Enantioselective Reactions of Silyl Ketene Acetals and Silyl Ketene Imines Catalyzed by Planar-Chiral Heterocycles

by

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B.S., College Honors, Applied Mathematics
University of California, Los Angeles, CA, 1999

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Submitted to the Department of
Chemistry in Partial Fulfillment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

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Massachusetts Institute of Technology
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ABSTRACT

The enantioselective C-acylation of cyclic silyl ketene acetals was achieved catalytically by employing planar-chiral heterocycles derived from 4-(pyrrolidino)pyridine. Key mechanistic features of this process involve activation of both the electrophile (acylating agent → acylpyridinium) and the nucleophile (silyl ketene acetal → enolate). This process accomodates a wide variety of aryl- and heteroaryl-substituted silyl ketene acetals, furnishing quaternary stereocenters with enantioselectivities up to 99%.

Further investigation of this process revealed that acyclic disubstituted silyl ketene acetals can also participate in this nucleophile-catalyzed process, furnishing enantioselectivities up to 97%. Isomeric mixtures of silyl ketene acetals are efficiently converted into the same enantiomer of the product β-ketoester, rendering this a stereoconvergent catalytic C-acylation process.

Silyl ketene imines were also shown to be suitable reaction partners in this catalytic enantioselective C-acylation reaction, affording nitriles bearing an adjacent quaternary stereocenter with enantioselectivies up to 83%. This process is also believed to proceed via activation of the electrophile (acylating agent → acylpyridinium) and the nucleophile (silyl ketene imine → nitrile anion), which is in direct analogy to the process developed for silyl ketene acetals. Application of this transformation to the enantioselective total synthesis of (*S*)-Verapamil was successfully achieved in 8 steps and 25% overall yield from commercially available 3,4-dimethoxyphenylacetonitrile. The key bond construction in this total synthesis involved enantioselective construction of the quaternary stereocenter via a catalytic C-acylation of a silyl ketene imine.

Thesis Supervisor: Gregory C. Fu
Title: Professor of Chemistry

ACKNOWLEDGMENTS

During the course of my education, I became increasingly aware that whatever success I achieved, or opportunities I was presented with were largely due to the efforts certain key individuals. This dissertation would not be as meaningful to me without acknowledging the people who played such a prominent role in my personal and professional maturity.

From my infancy to age 22, my grandmother, Mrs. Sultan B. Mermerian embodied the terms perseverance and tenacity. Having lost both her parents and her brother at a very young age, my grandmother had to learn very many of life's lessons in an orphanage. She amazed her mentors with the skills she acquired and the diligence she displaying in any tasks in which she engaged. Without parental figures in her life, she successfully assumed the role as mother and wife. In 1976, she immigrated to the United States and immediately became an integral part of my childhood development. My grandmother always taught me to be grateful for anything that I achieved, as it was a blessing from God. Her lifelong sacrifice has truly been an inspiration to me, as I could never envision living through the set of circumstances she overcame. While her passing in 1998 marked the end of her physical existence, the inspiration she left me with will never die.

Throughout high school, my guidance counselor, the late Mrs. Joyce R. Bryson, inspired me to assert myself in my academic endeavors. Her tireless efforts to promote my future education and unending encouragement helped me emerge from high school with the prospects of a prestigious college education at UCLA. While high school was a difficult time for me, both academically and emotionally, I emerged with great success, largely due to Mrs. Bryson.

As an undergraduate at UCLA, I was fortunate to have been part of a community that was so ambitious and academically driven. The transition from a small private Christian high school to an institution that has its own zip code was not easy. However, finding my professional niche was facilitated greatly by two people to whom I am indebted. Professor Michael Jung's creative and inspiring teaching style made me appreciate organic chemistry. At a time where I was stuck in an unsatisfying major, his class made me realize that I had the makings of an organic chemist, and hence pursued my passions accordingly. An even more significant figure in my scientific development was Professor Craig A. Merlic who graciously provided me with a position in his own research group and entrusted me with a highly sophisticated project. Craig Merlic was not only a great teacher, but also a great mentor in general. He had tremendous faith in me, and motivated me to work to my potential at all times. I know his endorsement of my abilities served as a critical factor in my acceptance to graduate school at MIT.

During my five years as a graduate student at MIT, there was one figure that probably had the most visible effect on my growth as a scientist: Professor Gregory C. Fu. The one lesson I valued the most, and will carry on into my future scientific career, is to always be on a steep slope of one's learning curve. Greg instilled in me the importance of questioning and understanding any piece of data one obtains empirically. I

truly feel blessed to have had a man who is so dedicated and concerned about his students' scientific development play a major role in my education. In addition, I am also fortunate to have been surrounded by such a talented group of colleagues in the Fu group. From this group, I owe a special thanks to Wade Downey and Ryan Wurz for their efforts in proofreading my thesis. I cannot thank them enough for their contributions toward the refinement of this document.

While a number of people were responsible for my development as a professional, I cannot neglect those who played a significant role in my personal growth. I am indebted to Michael Seeger, Leann Prentiss, Stan Zanarotti, Christopher Norris, Drew Bartley, and Paul Martinek for their continual friendship and their emotional nurturing of me during my less glamorous moments. I know that I can always count on these individuals for emotional support when things are at their worst. These people will always have a special meaning in my life, as they befriended me with no reservation and were present at a time where I was in need of emotional nurturing. I especially thank Christopher, Drew, and Paul for providing balance in my life during the last two years, as well as engaging in highly pivotal discussions about Laura Branigan and Melissa Manchester.

Finally, the three people who by far were the most instrumental in my personal and professional development are my sister Talin and my parents. First, I owe much to my sister Talin. She has always been a positive influence in my life, and gives of herself to anything she does. If there is one person in life that I can turn to who knows me best, it is she. I know that whenever I have a problem, she's there with abundant empathy to help me deal with it.

This brings me to acknowledge the people who gave me life and taught me how to make the most of it, namely my parents. Without any formal education, they both aspired to achieve professional success as a means to promoting my education (and that of my sister) and through it all instilled in me the important value of self-integrity. I cannot begin to thank my parents for all of their love-borne sacrifice and devotion to my growth as an individual. Every good thing that has come, or will come, my way has been, and will be, the product of my parent's efforts. They are not only great providers, but also outstanding teachers. Despite the many years of schooling that I have been through, I still think that the most intelligent people that I know are and will unequivocally be my parents, as they possess the unquantifiable wisdom of experience.

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ABBREVIATIONS

Ac	acetyl
app	apparent (^{1}H NMR splitting pattern default)
Br	bromo or bromide
Bz	benzoyl
Cp	cyclopentadienyl
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
DABCO	1,4-diaza-bicyclo[2.2.2]octane
DMAP	4-(dimethylamino)pyridine
d	doublet
dq	doublet of quartets
EtI	iodoethane
eq	equation
equiv	equivalent(s)
GC	gas chromatography
h	hour(s)
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared
LDA	lithium diisopropylamide
MeMgBr	methyl magnesium bromide
NMR	nuclear magnetic resonance
ppm	parts per million
PPY	4-(pyrrolidino)pyridine
q	quartet
r.t.	room temperature
sept	septet
t	triplet
TBS	*t*-butyldimethylsilyl
TMS	trimethylsilyl
TBSCl	*t*-butyldimethylsilyl chloride
TMSCl	chlorotrimethylsilane
TLC	thin-layer chromatograpy
wt.	Weight percentage.

Portions of this document have appeared or will appear in the following publications:

1) Mermerian, A. H.; Fu, G. C. Generation of All-Carbon Quaternary Stereocenters via Catalytic Asymmetric Acylations of Silyl Ketene Imines. Application to the Enantioselective Synthesis of Verapamil. *Angew. Chem., Int. Ed.* **2004**, *submitted.*

2) Mermerian, A. H.; Fu, G. C. Catalytic Enantioselective Synthesis of Quaternary Stereocenters via Intermolecular C-Acylation of Silyl Ketene Acetals: Dual Activation of the Electrophile and the Nucleophile. *J. Am. Chem. Soc.* **2003**, *125*, 4050-4051.

To Mom and Dad, with all my love

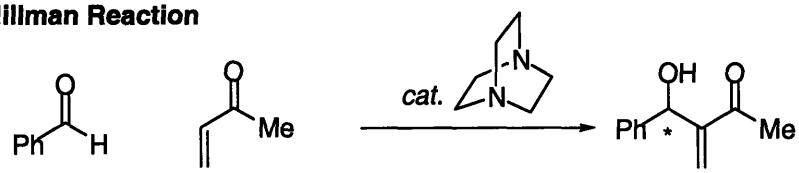
Chapter 1

Catalytic Enantioselective Synthesis of Quaternary Stereocenters via Intermolecular C-Acylation of Cyclic Silyl Ketene Acetals: Dual Activation of the Electrophile and the Nucleophile

Part A. Introduction to Nucleophilic Catalysis with Planar-Chiral Heterocycles

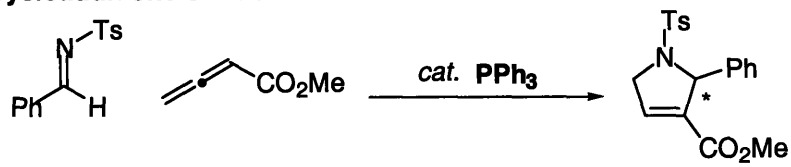
Although processes catalyzed by Lewis acids have been intensively investigated, corresponding reactions of Lewis bases have not received the same level of attention.[1] While attempts to develop enantioselective nucleophile-catalyzed processes have surfaced in recent years, this area remains relatively unexplored.[2] Many nucleophile-catalyzed processes are controlled by compounds that contain a nitrogen or phosphorus heteroatom. Examples include the catalytic use of DABCO in Baylis-Hillman reactions (1A.1),[3] the triphenylphosphine-catalyzed [3+2] cycloadditions of allenic esters with imines (1A.2),[4] and the acylation of secondary alcohols catalyzed by DMAP (1A.3).[5] In the first two examples, the catalyst has the ability to establish a new stereogenic center, while in the last example, the catalyst can effect a kinetic resolution of a racemic mixture of secondary alcohols.

Baylis-Hillman Reaction



(1A.1)

[3 + 2] Cycloadditions of Allenes with Imines



(1A.2)

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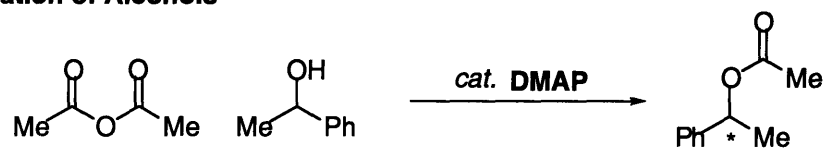
[1] For a comprehensive overview of Lewis acid-catalyzed processes, see: *Lewis Acids in Organic Synthesis*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000.

[2] For reviews, see: (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. Chem. Rev. 2003, 103, 2985-3012. (b) Spivey, A. C.; Maddaford, A. *Org. Prep. Proced. Int.* **2000**, *32*, 331-365.

[3] For representative accounts, see: (a) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007-5010. (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653-4670.

[4] (a) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031-5041. (b) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461-3464.

Acylation of Alcohols



(1A.3)

Nitrogen- and phosphorus-based nucleophilic catalysts have received considerable attention largely because asymmetric variants of such species are readily accessed. Examples of this are shown in Figure 1A.4, which classifies these compounds into two major categories. The first class is one in which the nucleophilic atom is sp^3 hybridized. Representative examples are Oriyama's proline-derived ligand **1.31**[6] and Vedejs's P-chiral bicyclic phosphine **1.32**,[7] which have both been employed in the kinetic resolution of secondary alcohols. Bicyclic catalyst **1.33** was utilized by Hatakeyama for enantioselective Baylis-Hillman reactions.[8]

The second class of chiral nucleophiles, consisting of nucleophilic catalysts containing an sp^2-hybridized nucleophilic atom, are exemplified by catalyst **1.34**, which was shown by Vedejs to effect the rearrangement of O-acylated enolates.[9] Spivey's biaryl catalyst **1.35** and Campbell's PPY-derived **1.36** were both used in the kinetic resolution of secondary alcohols.[10,11] One distinguishing feature of this class of catalysts includes the fact the nucleophilic atom is not itself a stereogenic center. In addition, placement of chiral information close to the site of nucleophilicity is more readily achieved in the sp^3-hybridized class of catalysts, implying that construction of an *effective* sp^2-hybridized nucleophilic catalyst poses a greater design challenge.

---

[5] Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.

[6] Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265-266.

[7] Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813-5814.

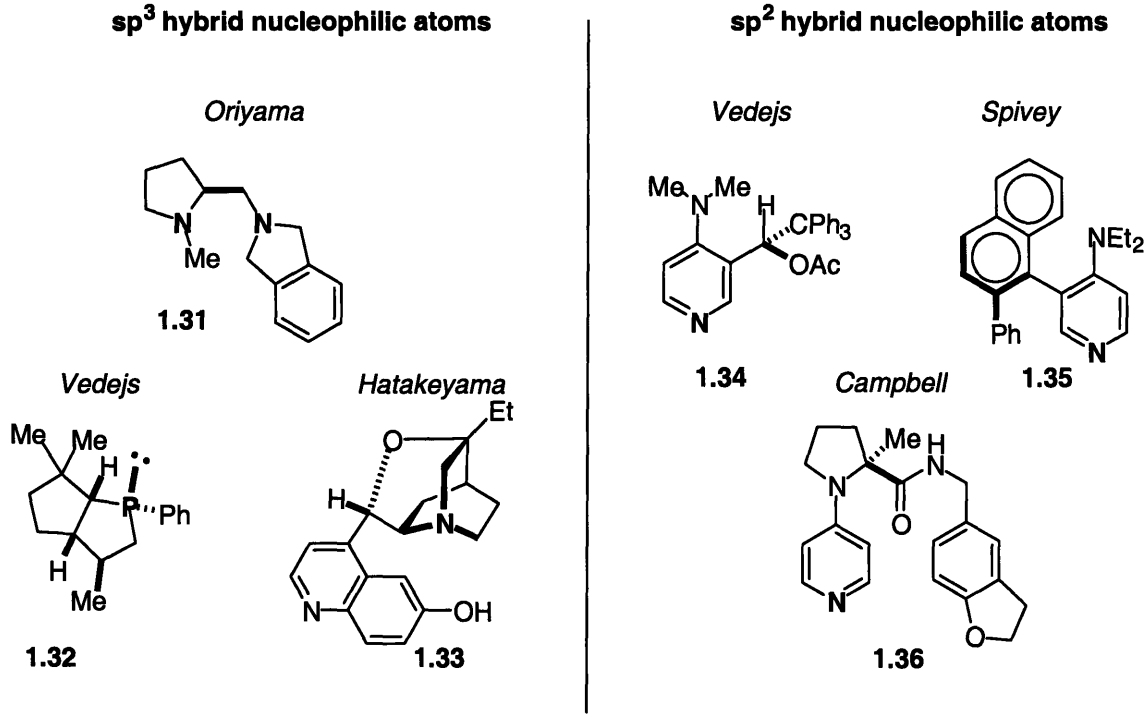
[8] Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103-3105.

[9] Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368-13369.

[10] Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844-3848.

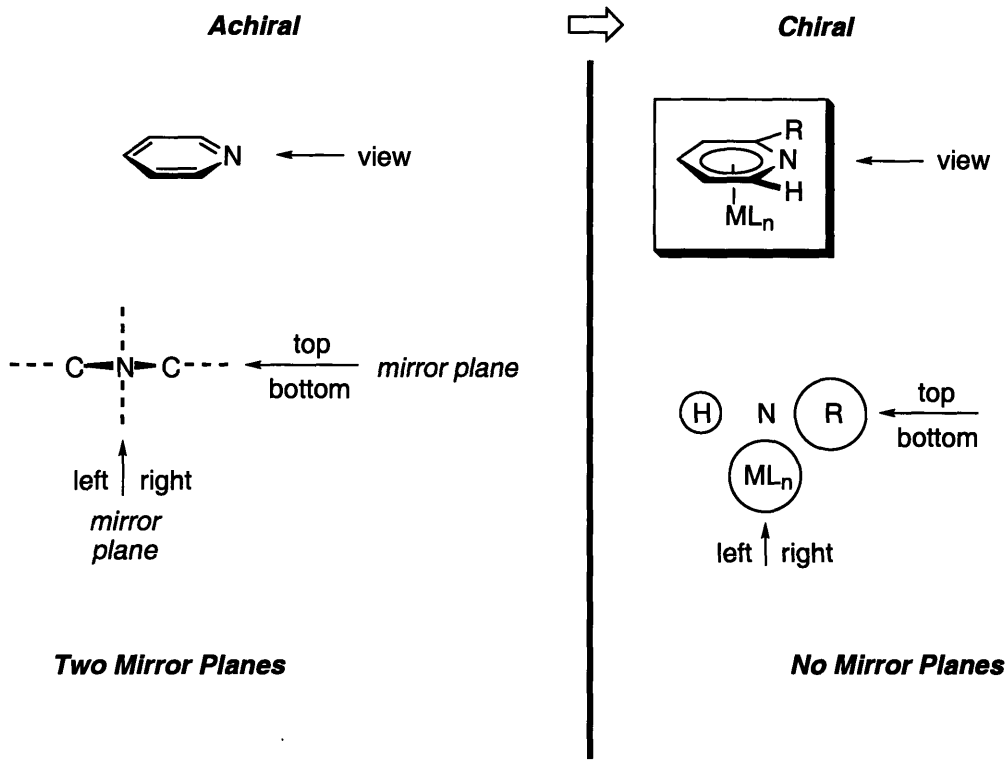
[11] Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154-3159.

Figure 1A.4. Examples of Chiral Nucleophilic Catalysts.



In designing a pyridine-derived enantioselective catalyst, the heterocycle must be desymmetrized by destruction of the two mirror planes (Figure 1A.5). As part of our ongoing research program, we sought to develop such a class of enantioselective nucleophilic catalysts that clearly differentiated left and right sides of the ring, as well as distinguished the top versus bottom face of the arene. Our solution was to first incorporate an ortho-substituent (left vs. right differention) and then complex the heterocycle to a transition metal (top vs. bottom differentiation).

Figure 1A.5. Desymmetrization of Pyridine.

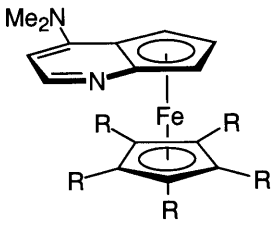


To combat the attenuated activity of an ortho-substituted pyridine catalyst, an amino group was installed at the para position, affording a DMAP-derived series of catalysts (Figure 1A.6).[12,13] Prior to the commencement of our research program towards the design of effective sp^2-hybridized nucleophilic catalysts, there were no chiral variants of DMAP, pyridine, or imidazole known to participate in asymmetric nucleophile-catalyzed processes. In response to this, and in light of the requirements necessary to desymmetrize a planar-based heterocyclic structure, catalysts **1.11-1.16** were developed.

