furnished the mixture of product and impurities (the desired aldehyde 40–70%

pure). It was used in the next step without further purification.



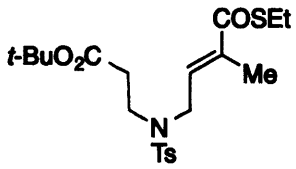
Benzyl (*E*)-4-((*N*-(3-(*tert*-butoxy)-3-oxopropyl)-4-methylphenyl)sulfonamido) but-2-enoate. Benzyl 2-(triphenyl-λ^5-phosphanylidene)acetate (1.2 equiv) was added to a round-bottom flask that contained 0.1 M solution of *tert*-butyl 3-((4-methyl-*N*-(2-oxoethyl)phenyl)sulfonamido)propanoate (1.0 equiv) in CH_2Cl_2. The resulting solution was stirred at r.t. for 12 h, and then it was concentrated under reduced pressure. The residue was then purified by column chromatography (10% EtOAc in hexanes→30% EtOAc in hexanes), which furnished the (*E*)-olefin (90% yield).

^{1}H NMR (500 MHz, CDCl3) δ 7.71–7.69 (m, 2H), 7.40–7.33 (m, 5H), 7.32–7.28 (m, 2H), 6.78 (dt, 1H, *J* =15.3 Hz, *J* = 6.2 Hz), 5.98 (dt, 1H, *J* =15.8 Hz, *J* = 1.6 Hz), 5.17 (s, 2H), 3.97 (dd, 2H, *J* = 5.9 Hz, *J* = 1.7 Hz), 3.39 (t, 2H, *J* = 7.2 Hz), 3.40–3.38 (m, 2H), 2.41 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (125 MHz, CDCl3) δ 170.6, 165.5, 143.9, 143.2, 136.7, 136.0, 130.0, 128.7, 128.43, 128.37, 127.4, 123.8, 81.3, 55.5, 49.6, 44.4, 35.5, 28.2, 21.6.

FT-IR (neat) 2978, 1724, 1455, 1341, 1267, 1161, 1095, 698 cm^{-1}.

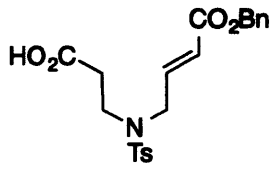
TOF-MS *m*/*z* $(M + NH_4)^+$ calcd for $C_{25}H_{35}N_2O_6S$: 491, found: 491.



***tert*-Butyl (*E*)-3-((*N*-(4-(ethylthio)-3-methyl-4-oxobut-2-en-1-yl)-4-methylphenyl) sulfonamido)propanoate.** *S*-Ethyl 2-(triphenyl-λ^5-phosphanylidene)propanethioate (1.2 equiv) was added to a round-bottom flask that contained 0.1 M solution of *tert*-butyl 3-((4-methyl-*N*-(2-oxoethyl)phenyl)sulfonamido)propanoate (1.0 equiv) in CH_2Cl_2. The resulting solution was stirred at r.t. for 12 h, and then it was concentrated under

reduced pressure. The residue was then purified by column chromatography (10% EtOAc in hexanes → 30% EtOAc in hexanes), which furnished the (*E*)-olefin (60% yield).

^{1}H NMR (500 MHz, CDCl3) δ 7.71 (d, 2H, *J* =8.4 Hz), 7.34–7.32 (m, 2H), 6.37 (td, 1H, *J* =6.7 Hz, *J* = 1.3 Hz), 4.03 (dd, 2H, *J* =6.2 Hz, *J* = 0.9 Hz), 3.42–3.39 (m, 2H), 2.89 (q, 2H, *J* = 7.4 Hz), 2.57 (t, 2H, *J* = 7.4 Hz), 2.43 (s, 3H), 1.87 (d, 3H, *J* = 1.8 Hz), 1.45 (s, 9H), 1.26 (t, 3H, *J* = 7.5 Hz).



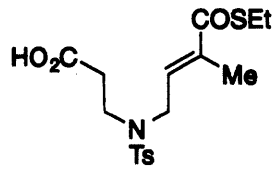
(*E*)-3-((*N*-(4-(Benzyloxy)-4-oxobut-2-en-1-yl)-4-methylphenyl)sulfonamido) propanoic acid. The title compound was prepared according to General Procedure B using benzyl (*E*)-4-((*N*-(3-(*tert*-butoxy)-3-oxopropyl)-4-methylphenyl)sulfonamido)but-2-enoate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.71–7.69 (m, 2H), 7.40–7.33 (m, 5H), 7.32–7.29 (m, 2H), 6.77 (dt, 1H, *J* =15.8 Hz, *J* = 5.4 Hz), 5.96 (dt, 1H, *J* =15.7 Hz, *J* = 1.7 Hz), 5.17 (s, 2H), 3.99 (dd, 2H, *J* = 5.6 Hz, *J* = 2.3 Hz), 3.41 (t, 2H, *J* = 7.2 Hz), 2.69 (t, 2H, *J* = 6.9 Hz), 2.42 (s, 3H).

^{13}C NMR (125 MHz, CDCl3) δ 175.5, 165.4, 144.1, 142.9, 136.4, 135.9, 130.0, 128.7, 128.47, 128.36, 127.4, 124.1, 66.6, 49.8, 44.0, 34.0, 21.6.

FT-IR (neat) 2980, 1714, 1336, 1277, 1159, 1095, 753 cm^{-1}.

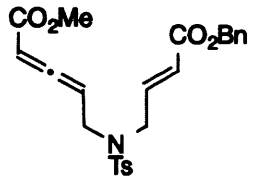
LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{21}H_{24}NO_6S$: 418, found: 418.



(*E*)-3-((*N*-(4-(Ethylthio)-3-methyl-4-oxobut-2-en-1-yl)-4-methylphenyl) sulfonamido)propanoic acid. The title compound was prepared according to General

Procedure B, using *tert*-butyl (*E*)-3-((*N*-(4-(ethylthio)-3-methyl-4-oxobut-2-en-1-yl)-4-methylphenyl)sulfonamido)propanoate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.71 (d, 2H, *J* =8.4 Hz), 7.35–7.33 (m, 2H), 6.38 (td, 1H, *J* =6.6 Hz, *J* = 1.6 Hz), 4.04 (dd, 2H, *J* =6.3 Hz, *J* = 1.3 Hz), 3.42 (t, 2H, J = 7.0 Hz), 2.90 (q, 2H, *J* = 7.5 Hz), 2.75 (t, 2H, *J* = 6.7 Hz), 2.44 (s, 3H), 1.87 (d, 3H, *J* = 1.4 Hz), 1.26 (t, 3H, *J* = 7.5 Hz).



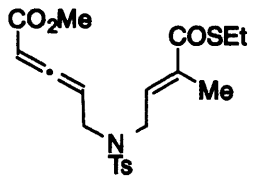
Methyl (*E*)-5-((*N*-(4-(benzyloxy)-4-oxobut-2-en-1-yl)-4-methylphenyl) sulfonamido)penta-2,3-dienoate. The title compound was synthesized according to General Procedure C/D from (*E*)-3-((*N*-(4-(benzyloxy)-4-oxobut-2-en-1-yl)-4-methylphenyl)sulfonamido)propanoic acid using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 34%. The title compound was isolated as a light yellow colorless oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.72–7.70 (m, 2H), 7.40–7.33 (m, 5H), 7.32–7.30 (m, 2H), 6.77 (dt, 1H, *J* =15.2 Hz, *J* = 6.2 Hz), 6.00 (dt, 1H, *J* =15.9 Hz, *J* = 1.3 Hz), 5.58 (dt, 1H, *J* =6.0 Hz, *J* = 2.2 Hz), 5.40 (dt, 1H, *J* =12.5 Hz, *J* = 3.7 Hz), 5.17 (s, 2H), 4.11–4.00 (m, 3H), 3.89–3.84 (m, 1H), 3.70 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (125 MHz, CDCl3) δ 213.0, 165.5, 165.4, 144.0, 142.5, 137.1, 136.0, 130.1, 128.7, 128.42, 128.35, 127.3, 124.2, 91.0, 89.6, 66.5, 52.2, 47.4, 45.5, 21.6.

FT-IR (neat) 2951, 1963, 1718, 1653, 1437, 1349, 1268, 1161, 1095, 1018 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{26}NO_6S$: 456, found: 456.



Methyl (*E*)-5-((*N*-(4-(ethylthio)-3-methyl-4-oxobut-2-en-1-yl)-4-methylphenyl)

sulfonamido)penta-2,3-dienoate. The title compound was synthesized according to General Procedure C/D from (*E*)-3-((*N*-(4-(Ethylthio)-3-methyl-4-oxobut-2-en-1-yl)-4-methylphenyl)sulfonamido)propanoic acid, using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 50%. The title compound was isolated as a colorless oil.

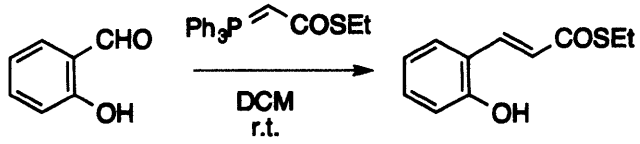
^{1}H NMR (500 MHz, CDCl3) δ 7.72 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 6.43 (td, 1H, *J* = 6.5 Hz, *J* = 1.4 Hz), 5.61 (dt, 1H, *J* = 6.0 Hz, *J* = 2.5 Hz), 5.51–5.47 (m, 1H), 4.13–4.03 (m, 2H), 4.01–3.92 (m, 2H), 3.72 (s, 3H), 2.90 (q, 2H, *J* = 7.7 Hz), 2.44 (s, 3H), 1.88 (s, 3H), 1.26 (t, 3H, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 212.8, 193.5, 165.6, 144.0, 139.1, 136.9, 133.2, 130.1, 127.3, 91.4, 89.7, 52.4, 45.6, 44.7, 23.6, 21.7, 14.7, 12.6.

FT-IR (neat) 2930, 1963, 1722, 1653, 1437, 1347, 1259, 1160, 1093, 1018 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{20}H_{26}NO_5S_2$: 424, found: 424.

4) A substrate for eq 3.2.3



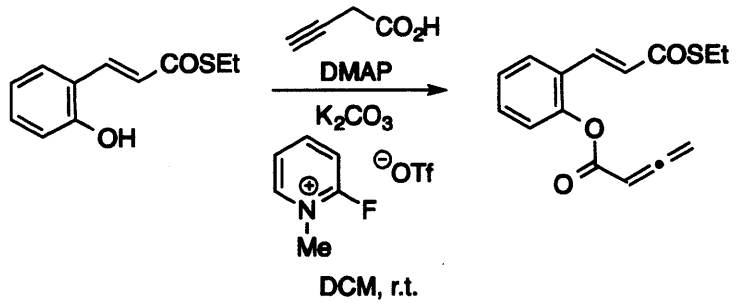
***S*-Ethyl (*E*)-3-(2-hydroxyphenyl)prop-2-enethioate.** *S*-Ethyl 2-(triphenyl-λ^5-phosphanylidene)propanethioate (1.2 equiv) was added to a round-bottom flask that contained 0.1 M solution of salicylaldehyde (1.0 equiv) in CH_2Cl_2. The resulting solution was stirred at r.t. for 12 h, and then it was concentrated under reduced pressure. The residue was then purified by column chromatography (hexanes→20% EtOAc in hexanes), which furnished the (*E*)-olefin (84% yield).

^{1}H NMR (500 MHz, CDCl3) δ 7.97 (d, 1H, *J* = 16.0 Hz), 7.49 (dd, 1H, *J* =8.0 Hz, *J* = 1.6 Hz), 7.28–7.24 (m, 1H), 6.96–6.86 (m, 3H), 6.37 (br s, 1H), 3.04 (q, 2H, *J* =7.5 Hz), 1.34 (t, 3H, *J* =7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 191.7, 155.6, 136.1, 131.8, 129.5, 125.9, 121.6, 121.2, 116.5, 23.6, 15.0.