---

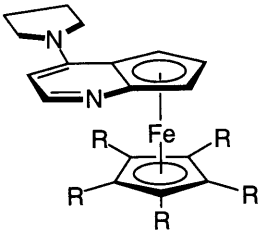
[12] For reviews on DMAP, see: (a) Höfle, G; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569-583. (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129-161.

[13] (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230-7231. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493.



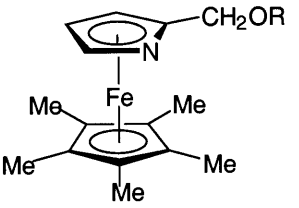
R = Me: (–)-**1.11**
Ph: (–)-**1.15**

DMAP-Derived



R = Me: (–)-**1.12**
Ph: (–)-**1.16**

PPY-Derived



R = Me: (+)-**1.13**
TBS: (+)-**1.14**

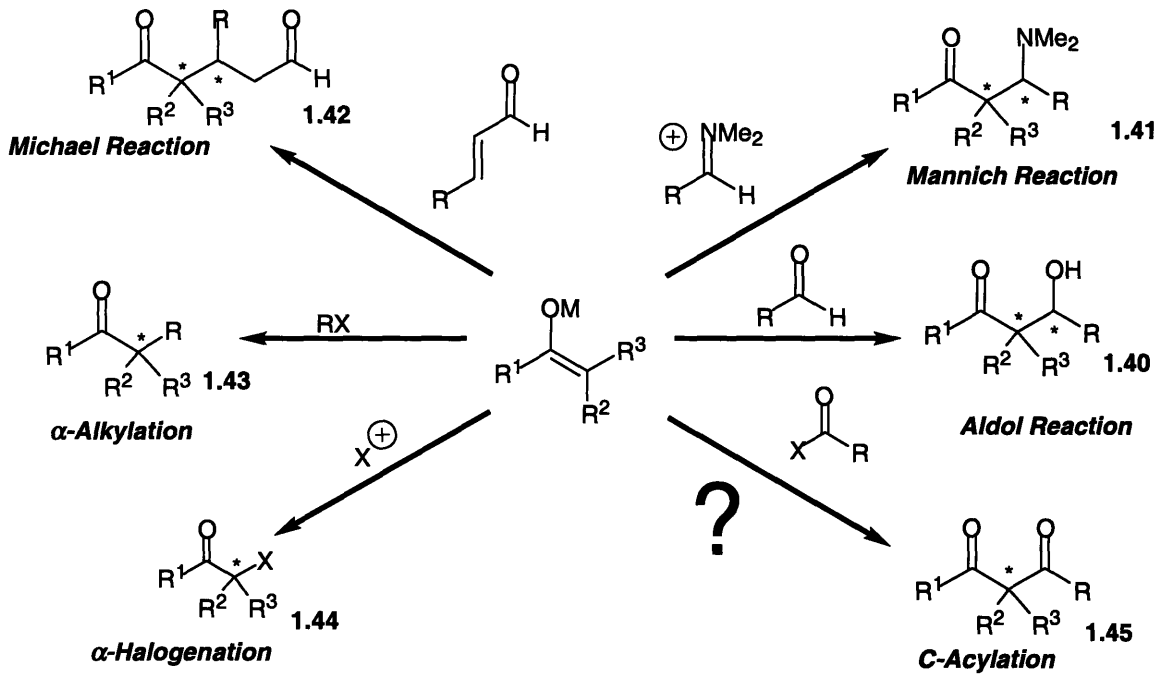
Azaferrocene-Derived

(1A.6)

Part B. Introduction to the Acylation of Enolates.

Catalytic enantioselective addition of enolates to a wide array of electrophiles has been intensively investigated with remarkable recent success (Figure 1B.1).[14] While reliable catalytic enantioselective methods have been described for the formation of products **1.40-1.44**, addition to acyl derivatives to furnish **1.45** was not reported prior to our investigations. This may be attributed to complications associated with the fundamental reactivity of enolates in the presence of acylating agents.

Figure 1B.1. Diversity of Enolate Reactions.



[14] For catalytic enantioselective accounts of the transformations shown in 1B.1, see: (a) Aldol reactions-Carriera, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 29.1. (b) Aldol reactions-Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1352-1374. (c) Mannich Reaction-Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180-8186. (d) Michael Reaction-Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194-6198. (e) Halogenation-Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790-4791. (f) Halogenation-Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038-6039.

In the presence of an acylating agent, an enolate may react at oxygen (O-acylation) or carbon (C-acylation), with a general kinetic preference for the O-acylation product.[15] A number of factors are thought to contribute to this product distribution, including enolate type (e.g., ketone-derived versus carboxylic acid-derived enolates), nature of the acylating agent, solvent, temperature, and reagent stoichiometry. Nonetheless, no general solution has been realized.[16] In addition, mixtures of O- and C-acylation products are often inseparable.

Despite the lack of catalytic asymmetric variants for the acylation of enolates, auxiliary-based approaches have been quite successful (Figure 1B.2). Oxazolidinone **1.46**, developed by Evans and coworkers, controls the C-acylation reaction with excellent diastereoselectivity and yield.[17] Yamaguchi and coworkers have employed auxiliary **1.47** with similar results.[18] More recently, Oppolzer and coworkers demonstrated the efficacy of cyclic sulfonamide **1.48** in this process.[19] It should be noted that the initial products of these reactions display remarkable configurational stability because enolization would lead to destabilizing A(1,3) interactions. While impressive selectivities have been obtained utilizing auxiliaries **1.46-1.48**, the products must be appropriately derivatized prior to auxiliary cleavage in order to prevent racemization.

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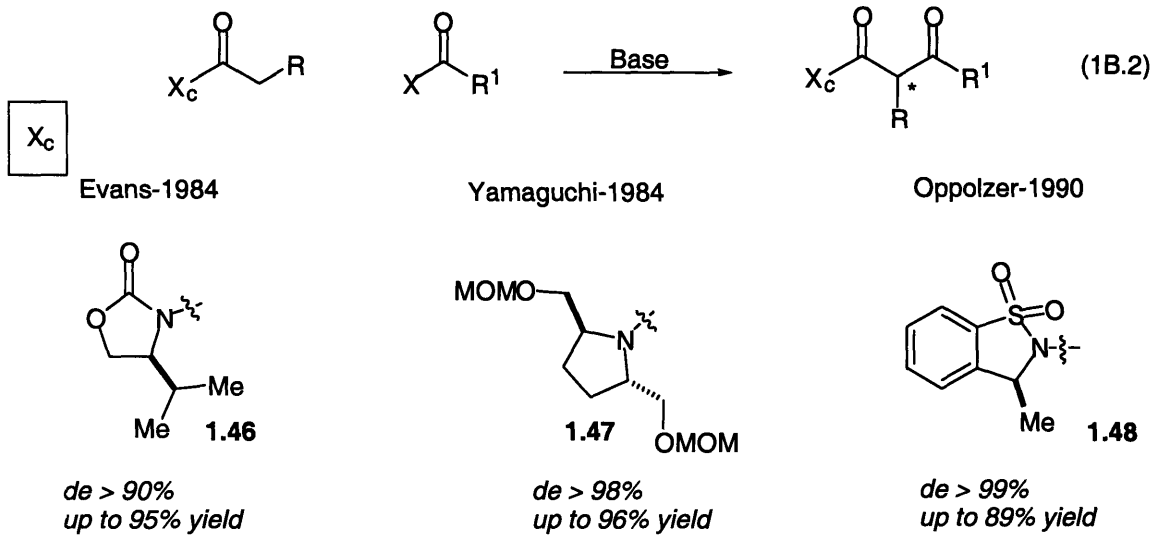
[15] For a review on the structure and reactivity of enolates, see: Jackman, L. M.; Lange, B. C. *Tetrahedron*, **1977**, *33*, 2737-2769.

[16] For a review on C- vs O-Acylation of enolates, see: (a) Black, T. H. *Org. Prep. Proced. Int.* **1989**, *21*, 179-217. For other references on the acylation of enolates, see: (b) Limat, D., Schlosser, M. *Tetrahedron*, **1995**, *51*, 5799-5806. (c) Tirpak, R. E.; Rathke, M. W. *J. Org. Chem.* **1982**, *47*, 5099-5102. (d) Kopka, I.; Rathke, M. W. *J. Org. Chem.* **1981**, *46*, 3771-3773.

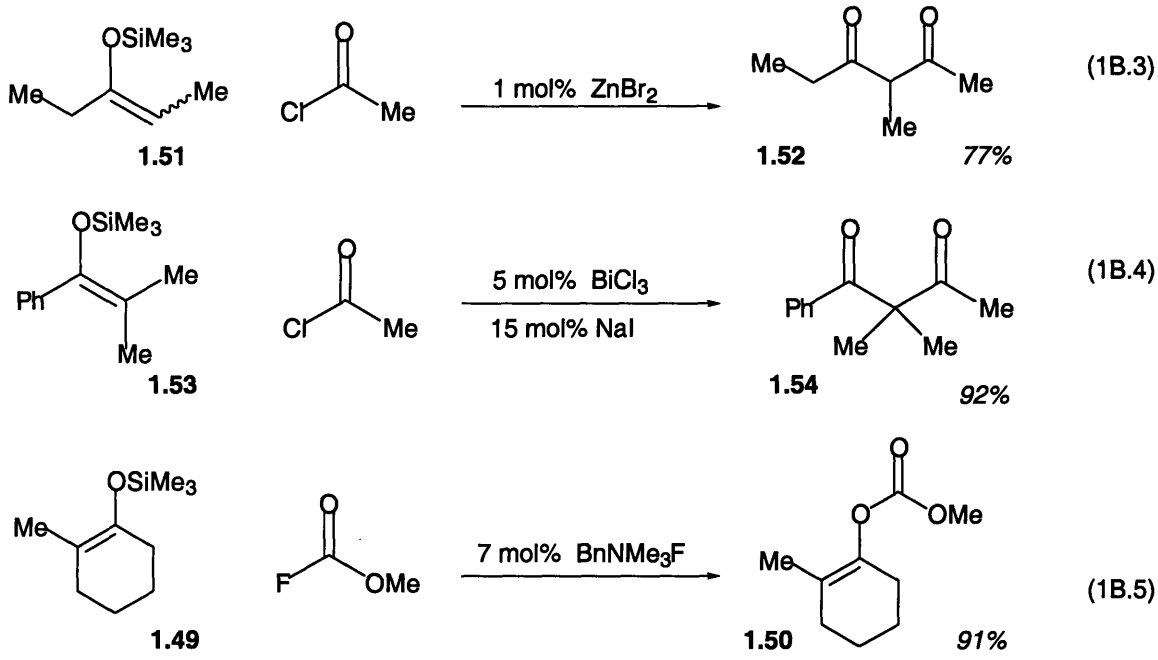
[17] Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154-1156.

[18] Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 6015-6016.

[19] Oppolzer, W.; Rodriguez, I.; Starkemann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019-5022.

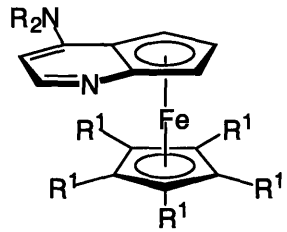


The catalytic C-acylation of enolsilanes has been effected with achiral Lewis acids such as $ZnBr_2$ and $BiCl_3$/NaI in good yield (1B.3 and 1B.4).[20]



[20] For $ZnBr_2$-catalyzed C-acylation processes, see: Fleming, I.; Iqbal, J.; Krebs, E.-P. *Tetrahedron* **1983**, *39*, 841-846, and references cited therein. For $BiCl_3$/NaI catalyzed C-acylation processes, see: Le Roux, C.; Mandrou, S.; Dubac, J. *J. Org. Chem.* **1996**, *61*, 3885-3887.

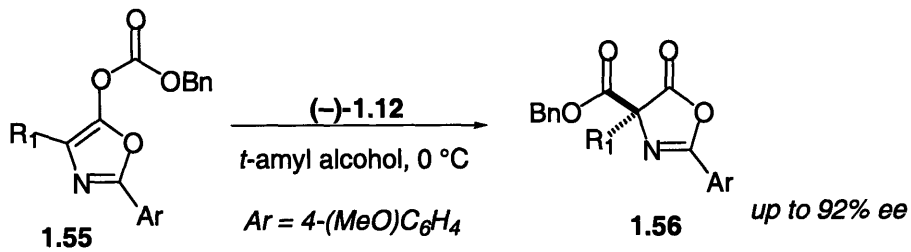
In contrast, Lewis bases such as fluoride lead instead to undesired O-acylation (1B.5).[21] Although these reactions were not asymmetric, we were intrigued by the use of disubstituted silyl enol ether **1.53** in 1B.4. We speculated that a quaternary center formed by the C-acylation of a disubstituted enolate might be constructed asymmetrically in the presence of a chiral catalyst. Accordingly, we decided to investigate enantioselective C-acylation reactions with planar-chiral derivatives of DMAP and PPY as nucleophilic catalysts.



NR_2 =	R^1 =	
dimethylamino	Me	**(–)-1.11**
pyrrolidino	Me	**(–)-1.12**
dimethylamino	Ph	**(–)-1.15**
pyrrolidino	Ph	**(–)-1.16**

(1B.6)

We were optimistic that these complexes could serve as effective enantioselective catalysts for the acylation of enolates. Early work in our group established that complex **1.12** effects the rearrangement of O-acylated azlactones to C-acylated derivatives (1B.7).[22] In order to develop an intermolecular version of this transformation, we turned to the reaction of enolsilanes with external acylating agents.[23]



(1B.7)

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[21] Olofson, R. A.; Cuomo, J. *Tetrahedron Lett.* **1980**, *21*, 819-822.

[22] Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532-11533. For a more recent example of this process with oxindole and benzofuranone-derived substrates, see: Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921-3924.

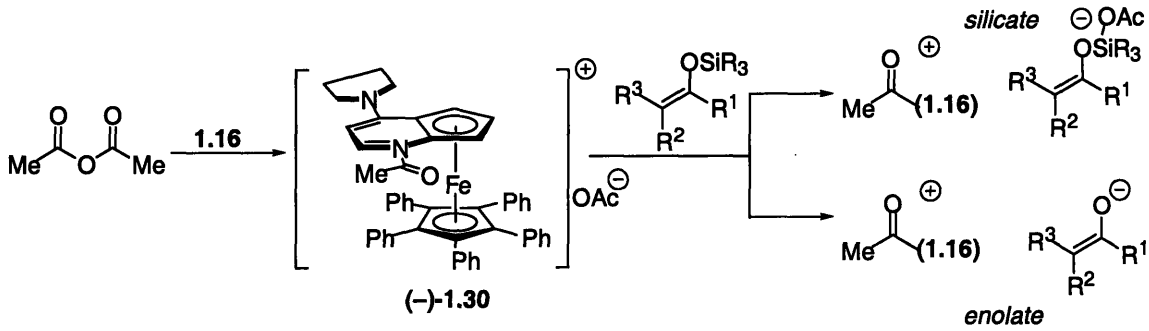
[23] For reviews on the chemistry of silyl enol ethers see: (a) Brownbridge, P. *Synthesis*, **1983**, 1-24. (b) Brownbridge, P. *Synthesis*, **1983**, 85-104.

In this chapter, we describe the discovery of an intermolecular C-acylation process for silyl ketene acetals, and provide data that helps elucidate the new mode of reactivity governing this process.

Part C. Results and Discussion

Our initial goal was to determine a set of conditions for the reaction of an enol silane with the acylated form of a planar-chiral catalyst.[24] Of particular interest was the counterion of the acylated catalyst, which we envisioned attacking at silicon to activate the enol silane (Figure 1C.1).[25] In this process, we anticipated activation of not only the electrophile (acylating agent → acylpyridinium), but also of the nucleophile (silyl ketene acetal → silicate or enolate).

Figure 1C.1. Possible Means of Dual Activation.



We began our investigation by surveying a wide variety of silyl enol ethers and silyl ketene acetals with a diverse array of acylating agents in the presence of catalyst **1.16**. Silyl enol ethers did not react, even under forcing conditions. The more nucleophilic silyl ketene acetals,[26] however, led to a very rapid uncatalyzed reaction with most acylating agents. Although both acid halides and chloroformates led to this

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[24] DMAP-derived planar-chiral heterocycles have been previously shown to activate anhydrides in the form of an acylpyridinium salt for the kinetic resolution of secondary alcohols. For references, see: (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230-7231. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493. (c) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.*, **1998**, *120*, 11532-11533. (d) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am Chem. Soc.* **1999**, *121*, 5091-5092.

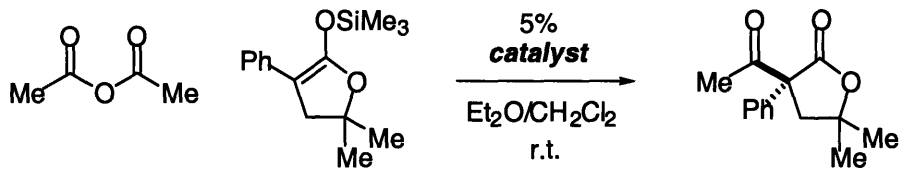
[25] For an account on the nucleophilic activation of silicon, see: Chuit, C.; Corriu, R.; Reyé, C. J. *J. Organomet. Chem.* **1988**, *358*, 57-66.

[26] A comparison of the nucleophilicities of various silyl enol ethers and silyl ketene acetals indicate that γ-butyrolactone derived silyl ketene acetals are among the most nucleophilic enolates, see: Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500-9512.

undesired background reaction, anhydrides did not react at all with alkyl-substituted silyl ketene acetals . After much investigation, we found that aryl-substituted silyl ketene acetals led to exclusive acylation on carbon with high enantioselectivity (~80% ee). After establishing this lead result, we sought to optimize the various reaction parameters.

A survey of various DMAP- and PPY-derived catalysts revealed that substitution on the lower ring dramatically influenced enantioselectivity (1C.2). Pentamethylcyclopentadienyl-substituted lower rings (Table 1C.2, entries 1 and 2) resulted in poor enantioselectivities, while pentaphenylcyclopentadienyl analogs (Table 1C.2, entries 3 and 4) performed better. In addition, pentamethylcyclopentadienyl-substituted catalysts **1.11** and **1.12** were prone to decomposition, possibly producing achiral fragments capable of catalyzing the acylation reaction, leading to an erosion in enantioselectivity. While the structure of the amino group did not lead to significant differences in stereoselectivity, catalysts bearing a pyrrolidino moiety (Table 1C.2, entries 2 and 4) reacted significantly faster than dimethylamino analogs. In light of these observations, we chose catalyst **(–)-1.16** for further study.

Table 1C.2. Enantioselectivity as a Function of Catalyst Structure.

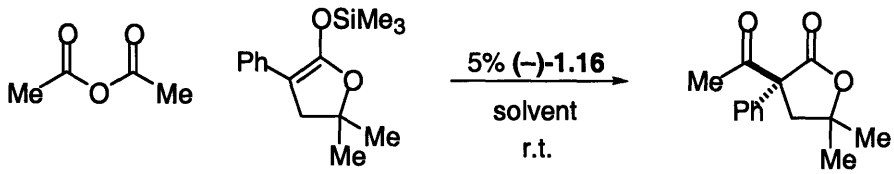


1.61 **1.71**

entry	catalyst	% ee
1	(–)-**1.11**	40
2	(–)-**1.12**	33
3	(–)-**1.15**	87
4	(–)-**1.16**	90

Solvent has been shown to be a critical variable in the acylation of enolates.[27] A preliminary solvent survey for the reaction of silyl ketene acetal **1.61** with catalyst **(–)-1.16** indicated that ethereal solvents furnished high enantioselectivities. An extensive secondary screen revealed that up to 90% ee could be obtained in *n*-butyl ether (Table

Table 1C.3. Enantioselectivity as a Function of Solvent



1.61 **1.71**

Entry	Solvent	% ee	
1	*n*-Bu_2O	90	*
2	Et_2O	88	*
3	*i*-Pr_2O	87	*
4	$(Me_3Si)_2O$	86	
5	*t*-BuOMe	82	*
6	1,4-Dioxane	80	*
7	DME	80	*
8	1,3-Dioxolane	79	*
9	THF	79	*
10	Thiophene	78	
11	Anisole	77	
12	*t*-BuOAc	76	*
13	$(MeOCH_2CH_2)_2O$	NR	
14	**Et_2O/CH_2Cl_2 (14:1)**	**89**	← ***78% conversion in 15 hours***
15	$Et_2O/PhCH_3$ (6.5:1)	88	

* *< 40% conversion in 24 hours*

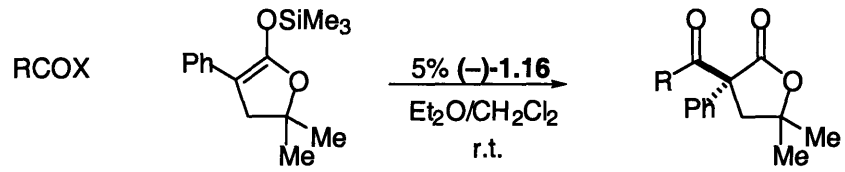
1C.3, entry 1). More practical diethyl ether afforded nearly the same selectivity (88% ee, Table 1C.3, entry 2). Sterically demanding ether-based solvents or solvents containing more than one oxygen (Table 1C.3, entries 3-13) furnished selectivities inferior to diethyl

[27] Jackman, J. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737-2769.

ether. While we were pleased with the stereoselectivity furnished by Et_2O, the reaction was sluggish and heterogeneous. To address this issue, we employed a binary solvent system comprised of ether and dichloromethane.[28] The percentage of dichloromethane added (~7%) was sufficient to render the reaction homogeneous, leading to significant rate enhancement without affecting the stereoselectivity (Table 1C.3, entry 14).

After determining the optimal reaction solvent, we conducted a survey of various acylating agents. Acetic anhydride provided 90% ee (Table 1C.4, entry 1), while the sterically demanding isobutyric anhydride (Table 1C.4, entry 2) was lower yielding and less selective. Benzoic anhydride (Table 1C.4, entry 3) afforded moderate enantioselectivity and good yield. Acid chlorides did participate in this process with good enantioselectivity, but yields were disappointing (Table 1C.4, entry 4). More reactive acylating agents such as trifluoroacetic anhydride and pyruvonitrile led to racemic products due to competing uncatalyzed processes (Table 1C.4, entries 5 and 6, respectively). The results of this survey prompted us to continue the reaction optimization with acetic anhydride as the acylating agent.

Table 1C.4. Enantioselectivity as a function of the Acylating Agent.



1.61

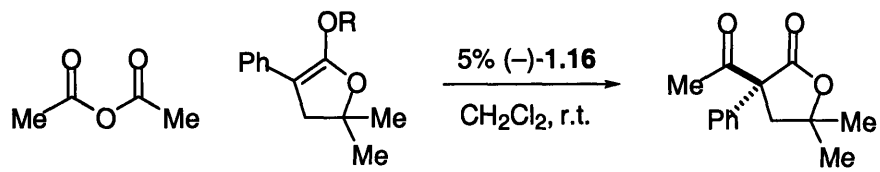
entry	RCOX	Product	% ee	% yield
1	Ac_2O	**1.71**	**90**	**80**
2	$(i\text{-PrCO})_2O$	**1.81**	**83**	**15**
3	$(PhCO)_2O$	**1.82**	**55**	**82**
4	AcCl	**1.71**	**73**	**43**
5	$(F_3CCO)_2O$	**1.83**	**0**	**56**
6	AcCN	**1.71**	**0**	**10**

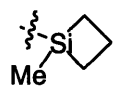
[28] Dichloromethane had been previously identified as a solvent that led to very rapid C-acylation.

Reactions performed at temperatures other than ambient conditions furnished slightly lower selectivities. In addition, reduced temperature (0 °C) led to a slower reaction rate, while conducting the acylation at elevated temperatures (40 °C) resulted in significant catalyst decomposition. Very little change (< 5%) in enantioselectivity was evident by altering the reaction concentration. Since reaction concentrations ≥ 200 mM appeared to be heterogeneous, we selected 76 mM as the optimal substrate concentration.

With the optimized reaction conditions in hand, we turned to variation of the silicon moiety. Upon investigating this process with a variety of silicon groups, however, we were surprised to see that there was essentially no change in stereoselectivity with various silicon groups (Table 1C.5). Reduced reaction rates were observed with more sterically demanding silicon groups (Table 1C.5, entries 1 and 2). While the silicon moiety is a critical element in this nucleophile-catalyzed process, the lack of enantio-differentiation imparted by this substructure indicates that it may not involved in the stereochemistry-determining step. Additional mechanistic observations to support these assertions will be discussed later in this chapter.

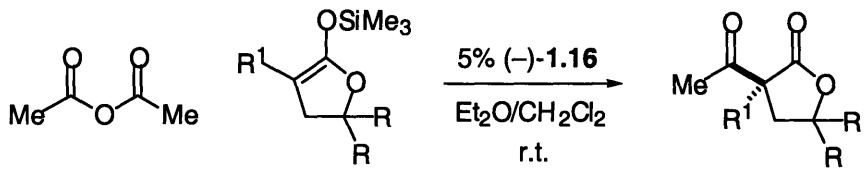
Table 1C.5. Enantioselectivity as a Function of the Silicon Moiety.



entry	R	substrate	% ee
1	$Si(i\text{-}Pr)_3$	**1.84**	82
2	$SiMe_2(Ph)$	**1.85**	79
3	$Si(n\text{-}Bu)_3$	**1.86**	79
4	$SiMe_3$	**1.61**	80
5		**1.87**	79

We next established that catalyst (–)-**1.16** effects the asymmetric intermolecular C-acylation of a range of silyl ketene acetals, furnishing new quaternary stereocenters with excellent enantiomeric excess (Table 1C.6).[29] Products derived from the O-acylation of silyl ketene acetals **1.61-1.69** were not observed. The method tolerated a variety of aromatic substituents, including heteroaromatic groups.[30] In addition, the catalyst could be recovered in almost quantitative yield.

Table 1C.6. Enantioselectivity as a Function of the Aromatic Substituent.



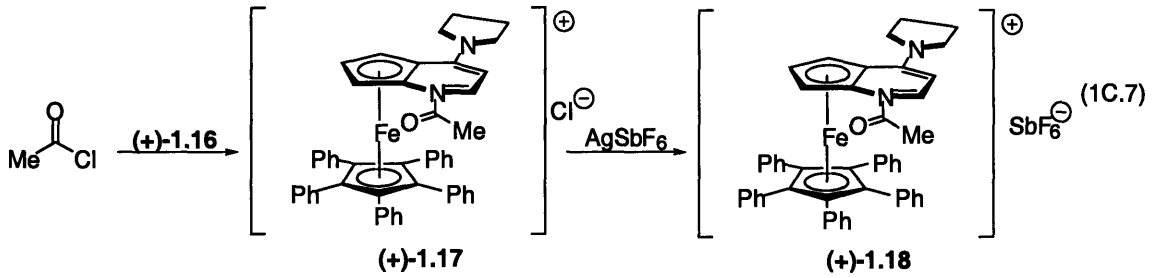
entry	R^1	substrate	R	product	% ee	% yield
1	Me	**1.60**	H	**1.70**	–	–
2	Ph	**1.61**	Me	**1.71**	90	80
3	4-(MeO)C_6H_4	**1.62**	Me	**1.72**	95	78
4	4-(F_3C)C_6H_4	**1.63**	H	**1.73**	90	84
5	*o*-tolyl	**1.64**	Me	**1.74**	95	89
6	1-naphthyl	**1.65**	Me	**1.75**	99	82
7	2-thiophene	**1.66**	Me	**1.76**	76	84
8	3-thiophene	**1.67**	Me	**1.77**	87	86
9	3-thiophene	**1.68**	H	**1.78**	80	73
10	3-(*N*-methylindolyl)	**1.69**	Me	**1.79**	94	92

Our next objective was to pursue experiments aimed at further elucidating the mechanism of this process. As described earlier with we anticipated that the counterion of the catalyst plays a distinct role by activating the silicon group (Figure 1C.1). To probe this assertion, we examined the reactivity of a silyl ketene acetal towards an

[29] For a recent review of catalytic asymmetric methods that generate quaternary stereocenters, see: Corey, E. J.; Guzman-Perez, A. *Angew Chem., Int. Ed. Engl.* **1998**, *37*, 388-401. See also: Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591-4597.

[30] Gem-dimethyl substitution is present for ease of substrate synthesis (double deprotonation of an arylacetic acid, followed by reaction with isobutylene oxide). As shown in Table 1C.5, these groups are not required for high stereoselectivity.

acylated catalytic species bearing a non-nucleophilic SbF_6 counterion, generated by treatment of acylpyridinium salt (+)-**1.17** with $AgSbF_6$ (1C.7).[31]



We employed acylpyridinium salt **(+)-1.18** as a stoichiometric acetylating agent in experiments designed to probe the nucleophilic capacity of the catalyst counterion in this C-acylation process (Table 1C.8). In the absence of catalyst, treatment of silyl ketene acetal **1.63** with acetic anhydride resulted in no detectable product formation after 60 hours at room temperature (Table 1C.8, entry 1).[32] In contrast, rapid C-acylation was observed in the presence of 5% (–)-**1.16** to furnish **1.73** ($t_{1/2}$ = 0.3 hours; Table 1C.8, entry 2). Upon treatment of **1.63** with acylpyridinium salt (+)-**1.18**, we observed no product formation after 60 hours at room temperature. This suggests that activation of the anhydride (Ac_2O → acylpyridinium) is not sufficient to effect acylation (Table 1C.8, entry 3). However, use of 5% $Me_4N[OAc]$ led to very rapid acylation of **1.63** (Table 1C.8, entry 5). These observations indicate that the combined effect of the acylpyridinium ion and the nucleophilic acetate ion are responsible for the significant rate acceleration and excellent enantioselectivity imparted by catalyst **1.16**.

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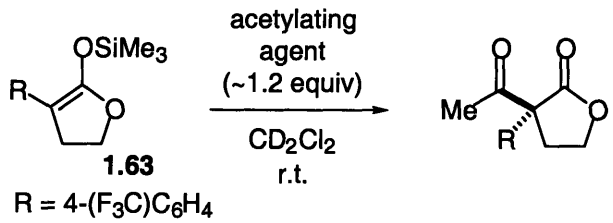
[31] Complex **1.17** is readily accessed by treatment of **1.16** with ≥ 1.0 equivalent of acetyl chloride.

[32] Because these reactions were monitored by ^1H NMR, CD_2Cl_2, rather than a mixture of d_{10}-Et_2O/CD_2Cl_2, was used. In CD_2Cl_2, the C-acylation process that is illustrated in Table 1C.8 proceeds in 87% ee (vs. 90% ee in Et_2O/CH_2Cl_2).

Table 1C.8. Evidence for a Dual-Activation Mechanism: Reactivity of 1.63 In Various Acetylation Systems.



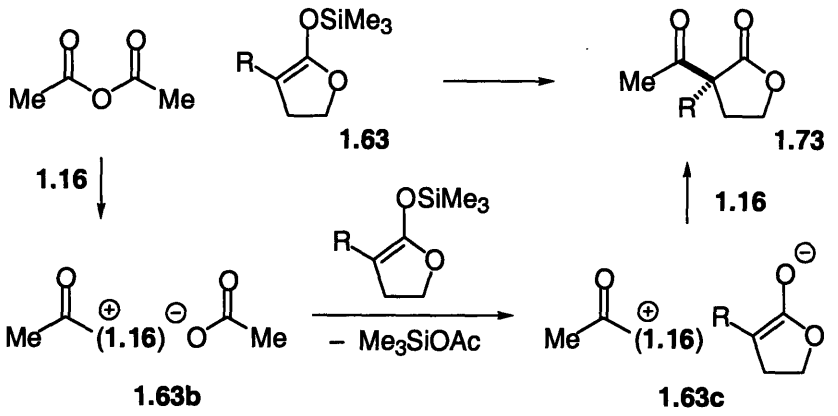
entry	acetylating agent	$t_{1/2}$ for reaction
1	Ac_2O	<2% conversion (60 h)
2	Ac_2O; 5% (–)-**1.16**	0.3 h
3	**(+)-1.18**	<2% conversion (60 h)
4	**(+)-1.18; 5%** (+)-**1.16**	<2% conversion (60 h)
5	Ac_2O; 5% $[Me_4N]OAc$	<0.1 h

We also conducted an experiment to probe whether the catalyst serves to activate the silicon moiety. Treatment of substrate **1.63** with acylpyridinium salt (+)-**1.18** in the presence of 5% (+)-**1.16** leads to no product after 60 hours at room temperature, indicating that the role of the catalyst is limited to activation of the electrophilic component (Table 1C.8, entry 4). This observation, taken together with the data presented in Table 1C.5, suggest that a silicate pathway is not likely during the formation of **1.73**.[33, 34]

With the support of these experiments, we believe the mechanistic pathway illustrated in Figure 1C.9. Acetic anhydride is initially converted to ion pair **1.63b**, which produces an acetate counterion, leading to the desilylation of **1.63** and formation of new ion pair **1.63c**. The components of this ion pair combine to form product **1.73** in enantioenriched form.

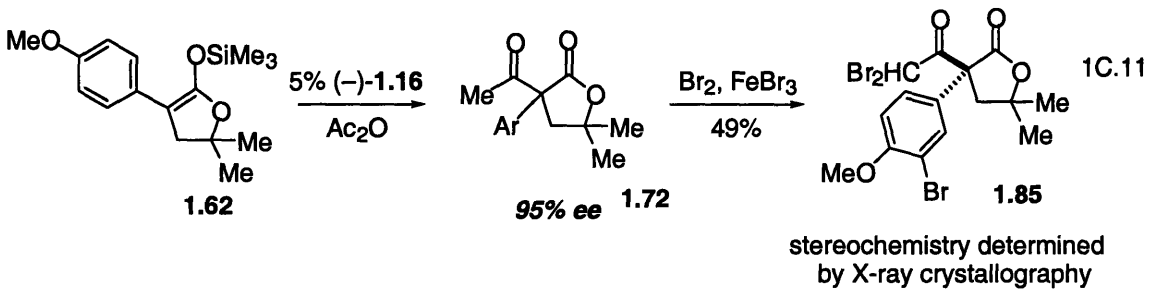
[33] The observation that only aromatic-substituted silyl ketene acetals furnish the desired product also supports a desilylation mechanism, as these substituents provide necessary stabilization for the enolate intermediate.

Figure 1C.9. Proposed Mechanism for the Acylation of 1.63 Catalyzed by 1.16.



The absolute configuration of the products obtained from this process was determined by derivatization of product **1.72**. Treatment of this β-dicarbonyl with Br_2 in the presence of $FeBr_3$ afforded tribromide **1.85**.[35] This crystalline β-dicarbonyl compound was analyzed by X-ray crystallography to elucidate the absolute configuration of the quaternary stereocenter to be as illustrated in Figure 1C.10.

Figure 1C.10. Absolute Configuration Determination.



[34] The byproduct, Me_4NSbF_6, does not interfere with the C-acylation process. Execution of the catalytic reaction with one equivalent of this salt leads to the same enantioselectivity shown in Table 1C.8, entry 2.

[35] The products from the C-acylation reaction were sensitive to nucleophiles. Addition of a nucleophilic species to the carbonyl of 1.72 led to a retro-Claisen process. This mode of reactivity will be further addressed in chapter 4.

Conclusions

We report the first catalytic enantioselective C-acylation process for silyl ketene acetals. Essential to the development of this process was exploiting the nucleophilic capacity of an acetate counterion, which serves to activate the silicon moiety. This process tolerates a wide array of sterically and electronically diverse aromatic substrates, including heteroaromatic substrates, and furnishes enantioselectivities up to 99% with no undesired O-acylation.

The nature of the silicon group influences the reaction kinetics, but does not exert a significant influence on the enantiomeric excess, suggesting that the silyl ketene acetal is desilylated to generate a more reactive enolate nucleophile. Furthermore, mechanistic studies suggest that the combination of the acylpyridinium ion and the acetate ion is responsible for the dramatic rate enhancement and excellent selectivities imparted by catalyst **1.16**.