FT-IR (neat) 3232, 1640, 1447, 1369, 1265, 978 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{11}H_{13}O_2S$: 209, found: 209.



(*E*)-2-(3-(Ethylthio)-3-oxoprop-1-en-1-yl)phenyl buta-2,3-dienoate. [95]

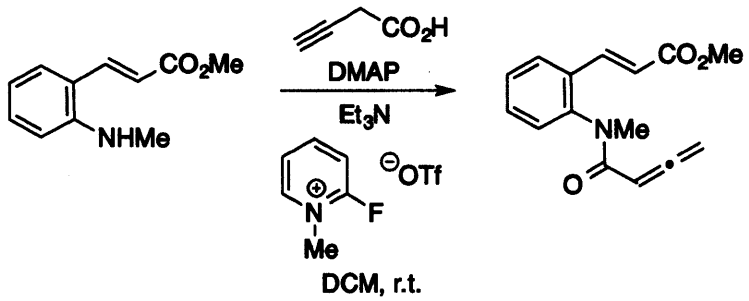
^1H NMR (500 MHz, CDCl3) δ 7.71 (d, 1H, J = 16 Hz), 7.64 (dd, 1H, J =7.5 Hz, J = 1.5 Hz), 7.43 (td, 1H, J = 7.5 Hz, J = 1.5 Hz), 7.29–7.26 (m, 1H), 7.22 (dd, 1H, J =8.0 Hz, J = 1.0 Hz), 6.76 (d, 1H, J =15.8 Hz), 5.87 (t, 1H, J =6.5 Hz), 5.44 (d, 2H, J =6.0 Hz), 3.02 (q, 2H, J =7.5 Hz), 1.33 (t, 3H, J =7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 217.2, 189.9, 163.7, 149.9, 133.9, 131.3, 128.3, 127.4, 127.1, 126.5, 123.4, 87.5, 80.2, 23.6, 14.9.

FT-IR (neat) 2987, 1967, 1734, 1663, 1613, 1209, 1119, 1024 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{15}H_{15}O_3S$: 275, found: 275.

5) Substrates for eq 3.2.4 and eq 3.2.5



[95] This substrate was prepared according to the procedure reported in ref 70c.

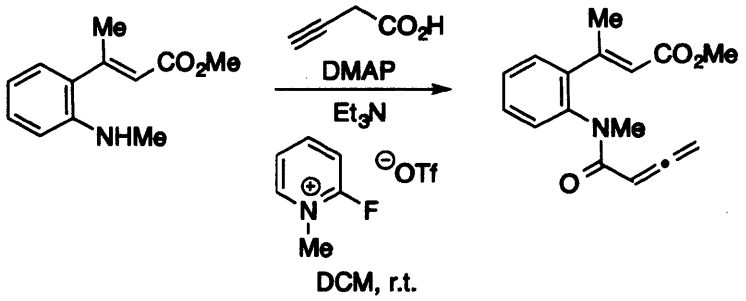
Methyl (*E*)-3-(2-(*N*-methylbuta-2,3-dienamido)phenyl)acrylate. Methyl (*E*)-3-(2-(methylamino)phenyl)acrylate (730 mg, 3.82 mmol), 3-butynoic acid (352mg, 4.19 mmol), 2-fluoro-1-methylpyridinium triflate (1.09g, 4.19 mmol), and a stir bar were combined in a 100-mL round-bottom flask, which was then evacuated and back-filled with nitrogen (three cycles). Triethylamine (1.12 mL) and CH_2Cl_2 (37 mL) were added in turn via syringe. The mixture was stirred at r.t. for 16 h, and then it was filtered through a short pad of silica (washed with CH_2Cl_2 (20 mL). The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (30% EtOAc in hexanes→50% EtOAc in hexanes), which furnished the product as a white solid (350 mg, 36%).

^{1}H NMR (500 MHz, CDCl3) δ 7.71–7.66 (m, 2H), 7.47–7.42 (m, 2H), 7.23 (dd, 1H, J = 8.0 Hz, J = 1.5 Hz), 6.46 (d, 1H, J = 15.8 Hz), 5.40 (t, 1H, J = 6.3 Hz), 5.04 (dd, 2H, J = 6.6 Hz, J = 1.3 Hz), 3.82 (s, 3H), 3.28 (s, 3H).

^{13}C NMR (125 MHz, CDCl3) δ 214.6, 166.8, 165.0, 143.1, 138.9, 132.8, 131.5, 129.5, 129.0, 127.9, 121.4, 88.4, 79.0, 52.0, 37.7.

FT-IR (neat) 2951, 1943, 1716, 1649, 1487, 1433, 1376, 1320, 1274, 1197, 1174 cm^{-1}.

LRMS (EI) m/z (M + H)$^+$ calcd for $C_{15}H_{16}NO_3$: 258, found: 258.



Methyl (*E*)-3-(2-(*N*-methylbuta-2,3-dienamido)phenyl)but-2-enoate. Methyl (*E*)-3-(2-(methylamino)phenyl)but-2-enoate (500 mg, 2.43 mmol), 3-butynoic acid (245 mg, 2.92 mmol), 2-fluoro-1-methylpyridinium triflate (763 mg, 2.92 mmol), and a stir bar were combined in a 100-mL round-bottom flask, which was then evacuated and back-filled with nitrogen (three cycles). Triethylamine (0.75 mL, 5.35 mmol) and CH_2Cl_2 (24

mL) were added in turn via syringe. The mixture was stirred at r.t. for 16 h, and then it was filtered through a short pad of silica (washed with CH_2Cl_2 (15 mL). The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (30% EtOAc in hexanes→50% EtOAc in hexanes), which furnished the product as a white solid (320 mg, 49%).

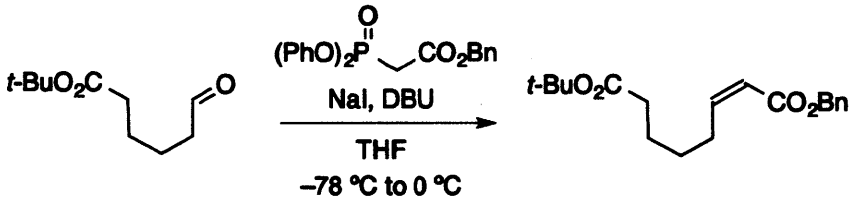
^{1}H NMR (500 MHz, CDCl3) δ 7.41–7.36 (m, 2H), 7.28–7.26 (m, 2H), 7.21–7.19 (m, 1H), 5.84 (s, 1H), 5.53 (t, 1H, J = 6.3 Hz), 5.07 (d, 2H, J = 6.5 Hz), 3.75 (s, 3H), 3.23 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (125 MHz, CDCl3) δ 214.6, 166.5, 164.7, 154.9, 142.2, 140.8, 129.62, 129.55, 129.3, 128.6, 120.7, 88.7, 79.1, 51.3, 37.6, 19.8.

FT-IR (neat) 2949, 1945, 1717, 1651, 1433, 1375, 1272, 1171 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{16}H_{18}NO_3$: 272, found: 272.

6) A substrate for eq 3.2.8



1-Benzyl 8-(*tert*-butyl) (Z)-oct-2-enedioate.[96] Sodium iodide (5.91 mmol, 885 mg) and DBU (899 mg, 5.91 mmol) were added to the 100-mL round-bottom flask that contained benzyl 2-(diphenoxyphosphoryl)acetate (1.87 g, 4.89 mmol) and THF (20 mL) at 0 °C. After 10 min, the mixture was cooled to –78 °C, and *tert*-butyl 6-oxohexanoate (1.0 g, 5.37 mmol) was added. After 10 min, the mixture was warmed up to 0 °C and stirred at 0°C for 2.5 h. The saturated solution of NH_4Cl (aq) was added, and the aqueous layer was extracted with Et_2O (10 mL x2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by column chromatography (eluted with hexanes→20% Et_2O in hexanes),

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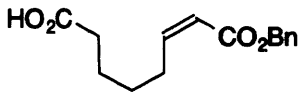
[96] Endo, K. *J. Org. Chem.* **2000**, *65*, 4745–4749.

which furnished the product as a light yellow oil (860 mg, 55%; minor (*E*) isomer should be carefully separated at this stage).

^{1}H NMR (500 MHz, CDCl3) δ 7.40–7.32 (m, 5H), 6.26 (dt, 1H, *J* =11.6 Hz, *J* = 7.4 Hz), 5.84 (dt, 1H, *J* =11.6 Hz, *J* = 1.9 Hz), 5.16 (s, 2H), 2.69 (qd, 2H, *J* = 7.3 Hz, *J* = 1.4 Hz), 2.23 (t, 2H, *J* = 7.3 Hz), 1.66–1.60 (m, 2H), 1.51–1.45 (m, 11H).

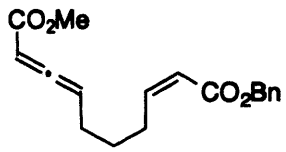
^{13}C NMR (125 MHz, CDCl3) δ 173.1, 166.2, 150.8, 136.3, 128.7, 128.35, 128.28, 119.8, 80.2, 65.9, 35.4, 28.8, 28.5, 28.3, 24.8.



(*Z*)-8-(Benzyloxy)-8-oxooct-6-enoic acid. The title compound was prepared according to General Procedure B, using 1-benzyl 8-(*tert*-butyl) (*Z*)-oct-2-enedioate. Yellow oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.40–7.33 (m, 5H), 6.25 (dt, 1H, *J* =11.6 Hz, *J* = 7.4 Hz), 5.86 (dt, 1H, *J* =11.4 Hz, *J* = 1.7 Hz), 5.17 (s, 2H), 2.71 (qd, 2H, *J* = 7.2 Hz, *J* = 1.8 Hz), 2.38 (t, 2H, *J* = 7.4 Hz), 1.72–1.66 (m, 2H), 1.55–1.49 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 166.3, 150.4, 136.2, 128.7, 128.4, 128.3, 120.0, 66.0, 33.8, 33.7, 28.7, 28.4, 24.3.



10-Benzyl 1-methyl (*Z*)-deca-2,3,8-trienedioate. The title compound was synthesized according to General Procedure C/D from (*Z*)-8-(benzyloxy)-8-oxooct-6-enoic acid, using methyl 2-(triphenyl-λ^5-phosphanylidene)acetate. The overall yield (2 steps) was 33%. The title compound was isolated as a colorless oil.

^{1}H NMR (500 MHz, CDCl3) δ 7.40–7.32 (m, 5H), 6.26 (dt, 1H, *J* =15.0 Hz, *J* = 5.8 Hz), 5.86 (dt, 1H, *J* =11.8 Hz, *J* = 1.8 Hz), 5.64–5.60 (m, 2H), 5.17 (s, 2H), 3.75 (s, 3H), 2.80–2.70 (m, 2H), 2.20–2.15 (m, 2H), 1.71–1.59 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 212.5, 166.8, 166.2, 150.2, 136.2, 128.7, 128.4, 128.3, 120.1, 95.1, 88.4, 65.9, 52.1, 28.5, 28.1, 27.2.

FT-IR (neat) 2947, 1960, 1718, 1642, 1437, 1261, 1155, 697 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{18}H_{21}O_4$: 301, found: 301.