Experimental

General

THF, CH_2Cl_2, and Et_2O were purified by passage through a neutral alumina column. Ac_2O was distilled from phosphorus pentoxide. Benzoic anhydride was recrystallized from Et_2O. $[Me_4N]OAc$ (Alfa Aesar) was purified by recrystallization from 2:1 CH_3CN/CH_2Cl_2. *n*-BuLi (Alfa Aesar) was titrated with diphenylacetic acid (Aldrich) prior to each use. Methylene chloride-d_2 (Cambridge Isotope Laboratories) was distilled from CaH_2. Phenylacetic acid (Aldrich), 4-methoxyphenylacetic acid (Avocado), 4-trifluoromethylphenylacetic acid (Avocado), *o*-tolylacetic acid (Avocado), naphthalene-1-acetic acid (Avocado), thiophene-2-acetic acid (Avocado), thiophene-3-acetic acid (Avocado), 1-methyl-3-indoleacetic acid (Aldrich), 1,3,2-dioxathiolane 2,2-dioxide (Aldrich), diisopropylamine (Aldrich), 1,4-dioxane (Aldrich), chlorotrimethylsilane (Avocado), chlorotributylsilane (Aldrich), chlorodimethylphenylsilane (Aldrich), chlorotriisopropylsilane (Aldrich), 1-chloro-1-methylsilacylcobutane (Aldrich), isobutylene oxide (TCI), chloroform (Mallinckrodt), pentane (Burdick & Jackson), hydrochloric acid (Fisher), bromine (Fluka), $FeBr_3$ (Strem), $AgSbF_6$ (Strem), oxalyl chloride (Aldrich), 2-methyl-2-propanol (Aldrich), NEt_3 (EM Science), *N,N*-dimethylformamide (Aldrich), 2-phenylbutyric acid (Aldrich), tetrabutylammonium chloride (TCI), acetonitrile (Aldrich), and absolute EtOH (Pharmco) were used as received. Catalysts **1-4** were prepared as previously reported.[36]

Analytical thin layer chromatography was performed with EM Reagents 0.25 mm silica gel 60 plates, and visualization was achieved with ultraviolet light and/or ceric

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[36] (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230-7231. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493. (c) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532-11533. (d) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091-5092.

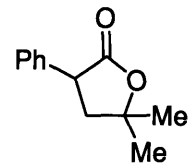
ammonium nitrate or potassium permanganate stains. Flash chromatography was performed with Sorbent Technologies silica gel 60 (230-400 mesh).

Optical rotations were acquired with a Jasco-1010 polarimeter. Infrared spectra were obtained on a Perkin-Elmer Series 2000 FT-IR spectrophotometer. Melting points (uncorrected) were acquired on a Thomas Hoover Unimelt capillary melting point apparatus.

^{1}H and ^{13}C nuclear magnetic resonance spectra were obtained on a Varian Unity 300, Varian Mercury 300, or Varian VXR 500 spectrometer at room temperature. ^{1}H NMR data are reported using the following notation: chemical shift in parts per million downfield from tetramethylsilane (δ scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, and app t = apparent triplet), integration, and coupling constant (Hz). ^{13}C chemical shifts are recorded in ppm downfield with respect to tetramethylsilane (δ scale), and were acquired with full proton decoupling.

All experiments were conducted under an argon or nitrogen atmosphere in oven-dried glassware with magnetic stirring, unless otherwise specified.

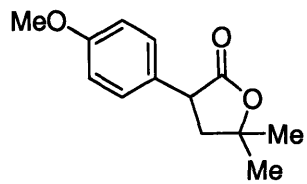
Preparation of Lactones



A solution of *n*-BuLi (2.45 M in hexanes; 75.6 mL, 185 mmol) was added via syringe to a –78 °C solution of diisopropylamine (25.9 mL, 185 mmol) in THF (100 mL). This solution was stirred at –78 °C for 45 minutes, and then a solution of phenylacetic acid (12.0 g, 88.1 mmol) in THF (75 mL) was added via cannula. The reaction mixture

was stirred at –78 °C for 20 minutes, then warmed to room temperature and stirred for 2 hours. The solution was then cooled to 0 °C, and neat isobutylene oxide (7.90 mL, 88.1 mmol) was added via syringe, resulting in a clear yellow solution, which was stirred for 12 hours at room temperature. Water (50 mL) was then added, resulting in a clear colorless solution, which was refluxed for 2 hours. Then, the reaction mixture was cooled to room temperature and washed with Et_2O (3 x 150 mL). The aqueous layer was diluted with 95% EtOH (100 mL), acidified with concentrated HCl (25 mL), and refluxed for 3 hours. Then, it was cooled to room temperature and extracted with $CHCl_3$ (3 x 200 mL). The $CHCl_3$ layer was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL), then dried (Na_2SO_4) and concentrated. The resulting white solid was recrystallized from Et_2O/pentane (9:1) to afford white crystals, which were collected, washed with pentane, and dried under vacuum (13.7 g, 82%).

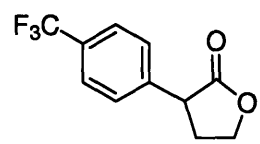
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.39 (m, 2H), 7.27-7.32 (m, 3H), 4.05 (dd, 1H, J=12.0, J=9.5), 2.59 (dd, 1H, J=12.5, J=9.5), 2.25 (app t, 1H, J=12.5), 1.56 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 137.2, 129.1, 128.3, 127.7, 82.3, 47.2, 44.4, 29.1, 27.2. FTIR (CH_2Cl_2) 3031, 2979, 2945, 1772, 1653, 1498, 1457, 1375, 1261, 1141 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{12}H_{14}O_2$ (M^+) 190.0994, found 190.0989. mp 63-66 °C.



A solution of *n*-BuLi (2.60 M in hexanes; 48.6 mL, 126 mmol) was added via syringe to a –78 °C solution of diisopropylamine (17.7 mL, 126 mmol) in THF (150 mL). This mixture was stirred at –78 °C for 30 minutes, then warmed to 0 °C. A solution of 4-

methoxyphenylacetic acid (7.00 g, 42.1 mmol) in THF (50 mL) was added via cannula, and the resulting mixture was warmed to 40 °C and stirred for 1 hour. Neat isobutylene oxide (7.90 mL, 88.1 mmol) was then added via syringe, and the resulting solution was refluxed for 18 hours. The reaction mixture was cooled to 0 °C, and water (100 mL) was added, resulting in a clear, colorless solution. This mixture was refluxed for 2 hours, then cooled to room temperature, diluted with water (100 mL), and washed with Et_2O (3 x 150 mL). The aqueous layer was diluted with absolute EtOH (100 mL), acidified with 6 N HCl (70 mL), and then refluxed for 4 hours. The mixture was cooled to room temperature and extracted with $CHCl_3$ (3 x 200 mL). The $CHCl_3$ layer was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL), dried ($MgSO_4$), and concentrated. The resulting yellow solid was recrystallized in 3 crops from Et_2O/CH_2Cl_2/pentane (5:4:50) to afford flocculent white needles, which were collected, washed with pentane, and dried under vacuum (7.79 g, 84%).

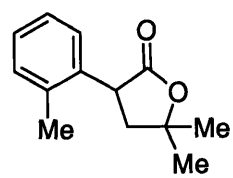
^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, 2H, J=8.5), 6.90 (d, 2H, J=9.0), 3.99 (dd, 1H, J=12.0, J=9.5), 3.80 (s, 3H), 2.55 (dd, 1H, J=12.5, J=9.0), 2.20 (dd, 1H, J=12.5, J=12.0), 1.54 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 159.1, 129.3, 129.1, 114.5, 82.2, 55.5, 46.4, 44.4, 29.1, 27.1. FTIR (CH_2Cl_2) 2975, 2935, 2838, 1771, 1653, 1615, 1516, 1375, 1250, 1139 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{13}H_{16}O_3$ (M^+) 220.1094, found 220.1090. mp 64-68 °C.



A solution of *n*-BuLi (2.80 M in hexanes; 6.32 mL, 17.7 mmol) was added via syringe to a –78 °C solution of diisopropylamine (2.48 mL, 17.7 mmol) in THF (50 mL).

The reaction mixture was stirred at –78 °C for 45 minutes, after which a solution of 4-trifluoromethylphenylacetic acid (1.72 g, 8.43 mmol) in THF (10 mL) was added via cannula, resulting in a deep-red solution. This mixture was stirred for 45 minutes at –78 °C, after which 1,3,2-dioxathiolane 2,2-dioxide (1.05 g, 8.43 mmol) in THF (10 mL) was added via cannula. The resulting mixture was stirred at –78 °C for 10 minutes, warmed to room temperature, and then refluxed for 12 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added, and the solution was refluxed for 1 hour. The reaction mixture was then cooled to room temperature and extracted with Et_2O (3 x 100 mL). The organic layer was dried over $MgSO_4$ and concentrated to a yellow liquid, which was purified by flash chromatography (Et_2O), furnishing a clear, light-yellow oil (1.27 g, 65%).

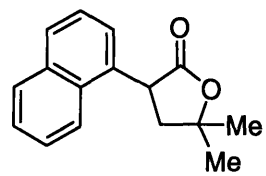
^1H NMR (500 MHz, C_6D_6) δ 7.32 (d, 2H, J=8.0), 6.87 (d, 2H, J=8.0), 3.58 (ddd, 1H, J=11.5, J=8.5, J=3.0), 3.37 (m, 1H), 2.92 (dd, 1H, J=15.5, J=9.5), 1.37-1.54 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 140.7, 130.1 (q, J=32.8), 128.6, 126.0 (q, J=3.4), 124.2 (q, J=272), 66.7, 45.5, 31.5. FTIR (neat) 2996, 2915, 1772, 1620, 1421, 1375, 1327, 1116 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{11}H_9F_3O_2$ (M^+) 220.1094, found 220.1090. bp 145-147 °C (0.5 mm Hg).



A solution of *n*-BuLi (2.65 M in hexanes; 27.6 mL, 73.3 mmol) was added via syringe to a –78 °C solution of diisopropylamine (10.3 mL, 73.3 mmol) in THF (80 mL). The mixture was stirred at –78 °C for 30 minutes and then warmed to 0 °C. A solution of *o*-tolylacetic acid (5.00 g, 33.3 mmol) in THF (20 mL) was then added via cannula. The

reaction mixture was warmed to 40 °C and stirred for 1 hour, and then neat isobutylene oxide (3.00 mL, 88.1 mmol) was added via syringe. The resulting solution was stirred at 0 °C for 1 hour, then refluxed for 18 hours. The solution was cooled to 0 °C, water (50 mL) was added, and the reaction mixture was refluxed for 2 hours. It was then cooled to room temperature, diluted with water (100 mL), and washed with Et_2O (3 x 50 mL). The aqueous layer was diluted with absolute EtOH (50 mL), acidified with 6 N HCl (200 mL), and refluxed for 2 hours. The reaction mixture was then cooled to room temperature and extracted with $CHCl_3$ (3 x 200 mL). The $CHCl_3$ layer was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL), dried (Na_2SO_4), and concentrated. The resulting yellow solid was recrystallized in 2 crops from Et_2O/pentane (1:10) to afford white crystals, which were collected, washed with pentane, and dried under vacuum (4.14 g, 61%).

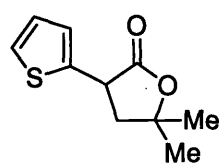
^1H NMR (500 MHz, $CDCl_3$) δ 7.17-7.27 (m, 4H), 4.21 (dd, 1H, J=11.0, J=9.0), 2.57 (dd, 1H, J=12.5, J=9.5), 2.36 (s, 3H), 2.13 (dd, 1H, J=12.5, J=11.5), 1.55 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 136.4, 136.0, 130.9, 128.0, 127.7, 126.9, 82.4, 44.7, 43.8, 29.2, 27.4, 19.9. FTIR (CH_2Cl_2) 3019, 2983, 1750, 1653, 1497, 1457, 1377, 1278, 1144 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{13}H_{16}O_2$ (M^+) 204.1145, found 204.1136. mp 64-66 °C.



A solution of *n*-BuLi (2.65 M in hexanes; 30.4 mL, 80.6 mmol) was added via syringe to a –78 °C solution of diisopropylamine (8.15 mL, 80.6 mmol) in THF (100 mL). The mixture was stirred at –78 °C for 30 minutes and then warmed to 0 °C. A

solution of naphthalene-1-acetic acid (5.00 g, 26.9 mmol) in THF (20 mL) was then added via cannula, resulting in a bright-orange solution. The reaction mixture was warmed to 50 °C and stirred for 1 hour. Then, neat isobutylene oxide (2.40 mL, 26.9 mmol) was added via syringe. The resulting deep-red solution was stirred at 60 °C for 12 hours. The solution was cooled to 0 °C, diluted with water (60 mL), and then refluxed for 2 hours. It was then cooled to room temperature, diluted with water (100 mL), and washed with Et_2O (3 x 50 mL). The aqueous layer was diluted with absolute EtOH (75 mL), acidified with 6 N HCl (50 mL), and refluxed for 2 hours. Then, it was cooled to room temperature and extracted with $CHCl_3$ (3 x 200 mL). The $CHCl_3$ layer was successively washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and NaCl (1 x 100 mL), dried ($MgSO_4$), and concentrated. The resulting yellow solid was recrystallized in 2 crops from CH_2Cl_2/pentane (1:5) to afford white crystals, which were collected, washed with pentane, and dried under vacuum (5.53 g, 86%).

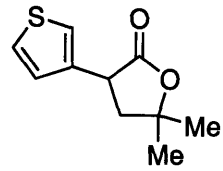
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.91 (m, 3H), 7.44-7.58 (m, 4H), 4.73 (dd, 1H, J=10.5, J=9.6), 2.74 (dd, 1H, J=12.9, J=9.3), 2.30 (dd, 1H, J=12.9, J=10.5), 1.60 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 134.2, 133.8, 131.4, 129.4, 128.5, 126.6, 126.0, 125.8, 123.0, 82.7, 44.7, 44.2, 29.2, 27.7. FTIR (CH_2Cl_2) 3053, 2975, 2932, 1763, 1653, 1512, 1457, 1375, 1268, 1138 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{16}H_{16}O_2$ (M^+) 240.1145, found 220.1140. mp 122-125 °C.



A solution of *n*-BuLi (2.60 M in hexanes; 38.8 mL, 101 mmol) was added via syringe to a –78 °C solution of diisopropylamine (14.2 mL, 101 mmol) in THF (150 mL).

The mixture was stirred at –78 °C for 30 minutes and then warmed to 0 °C. A solution of thiophene-2-acetic acid (7.00 g, 49.2 mmol) in THF (50 mL) was added via cannula, and the mixture was warmed to 40 °C and stirred for 1 hour. Neat isobutylene oxide (4.44 mL, 49.2 mmol) was added via syringe, and the resulting solution was refluxed for 18 hours. Water (100 mL) was then added, and the reaction mixture was refluxed for 2 hours. It was then cooled to room temperature and washed with Et_2O (3 x 150 mL). The aqueous layer was diluted with absolute EtOH (100 mL), acidified with 1N HCl (75 mL), and refluxed for 2 hours. It was then cooled to room temperature and extracted with $CHCl_3$ (3 x 200 mL). The $CHCl_3$ layer was washed successively with saturated aqueous $NaHCO_3$ (2 x 100 mL) and NaCl (2 x 100 mL), dried ($MgSO_4$), and concentrated. The resulting tan solid was recrystallized in 2 crops from CH_2Cl_2/pentane (3:10) to afford light-tan crystals, which were collected, washed with pentane, and dried under vacuum (8.60 g, 89%).

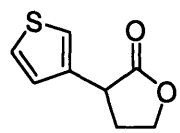
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, 1H, J=5.1, J=1.2), 6.97-7.03 (m, 2H), 4.27 (ddd, 1H, J=12.6, J=11.7, J=1.2), 2.67 (dd, 1H, J=12.6, J=9.0), 2.34 (dd, 1H, J=12.9, J=11.4), 1.54 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ 175.0, 138.6, 126.9, 125.6, 124.9, 82.5, 43.7, 42.1, 28.7, 26.9. FTIR (CH_2Cl_2) 3102, 2972, 2931, 2870, 1759, 1653, 1456, 1375, 1300, 1139 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{10}H_{12}O_2S$ (M^+) 196.0553, found 196.0561. mp 61-63 °C.



A solution of *n*-BuLi (2.65 M in hexanes; 16.7 mL, 44.3 mmol) was added via syringe to a –78 °C solution of diisopropylamine (6.21 mL, 44.3 mmol) in THF (70 mL).

The mixture was stirred at –78 °C for 30 minutes and then warmed to 0 °C. A solution of thiophene-3-acetic acid (3.00 g, 21.1 mmol) in THF (10 mL) was added via cannula, and the reaction mixture was warmed to 50 °C and stirred for 40 minutes. Neat isobutylene oxide (1.90 mL, 21.1 mmol) was added via syringe, and the resulting solution was stirred at 50 °C for 12 hours. Water (100 mL) was added, and the reaction mixture was refluxed for 2 hours. It was then cooled to room temperature and washed with Et_2O (3 x 150 mL). The aqueous layer was diluted with absolute EtOH (50 mL), acidified with 2 N HCl (75 mL), and refluxed for 2 hours. Then, it was cooled to room temperature and extracted with $CHCl_3$ (4 x 200 mL). The $CHCl_3$ layer was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL), dried (Na_2SO_4), and concentrated to afford a gold oil, which was purified by flash chromatography (25% Et_2O/75% pentane _ 40% Et_2O/60% pentane) to provide a clear, light-yellow oil (2.91 g, 70%).

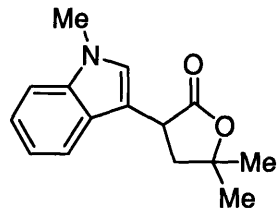
^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, 1H, J=5.1, J=2.7), 7.23-7.26 (m, 1H), 7.09 (dd, 1H, J=5.1, J=1.2), 4.12 (dd, 1H, J=11.4, J=9.0), 2.58 (dd, 1H, J=12.6, J=9.0), 2.25 (app t, 1H, J=12.0), 1.52 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 136.7, 127.0, 126.3, 122.1, 82.4, 42.9, 42.1, 28.8, 26.9. FTIR (neat) 3105, 2977, 2934, 1762, 1456, 1375, 1261, 1140 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{10}H_{12}O_2S$ (M^+) 196.0553, found 196.0557.



A solution of *n*-BuLi (2.65 M in hexanes; 16.0 mL, 42.3 mmol) was added via syringe to a –78 °C solution of diisopropylamine (5.93 mL, 42.3 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 45 minutes, and then a solution of thiophene-3-acetic acid (2.86 g, 20.1 mmol) in THF (20 mL) was added via cannula. The mixture was

stirred for 20 minutes at –78 °C, warmed to room temperature, and stirred for 45 minutes. A solution of 1,3,2-dioxathiolane 2,2-dioxide (2.50 g, 20.1 mmol) in THF (20 mL) was added via syringe. 1,2-Dimethoxyethane (15 mL) was added, and the resulting solution was refluxed for 16 hours. Water (20 mL) was then added, and the resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was washed successively with saturated aqueous $NaHCO_3$ (2 x 100 mL) and NaCl (1 x 50 mL), and then it was concentrated, affording a yellow liquid. Purification by flash chromatography (50% Et_2O/50% pentane _ 75% Et_2O/25% pentane) provided a clear, light-yellow oil (1.86 g, 55%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, 1H, J=4.8, J=3.0), 7.24-7.26 (m, 1H), 7.10 (dd, 1H, J=4.8, J=1.2), 4.47 (ddd, 1H, J=12.3, J=8.7, J=3.6), 4.35 (ddd, 1H, J=15.6, J=9.0, J=6.6), 3.91 (dd, 1H, J=9.6, J=9.0), 2.68-2.79 (m, 1H), 2.40-2.53 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 136.3, 126.9, 126.4, 122.1, 66.7, 40.7, 30.6. FTIR (neat) 3103, 2990, 2910, 1772, 1482, 1373, 1156, 1024 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_8H_8O_2S$ $(M+Na)^+$ 191.0137, found 191.0141.

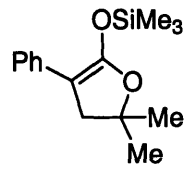


A solution of *n*-BuLi (2.96 M in hexanes; 19.6 mL, 58.1 mmol) was added via syringe to a –78 °C solution of diisopropylamine (8.15 mL, 58.1 mmol) in THF (50 mL). The mixture was stirred at –78 °C for 40 minutes, and then a solution of 1-methyl-indole-3-acetic acid (5.00 g, 26.4 mmol) in THF (20 mL) was added via cannula. The mixture was stirred at –78° C for 75 minutes, and then neat isobutylene oxide (2.38 mL, 26.4 mmol) was added via syringe. The resulting solution was warmed to room temperature

and stirred for 12 hours. Water (100 mL) was then added, and the resulting solution was refluxed for 2 hours. It was then cooled to room temperature, washed with Et_2O (3 x 150 mL), diluted with water (160 mL) and absolute EtOH (50 mL), and acidified with 6 N HCl (70 mL). This reaction mixture was refluxed for 4 hours and then cooled to room temperature and extracted with $CHCl_3$ (3 x 200 mL). The $CHCl_3$ layer was successively washed with saturated aqueous $NaHCO_3$ (3 x 100 mL) and water (2 x 100 mL), dried (Na_2SO_4), and concentrated. The resulting brown solid was recrystallized in 2 crops from EtOH/H_2O (1:1) to afford dark-tan crystals, which were collected, washed with pentane, and dried under vacuum (5.09 g, 79%).

^{1}H NMR (300 MHz, C_6D_6) δ 7.54 (d, 1H, J=7.2), 7.16-7.29 (m, 2H), 7.03 (d, 1H, J=7.8), 6.95 (s, 1H), 4.00 (dd, 1H, J=10.2, J=9.9), 2.91 (s, 3H), 2.11 (dd, 1H, J=12.3, J=9.3), 1.87 (dd, 1H, J=12.3, J=11.1), 1.10 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 137.4, 127.1, 126.7, 122.0, 119.4, 118.9, 110.0, 109.7, 82.5, 43.5, 38.9, 38.8, 29.1, 27.2. FTIR (CH_2Cl_2) 3055, 2975, 2934, 1770, 1653, 1558, 1474, 1375, 1256, 1140 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{15}H_{17}NO_2$ (M^+) 243.1254, found 243.1255. mp 121-122 °C.

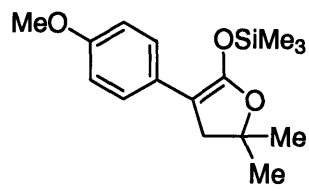
Preparation of Silyl Ketene Acetals



General procedure, (**1.61**). A solution of *n*-BuLi (2.45 M in hexanes; 9.00 mL, 22.1 mmol) was added via syringe to a –78 °C solution of diisopropylamine (3.10 mL, 22.1 mmol) in THF (10 mL). The mixture was stirred at –78 °C for 45 minutes, and then a solution of the lactone (4.0 g, 21.0 mmol) in THF (10 mL) was added via cannula. The mixture was stirred at –78 °C for 60 minutes, and then Me_3SiCl (2.80 mL, 22.1 mmol)

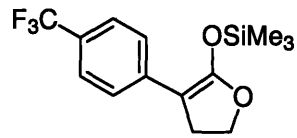
was added, resulting in a clear, light-yellow solution which was warmed to room temperature and stirred for 3 hours. The THF was then removed, and the residue was taken up in pentane and filtered. The solvent was removed, and the yellow liquid was purified by fractional distillation (126-128 °C, 0.5 mm Hg) to afford **1.61** as a clear, colorless liquid (2.01 g, 37%).

^{1}H NMR (300 MHz, C_6D_6) δ 7.70-7.75 (m, 2H), 7.43-7.49 (m, 2H), 7.14-7.19 (m, 1H), 2.67 (s, 2H), 1.29 (s, 6H), 0.35 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6) δ 153.8, 137.3, 129.5, 128.8, 124.3, 123.3, 82.0, 43.9, 29.2, 1.0. FTIR (CH_2Cl_2) 2900, 2849, 1662, 1659, 1600, 1502, 1461, 1371, 1170, 1161, 1068, 1004, 983, 857 cm^{-1}. bp 126-128 °C (0.5 mm Hg). HRMS (EI, *m/z*) calcd. for $C_{15}H_{22}O_2Si$ (M^+) 262.1384, found 262.1384.



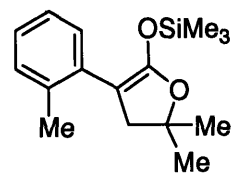
(**1.62**). The general procedure was followed, using *n*-BuLi (2.80 M in hexanes; 3.40 mL, 9.53 mmol), diisopropylamine (0.965 mL, 9.53 mmol), lactone (2.00 g, 9.08 mmol), and Me_3SiCl (1.25 mL, 9.53 mmol) in THF (25 mL). Purification by chromatography on Florisil (pentane) inside a glove box afforded **1.62** as a white crystalline solid (1.98 g, 75%).

^{1}H NMR (300 MHz, C_6D_6) δ 7.25 (dd, 2H, J=6.9, J=2.1), 6.81 (dd, 2H, J=6.9, J=2.1), 3.77 (s, 3H), 1.43 (s, 6H), 0.33 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6) δ 156.2, 152.2, 129.8, 125.1, 114.1, 81.6, 81.4, 55.7, 43.9, 29.0, 0.7. FTIR (CH_2Cl_2) 3152, 3007, 2899, 1669, 1666, 1514, 1369, 1240, 1168, 1093, 991 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{16}H_{24}O_3Si$ (M^+) 292.1489, found 292.1480. mp 54-56 °C.



(**1.63**). The general procedure was followed, using *n*-BuLi (2.80 M in hexanes; 2.30 mL, 6.48 mmol), diisopropylamine (0.910 mL, 6.48 mmol), lactone (1.42 g, 6.17 mmol), and Me_3SiCl (0.822 mL, 6.48 mmol) in THF (30 mL). Purification by chromatography on Florisil (pentane) inside a glove box afforded **1.63** as a white crystalline solid (1.21 g, 65%).

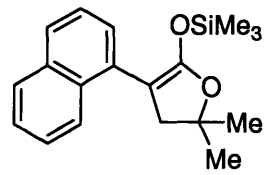
^1H NMR (300 MHz, C_6D_6) δ 7.51 (dd, 2H, J=9.0, J=0.9), 7.37 (dd, 2H, J=9.0, J=0.9), 3.80 (t, 2H, J=8.4), 2.40 (t, 2H, J=8.1), 0.20 (s, 9H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 157.9, 140.7, 129.2, 125.5 (q, J=4.0), 124.4 (q, J=32.4), 123.9, 82.4, 67.6, 30.4, 0.7. FTIR (CH_2Cl_2) 3152, 3008, 1658, 1607, 1529, 1327, 1192, 1121, 1067, 990 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{14}H_{17}F_3O_2Si$ (M^+) 302.0944, found 302.0944. mp 43-44 °C.



(**1.64**). The general procedure was followed, using *n*-BuLi (2.80 M in hexanes; 1.39 mL, 3.89 mmol), diisopropylamine (0.545 mL, 3.89 mmol), lactone (0.795 g, 3.89 mmol), and Me_3SiCl (0.494 mL, 3.89 mmol) in THF (22 mL). Purification by chromatography on Florisil (pentane) inside a glove box afforded **1.64**, as a clear, colorless oil (0.865 g, 81%).

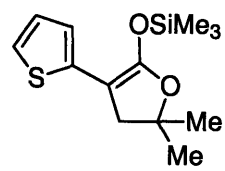
^1H NMR (300 MHz, C_6D_6) δ 7.30-7.33 (m, 1H), 6.99-7.15 (m, 3H), 2.62 (s, 2H), 2.56 (s, 3H), 1.22 (s, 6H), 0.10 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6) δ 152.1, 136.9, 136.1, 131.0, 129.5, 126.1, 126.0, 82.7, 81.4, 46.7, 28.6, 21.6, 0.7. FTIR (CH_2Cl_2) 2971, 1688, 1679,

1598, 1461, 1354, 1169, 1084, 994, 857 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{16}H_{24}O_2Si$ $(M+H)^+$ 277.1618, found 277.1624.



(**1.65**). The general procedure was followed, using *n*-BuLi (2.80 M in hexanes; 1.78 mL, 4.98 mmol), diisopropylamine (0.698 mL, 4.98 mmol), lactone (1.14 g, 4.74 mmol), and Me_3SiCl (0.632 mL, 4.98 mmol) in THF (25 mL). Purification by chromatography on Florisil (pentane) inside a glove box afforded **1.65** as a white solid (0.709 g, 48%).

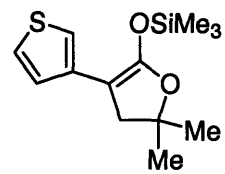
^1H NMR (300 MHz, C_6D_6) δ 8.31 (ddt, 1H, J=8.1, J=0.1), 7.66 (ddt, 1H, J=8.1, J=0.6), 7.53 (d, 1H, J=8.1), 7.24-7.39 (m, 4H), 2.76 (s, 2H), 1.27 (s, 6H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, C_6D_6) δ 152.9, 135.2, 135.0, 132.7, 129.1, 127.9, 126.7, 126.3, 126.11, 126.06, 125.4, 81.8, 81.6, 47.3, 28.7, 0.7. FTIR (CH_2Cl_2) 3054, 2985, 1558, 1540, 1506, 1456, 1420, 1265, 856 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{19}H_{24}O_2Si$ (M^+) 312.1540, found 312.1549. mp 86-89 °C.



(**1.66**). A solution of *n*-BuLi (2.80 M in hexanes; 2.78 mL, 7.79 mmol) was added via syringe to a –78 °C solution of diisopropylamine (1.10 mL, 7.79 mmol) in THF (15 mL). The mixture was stirred at –78 °C for 45 minutes, and then a solution of lactone (1.53 g, 7.79 mmol) in THF (10 mL) was added via cannula. The mixture was stirred at

–78 °C for 60 minutes, after which Me_3SiCl (0.988 mL, 7.79 mmol) was added, resulting in a clear, light-yellow solution, which was warmed to room temperature and stirred for 3 hours. The THF was then removed, and the yellow residue was taken up in pentane and filtered. The pentane was removed, and the yellow residue was taken into a glove box and purified by chromatography on activated Florisil (pentane), which afforded **1.66** as a clear, colorless oil (1.02 g, 49%).

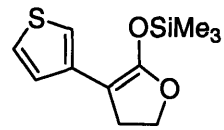
^1H NMR (500 MHz, C_6D_6) δ 6.88-6.95 (m, 2H), 6.68 (dd, 1H, J=3.3, J=1.5), 2.53 (s, 2H), 1.14 (s, 6H), 0.27 (s, 9H). ^{13}C NMR (75 MHz, C_6D_6) δ 152.8, 140.3, 127.1, 120.8, 118.8, 82.8, 81.3, 44.2, 28.8, 0.8. FTIR (CH_2Cl_2) 2963, 2901, 2851, 1678, 1665, 1520, 1461, 1369, 1238, 1166, 1091, 1043, 939 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{13}H_{20}O_2SSi$ $(M+H)^+$ 269.1026, found 269.1030.



(**1.67**). The general procedure was followed, using *n*-BuLi (2.65 M in hexanes; 2.17 mL, 5.76 mmol), diisopropylamine (0.807 mL, 5.76 mmol), lactone (1.13 g, 5.76 mmol), and Me_3SiCl (0.731 mL, 5.76 mmol) in THF (25 mL). Purification by chromatography on Florisil (pentane) inside a glove box afforded **1.67** as a clear, colorless oil (0.824 g, 53%).

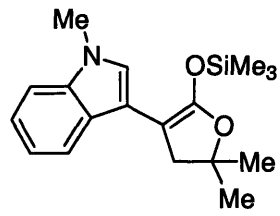
^1H NMR (300 MHz, C_6D_6) δ 7.57 (dd, 1H, J=5.1, J=1.2), 7.08 (dd, 1H, J=5.4, J=3.0), 6.68 (dd, 1H, J=2.7, J=1.2), 2.48 (s, 2H), 1.18 (s, 6H), 0.22 (s, 9H). ^{13}C NMR (75 MHz, C_6D_6) δ 152.5, 138.0, 126.1, 125.3, 114.1, 82.0, 80.7, 44.1, 28.9, 0.8. FTIR (CH_2Cl_2) 2962, 2900, 2849, 1689, 1679, 1527, 1461, 1382, 1370, 1342, 1228, 1198,

1163, 1098, 1016, 914 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{13}H_{20}O_2SSi$ (M^+) 268.0948, found 268.0941.



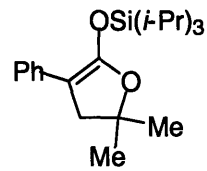
(**1.68**). A solution of *n*-BuLi (2.46 M in hexanes; 7.24 mL, 17.8 mmol) was added via syringe to a –78 °C solution of diisopropylamine (2.49 mL, 17.8 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 45 minutes, after which a solution of the lactone (2.85 g, 16.9 mmol) in THF (15 mL) was added via cannula. The mixture was stirred at –78 °C for 60 minutes, and then Me_3SiCl (2.26 mL, 17.8 mmol) was added, resulting in a clear, light-yellow solution, which was warmed to room temperature and stirred for 3 hours. The THF was then removed, and the orange residue was taken up in pentane and filtered. The solvent was removed, and the orange liquid was purified by fractional distillation (127 °C, 1.0 mm Hg), which afforded **1.68** as a clear, colorless oil (1.50 g, 45%).

^1H NMR (500 MHz, C_6D_6) δ 7.57 (dd, 1H, J=5.0, J=1.0), 7.07 (dd, 1H, J=5.0, J=3.0), 6.66 (dd, 1H, J=3.0, J=1.5), 3.87 (t, 2H, J=9.0), 2.52 (t, 2H, J=8.0), 0.22 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6) δ 137.5, 128.7, 126.0, 125.5, 114.5, 81.2, 67.1, 31.1, 0.7. FTIR (CH_2Cl_2) 3008, 2961, 2902, 2856, 1688, 1679, 1528, 1365, 1327, 1254, 1191 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{11}H_{16}O_2SSi$ $(M+H)^+$ 241.0713, found 241.0713. bp 127-128 °C (1.0 mm Hg).



(**1.69**). The general procedure was followed, using *n*-BuLi (2.80 M in hexanes; 1.03 mL, 2.89 mmol), diisopropylamine (0.405 mL, 2.89 mmol), lactone (0.704 g, 2.89 mmol), and Me_3SiCl (0.367 mL, 2.89 mmol) in THF (20 mL). Purification by chromatography on Florisil (pentane) inside a glove box afforded **1.69** as a viscous yellow oil (0.270 g, 30%).

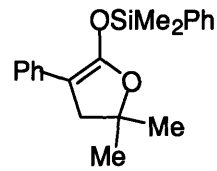
^{1}H NMR (300 MHz, C_6D_6) δ 8.37-8.42 (m, 1H), 7.32-7.41 (m, 2H), 7.12-7.18 (m, 1H), 6.92 (s, 1H), 3.09 (s, 3H), 2.97 (s, 2H), 1.37 (s, 6H), 0.36 (s, 9H). ^{13}C NMR (75 MHz, C_6D_6) δ 150.7, 137.9, 127.8, 124.6, 123.0, 122.1, 119.1, 111.9, 109.7, 81.5, 78.4, 45.7, 32.3, 29.1, 1.0. FTIR (CH_2Cl_2) 2970, 2880, 1691, 1680, 1547, 1534, 1479, 1369, 1320, 1173, 1062 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{18}H_{25}NO_2Si$ $(M+H)^+$ 316.1727, found 316.1738.



(**1.84**). A solution of *n*-BuLi (2.65 M in hexanes; 0.592 mL, 1.57 mmol) was added via syringe to a –78 °C solution of diisopropylamine (0.220 mL, 1.57 mmol) in THF (10 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of the lactone (0.300 g, 1.57 mmol) in THF (5 mL) was added via cannula. The mixture was stirred at –78 °C for 60 minutes, and then chlorotriisopropylsilane (0.336 mL, 1.57 mmol) was added, resulting in a clear, light-yellow solution which was warmed to room temperature and stirred for 12 hours. The THF was then removed, and the residue was

taken up in pentane and filtered. The solvent was removed, and the yellow oil, **1.84**, was used without purification (0.370 g, 68%).

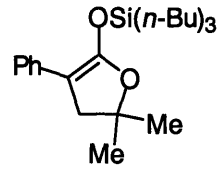
^{1}H NMR (500 MHz, C_6D_6) δ 7.59 (dd, 2H, J=7.5, J=3.0), 7.33 (m, 2H), 7.01 (ddt, 1H, J=7.5, J=7.0, J=1.0), 2.54 (s, 2H), 1.22 (sept, 3H, J=7.0), 1.16 (s, 6H), 1.12 (d, 18H, J=7.0). ^{13}C NMR (125 MHz, C_6D_6) δ 153.2, 137.4, 128.8, 124.7, 123.6, 81.7, 81.4, 44.1, 29.0, 18.4, 13.4. FTIR 3056, 3032, 2945, 2893, 2867, 1662, 1600, 1501, 1464, 1374, 1279, 1169, 1110, 1100, 1068, 1005, 985, 883, 821 (neat) cm^{-1}. HRMS (EI, *m/z*) submitted.



(**1.85**). A solution of *n*-BuLi (2.92 M in hexanes; 2.84 mL, 8.28 mmol) was added via syringe to a –78 °C solution of diisopropylamine (1.16 mL, 8.28 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 35 minutes, and then a solution of the lactone (1.50 g, 7.89 mmol) in THF (10 mL) was added via cannula. The mixture was stirred at –78 °C for 60 minutes, and then chlorodimethylphenylsilane (1.46 mL, 8.68 mmol) was added, resulting in a clear, light-yellow solution which was warmed to room temperature and stirred for 12 hours. The THF was then removed, and the residue was taken up in pentane and filtered. The solvent was removed, and the yellow oil, **1.85**, was used without purification (2.19 g, 86%).