IV. Intramolecular [3 + 2] Cycloaddition Reactions

General Procedure. Catalyst was added to an oven-dried 20-mL vial equipped with a stir bar. This vial was capped with a septum-lined cap, and then it was evacuated and back-filled with nitrogen (three cycles). Next, the ene-allene substrate was added via a syringe as a solution in toluene (0.1 M; anhydrous). This reaction mixture was stirred at room temperature. After 24 h, an aqueous solution of hydrogen peroxide (10%; 1 mL) was added, and the mixture was stirred for 10 min. Then an aqueous solution of $Na_2S_2O_3$ (saturated; 2 mL) was added, and the mixture was stirred for additional 10 min. The aqueous layer was extracted with EtOAc (5 mL x3), and the combined organic layers were dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by column chromatography.

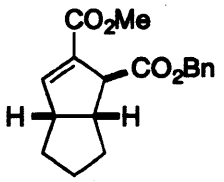


Table 3.2, entry 1. This compound was prepared according to the general procedure, using 10-benzyl 1-methyl (*E*)-deca-2,3,8-trienedioate (135 mg, 0.45 mmol), (*S*)-**3.7** (27.0 mg, 0.045 mmol), and toluene (4.50 mL). After purification by flash chromatography (eluted with hexanes→20% Et_2O and 20% acetone in hexanes), the title compound was isolated as a colorless oil (109 mg, 81% yield) with 98% ee.

HPLC analysis of the product: Daicel CHIRALCEL AD-H column; solvent system: 3% 2-propanol in hexanes; 1.0 mL/min; retention times: 14.3 min (minor), 15.6 min (major).

The second run was performed with (*R*)-**3.7**. The product was isolated as a colorless oil (114 mg, 84% yield) with 96% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.38–7.30 (m, 5H), 6.76 (dd, 1H, *J* =1.8 Hz, *J* = 2.8 Hz), 5.15 (s, 2H), 3.65 (s, 3H), 3.53–3.51 (m, 1H), 3.44–3.38 (m, 1H), 2.85–2.80 (m, 1H), 1.87–1.81 (m, 1H), 1.76–1.71 (m, 1H), 1.58–1.48 (m, 4H).

^{13}C NMR (125 MHz, CDCl3) δ 174.1, 164.8, 149.9, 136.4, 133.3, 128.4, 128.0, 127.9, 66.5, 57.6, 51.6, 50.7, 47.3, 34.9, 30.9, 25.3.

FT-IR (neat) 2949, 1718, 1635, 1437, 1266, 1163, 1101, 1012 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{18}H_{21}O_4$: 301, found: 301.

$[\alpha]^{25}_D$ = –94 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

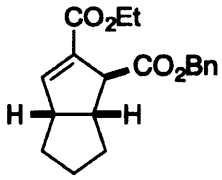


Table 3.2, entry 2. The title compound was prepared according to the general procedure, using 10-benzyl 1-ethyl (*E*)-deca-2,3,8-trienedioate (142 mg, 0.45 mmol), (*S*)-**3.7** (27.0 mg, 0.045 mmol), and toluene (4.50 mL). After purification by flash chromatography (eluted with hexanes→20% Et_2O and 20% acetone in hexanes), the title compound was isolated as a colorless oil (120 mg, 85% yield) with 98% ee.

HPLC analysis of the product: Daicel CHIRALCEL AD-H column; solvent system: 3% 2-propanol in hexanes; 1.0 mL/min; retention times: 12.1 min (minor), 14.3 min (major).

The second run was performed with (*R*)-**3.7**. The product was isolated as a colorless oil (122 mg, 86% yield) with 97% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.38–7.32 (m, 5H), 6.77 (s, 1H), 5.16 (s, 2H), 4.16–4.11 (m, 2H), 3.54 (s, 1H), 3.44–3.40 (m, 1H), 2.86–2.82 (m, 1H), 1.89–1.82 (m, 1H), 1.79–1.70 (m, 1H), 1.60–1.49 (m, 4H), 1.21 (t, 3H, *J* =7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 174.2, 164.4, 149.6, 136.4, 133.6, 128.6, 128.2, 128.1, 66.5, 60.5, 57.6, 50.7, 47.3, 34.9, 30.9, 25.3, 14.3.

FT-IR (neat) 2951, 1718, 1636, 1372, 1263, 1162, 1098, 1021 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{19}H_{23}O_4$: 315, found: 315.

$[\alpha]^{25}_D$ = –85 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

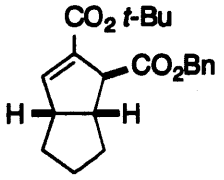


Table 3.2, entry 3. The title compound was prepared according to the general procedure, using 10-benzyl 1-(*tert*-butyl) (*E*)-deca-2,3,8-trienedioate (137 mg, 0.40 mmol), (*S*)-**3.7** (24.0 mg, 0.040 mmol), and toluene (4.0 mL). After purification by flash chromatography (eluted with hexanes→20% Et_2O and 20% acetone in hexanes), the title compound was isolated as a colorless oil (116 mg, 85% yield) with 98% ee.

HPLC analysis of the product: Daicel CHIRALCEL AD-H column; solvent system: 3% 2-propanol in hexanes; 1.0 mL/min; retention tixmes: 9.5 min (minor), 12.1 min (major).

The second run was performed with (*R*)-**3.7**. The product was isolated as a colorless oil (114 mg, 83% yield) with 97% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.37–7.31 (m, 5H), 6.68 (dd, 1H, J = 1.5 Hz, J = 2.5 Hz), 5.20–5.10 (m, 2H), 3.49–3.47 (m, 1H), 3.41–3.38 (m, 1H), 2.84–2.79 (m, 1H), 1.87–1.80 (m, 1H), 1.77–1.68 (m, 1H), 1.59–1.48 (m, 4H), 1.42 (s, 9H).

^{13}C NMR (125 MHz, CDCl3) δ 174.4, 163.7, 148.8, 136.3, 135.0, 128.6, 128.2 (2), 80.8, 66.5, 57.6, 50.5, 47.3, 35.0, 30.9, 28.2, 25.3.

FT-IR (neat) 2951, 1735, 1709, 1367, 1271, 1163, 1101 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{21}H_{27}O_4$: 343, found: 343.

$[\alpha]^{25}_D$ = –78 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

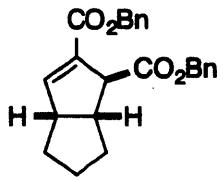


Table 3.2, entry 4. The title compound was prepared according to the general procedure, using 10-benzyl 1-benzyl (*E*)-deca-2,3,8-trienedioate (140 mg, 0.37 mmol),

(*S*)-**3.7** (22.0 mg, 0.037 mmol), and toluene (3.70 mL). After purification by flash chromatography (eluted with hexanes→20% Et_2O in hexanes), the title compound was isolated as a colorless oil (128 mg, 91% yield) with 98% ee.

HPLC analysis of the product: Daicel CHIRALCEL IB column; solvent system: 10% 2-propanol in hexanes; 1.0 mL/min; retention times: 8.9 min (minor), 11.3 min (major).

The second run was performed with (*R*)-**3.7**. The product was isolated as a colorless oil (125 mg, 89% yield) with 98% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.36–7.29 (m, 10H), 6.83 (dd, 1H, J = 2.6 Hz, J = 1.6 Hz), 5.13 (s, 2H), 5.10 (d, 2H, J = 8.1 Hz), 3.56 (td, 1H, J = 3.0 Hz, J = 1.6 Hz), 3.45–3.40 (m, 1H), 2.87–2.82 (m, 1H), 1.89–1.80 (m, 1H), 1.76–1.69 (m, 1H), 1.59–1.50 (m, 4H).

^{13}C NMR (125 MHz, CDCl3) δ 174.2, 164.1, 150.4, 136.3, 136.2, 133.3, 128.63, 128.61, 128.22, 128.17, 128.1, 66.6, 66.3, 57.5, 50.8, 47.4, 34.9, 30.9, 25.4.

FT-IR (neat) 2950, 1718, 1636, 1454, 1262, 1164, 1089, 1011 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{24}H_{25}O_4$: 377, found: 377.

$[\alpha]^{25}_D$ = –68 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

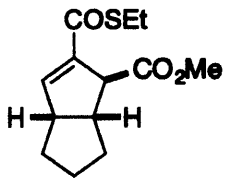


Table 3.2, entry 5. The title compound was prepared according to the general procedure, using methyl (*E*)-10-(ethylthio)-10-oxodeca-2,3,8-trienoate (114 mg, 0.45 mmol), (*S*)-**3.7** (27.0 mg, 0.045 mmol), and toluene (4.50 mL). After purification by flash chromatography (eluted with hexanes→20% Et_2O and 20% acetone in hexanes), the title compound was isolated as a colorless oil (99 mg, 87% yield) with 91% ee.

HPLC analysis of the product: Daicel CHIRALCEL AS-H column; solvent system: 5% 2-propanol in hexanes; 1.0 mL/min; retention times: 6.1 min (minor), 7.5 min (major).

The second run was performed with (*R*)-**3.7**. The product was isolated as a colorless oil (102 mg, 89% yield) with 94% ee.

^{1}H NMR (500 MHz, CDCl3) δ 6.83 (dd, 1H, J = 2.9 Hz, J = 1.5 Hz), 3.73 (s, 3H), 3.68–3.67 (m, 1H), 3.47–3.42 (m, 1H), 2.88 (qd, 2H, J = 7.4 Hz, J = 1.0 Hz), 2.80–2.76 (m, 1H), 1.90–1.85 (m, 1H), 1.78–1.73 (m, 1H), 1.59–1.49 (m, 4H), 1.25 (t, 3H, J = 7.0 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 200.9, 164.6, 151.5, 133.0, 66.0, 51.7, 50.6, 48.1, 34.9, 30.8, 25.2, 23.4, 14.7.

FT-IR (neat) 2950, 1721, 1685, 1437, 1265, 1088, 1023 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{13}H_{19}O_3S$: 255, found: 255.

$[\alpha]^{25}_D$ = –180 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

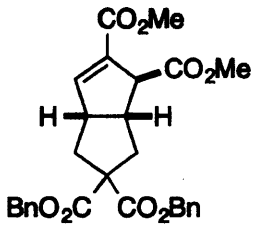


Table 3.2, entry 6. The title compound was prepared according to the general procedure, using 4,4-dibenzyl 1,8-dimethyl (*E*)-octa-1,6,7-triene-1,4,4,8-tetracarboxylate (123 mg, 0.25 mmol), (*S*)-**3.7** (15.0 mg, 0.025 mmol), and toluene (2.50 mL). Reaction temperature: 40 °C. After purification by flash chromatography (eluted with hexanes→40% Et_2OAc in hexanes), the title compound was isolated as a colorless oil (108 mg, 88% yield) with 97% ee.

HPLC analysis of the product: Daicel CHIRALCEL IA column; solvent system: 15% 2-propanol in hexanes; 1.0 mL/min; retention times: 13.2 min (minor), 18.7 min (major).

The second run was performed with (*R*)-**3.7**. The product was isolated as a colorless oil (107 mg, 87% yield) with 97% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.33–7.31 (m, 6H), 7.26–7.22 (m, 4H), 6.76 (dd, 1H, J =2.4 Hz, J = 1.4 Hz), 5.16–5.04 (m, 4H), 3.74 (s, 3H), 3.69 (s, 3H), 3.63–3.61 (m, 1H), 3.59–3.54 (m, 1H), 2.91 (qd, 1H, J = 8.1 Hz, J = 2.5 Hz), 2.68–2.59 (m, 2H), 2.11–2.07 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 173.8, 171.2, 170.6, 164.5, 148.4, 135.50, 135.47, 133.0, 128.71, 128.69, 128.49, 128.46, 128.2, 128.1, 67.53, 67.47, 61.4, 56.0, 52.3, 51.8, 50.0, 46.3, 41.0, 37.8.

FT-IR (neat) 2950, 1730, 1496, 1437, 1240, 1165, 1104, 1027 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{28}H_{29}O_8$: 493, found: 493.

$[\alpha]^{25}_D = -74$ (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

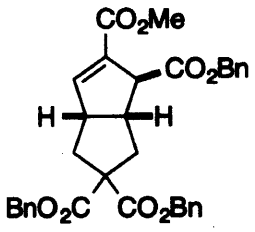


Table 3.2, entry 7. The title compound was prepared according to the general procedure, using 1,4,4-tribenzyl 8-methyl (*E*)-octa-1,6,7-triene-1,4,4,8-tetracarboxylate (142 mg, 0.25 mmol), (*S*)-**3.7** (15.0 mg, 0.025 mmol), and toluene (2.50 mL). After purification by flash chromatography (eluted with hexanes→30% EtOAc in hexanes), the title compound was isolated as a colorless oil (128 mg, 90% yield) with 95% ee.

HPLC analysis of the product: Daicel CHIRALCEL IA column; solvent system: 15% 2-propanol in hexanes; 1.0 mL/min; retention times: 25.9 min (minor), 31.1 min (major).

The second run was performed with (*R*)-**3.7**. The product was isolated as a colorless oil (121 mg, 85% yield) with 94% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.39–7.30 (m, 11H), 7.26–7.22 (m, 4H), 6.76 (dd, 1H, J =2.4 Hz, J = 1.5 Hz), 5.13 (d, 2H, J = 2.7 Hz), 5.12 (d, 2H, J = 4.9 Hz), 5.06 (d, 2H, J = 3.7 Hz), 3.68–3.67 (m, 1H), 3.66 (s, 3H), 3.59–3.54 (m, 1H), 3.00–2.90 (m, 1H), 2.67–2.59 (m, 2H), 2.14–2.09 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 173.2, 171.1, 170.6, 164.4, 148.4, 136.1, 135.5, 133.1, 128.71, 128.69, 128.65, 128.49, 128.46, 128.3, 128.2, 128.12, 128.10, 67.54, 67.48, 66.8, 61.4, 56.3, 51.8, 50.0, 46.3, 41.0, 37.8, 30.5.

FT-IR (neat) 2950, 1729, 1455, 1242, 1165, 1105, 1028 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{34}H_{33}O_8$: 569, found: 569.

$[\alpha]^{25}_D = -68$ (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

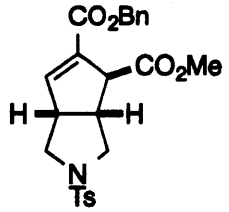


Table 3.2, entry 8. The title compound was prepared according to the general procedure, using methyl (*E*)-5-((*N*-(4-(benzyloxy)-4-oxobut-2-en-1-yl)-4-methylphenyl)sulfonamido)penta-2,3-dienoate (137 mg, 0.30 mmol), (*S*)-**3.7** (18.0 mg, 0.030 mmol), and toluene (3.00 mL). After purification by flash chromatography (eluted with 10% EtOAc in hexanes→30% EtOAc in hexanes), the title compound was isolated as a sticky white solid (131 mg, 96% yield) with 94% ee.

HPLC analysis of the product: Daicel CHIRALCEL IA column; solvent system: 40% 2-propanol in hexanes; 1.0 mL/min; retention times: 13.4 min (minor), 22.1 min (major).

The second run was performed with (*R*)-**3.7**. The product was isolated as a sticky white solid (129 mg, 94% yield) with 93% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.68–7.66 (m, 2H), 7.39–7.30 (m, 7H), 6.66 (t, 1H, *J* =2.0 Hz), 5.13 (d, 2H, *J* =1.6 Hz), 3.70–3.69 (m, 1H), 3.67 (s, 3H), 3.57–3.52 (m, 1H), 3.24–3.16 (m, 3H), 3.08 (dd, 1H, *J* =10.0 Hz, *J* =8.3 Hz), 3.01–2.95 (m, 1H), 2.45 (s, 3H).

^{13}C NMR (125 MHz, CDCl3) δ 172.6, 163.9, 145.5, 144.1, 135.8, 135.3, 129.8, 128.7, 128.4, 128.2, 128.1, 127.3, 67.0, 56.1, 54.5, 51.8, 51.3, 49.8, 45.9, 21.7.

FT-IR (neat) 2950, 1735, 1437, 1346, 1270, 1162, 1013, 663 cm^{-1}.

LRMS (EI) *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{26}NO_6S$: 456, found: 456.

$[\alpha]^{25}_D$ = –58 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

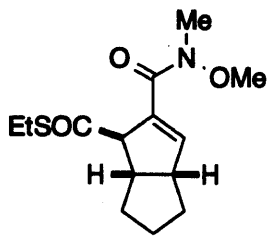


Table 3.3, entry 3. The title compound was prepared according to the general procedure, using *S*-ethyl (*E*)-10-(methoxy(methyl)amino)-10-oxodeca-2,7,8-trienethioate (128 mg, 0.45 mmol), (*S*)-**3.2** (33.0 mg, 0.090 mmol), and toluene (4.50 mL). After purification by flash chromatography (eluted with 20% EtOAc in hexanes→ 40% EtOAc in hexanes), the title compound was isolated as a light yellow oil (82 mg, 64% yield) with 89% ee.

HPLC analysis of the product: Daicel CHIRALCEL AS-H column; solvent system: 10% 2-propanol in hexanes; 1.0 mL/min; retention times: 8.4 min (minor), 10.7 min (major).

The second run was performed with (*S*)-**3.2**. The product was isolated as a light yellow oil (86 mg, 67% yield) with 89% ee.

^{1}H NMR (500 MHz, CDCl3) δ 6.62 (s, 1H), 3.90–3.88 (m, 1H), 3.69 (s, 3H), 3.49–3.44 (m, 1H), 3.26 (s, 3H), 2.93–2.82 (m, 2H), 2.74 (tt, 1H, J = 8.1 Hz, J = 3.7 Hz), 1.91–1.83 (m, 1H), 1.80–1.71 (m, 1H), 1.63–1.49 (m, 4H), 1.25 (t, 3H, J = 7.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 201.2, 165.0, 146.7, 133.7, 68.0, 61.1, 51.2, 46.5, 34.9, 33.3, 31.2, 25.2, 23.4, 14.7.

FT-IR (neat) 2934, 1645, 1418, 1381, 1263, 1019, 799, 744 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{14}H_{22}NO_3S$: 284, found: 284.

$[\alpha]^{25}_D$ = +137 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.2**).

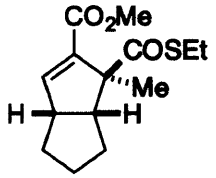


Table 3.4, entry 1. The title compound was prepared according to the general procedure, using methyl (*E*)-10-(ethylthio)-9-methyl-10-oxodeca-2,3,8-trienoate (121 mg, 0.45 mmol), (*S*)-**3.2** (33.0 mg, 0.090 mmol), and toluene (4.50 mL). After purification by flash chromatography (eluted with hexanes→20% Et_2O and 20% acetone in hexanes), the title compound was isolated as a colorless oil (68 mg, 56% yield) with 97% ee.

HPLC analysis of the product: Daicel CHIRALCEL OD-H column; solvent system: 5% 2-propanol in hexanes; 1.0 mL/min; retention times: 5.8 min (minor), 12.3 min (major).

^{1}H NMR (500 MHz, CDCl3) δ 6.90 (d, 1H, J = 2.4 Hz), 3.73 (s, 3H), 3.45–3.40 (m, 1H), 2.88–2.75 (m, 3H), 1.89–1.81 (m, 1H), 1.65–1.49 (m, 5H), 1.47 (s, 3H), 1.22 (t, 3H, J = 7.4 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 204.4, 164.7, 152.3, 137.0, 64.0, 52.7, 51.6, 49.2, 30.7, 29.1, 26.5, 23.6, 17.8, 14.6.

FT-IR (neat) 2951, 1721, 1683, 1436, 1262, 1061, 967, 793 cm^{-1}.

LRMS (EI) m/z (M + H)$^+$ calcd for $C_{14}H_{21}O_3S$: 269, found: 269.

$[\alpha]^{25}_D$ = +192 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.2**).

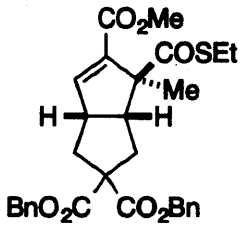


Table 3.4, entry 2. The title compound was prepared according to the general procedure, using 5,5-dibenzyl 1-methyl (*E*)-9-(ethylthio)-8-methyl-9-oxonona-1,2,7-triene-1,5,5-tricarboxylate (97 mg, 0.18 mmol), (*S*)-**3.7** (11.0 mg, 0.018 mmol), and toluene (1.80 mL). Reaction time: 48 h. After purification by flash chromatography (eluted with hexanes→30% EtOAc in hexanes), the title compound was isolated as a colorless oil (90 mg, 93% yield) with 98% ee.

HPLC analysis of the product: Daicel CHIRALCEL OD-H column; solvent system: 10% 2-propanol in hexanes; 1.0 mL/min; retention times: 11.6 min (minor), 16.5 min (major).

The second run was performed with (*R*)-**3.7**. The product was isolated as a colorless oil (89 mg, 92% yield) with 98% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.33–7.31 (m, 6H), 7.26–7.22 (m, 4H), 6.76 (dd, 1H, J =2.4 Hz, J = 1.4 Hz), 5.16–5.04 (m, 4H), 3.74 (s, 3H), 3.69 (s, 3H), 3.63–3.61 (m, 1H), 3.59–3.54 (m, 1H), 2.91 (qd, 1H, J = 8.1 Hz, J = 2.5 Hz), 2.68–2.59 (m, 2H), 2.11–2.07 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 203.4, 171.1, 170.7, 164.4, 150.7, 136.8, 135.5, 128.73, 128.72, 128.51, 128.49, 128.2, 67.6, 67.5, 64.0, 61.5, 51.8, 51.7, 47.9, 37.6, 35.9, 30.5, 23.8, 17.8, 14.5.

FT-IR (neat) 2951, 1724, 1676, 1454, 1238, 1172, 1066, 966 cm^{-1}.

TOF-MS m/z $(M + Na)^+$ calcd for $C_{30}H_{32}O_7SNa$: 559, found: 559.

$[\alpha]^{25}_D = -146$ (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

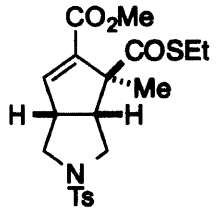


Table 3.4, entry 3. The title compound was prepared according to the general procedure, using methyl (*E*)-5-((*N*-(4-(ethylthio)-3-methyl-4-oxobut-2-en-1-yl)-4-methylphenyl)
sulfonamido)penta-2,3-dienoate (127 mg, 0.30 mmol), (*S*)-**3.2** (11.0 mg, 0.030 mmol), and toluene (3.00 mL). After purification by flash chromatography (eluted with 10% EtOAc in hexanes→30% EtOAc in hexanes), the title compound was isolated as a sticky yellow solid (97 mg, 76% yield) with 94% ee.

HPLC analysis of the product: Daicel CHIRALCEL AD-H column; solvent system: 40% 2-propanol in hexanes; 1.0 mL/min; retention times: 13.2 min (minor), 23.4 min (major).