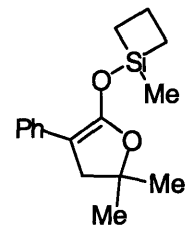
^{1}H NMR (500 MHz, C_6D_6) δ 7.58 (m, 4H), 7.28 (m, 2H), 6.99-7.19 (m, 4H), 2.49 (s, 2H), 1.07 (s, 6H), 0.46 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 153.2, 134.2, 133.7, 130.6, 130.0, 129.2, 128.9, 128.8, 124.7, 123.7, 83.1, 81.7, 43.8, 28.8, -0.19. FTIR (neat)

3084, 2976, 1677, 1604, 1454, 1257, 1118, 1054, 952, 831 cm^{-1}. HRMS (EI, *m/z*) submitted.



(**1.86**). A solution of *n*-BuLi (3.24 M in hexanes; 2.56 mL, 8.28 mmol) was added via syringe to a –78 °C solution of diisopropylamine (1.16 mL, 8.28 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 35 minutes, and then a solution of the lactone (1.50 g, 7.89 mmol) in THF (10 mL) was added via cannula. The mixture was stirred at –78 °C for 60 minutes, and then chlorotributylsilane (2.75 mL, 10.3 mmol) was added, resulting in a clear, light-yellow solution which was warmed to room temperature and stirred for 12 hours. The THF was then removed, and the residue was taken up in pentane and filtered. The solvent was removed, and the yellow oil, **1.86**, was used without purification (2.46 g, 80%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.59 (m, 2H), 7.33 (m, 2H), 7.01 (ddt, 1H, J=7.5, J=7.0, J=1.5), 2.55 (s, 2H), 1.44 (m, 6H), 1.35 (m, 6H), 1.20 (s, 6H), 0.88 (t, 9H, J=7.5), 0.82 (m, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 153.1, 136.9, 128.3, 124.2, 123.1, 81.7, 81.0, 43.4, 28.5, 26.7, 25.4, 14.4, 13.8. FTIR (neat) 2958, 2925, 2872, 1665, 1602, 1376, 1277, 1169, 985, 823 cm^{-1}. HRMS (EI, *m/z*) submitted.



(**1.87**). A solution of *n*-BuLi (2.92 M in hexanes; 2.84 mL, 8.28 mmol) was added via syringe to a –78 °C solution of diisopropylamine (1.16 mL, 8.28 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of the lactone (1.50 g, 7.89 mmol) in THF (10 mL) was added via cannula. The mixture was stirred at –78 °C for 60 minutes, and then 1-chloro-1methylsilacyclobutane (1.26 mL, 10.3 mmol) was added, resulting in a clear, light-yellow solution which was warmed to room temperature and stirred for 2 hours. The THF was then removed, and the residue was taken up in pentane and filtered. The solvent was removed, and the clear oil, **1.87**, was isolated as a mixture (3.4/1 product/starting material based on ^{1}H NMR and crude mass) without further purification (1.17 g, 54%).

^{1}H NMR (300 MHz, C_6D_6) δ 7.55 (m, 2H), 7.29 (m, 2H), 7.00 (tt, 1H, J=7.2, J=1.5), 2.53 (s, 2H), 2.00 (m, 2H), 1.55 (m, 4H), 1.15 (s, 6H), 0.30 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 152.9, 136.5, 128.4, 124.3, 123.4, 82.7, 81.4, 43.4, 28.4, 19.4, 14.4, -0.37. FTIR (neat) 2973, 2933, 1666, 1601, 1500, 1449, 1275, 1122, 985, 870, 793 695 cm^{-1}. HRMS (EI, *m/z*) submitted.

Enantioselectivity as a Function of Catalyst (1C.2)

General. Although several of the silyl ketene acetals were purified by chromatography on Florisil inside a glove box, this level of purity is not essential for catalytic enantioselective C-acylations–we have used unpurified silyl ketene acetals, and they furnish the same ee. However, we routinely purify the silyl ketene acetals in order to accurately determine the yields of the acylation reactions.

Unless otherwise specified, all reactions are the average of two runs. These acylations were set up in a glove box, due to the moisture sensitivity of the trimethylsilyl

ketene acetals, which results in lower yields when reactions are set up without a glove box.

Table 1C.2, entry 1. A solution of (–)-**1.11** (2.7 mg, 0.0077 mmol) in 1.4 mL of Et_2O/CH_2Cl_2 (14:1) was added to a 20-mL vial containing silyl ketene acetal **1.61** (28 mg, 0.11 mmol). The pink mixture was stirred for 5 minutes at room temperature, after which Ac_2O (0.013 mL, 0.14 mmol) was added, resulting in a bright-gold solution. The vial was capped and removed from the glove box. After stirring for 24 hours at room temperature, the reaction mixture was purified directly by flash chromatography (25% Et_2O/75% pentane). Product **1.71** was analyzed by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 110 °C, 1.0 mL/min, retention times of enantiomers: 40.2 min (minor), 41.9 min (major)), which showed 42% ee.

Run 2: silyl ketene acetal **1.61** (47 mg, 0.18 mmol), (–)-**1.11** (3.2 mg, 0.0091 mmol), Ac_2O (0.022 mL, 0.23 mmol), and 2.4 mL of Et_2O/CH_2Cl_2 (14:1); 37% ee.

Table 1C.2, entry 2. A solution of (–)-**1.12** (2.6 mg, 0.0069 mmol) in 1.8 mL of Et_2O/CH_2Cl_2 (14:1) was added to a 20-mL vial containing silyl ketene acetal **1.61** (36 mg, 0.14 mmol). The pink mixture was stirred for 5 minutes at room temperature, after which Ac_2O (0.017 mL, 0.18 mmol) was added, resulting in a bright-gold solution. The vial was capped and removed from the glove box. After stirring for 24 hours at room temperature, the reaction mixture was purified directly by flash chromatography (25% Et_2O/75% pentane). The product was analyzed by chiral GC, which showed 31% ee.

Run 2: silyl ketene acetal **1.61** (42 mg, 0.16 mmol), (–)-**1.12** (3.0 mg, 0.0080 mmol), Ac_2O (0.019 mL, 0.21 mmol), and 2.1 mL of Et_2O/CH_2Cl_2 (14:1); 34% ee.

Table 1C.2, entry 3. A solution of (–)-**1.15** (4.2 mg, 0.0064 mmol) in 1.7 mL of Et_2O/CH_2Cl_2 (14:1) was added to a 20-mL vial containing silyl ketene acetal **1.61** (33 mg, 0.13 mmol). The pink mixture was stirred for 5 minutes at room temperature, after which Ac_2O (0.016 mL, 0.17 mmol) was added. The vial was capped and removed from the glove box. After stirring for 24 hours at room temperature, the reaction mixture was purified directly by flash chromatography (25% Et_2O/75% pentane). The product was analyzed by chiral GC, which showed 87% ee.

Run 2: silyl ketene acetal **1.61** (32 mg, 0.12 mmol), (–)-**1.15** (4.0 mg, 0.0061 mmol), Ac_2O (0.015 mL, 0.16 mmol), and 1.6 mL of Et_2O/CH_2Cl_2 (14:1); 87% ee.

Table 1C.2, entry 4. The experimental procedure and the characterization data are located for Table 1C.6, entry 1.

Enantioselectivity as a Function of the Acylating Agent (1C.4)

General Procedure. A solution of catalyst (0.05 equiv) in Et_2O/CH_2Cl_2 (14:1) was added to a 20-mL vial containing silyl ketene acetal **1.61** (1.0 equiv). The resulting solution was stirred for 5 minutes at room temperature, after which the acylating agent (1.3 equiv) was added. The vial was capped and removed from the glove box, and the reaction mixture was stirred for 24 hours at room temperature. The product was then purified directly by flash chromatography (25% Et_2O/75% pentane). The catalyst was recovered by eluting with 3 volumes of CH_2Cl_2, followed by 10% Et_3N/90% EtOAc. The ee of the product was determined either by chiral HPLC or by chiral GC.

Table 1C.4, entry 1. See Table 1C.6, entry 1 for experimental information and characterization data.

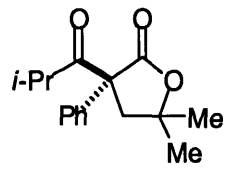


Table 1C.4, entry 2. The general procedure was followed, using silyl ketene acetal **1.61** (0.032 g, 0.12 mmol), isobutyric anhydride (0.026 mL, 0.16 mmol), (–)-**1.16** (0.0041 g, 0.0060 mmol), and 1.6 mL of Et_2O/CH_2Cl_2 (14:1) to produce 16% (0.0051 g, 0.020 mmol) of **1.81** as a clear, colorless oil which was shown by chiral HPLC (Daicel CHIRACEL OD, 4.6 mm x 25 cm, hexane/isopropanol 99:1, 1.0 mL/min, retention times of enantiomers: 5.81 min (minor), 6.24 min (major)) to have an 86%ee.

For run 2, silyl ketene acetal **1.61** (0.030 g, 0.12 mmol), isobutyric anhydride (0.025 mL, 0.15 mmol), and (+)-**1.16** (0.0040 g, 0.0058 mmol) in 1.6 mL of Et_2O/CH_2Cl_2 (14:1) furnished 14% of **1.71** (0.0042 g, 0.016 mmol), which was shown by chiral HPLC to have 79% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.45 (m, 5H), 3.47 (d, 1H, J=13.2), 3.39 (h, 1H, J=6.6), 2.29 (s, 3H), 2.24 (s, 3H), 1.07 (d, 3H, J=6.6), 0.750 (d, 3H, J=6.9). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 172.5, 137.5, 129.3, 128.2, 127.1, 82.4, 67.9, 44.7, 36.6, 29.4, 28.8, 21.2, 20.8. FTIR (neat) 3056, 2983, 1751, 1716, 1653, 1376, 1266, 1148, 1110, cm^{-1}. HRMS (ESI, *m/e*) calcd. for $C_{16}H_{20}O_3$ $(M+H)^+$ 261.1485, found 261.1486. $[\alpha]^{20}_D = +107°$ (c=0.77, CH_2Cl_2; for product with 86% ee).

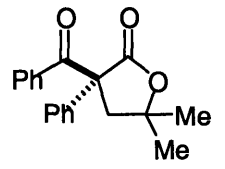


Table 1C.4, entry 3. The general procedure was followed, using silyl ketene acetal **1.61** (0.032 g, 0.12 mmol), benzoic anhydride (anhydride (0.026 g, 0.16 mmol), (–)-**1.16** (0.0036 g, 0.0052 mmol), and 1.4 mL of Et_2O/CH_2Cl_2 (14:1) to produce 84% 0.026 g,

0.089 mmol) of **1.82** as a white solid which was shown by chiral HPLC (Daicel CHIRACEL OD, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 5.44 min (minor), 5.93 min (major)) to have an 57%ee.

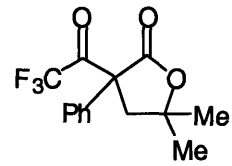
For run 2, silyl ketene acetal **1.61** (0.017 g, 0.064 mmol), benzoic anhydride (0.019 g, 0.083 mmol), and (+)-**1.16** (0.0022 g, 0.0032 mmol) in 1.0 mL of Et_2O/CH_2Cl_2 (14:1) furnished 79% of **1.82** (0.015 g, 0.051 mmol), which was shown by chiral HPLC to have 52% ee.

^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, 1H, J=8.5, J=1.0), 7.26-7.44 (m, 9H), 3.55 (d, 1H, J=13.5), 2.48 (d, 1H, J=13.5), 1.461 (s, 3H), 1.456 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 172.9, 139.8, 134.4, 133.1, 131.5, 129.6, 128.1, 126.9, 82.4, 68.1, 47.1, 30.1, 28.6. FTIR (CH_2Cl_2) 3061, 2980, 1772, 1761, 1675, 1653, 1558, 1506, 1456, 1375, 1269, 1235, 1183, 1140, 977 cm^{-1}. HRMS (ESI, *m/e*) calcd. for $C_{19}H_{18}O_3$ $(M+H)^+$ 295.1329, found 295.1335. $[\alpha]^{20}_D = -283°$ (c=0.12, CH_2Cl_2; for product with 52% ee). mp. 103°C.

Table 1C.2, entry 4. The general procedure was followed, using silyl ketene acetal **1.61** (0.031 g, 0.12 mmol), acetyl chloride (0.0011 mL, 0.16 mmol), (–)-**1.16** (0.0041 g, 0.0060 mmol), and 1.6 mL of Et_2O/CH_2Cl_2 (14:1) to produce 32% (0.0088 g, 0.038 mmol) of **1.71** as a white crystalline solid which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 110°C, 1.0 mL/min, retention times of enantiomers: 42.0 min (major), 41.3 min (minor)) to have a 73%ee.

For run 2, silyl ketene acetal **1.61** (0.032 g, 0.12 mmol), acetyl chloride (0.0011 mL, 0.16 mmol), and (+)-**1.16** (0.0042 g, 0.0061 mmol) in 1.6 mL of Et_2O/CH_2Cl_2 (14:1) furnished 54% of **1.71** (0.015 g, 0.065 mmol), which was shown by chiral HPLC to have 73% ee.

For characterization data, see Table 1C.6, entry 1.



(Table 1C.4, entry 5). The general procedure was followed, using silyl ketene acetal **1.61** (0.040 g, 0.15 mmol), trifluoroacetic anhydride (0.028 mL, 0.20 mmol), (–)-**1.16** (0.0052 g, 0.0076 mmol), and 2.0 mL of Et_2O/CH_2Cl_2 (14:1) to produce 54% 0.019 g, 0.067 mmol) of **1.83** as a white crystalline solid which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 110°C, 1.0 mL/min, retention times of enantiomers: 35.2 min , 38.5 min) to have a 0%ee.

For run 2, silyl ketene acetal **1.61** (0.031 g, 0.12 mmol), trifluoroacetic anhydride (0.022 mL, 0.16 mmol), and (+)-**1.16** (0.0041 g, 0.0060 mmol) in 1.6 mL of Et_2O/CH_2Cl_2 (14:1) furnished 58% of **1.83** ((0.016 g, 0.057 mmol), which was shown by chiral GC to have 0% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.61 (m, 2H), 7.36-7.42 (m, 3H), 3.07 (d, 1H, J=13.5), 2.97 (d, 1H, J=13.5), 1.54 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 235.5, 177.7, 129.6, 129.0, 128.8, 128.4, 122.3 (q, J=287), 84.6, 58.2, 42.5, 29.7, 27.8. FTIR (CH_2Cl_2) 3063, 3030, 2977, 1770, 1494, 1449, 1388, 1374,1251, 1192, 1147, 1054, 1012, 968 cm^{-1}. HRMS (ESI, *m/e*) calcd. for $C_{14}H_{13}F_3O_3$ $(M+Na)^+$ 309.0709, found 309.0700. mp. 122-124°C.

Table 1C.2, entry 6. The general procedure was followed, using silyl ketene acetal **1.61** (0.026 g, 0.10 mmol), pyruvonitrile (0.0089 g, 0.13 mmol), (–)-**1.16** 0.0034 g, 0.0050 mmol), and 1.3 mL of Et_2O/CH_2Cl_2 (14:1) to produce 7% (0.015 g, 0.0065 mmol) of **1.71**

as a white crystalline solid which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 110°C, 1.0 mL/min, retention times of enantiomers: 42.0 min (major), 41.3 min (minor)) to have a 0%ee.

For run 2, silyl ketene acetal **1.61** (0.031 g, 0.12 mmol), pyruvonitrile (0.0011 g, 0.16 mmol), and (+)-**1.16** (0.0041 g, 0.0060 mmol) in 1.6 mL of Et_2O/CH_2Cl_2 (14:1) furnished 13% of **1.71** (0.0038 g, 0.016 mmol), which was shown by chiral HPLC to have 0% ee.

For characterization data, see Table 1C.6, entry 1.

Enantioselectivity as a Function of the Aromatic Substituent (Table 1.C6)

General. Although several of the silyl ketene acetals were purified by chromatography on Florisil inside a glove box, this level of purity is not essential for catalytic enantioselective C-acylations–we have used unpurified silyl ketene acetals, and they furnish the same ee. However, we routinely purify the silyl ketene acetals in order to accurately determine the yields of the acylation reactions.

Unless otherwise specified, all reactions are the average of two runs (one run with each enantiomer of the catalyst). The acylations were set up in a glove box (exceptions: Table 1C.6, entries 2 and 5), due to the moisture sensitivity of the trimethylsilyl ketene acetals, which results in lower yields when reactions are set up without a glove box.

General Procedure. A solution of catalyst (0.05 equiv) in Et_2O/CH_2Cl_2 (14:1) was added to a 20-mL vial containing the silyl ketene acetal (1.0 equiv). The resulting solution was stirred for 5 minutes at room temperature, after which Ac_2O (1.3 equiv) was added. The vial was capped and removed from the glove box, and the reaction mixture was stirred for 24 hours at room temperature. The product was then purified directly by

flash chromatography (25% Et_2O/75% pentane). The catalyst was recovered by eluting with 3 volumes of CH_2Cl_2, followed by 10% Et_3N/90% EtOAc. The ee of the product was determined either by chiral HPLC or by chiral GC.

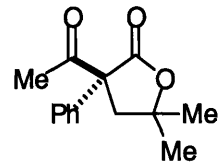


Table 1C.6, entry 2. The general procedure was followed, using silyl ketene acetal **1.61** (0.164 g, 0.626 mmol), Ac_2O (0.0768 mL, 0.814 mmol), (+)-**1.16** (0.0215 g, 0.0313 mmol), and 8.2 mL of Et_2O/CH_2Cl_2 (14:1) to produce 78% (0.113 g, 0.487 mmol) of white crystalline solid **1.71**, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 110 °C, 1.0 mL/min, retention times of enantiomers: 42.0 min (major), 41.3 min (minor)) to have 90% ee.

^1H NMR (300 MHz, C_6D_6) δ 7.30-7.34 (m, 2H), 6.92-7.04 (m, 3H), 3.25 (d, 1H, J=13.5), 2.10 (s, 3H), 1.82 (d, 1H, J=13.5), 1.04 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 172.8, 138.9, 129.6, 128.3, 126.7, 82.6, 68.6, 44.7, 29.1, 28.9, 26.5. FTIR (CH_2Cl_2) 2983, 2932, 1750, 1718, 1559, 1455, 1373, 1275, 1182, 1151, 1097 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{16}O_3$ $(M+Na)^+$ 255.0992, found 255.0993. $[\alpha]^{20}_D = -213°$ (c=0.89, CH_2Cl_2; for product with 90% ee). mp 64-66 °C.