The second run was performed with (*S*)-**3.2**. The product was isolated as a sticky yellow solid (110 mg, 80% yield) with 94% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.68 (d, 2H, J = 8.0 Hz), 7.35 (d, 2H, J = 8.2 Hz), 6.80 (d, 1H, J = 2.5 Hz), 3.74 (s, 3H), 3.54 (tt, 1H, J = 8.4 Hz, J = 2.8 Hz), 3.38 (dd, 1H, J = 9.5 Hz, J = 3.5 Hz), 3.26 (dd, 1H, J = 10.0 Hz, J = 3.0 Hz), 3.04 (t, 1H, J = 9.4 Hz), 2.97–2.87 (m, 2H), 2.86–2.78 (m, 2H), 2.45 (s, 3H), 1.53 (s, 3H), 1.20 (t, 3H, J = 7.4 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 203.1, 163.8, 147.2, 144.1, 139.6, 131.8, 129.9, 128.2, 63.9, 51.9, 51.4, 50.8, 49.5, 48.3, 23.7, 21.7, 17.7, 14.5.

FT-IR (neat) 2950, 1718, 1675, 1345, 1163, 967 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{20}H_{26}NO_5S_2$: 424, found: 424.

$[\alpha]^{25}_D$ = +97 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.2**).

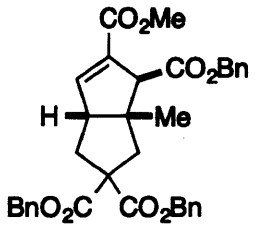


Table 3.4, entry 4. The title compound was prepared according to the general procedure, using 1,4,4-tribenzyl 8-methyl (*E*)-2-methylocta-1,6,7-triene-1,4,4,8-tetracarboxylate (117 mg, 0.20 mmol), (*S*)-**3.6** (7.80 mg, 0.020 mmol), and toluene (2.0 mL). After purification by flash chromatography (eluted with hexanes→30% Et_2OAc in hexanes), the title compound was isolated as a colorless oil (112 mg, 96% yield) with 89% ee.

HPLC analysis of the product: Daicel CHIRALCEL IA column; solvent system: 15% 2-propanol in hexanes; 1.0 mL/min; retention times: 24.5 min (minor), 30.9 min (major).

The second run was performed with (*R*)-**3.6**. The product was isolated as a colorless oil (108 mg, 92% yield) with 90% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.36–7.30 (m, 11H), 7.24–7.22 (m, 4H), 6.71 (dd, 1H, J =2.3 Hz, J = 1.4 Hz), 5.14 (d, 2H, J =2.6 Hz), 5.10 (d, 2H, J =4.1 Hz), 5.03 (s, 2H), 3.75 (dd, 1H, J =2.6 Hz, J = 1.5 Hz), 3.65 (s, 3H), 3.08 (dq, 1H, J =8.5 Hz, J = 2.9 Hz), 2.61–2.56 (m, 2H), 2.42–2.35 (m, 2H), 1.04 (s, 3H).

^{13}C NMR (125 MHz, CDCl3) δ 171.8, 171.7, 171.1, 164.4, 148.6, 136.0, 135.5, 133.6, 128.71, 128.69, 128.65, 128.63, 128.57, 128.51, 128.47, 128.34, 128.31, 128.2, 67.62, 67.60, 66.6, 61.6, 61.2, 58.0, 53.2, 51.7, 49.3, 37.3, 23.4.

FT-IR (neat) 2952, 1730, 1498, 1456, 1332, 1248, 1171, 751 cm^{-1}.

LRMS (EI) m/z $(M + H)^+$ calcd for $C_{35}H_{35}O_8$: 583, found: 583.

$[\alpha]^{25}_D$ = –98 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.6**).

Eq 3.2.3. The title compound was prepared according to the general procedure, using methyl (*E*)-10-(ethylthio)-10-oxodeca-2,3,8-trienoate (123 mg, 0.45 mmol), (*S*)-**3.3** (27.0 mg, 0.045 mmol), and toluene (4.50 mL). After purification by flash chromatography (eluted with hexanes→20% EtOAc in hexanes), the title compound was isolated as a light yellow solid (105 mg, 85% yield) with 96% ee.

HPLC analysis of the product: Daicel CHIRALCEL OJ-H column; solvent system: hexanes; 1.0 mL / min; retention times: 34.5 min (major), 51.2 min (minor).

The second run was performed with (*R*)-**3.3**. The product was isolated as a yellow solid (109 mg, 88% yield) with 95% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.29–7.23 (m, 2H), 7.16 (td, 1H, *J* =7.5 Hz, *J* = 1.5 Hz), 7.09 (dd, 1H, *J* =8.0 Hz, *J* = 1.5 Hz), 6.91 (q, 1H, *J* = 5 Hz), 4.65 (q, 1H, *J* =5.0 Hz), 3.69 (q, 1H, *J* =10 Hz), 3.10–3.03 (m, 3H), 2.98–2.94 (m, 1H), 1.36 (t, 3H, *J* = 7.7 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 200.1, 160.1, 150.9, 142.4, 130.7, 128.7, 126.3, 125.8, 125.1, 117.4, 60.5, 45.6, 38.6, 24.0, 14.8.

FT-IR (neat) 2929, 1754, 1678, 1452, 1222, 1180, 1069, 967, 756 cm^{-1}.

LRMS (EI) *m* / *z* (M + H)$^+$ calcd for $C_{15}H_{15}O_3S$: 275, found: 275.

$[\alpha]^{25}_D$ = –114 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.3**).

Eq 3.2.4. The title compound was prepared according to the general procedure, using methyl (*E*)-3-(2-(*N*-methylbuta-2,3-dienamido)phenyl)acrylate (116 mg, 0.45 mmol), (*S*)-**3.7** (54.0 mg, 0.090 mmol), and toluene (9.0 mL). After purification by flash

chromatography (eluted with 20% EtOAc in hexanes→50% EtOAc in hexanes), the title compound was isolated as a white solid (107 mg, 92% yield) with 70% ee.

HPLC analysis of the product: Daicel CHIRALCEL AD-H column; solvent system: 20% 2-propanol in hexanes; 1.0 mL/min; retention times: 9.1 min (major), 13.8 min (minor).

^{1}H NMR (500 MHz, CDCl3) δ 7.30–7.25 (m, 2H), 7.09 (td, 1H, J = 7.7 Hz, J = 0.9 Hz), 7.0 (d, 1H, J = 7.9 Hz), 6.67 (q, 1H, J = 2.8 Hz), 4.50–4.46 (m, 1H), 3.85 (s, 3H), 3.49 (q, 1H, J = 9.0 Hz), 3.41 (s, 3H), 3.01–2.87 (m, 2H).

^{13}C NMR (125 MHz, CDCl3) δ 175.1, 162.0, 139.6, 136.8, 134.6, 128.5, 127.8, 125.9, 123.4, 114.9, 52.6, 51.1, 47.1, 37.1, 29.7.

FT-IR (neat) 2951, 1733, 1661, 1600, 1456, 1353, 1276, 1218, 755 cm^{-1}.

LRMS (EI) m/z (M + H)$^+$ calcd for $C_{15}H_{16}NO_3$: 258, found: 258.

$[\alpha]^{25}_D$ = –80 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

Eq 3.2.5. The title compound was prepared according to the general procedure, using methyl (*E*)-3-(2-(*N*-methylbuta-2,3-dienamido)phenyl)but-2-enoate (122 mg, 0.45 mmol), (*S*)-**3.7** (27.0 mg, 0.045 mmol), and toluene (4.50 mL). After purification by flash chromatography (eluted with 10% EtOAc in hexanes→50% EtOAc in hexanes), the title compound was isolated as a white solid (109 mg, 89% yield) with 90% ee.

HPLC analysis of the product: Daicel CHIRALCEL AD-H column; solvent system: 20% 2-propanol in hexanes; 1.0 mL/min; retention times: 6.3 min (major), 7.7 min (minor).

The second run was performed with (*R*)-**3.7**. The product was isolated as a white solid (112 mg, 92% yield) with 90% ee.

^{1}H NMR (500 MHz, CDCl3) δ 7.90 (dd, 1H, J =7.8 Hz, J = 1.5 Hz), 7.30–7.27 (m, 1H), 7.13 (td, 1H, J =7.6 Hz, J = 1.2 Hz), 7.01 (dd, 1H, J =8.2 Hz, J = 1.1 Hz), 6.66 (dd, 1H,

J =3.3 Hz, J = 2.1 Hz), 3.87 (s, 3H), 3.71 (t, 1H, J = 9.5 Hz), 3.42 (s, 3H), 3.18 (ddd, 1H, J = 18.6 Hz, J = 9.7 Hz, J = 2.1 Hz), 2.76 (ddd, 1H, J = 18.5 Hz, J = 8.9 Hz, J = 3.1 Hz), 1.25 (s, 3H).

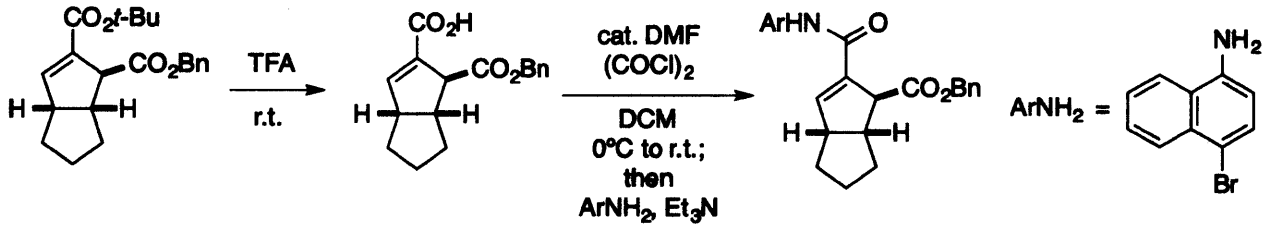
^{13}C NMR (125 MHz, CDCl3) δ 173.4, 161.8, 139.6, 138.5, 136.2, 135.0, 127.7, 126.1, 123.7, 115.0, 54.7, 52.2, 51.0, 34.7, 29.6, 24.0.

FT-IR (neat) 2952, 1732, 1661, 1599, 1447, 1355, 1277, 1204, 756 cm^{-1}.

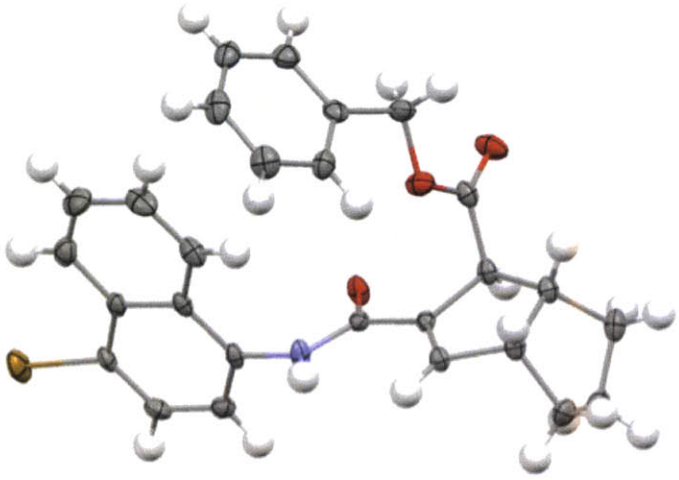
LRMS (EI) m/z (M + H)$^+$ calcd for $C_{16}H_{18}NO_3$: 272, found: 272.

$[\alpha]^{25}_D$ = +13 (c = 1.0, $CHCl_3$; obtained with (*S*)-**3.7**).

V. Assignment of the Absolute Stereochemistry



Benzyl (1*S*,3a*S*,6a*R*)-2-((4-bromonaphthalen-1-yl)carbamoyl)-1,3a,4,5,6,6a-hexa hydropentalene-1-carboxylate (derived from the product of Table 3.2, entry 3). 1-Benzyl 2-(*tert*-butyl) (1*S*,3a*S*,6a*R*)-1,3a,4,5,6,6a-hexahydropentalene-1,2-dicarboxylate (17 mg, 0.05 mmol; 98% ee, obtained with (*S*)-**3.7**) was treated with TFA (0.5 mL), and this mixture was stirred at r.t. for 12 h. Toluene (2 mL) was added to the mixture, which was then concentrated under reduced pressure. The residue was added to a 4-mL vial which was then evacuated and back-filled with nitrogen (three cycles). CH_2Cl_2 (0.5 mL) and a drop of dimethylformamide were added via syringe in turn. The mixture was cooled to 0 °C, and then oxalyl chloride (5 μL) was added. This mixture was stirred at r.t. for 1 h. Next, Et_3N (11 μL) and 4-bromonaphthalen-1-amine (10 mg) were added. This mixture was stirred at r.t. for 16 h and then concentrated under reduced pressure. The residue was purified by preparative TLC, which furnished the product as a off-white crystalline solid. X-ray quality crystals were grown from CH_2Cl_2/pentane. The absolute stereochemistry was assigned by X-ray crystallography.



A suitable crystal of $C_{27}H_{24}BrNO_3$ was selected for analysis. All measurements were made on a Bruker APEX-II CCD with filtered Mo-Kα radiation at a temperature of 100 K. Using Olex2,[1] the structure was solved with the ShelXS[2] structure solution program using Direct Methods and refined with the ShelXL[2] refinement package using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

1. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J Appl Crystallogr* **2009**, *42*, 339.
2. Sheldrick, G. M. *Acta Crystallogr A* **2008**, *64*, 112.

Table 1. Crystal data and structure refinement for a14003.

Identification code	a14003	
Empirical formula	$C_{27}H_{24}BrNO_3$	
Formula weight	490.38	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P\ 2_12_12_1$	
Unit cell dimensions	a = 9.6703(10) Å	α = 90°.
	b = 9.7969(10) Å	β = 90 °.
	c = 23.238(2) Å	γ = 90 °.
Volume	2201.5(4) $Å^3$	

Z	4
Density (calculated)	1.480 Mg/m^3
Absorption coefficient	1.897 mm^{-1}
F(000)	1008
Crystal size	0.2 x 0.12 x 0.1 mm^3
Theta range for data collection	1.753 to 27.539°.
Index ranges	-12<=h<=10, -12<=k<=12, -30<=l<=30
Reflections collected	46998
Independent reflections	5069 [R(int) = 0.0459]
Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7456 and 0.6559
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5069 / 0 / 289
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0282, wR2 = 0.0652
R indices (all data)	R1 = 0.0338, wR2 = 0.0668
Absolute structure parameter (Flack)	0.012(3)
Largest diff. peak and hole	0.684 and -0.273 $e/Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for a14003. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	-701(1)	-8476(1)	-229(1)	32(1)
O(1)	-508(2)	-7325(2)	2600(1)	22(1)
O(2)	-2555(2)	-6488(2)	3925(1)	30(1)
O(3)	-2723(2)	-8665(2)	3637(1)	26(1)
N(1)	-68(3)	-9504(2)	2348(1)	21(1)
C(1)	-499(3)	-7848(2)	3809(1)	16(1)
C(2)	-59(3)	-8873(3)	3358(1)	15(1)

C(3)	430(3)	-10019(3)	3581(1)	17(1)
C(4)	484(3)	-9988(3)	4231(1)	20(1)
C(5)	-104(3)	-8556(3)	4392(1)	19(1)
C(6)	1058(3)	-7841(3)	4719(1)	26(1)
C(7)	2370(3)	-8507(4)	4493(1)	33(1)
C(8)	1980(3)	-10014(3)	4465(1)	30(1)
C(9)	-221(3)	-8502(3)	2738(1)	16(1)
C(10)	-2020(3)	-7548(3)	3795(1)	19(1)
C(11)	-4207(3)	-8580(3)	3660(1)	26(1)
C(12)	-4786(3)	-9764(3)	3330(1)	22(1)
C(13)	-4131(3)	-11024(3)	3321(1)	25(1)
C(14)	-4714(3)	-12115(3)	3040(1)	31(1)
C(15)	-5957(3)	-11963(3)	2749(1)	30(1)
C(16)	-6593(3)	-10714(3)	2745(1)	29(1)
C(17)	-6019(3)	-9611(3)	3035(1)	26(1)
C(18)	-244(3)	-9255(3)	1745(1)	17(1)
C(19)	841(3)	-8794(3)	1425(1)	21(1)
C(20)	680(3)	-8562(3)	830(1)	22(1)
C(21)	-562(3)	-8781(3)	579(1)	18(1)
C(22)	-1735(3)	-9242(3)	888(1)	18(1)
C(23)	-1546(3)	-9510(3)	1490(1)	17(1)
C(24)	-2676(3)	-10035(3)	1808(1)	25(1)
C(25)	-3926(3)	-10247(3)	1552(1)	31(1)
C(26)	-4111(3)	-9957(3)	963(1)	32(1)
C(27)	-3045(3)	-9469(3)	643(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for a14003.

Br(1)-C(21)	1.907(2)
O(1)-C(9)	1.229(3)
O(2)-C(10)	1.199(3)
O(3)-C(10)	1.339(3)
O(3)-C(11)	1.438(3)

N(1)-C(9)	1.345(3)
N(1)-C(18)	1.433(3)
C(1)-C(2)	1.513(3)
C(1)-C(5)	1.569(3)
C(1)-C(10)	1.501(4)
C(2)-C(3)	1.325(4)
C(2)-C(9)	1.493(3)
C(3)-C(4)	1.510(3)
C(4)-C(5)	1.559(4)
C(4)-C(8)	1.546(4)
C(5)-C(6)	1.528(4)
C(6)-C(7)	1.521(4)
C(7)-C(8)	1.525(5)
C(11)-C(12)	1.500(4)
C(12)-C(13)	1.387(4)
C(12)-C(17)	1.383(4)
C(13)-C(14)	1.374(4)
C(14)-C(15)	1.387(5)
C(15)-C(16)	1.370(5)
C(16)-C(17)	1.389(4)
C(18)-C(19)	1.362(4)
C(18)-C(23)	1.413(4)
C(19)-C(20)	1.409(3)
C(20)-C(21)	1.352(4)
C(21)-C(22)	1.416(4)
C(22)-C(23)	1.437(3)
C(22)-C(27)	1.407(4)
C(23)-C(24)	1.415(4)
C(24)-C(25)	1.362(4)
C(25)-C(26)	1.410(4)
C(26)-C(27)	1.358(4)

C(10)-O(3)-C(11)	116.6(2)
C(9)-N(1)-C(18)	121.5(2)
C(2)-C(1)-C(5)	103.7(2)
C(10)-C(1)-C(2)	113.0(2)

C(10)-C(1)-C(5)	110.1(2)
C(3)-C(2)-C(1)	113.0(2)
C(3)-C(2)-C(9)	128.5(2)
C(9)-C(2)-C(1)	118.5(2)
C(2)-C(3)-C(4)	112.8(2)
C(3)-C(4)-C(5)	104.2(2)
C(3)-C(4)-C(8)	112.5(2)
C(8)-C(4)-C(5)	105.8(2)
C(4)-C(5)-C(1)	106.18(19)
C(6)-C(5)-C(1)	113.9(2)
C(6)-C(5)-C(4)	105.3(2)
C(7)-C(6)-C(5)	104.2(2)
C(6)-C(7)-C(8)	102.9(2)
C(7)-C(8)-C(4)	103.3(2)
O(1)-C(9)-N(1)	122.2(2)
O(1)-C(9)-C(2)	120.3(2)
N(1)-C(9)-C(2)	117.5(2)
O(2)-C(10)-O(3)	123.9(3)
O(2)-C(10)-C(1)	125.9(2)
O(3)-C(10)-C(1)	110.1(2)
O(3)-C(11)-C(12)	107.9(2)
C(13)-C(12)-C(11)	121.7(3)
C(17)-C(12)-C(11)	119.4(3)
C(17)-C(12)-C(13)	118.9(3)
C(14)-C(13)-C(12)	120.8(3)
C(13)-C(14)-C(15)	120.3(3)
C(16)-C(15)-C(14)	119.2(3)
C(15)-C(16)-C(17)	120.8(3)
C(12)-C(17)-C(16)	120.0(3)
C(19)-C(18)-N(1)	119.9(2)
C(19)-C(18)-C(23)	121.1(2)
C(23)-C(18)-N(1)	119.0(2)
C(18)-C(19)-C(20)	120.2(3)
C(21)-C(20)-C(19)	119.7(2)
C(20)-C(21)-Br(1)	117.60(19)
C(20)-C(21)-C(22)	122.9(2)

C(22)-C(21)-Br(1)	119.5(2)
C(21)-C(22)-C(23)	116.8(2)
C(27)-C(22)-C(21)	124.6(2)
C(27)-C(22)-C(23)	118.6(3)
C(18)-C(23)-C(22)	119.2(2)
C(18)-C(23)-C(24)	122.3(2)
C(24)-C(23)-C(22)	118.4(3)
C(25)-C(24)-C(23)	120.9(3)
C(24)-C(25)-C(26)	120.3(3)
C(27)-C(26)-C(25)	120.4(3)
C(26)-C(27)-C(22)	121.2(3)

3.5. ^{1}H NMR Spectra of Selected Compounds

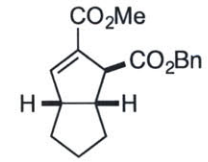
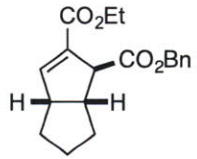


Table 3.2, entry 1



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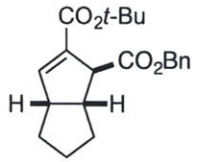


Table 3.2, entry 3

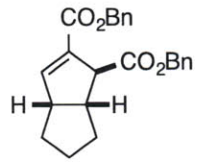
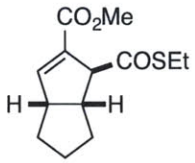


Table 3.2, entry 4



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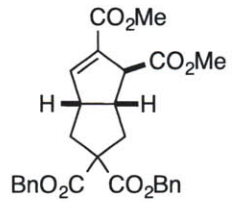

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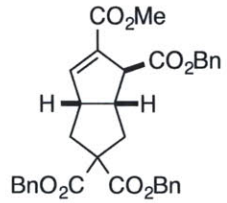