For run 2 (inside a glove box), silyl ketene acetal **1.61** (0.153 g, 0.582 mmol), Ac_2O (0.0714 mL, 0.757 mmol), and (–)-**1.16** (0.0200 g, 0.0290 mmol) in 7.7 mL of Et_2O/CH_2Cl_2 (14:1) furnished 81% of **1.71** (0.109 g, 0.470 mmol), which was shown by chiral GC to have 90% ee.

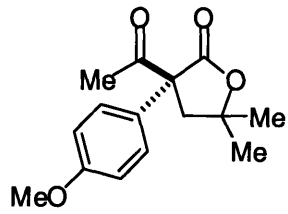


Table 1C.6, entry 3. The general procedure was followed, without the use of a glove box, with silyl ketene acetal **1.62** (0.148 g, 0.506 mmol), Ac_2O (0.0621 mL, 0.658 mmol), (+)-**1.16** (0.0174 g, 0.0253 mmol), and 6.7 mL of Et_2O/CH_2Cl_2 (14:1) to produce 76% (0.101 g, 0.385 mmol) of colorless crystalline solid **1.72**, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 120 °C, 1.0 mL/min, retention times of enantiomers: 105 min (major), 108 min (minor)) to have 95% ee.

^1H NMR (500 MHz, C_6D_6) δ 7.23 (d, 2H, J=9.0), 6.61 (d, 2H, J=9.0), 3.21 (d, 1H, J=13.5), 3.17 (s, 3H), 2.12 (s, 3H), 1.83 (d, 1H, J=13.5), 1.04 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 173.0, 160.0, 131.8, 128.5, 115.2, 81.8, 68.2, 55.1, 45.0, 29.0, 28.8, 26.2. FTIR (CH_2Cl_2) 2979, 2937, 2839, 1751, 1716, 1609, 1512, 1457, 1375, 1356, 1254, 1183, 1031 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{15}H_{18}O_4$ (M^+) 262.1200, found 262.1196. $[\alpha]^{20}_D = -235°$ (c=1.0, CH_2Cl_2; for product with 95% ee). mp 47-49 °C.

For run 2 (inside a glove box), silyl ketene acetal **1.62** (0.150 g, 0.513 mmol), Ac_2O (0.0629 mL, 0.667 mmol), and (–)-**1.16** (0.0176 g, 0.0260 mmol) in 6.8 mL of Et_2O/CH_2Cl_2 (14:1) furnished 80% of **1.72** (0.107 g, 0.408 mmol), which was shown by chiral GC to have 95% ee.

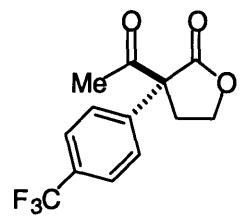


Table 1C.6, entry 4. The general procedure was followed, using silyl ketene acetal **1.63** (0.141 g, 0.466 mmol), Ac_2O (0.0572 mL, 0.606 mmol), (+)-**1.16** (0.0160 g, 0.0233 mmol), and 6.1 mL of Et_2O/CH_2Cl_2 (14:1) to produce 85% (0.108 g, 0.394 mmol) of aclear, colorless oil **1.73**, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 150 °C, 1.0 mL/min, retention times of enantiomers: 9.48 min (major), 12.9 min (minor)) to have 90% ee.

^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, 2H, J=8.7, J=0.6), 7.56 (dd, 2H, J=8.7, J=0.6), 4.22-4.36 (m, 2H), 3.35-3.44 (m, 1H), 2.39 (ddd, 1H, J=13.2, J=7.5, J=7.5), 2.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 173.0, 140.6, 130.8 (q, J=32.8), 127.4, 126.5 (q, J=4.0) 123.8 (q, J=272.4), 65.9, 65.8, 33.4, 26.5. FTIR (CH_2Cl_2) 3077, 3001, 2921, 1771, 1717, 1617, 1414, 1360, 1328, 1328, 1120, 1069, 1019, 843 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{13}H_{11}F_3O_3$ $(M+Na)^+$ 295.0552, found 295.0555. $[\alpha]^{20}_D = -150°$ (c=0.32, CH_2Cl_2; for product with 90% ee).

For run 2, silyl ketene acetal **1.63** (0.150 g, 0.496 mmol), Ac_2O (0.0609 mL, 0.645 mmol), and (–)-**1.16** (0.0170 g, 0.0248 mmol) in 6.5 mL of Et_2O/CH_2Cl_2 (14:1) furnished 83% of **1.73** (0.111 g, 0.408 mmol), which was shown by chiral GC to have 90% ee.

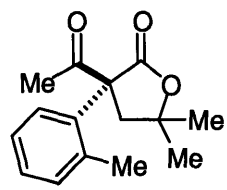


Table 1C.6, entry 5. The general procedure was followed, using silyl ketene acetal **1.64** (0.150 g, 0.543 mmol), Ac_2O (0.0666 mL, 0.706 mmol), (–)-**1.16** (0.0186 g, 0.0270 mmol), and 7.1 mL of Et_2O/CH_2Cl_2 (14:1), except that the reaction was stirred for 36 hours at room temperature. The reaction produced 87% (0.117 g, 0.475 mmol) of white

crystalline solid **1.74**, which was shown by chiral HPLC (Daicel CHIRALPAK AD, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 4.51 min (minor), 5.10 min (major)) to have 94% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.49 (m, 1H), 7.16-7.28 (m, 3H), 3.56 (d, 1H, J=13.2), 2.21 (s, 3H), 2.10 (d, 1H, J=13.2), 2.09 (s, 3H), 1.51 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 173.0, 138.6, 135.4, 132.7, 128.4, 127.9, 127.0, 83.0, 69.5, 43.5, 29.5, 29.4, 27.2, 20.2. FTIR (CH_2Cl_2) 3065, 2978, 2934, 2875, 1750, 1716, 1456, 1375, 1271, 1182, 1143, 1104, 1036, 961 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{18}O_3$ $(M+Na)^+$ 269.1148, found 269.1141. $[\alpha]^{20}_D$ = + 256° (c=0.39, CH_2Cl_2; for product with 94% ee). mp 67-68 °C.

For run 2, silyl ketene acetal **1.64** (0.155 g, 0.562 mmol), Ac_2O (0.0689 mL, 0.731 mmol), and (+)-**1.16** (0.0193 g, 0.0281 mmol) in 7.4 mL of Et_2O/CH_2Cl_2 (14:1) furnished 90% of **1.74** (0.125 g, 0.509 mmol), which was shown by chiral HPLC to have 96% ee.

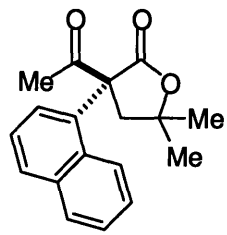


Table 1C.6, entry 6. The general procedure was followed, using silyl ketene acetal **1.65** (0.150 g, 0.480 mmol), Ac_2O (0.0589 mL, 0.624 mmol), (–)-**1.16** (0.0165 g, 0.0240 mmol), and 6.3 mL of Et_2O/CH_2Cl_2 (14:1) to produce 79% (0.107 g, 0.379 mmol) of white crystalline solid **1.75**, which was shown by chiral HPLC (Daicel CHIRALCEL OD, 4.6 mm x 25 cm, hexane/isopropanol 99:1, 1.0 mL/min, retention times of enantiomers: 8.68 min (minor), 9.76 min (major)) to have 99% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.93 (m, 2H), 7.75 (dd, 1H, J=6.3, J=0.9), 7.39-7.55 (m, 4H), 3.80 (d, 1H, J=13.2), 2.35 (d, 1H, J=13.2), 2.10 (s, 3H), 1.57 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 173.1, 135.9, 134.9, 130.3, 129.9, 129.5, 127.4, 126.32, 126.31, 125.7, 123.5, 83.4, 69.3, 44.2, 29.5, 29.4, 27.4. FTIR (CH_2Cl_2) 3061, 3001, 2981, 1747, 1715, 1559, 1456, 1388, 1351, 1272, 1179, 1149, 1132, 1064, 953 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{18}H_{18}O_3$ (M^+) 282.1250, found 282.1259. $[\alpha]^{20}_D$ = +349° (c=0.64, CH_2Cl_2; for product with 99% ee). mp 123-126 °C.

For run 2 (outside a glove box), the silyl ketene acetal **1.65** (0.155 g, 0.495 mmol), Ac_2O (0.0607 mL, 0.644 mmol), and (+)-**1.16** (0.0170 g, 0.0248 mmol) in 6.5 mL of Et_2O/CH_2Cl_2 (14:1) furnished 84% of **1.75** (0.117 g, 0.415 mmol), which was shown by chiral HPLC to have 99% ee.

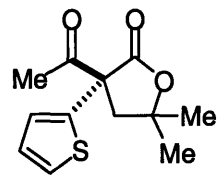


Table 1C.6, entry 7. The general procedure was followed, using silyl ketene acetal **1.66** (0.140 g, 0.521 mmol), Ac_2O (0.0639 mL, 0.678 mmol), (+)-**1.16** (0.0179 g, 0.0261 mmol), and 6.9 mL of Et_2O/CH_2Cl_2 (14:1) to produce 86% (0.108 g, 0.453 mmol) of clear, colorless oil **1.76**, which was shown by chiral HPLC (Daicel CHIRALCEL OD, 4.6 mm x 25 cm, hexane/isopropanol 99:1, 1.0 mL/min, retention times of enantiomers: 8.79 min (major), 9.99 min (minor)) to have 75% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, 1H, J=5.1, J=1.2), 7.17 (dd, 1H, J=3.6, J=1.2), 7.20 (dd, 1H, J=5.1, J=3.6), 3.41 (d, 1H, J=13.2), 2.41 (d, 1H, J=13.2), 2.33 (s, 3H), 1.45 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 172.4, 140.6, 127.5, 126.7, 126.4, 83.2, 65.0, 45.1, 29.1, 28.5, 25.6. FTIR (neat) 3109, 2980, 2935,

1757, 1717, 1456, 1376, 1272, 1132, 961 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{12}H_{14}O_3S$ $(M+Na)^+$ 261.0556, found 261.0566. $[\alpha]^{20}_D = -154°$ (c=0.54, CH_2Cl_2; for product with 75% ee).

For run 2, the silyl ketene acetal **1.66** (0.158 g, 0.588 mmol), Ac_2O (0.0721 mL, 0.764 mmol), and (–)-**1.16** (0.0202 g, 0.0290 mmol) in 7.7 mL of Et_2O/CH_2Cl_2 (14:1) furnished 81% of **1.76** (0.113 g, 0.474 mmol), which was shown by chiral HPLC to have 77% ee.

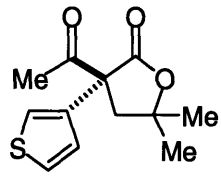


Table 1C.6, entry 8. The general procedure was followed, using silyl ketene acetal **1.67** (0.148 g, 0.551 mmol), Ac_2O (0.0675 mL, 0.716 mmol), (+)-**1,16** (0.0189 g, 0.0275 mmol), and 7.2 mL of Et_2O/CH_2Cl_2 (14:1) to produce 84% (0.110 g, 0.460 mmol) of a clear, colorless oil **1.77**, which was shown by chiral HPLC (Daicel CHIRALCEL OD, 4.6 mm x 25 cm, hexane/isopropanol 99:1, 1.0 mL/min, retention times of enantiomers: 8.99 min (major), 9.84 min (minor)) to have 86% ee.

^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, 1H, J=3.0, J=1.2), 7.36 (dd, 1H, J=5.1, J=3.0), 6.97 (dd, 1H, J=5.1, J=1.2), 3.34 (d, 1H, J=13.5), 2.31 (d, 1H, J=13.5), 2.25 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 173.1, 138.2, 127.6, 126.1, 123.0, 82.8, 65.4, 43.9, 29.1, 28.7, 26.0. FTIR (neat) 3109, 2980, 2935, 1752, 1717, 1456, 1375, 1272, 1180, 1131, 1096, 960 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{12}H_{14}O_3S$ $(M+Na)^+$ 261.0556, found 261.0565. $[\alpha]^{20}_D = -209°$ (c=0.64, CH_2Cl_2; for product with 86% ee).

For run 2, the silyl ketene acetal **1.67** (0.133 g, 0.495 mmol), Ac_2O (0.0607 mL, 0.644 mmol), and (–)-**1.16** (0.0170 g, 0.0248 mmol) in 6.5 mL of Et_2O/CH_2Cl_2 (14:1) furnished 88% of **1.77** (0.104 g, 0.436 mmol), which was shown by chiral HPLC to have 88% ee.

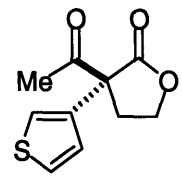


Table 1C.6, entry 9. The general procedure was followed, using silyl ketene acetal **1.68** (0.163 g, 0.679 mmol), Ac_2O (0.0832 mL, 0.882 mmol), (–)-**1.16** (0.0233 g, 0.0340 mmol), and 8.9 mL of Et_2O/CH_2Cl_2 (14:1) to produce 70% (0.100 g, 0.476 mmol) of clear, colorless oil **1.78**, which was shown by chiral HPLC (Daicel CHIRALPAK AD, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 7.25 min (minor), 7.91 min (major)) to have 80% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, 1H, J=2.7, J=2.4), 7.39 (dd, 1H, J=5.1, J=2.7), 7.04 (dd, 1H, J=5.1, J=2.4), 4.22-4.35 (m, 2H), 3.27-3.35 (m, 1H), 2.42 (d app t, 1H, J=12.9, J=7.5), 2.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 174.3, 137.0, 128.1, 126.7, 124.0, 66.7, 63.4, 33.3, 26.7. FTIR (neat) 3108, 2978, 2917, 1771, 1716, 1456, 1419, 1373, 1162 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{10}H_{10}O_3S$ $(M+Na)^+$ 233.0243, found 233.0244. $[\alpha]^{20}_D = +174°$ (c=0.23, CH_2Cl_2; for product with 80% ee).

For run 2, silyl ketene acetal **1.68** (0.162 g, 0.673 mmol), Ac_2O (0.0825 mL, 0.875 mmol), and (+)-**1.16** (0.0231 g, 0.0336 mmol) in 8.9 mL of Et_2O/CH_2Cl_2 (14:1) furnished 76% of **1.78** (0.108 g, 0.514 mmol), which was shown by chiral HPLC to have 80% ee.

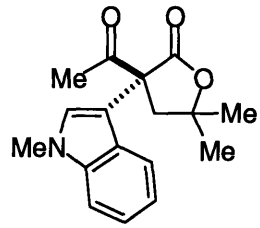


Table 1C.6, entry 9. The general procedure was followed, using silyl ketene acetal **1.69** (0.163 g, 0.518 mmol), Ac_2O (0.0636 mL, 0.674 mmol), (–)-**1.16** (0.0178 g, 0.0260 mmol), and 6.8 mL of Et_2O/CH_2Cl_2 (14:1) to produce 94% (0.139 g, 0.489 mmol) of white crystalline solid **1.79**, which was shown by chiral HPLC (Daicel CHIRALCEL OD, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 6.10 min (minor), 7.20 min (major)) to have 95% ee.

For run 2, silyl ketene acetal **1.69** (0.139 g, 0.440 mmol), Ac_2O (0.0539 mL, 0.572 mmol), and (+)-**1.16** (0.0151 g, 0.0220 mmol) in 5.8 mL of Et_2O/CH_2Cl_2 (14:1) furnished 87% of **1.79** (0.109 g, 0.383 mmol), which was shown by chiral HPLC to have 92% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.38 (m, 4H), 7.07-7.13 (m, 1H), 3.81 (s, 3H), 3.61 (d, 1H, J=13.2), 2.36 (d, 1H, J=13.2), 2.23 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) _ 201.9, 173.7, 137.6, 127.6, 125.3, 122.5, 120.2, 119.3, 112.3, 109.9, 83.3, 63.1, 42.8, 33.1, 29.6, 28.9, 25.7. FTIR (CH_2Cl_2) 3125, 3056, 2978, 2934, 1751, 1716, 1540, 1473, 1457, 1375, 1272, 1146, 1071, 965 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{17}H_{19}NO_3$ (M^+) 285.1360, found 285.1357. $[\alpha]^{20}_D = -348°$ (c=0.62, CH_2Cl_2; for product with 92% ee). mp 84-87 °C.

Mechanistic Studies (Table 1.C8)

Table 1C.8, entry 1. A solution of **1.63** (0.020 g, 0.066 mmol) and 1,4-dioxane (internal standard; 0.0011 mL, 0.013 mmol) in CD_2Cl_2 (0.80 mL) was added to a screwcap NMR tube. Immediately prior to data acquisition, Ac_2O (0.0062 mL, 0.066 mmol) was added. The reaction was monitored by ^1H NMR spectroscopy after reaction times of 5 minutes, 30 minutes, 3.5 hours, 30 hours, 60 hours, and 100 hours. All of the spectra showed only unreacted starting materials.

Table 1C.8, entry 2. A solution of **1.63** (0.020 g, 0.066 mmol) in CD_2Cl_2 (0.30 mL) and a solution of (–)-**1.16** (0.0023 mg, 0.0033 mmol) and 1,4-dioxane (internal standard; 0.56 μL, 0.0066 mmol) in CD_2Cl_2 (0.40 mL) were added in turn to a screwcap NMR tube. Immediately prior to data acquisition, a solution of Ac_2O (0.0063 mL, 0.0662 mmol) in CD_2Cl_2 (0.10 mL) was added. The reaction was monitored by ^1H NMR. Spectra were collected every 2 minutes for the first 50 minutes; the data showed a $t_{1/2}$ of 17 minutes. The reaction mixture was passed through a plug of silica gel (CH_2Cl_2 as the eluent) and concentrated. The product was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 150 °C, 1.0 mL/min, retention times of enantiomers: 9.48 min (major), 12.9 min (minor)) to have 87% ee.

Table 1C.8, entry 3.[37] Inside a glove box, acetyl chloride (0.0010 mL, 0.13 mmol) was added to a deep-purple solution of (+)-**1.16** (0.035 g, 0.051 mmol) in CH_2Cl_2 (5 mL). After ~15 minutes, the CH_2Cl_2 and excess acetyl chloride were removed by vacuum. The resulting blue-green solid (+)-**1.17** was dissolved in CH_2Cl_2 (2 mL) and then

[37] The DMAP analogue of this complex has been prepared and fully characterized, including an X-ray crystal structure: Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091-5092.

evaporated to dryness (to remove residual acetyl chloride). A solution of $AgSbF_6$ (0.018 g, 0.052 mmol) in acetonitrile (3 mL) was added. The resulting mixture was filtered through an acrodisc to remove the AgCl, then evaporated to provide a green residue, which was washed several times with CH_2Cl_2/pentane (1:1) to afford a crystalline green solid (+)-**1.18** (0.049 g, 0.051 mmol) in quantitative yield.