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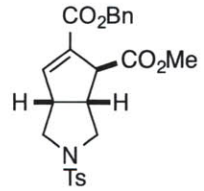
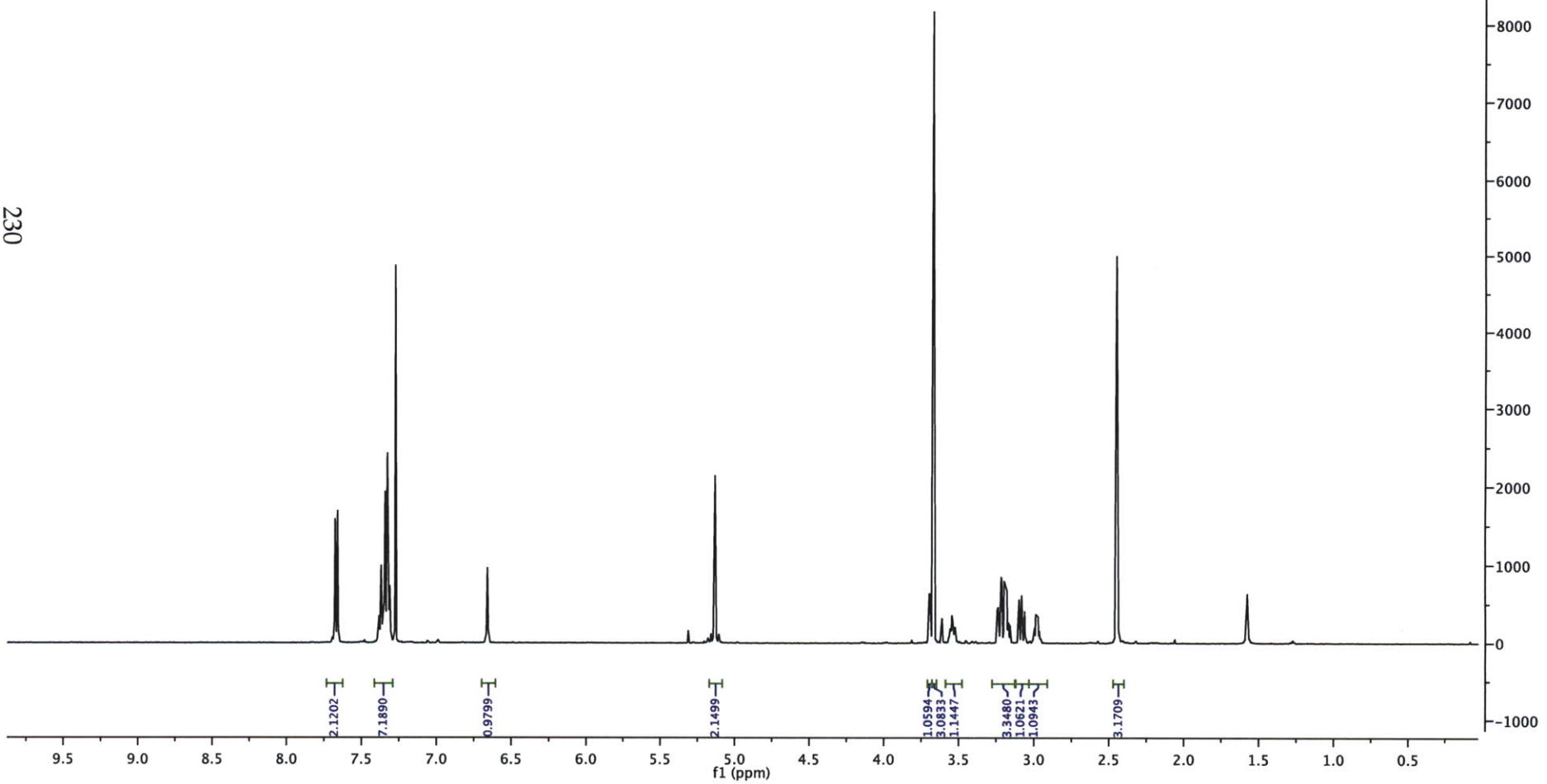


Table 3.2, entry 8



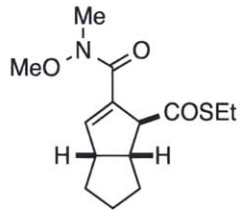


Table 3.3, entry 3

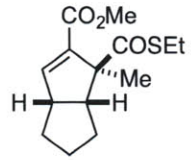
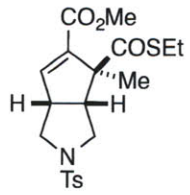


Table 3.4, entry 1

Table 3.4, entry 2



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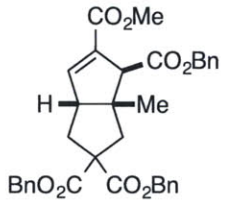
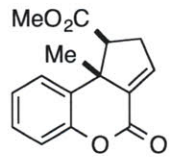
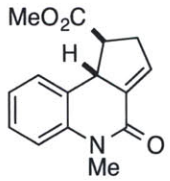


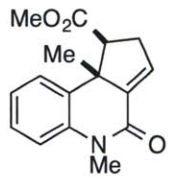
Table 3.4, entry 4



eq 3.2.3



eq 3.2.4


MeO2C
Me
N
Me
O

eq 3.2.5

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0.7656
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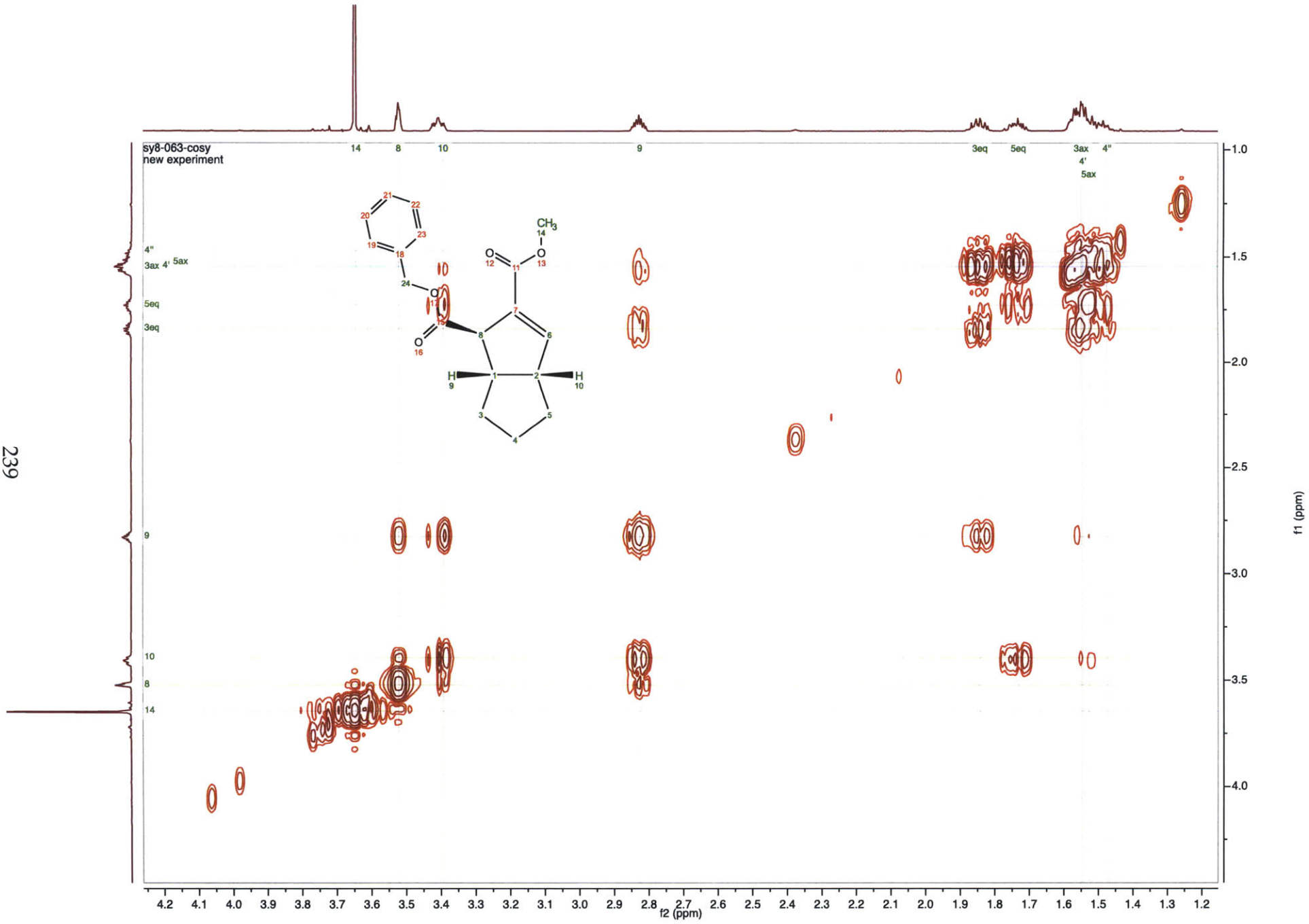
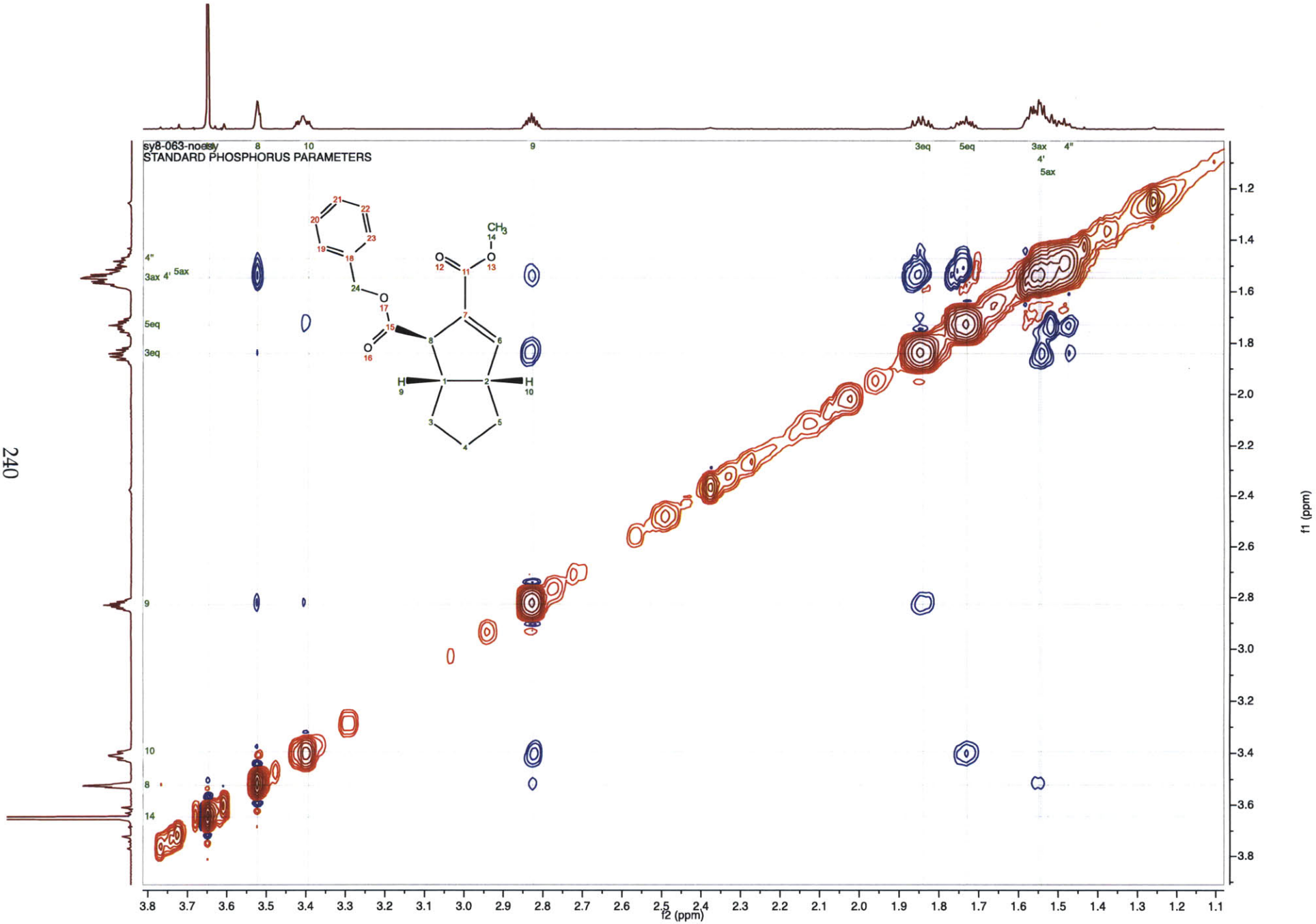
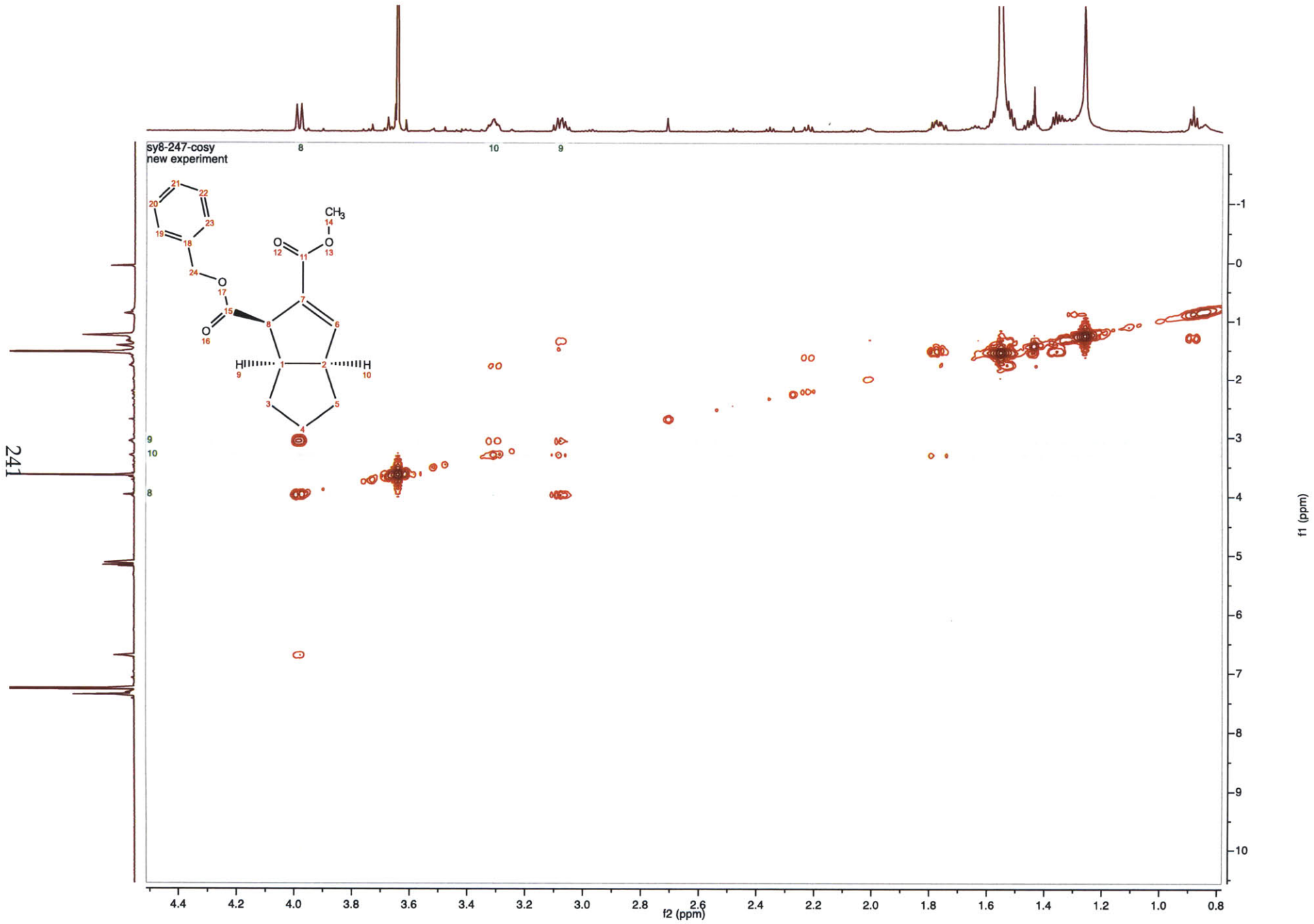
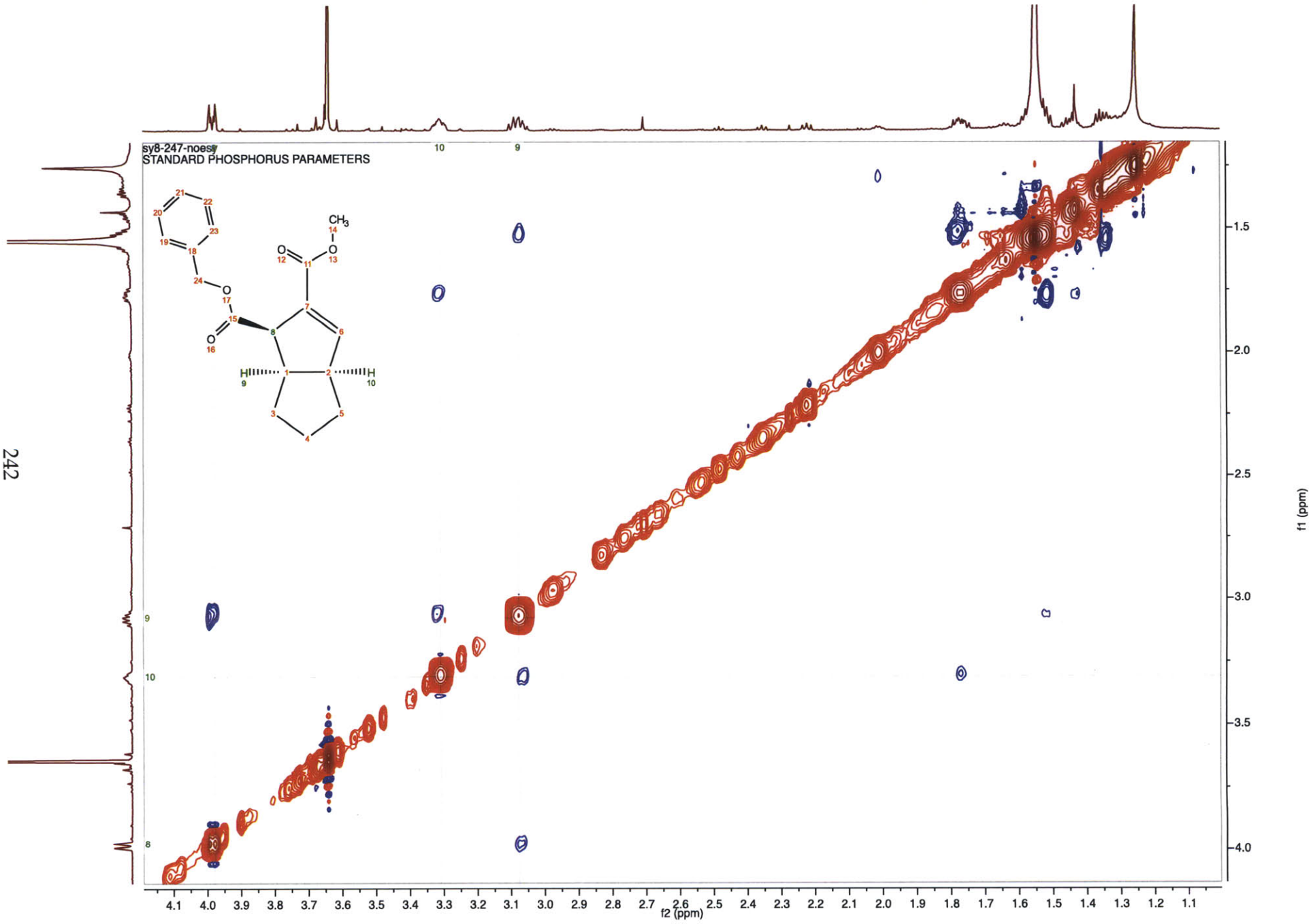
3.0357
1.0720
3.1499
1.1278
1.1098
f1 (ppm)


sy8-063-cosy
new experiment
14
8
10
9
3eq
5eq
3ax
4'
4"
5ax
4"
3ax 4' 5ax
5eq
3eq
9
10
8
14
f2 (ppm)
f1 (ppm)


sy8-063-noesy
STANDARD PHOSPHORUS PARAMETERS
f2 (ppm)
f1 (ppm)


sy8-247-cosy
new experiment
8
10
9
f2 (ppm)
f1 (ppm)


sy8-247-noesy
STANDARD PHOSPHORUS PARAMETERS
f2 (ppm)
f1 (ppm)

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Education

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- **Korea Advanced Institute of Science and Technology,** B.S., Chemistry (*Summa Cum Laude*), 2009

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2009 – 2012	**Research Assistant with Professor Gregory C. Fu**
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2008 – 2009	**Undergraduate Researcher with Professor Sukbok Chang**
	Korea Advanced Institute of Science and Technology (KAIST)

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2009 Fall	**Teaching Assistant**, Biochemistry and Organic Laboratory, MIT

Honors and Awards

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2010	**Outstanding Graduate Student Teaching Award**, Department of Chemistry, MIT
2009 – 2010	**Moore Fellowship**, Department of Chemistry, MIT
2009	**Excellence Award**, Undergraduate Research Program, KAIST
2005 – 2009	**Merit-Based Academic Scholarship**, KAIST

Publications

1. **Lee, S. Y.**; Neufeind, S.; Fu, G. C. "Enantioselective Nucleophile-Catalyzed Synthesis of Tertiary Alkyl Fluorides via the α-Fluorination of Ketenes: Synthetic and Mechanistic Studies" *J. Am. Chem. Soc.* **2014**, *136,* 8899–8902.
2. **Lee, S. Y.**; Murphy, J. M.; Ukai, A.; Fu, G. C. "Nonenzymatic Dynamic Kinetic Resolution of Secondary Alcohols via Enantioselective Acylation: Synthetic and Mechanistic Studies" *J. Am. Chem. Soc.* **2012**, *134,* 15149–15153.

(Highlights in Angewandte: Díaz-Álvarez, A. E.; Mesas-Sánchez, L.; Dinér, P. "Non-Enzymatic Dynamic Kinetic Resolution of Secondary Aryl Alcohols: Planar Chiral Ferrocene and Ruthenium Catalysts in Cooperation" *Angew. Chem., Int. Ed.* **2013**, *52*, 502–504.*)*

3. Cho, S. H.; Kim, J. Y.; **Lee, S. Y.**; Chang, S. "Silver-Mediated Direct Amination of Benzoxazoles: Tuning the Amino Group Source from Formamides to Parent Amines" *Angew. Chem., Int. Ed.* **2009**, *48*, 9127–9130. (*Hot paper*)
4. Kim, J.; **Lee, S. Y.**; Lee, J.; Do, Y.; Chang, S. "Synthetic Utility of Ammonium Salts in the Cu-Catalyzed Three-Component Reaction as a Facile Coupling Partner" *J. Org. Chem.* **2008**, *73,* 9454–9457.

Presentations

1. "Asymmetric Catalysis with Ferrocene Based Planar-Chiral DMAP Derivatives: Synthetic and Mechanistic Studies" *Caltech Inorganic-Organometallics Seminar,* Pasadena, CA, United States, November 1, **2013**. (*Oral presentation*)
2. "Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides by α-Fluorinations of Ketenes: Synthetic and Mechanistic Studies" *Caltech Chemistry & Chemical Engineering Student Seminar Day*, Pasadena, CA, United States, October 4, **2013**. (*Oral presentation*)
3. "Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides by α-Fluorinations of Ketenes: Synthetic and Mechanistic Studies" *43rd National Organic Chemistry Symposium*, Seattle, WA, United States, June 23–27, **2013**. (*Poster presentation*)
4. "Asymmetric Catalysis with Planar-Chiral DMAP Derivatives" *MIT Chemistry Graduate Research Symposium*, Cambridge, MA, United States, May 29, **2013**. (*Oral presentation*)
5. "Nonenzymatic Dynamic Kinetic Resolution of Alcohols Catalyzed by Planar-Chiral DMAP Derivatives" *243rd ACS National Meeting,* San Diego, CA, United States, March 25–29, **2012**. (*Oral presentation*)