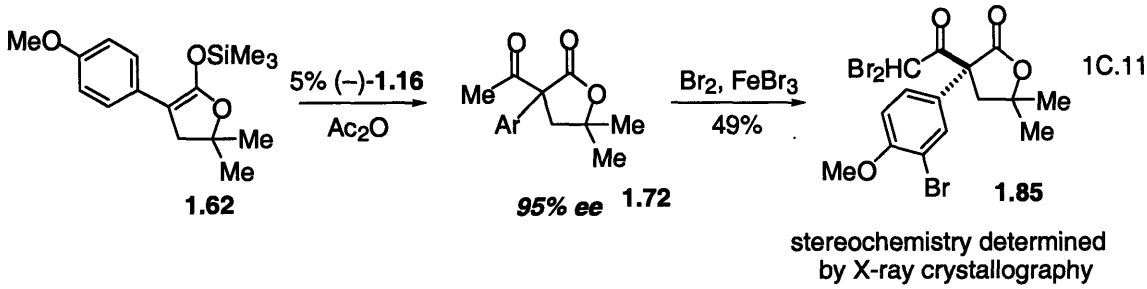
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.15 (d, 1H, J=8.1), 7.26 (t, 5H, J=7.5), 7.12 (t, 10H, J=7.5), 6.86 (d, 10H, J=7.5), 6.41 (dd, 1H, J=3.0, J=1.2), 6.28 (d, 1H, J=8.4), 5.10 (dd, 1H, J=3.0, J=1.2), 4.89 (t, 1H, J=3.0), 3.63-3.90 (m, 4H), 2.45 (s, 3H), 2.05-2.31 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 165.6, 141.1, 133.5, 132.4, 128.0, 127.9, 101.5, 100.4, 88.4, 82.7, 71.8, 70.4, 70.2, 54.5, 53.9, 26.2, 24.8, 23.6. FTIR (KBr) 3056, 1735, 1609, 1560, 1507, 1219, 1173, 990, 702, 658 cm^{-1}. Anal. Calcd. for $C_{49}H_{41}F_6FeN_2OSb$ (965.5): C, 60.96; H, 4.28; N, 2.90. Found: C, 60.66; H, 3.90; N, 2.76. $[\alpha]^{25}_D$ = +72° (c=0.09, CH_2Cl_2; for product with >99% ee). mp 242-244 °C.

A solution of (+)-**1.18** (0.049 g, 0.051 mmol) and 1,4-dioxane (internal standard; 0.0011 mL, 0.013 mmol) in CD_2Cl_2 (0.50 mL) was added to a screwcap NMR tube. Immediately prior to data acquisition, a solution of the silyl ketene acetal (0.015 g, 0.051 mmol) in CD_2Cl_2 (0.30 mL) was added. The reaction was monitored by ^{1}H NMR spectroscopy after reaction times of 5 minutes, 72 minutes, 10 hours, and 60 hours. All of the spectra showed only unreacted starting materials.

Table 1C.8, entry 4. A stock solution of the silyl ketene acetal was prepared by the addition of CD_2Cl_2 (1.0 mL) and 1,4-dioxane (internal standard; 6.0 μL) to the silyl ketene acetal (42.0 mg, 0.138 mmol). Another stock solution was prepared by the addition of CD_2Cl_2 (1 mL) to Me_4N[OAc] (5.3 mg, 0.040 mmol). To a screwcap NMR tube was added 0.35 mL of the stock solution of the silyl ketene acetal, then CD_2Cl_2

(0.40 mL), and then 62 μL of the stock solution of $Me_4N[OAc]$. After ~15 minutes, neat Ac_2O (6.1 μL, 0.064 mmol) was added. A ^1H NMR spectrum after 2 minutes indicated ~80% conversion to product (versus 1,4-dioxane).

Determination of the Absolute Configuration of the Product



(**1.85**). $FeBr_3$ (0.0100 g, 0.0330 mmol) and a solution of bromine (0.0569 mL, 1.12 mmol) in $CHCl_3$ (1.50 mL) were added in turn to a solution of lactone **1.72** (0.0975 g, 0.372 mmol) in $CHCl_3$ (2.0 mL). The resulting mixture was stirred at room temperature for 34 hours, after which additional $FeBr_3$ (0.0150 g, 0.0507 mmol) and bromine (0.0300 mL, 0.588 mmol) were added. The mixture was stirred at room temperature for 30 hours, and then it was poured into saturated aqueous $Na_2S_2O_3$ and extracted with Et_2O (3 x 20 mL). The organic layer was washed with water (1 x 30 mL) and dried over Na_2SO_4. The solvent was removed, and the resulting off-white solid was purified by flash chromatography (25% Et_2O/75% pentane), which furnished 49% of white crystalline solid **1.85** (0.0890 g, 0.212 mmol).

^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 1H, J=2.7), 7.37 (dd, 1H, J=9.0, J=3.0), 6.92 (d, 1H, J=8.7), 6.57 (s, 1H), 3.94 (s, 3H), 3.43 (d, 1H, J=13.5), 2.36 (d, 1H, J=13.5), 1.50 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 171.5, 156.7, 132.4, 128.5, 127.8, 113.2, 112.5, 83.7, 65.2, 56.6, 45.2, 36.1, 29.1, 28.7. FTIR (CH_2Cl_2) 3029,

2982, 2943, 2904, 2483, 1749, 1733, 1559, 1540, 1497, 1457, 1388, 1273, 1199 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{15}Br_3O_4$ $(M+H)^+$ 496.8613, found 496.8613. $[\alpha]^{20}_D$ = +235° (c=0.25, CH_2Cl_2; for product with 95% ee). mp 148-152 °C.

X-ray quality crystals were grown from Et_2O/pentane, and the configuration of the quaternary center was assigned as (R) by single crystal X-ray diffraction.

X-ray Crystal Structure

A colorless solution of the lactone in Et_2O was prepared. Crystals suitable for X-ray structural analysis were obtained by pentane diffusion. A clear, colorless block of dimensions 0.57 x 0.18 x 0.09 mm^3 was mounted under STP and transferred to a Bruker AXS/CCD three-circle diffractometer (χ fixed at 54.78°) equipped with a cold stream of N_2 gas. An initial unit cell was determined by harvesting reflections $I > 20\ \sigma\ (I)$ from 45 x 10-s frames of 0.30° ω scan data with monochromated Mo K_α radiation ($\lambda = 0.71073$ Å). The cell thus determined was orthorhombic.

A hemisphere of data was then collected using ω scans of 0.30° and 10-s frames. The raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. Actual integration was performed with constant spot sizes of 1.6° in the detector plane and 0.6° in ω. The data that were collected (6854 total reflections, 2473 unique, $R_{int} = 0.2631$) had the following Miller index ranges: –7 to 7 in h, –13 to 12 in k, and –13 to 22 in l. The data were corrected for Lorentz and polarization effects. No absorption correction was applied.

All aspects of the solution and refinement were handled by SHELXTL NT version 5.10.[38] The structure was solved by direct methods in the orthorhombic space group P2(1)2(1)2(1), a = 6.7476(8) Å; b = 12.5932(15) Å; c = 20.305(2) Å; $\alpha = 90°$; $\beta = 90°$; $\gamma = 90°$, and refined using standard difference Fourier techniques. Final, full-matrix least-squares refinement (2473 data for 203 parameters) on F^2 yielded residuals of R_1 and wR_2 of 0.0878 and 0.2031 for data $I > 2\sigma\ (I)$, and 0.0906 and 0.2070, respectively, for all data. During the final refinement, all non-hydrogen atoms were treated anisotropically. Hydrogen atoms were included in calculated positions and refined isotropically on a

[38] SHELXTL: Bruker AXS, Inc., SHELXTLTM Reference Manual Version 5.1, 1997.

riding model. A secondary extinction coefficient of 0.021(3) was used in the refinement. Residual electron density amounted to a maximum of 1.886 e/Å^3 and a minimum of –2.216 e/Å^3.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-178106. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; E-mail: deposit@ccdc.cam.ac.uk).

Tables 1-6 provide the full crystallographic data for the X-ray structure.

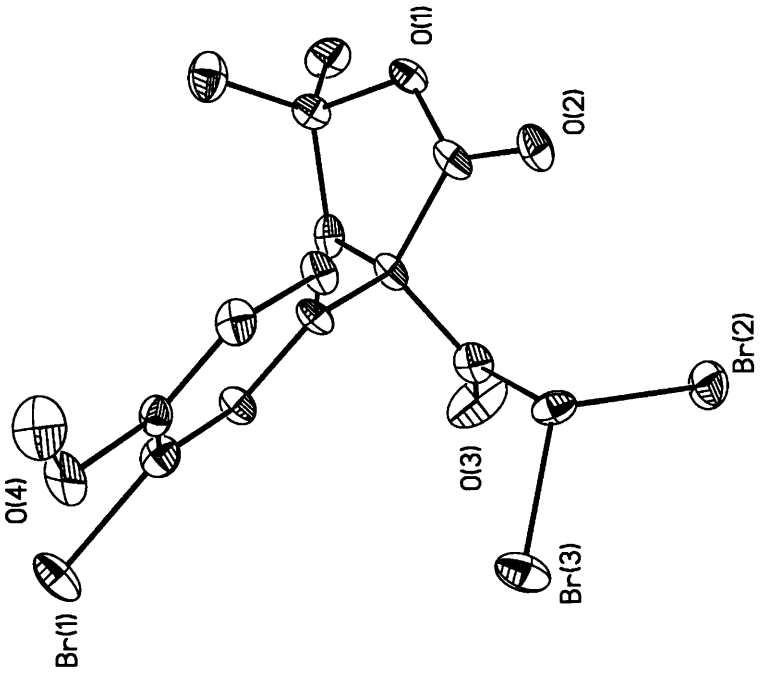

O(1)
O(2)
Br(2)
O(3)
Br(3)
O(4)
Br(1)

Table 1. Crystal data and structure refinement for 02015am2.

Identification code	02015am2	
Empirical formula	C15 H15 Br3 O4	
Formula weight	499.00	
Temperature	183(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.7476(8) Å	$\alpha = 90°$.
	b = 12.5932(15) Å	$\beta = 90°$.
	c = 20.305(2) Å	$\gamma = 90°$.
Volume	1725.4(3) $Å^3$	
Z	4	
Density (calculated)	1.921 Mg/m^3	
Absorption coefficient	7.027 mm^{-1}	
F(000)	968	
Crystal size	0.09 x 0.18 x 0.57 mm^3	
Theta range for data collection	3.18 to 23.29°.	
Index ranges	-7<=h<=7, -13<=k<=12, -13<=l<=22	
Reflections collected	6854	
Independent reflections	2473 [R(int) = 0.2631]	
Completeness to theta = 23.29°	99.5 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2473 / 0 / 203	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0878, wR2 = 0.2031	
R indices (all data)	R1 = 0.0906, wR2 = 0.2070	
Absolute structure parameter	0.00(3)	
Extinction coefficient	0.021(3)	
Largest diff. peak and hole	1.886 and -2.216 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 02015am2.

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

	x	y	z	U(eq)
Br(1)	1390(2)	3465(1)	8123(1)	38(1)
Br(2)	10818(2)	2670(1)	5866(1)	43(1)
Br(3)	7911(2)	1921(1)	7011(1)	43(1)
O(4)	4226(15)	4690(7)	8955(3)	33(2)
O(1)	7270(13)	6259(6)	5707(4)	30(2)
O(3)	6186(19)	2986(7)	5694(4)	52(3)
O(2)	9753(12)	5380(7)	6174(4)	33(2)
C(10)	4873(18)	4746(9)	8315(5)	22(2)
C(9)	3690(20)	4192(9)	7855(5)	29(3)
C(8)	4205(18)	4191(9)	7202(5)	24(2)
C(7)	5892(18)	4715(8)	6980(5)	23(2)
C(12)	7078(18)	5243(9)	7433(5)	24(2)
C(11)	6507(17)	5260(9)	8104(5)	27(2)
C(13)	5230(20)	5340(11)	9432(5)	40(3)
C(15)	8790(20)	3108(9)	6485(5)	28(3)
C(14)	7020(20)	3539(10)	6086(5)	29(3)
C(2)	6368(18)	4665(9)	6238(5)	21(2)
C(1)	8017(18)	5464(9)	6051(5)	26(3)
C(4)	5058(19)	6211(9)	5644(5)	25(2)
C(3)	4696(17)	5021(9)	5785(5)	26(2)
C(5)	4160(20)	6940(11)	6127(6)	41(3)
C(6)	4650(20)	6524(10)	4938(6)	40(3)

Table 3. Bond lengths [Å] and angles [°] for 02015am2.

Br(1)-C(9)	1.884(13)
Br(2)-C(15)	1.939(12)
Br(3)-C(15)	1.930(11)
O(4)-C(10)	1.373(13)
O(4)-C(13)	1.437(15)
O(1)-C(1)	1.321(15)
O(1)-C(4)	1.499(16)
O(3)-C(14)	1.198(14)
O(2)-C(1)	1.203(16)
C(10)-C(11)	1.348(17)
C(10)-C(9)	1.412(17)
C(9)-C(8)	1.371(16)
C(8)-C(7)	1.391(17)
C(7)-C(12)	1.388(16)
C(7)-C(2)	1.542(13)
C(12)-C(11)	1.417(15)
C(15)-C(14)	1.543(18)
C(14)-C(2)	1.516(16)
C(2)-C(3)	1.524(17)
C(2)-C(1)	1.548(15)
C(4)-C(5)	1.475(18)
C(4)-C(6)	1.513(15)
C(4)-C(3)	1.544(17)
C(10)-O(4)-C(13)	117.4(11)
C(1)-O(1)-C(4)	113.2(9)
C(11)-C(10)-O(4)	125.8(11)
C(11)-C(10)-C(9)	119.3(10)
O(4)-C(10)-C(9)	114.9(11)
C(8)-C(9)-C(10)	119.8(12)
C(8)-C(9)-Br(1)	119.2(9)
C(10)-C(9)-Br(1)	121.0(9)
C(9)-C(8)-C(7)	121.3(11)
C(12)-C(7)-C(8)	119.0(9)
C(12)-C(7)-C(2)	123.1(10)
C(8)-C(7)-C(2)	117.9(10)
C(7)-C(12)-C(11)	119.2(11)
C(10)-C(11)-C(12)	121.4(10)
C(14)-C(15)-Br(3)	109.0(9)
C(14)-C(15)-Br(2)	107.8(7)

Br(3)-C(15)-Br(2)	110.8(5)
O(3)-C(14)-C(2)	122.9(12)
O(3)-C(14)-C(15)	120.5(11)
C(2)-C(14)-C(15)	116.5(10)
C(14)-C(2)-C(3)	111.5(9)
C(14)-C(2)-C(7)	107.3(9)
C(3)-C(2)-C(7)	115.0(10)
C(14)-C(2)-C(1)	110.5(10)
C(3)-C(2)-C(1)	101.1(9)
C(7)-C(2)-C(1)	111.3(9)
O(2)-C(1)-O(1)	123.3(10)
O(2)-C(1)-C(2)	126.3(11)
O(1)-C(1)-C(2)	110.4(10)
C(5)-C(4)-O(1)	109.2(10)
C(5)-C(4)-C(6)	113.1(10)
O(1)-C(4)-C(6)	104.6(10)
C(5)-C(4)-C(3)	114.5(10)
O(1)-C(4)-C(3)	100.5(10)
C(6)-C(4)-C(3)	113.5(9)
C(2)-C(3)-C(4)	106.3(10)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 02015am2.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	33(1)	61(1)	19(1)	6(1)	3(1)	-13(1)
Br(2)	46(1)	47(1)	34(1)	-2(1)	15(1)	9(1)
Br(3)	49(1)	48(1)	32(1)	15(1)	-4(1)	-14(1)
O(4)	43(5)	53(5)	3(3)	-2(3)	6(4)	4(4)
O(1)	31(5)	34(4)	24(4)	7(3)	7(3)	-6(4)
O(3)	75(8)	36(4)	45(5)	-23(4)	-42(6)	4(5)
O(2)	19(4)	50(5)	29(4)	4(4)	0(3)	-1(4)
C(10)	24(6)	27(5)	15(5)	0(4)	1(4)	6(5)
C(9)	34(6)	28(5)	24(5)	-5(5)	-1(5)	1(5)
C(8)	27(6)	31(5)	12(5)	-1(4)	1(5)	-4(5)
C(7)	27(6)	34(5)	8(5)	7(5)	3(5)	-4(5)
C(12)	24(6)	39(6)	7(4)	5(4)	-1(5)	1(5)
C(11)	29(6)	31(6)	21(5)	-12(5)	-3(5)	-3(5)
C(13)	49(9)	52(7)	17(6)	-16(6)	-7(5)	-2(7)
C(15)	44(8)	23(5)	19(5)	3(5)	-4(5)	2(6)
C(14)	37(7)	40(6)	10(5)	1(5)	0(5)	0(6)
C(2)	26(6)	31(5)	6(4)	-7(4)	4(4)	-8(5)
C(1)	33(7)	36(6)	9(5)	-11(5)	8(5)	-14(6)
C(4)	28(6)	32(6)	15(5)	6(5)	-6(4)	-3(5)
C(3)	23(6)	40(6)	14(5)	-7(5)	-1(5)	4(5)
C(5)	30(7)	50(7)	43(7)	-11(7)	-3(6)	3(6)
C(6)	53(9)	39(7)	28(6)	15(5)	-8(6)	9(7)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 02015am2.

	x	y	z	U(eq)
H(8)	3393	3825	6895	28
H(12)	8257	5589	7294	28
H(11)	7292	5641	8412	32
H(13A)	6663	5266	9377	59
H(13B)	4852	5112	9877	59
H(13C)	4848	6084	9369	59
H(15)	9320	3678	6779	34
H(3A)	3395	4918	6001	31
H(3B)	4714	4609	5370	31
H(5A)	4529	6719	6574	61
H(5B)	2712	6920	6083	61
H(5C)	4633	7663	6047	61
H(6A)	3341	6254	4806	60
H(6B)	5665	6220	4651	60
H(6C)	4662	7299	4899	60

Table 6. Torsion angles [°] for 02015am2.

C(13)-O(4)-C(10)-C(11)	8.2(17)
C(13)-O(4)-C(10)-C(9)	-172.7(11)
C(11)-C(10)-C(9)-C(8)	-0.6(17)
O(4)-C(10)-C(9)-C(8)	-179.7(11)
C(11)-C(10)-C(9)-Br(1)	-179.8(9)
O(4)-C(10)-C(9)-Br(1)	1.0(14)
C(10)-C(9)-C(8)-C(7)	0.9(17)
Br(1)-C(9)-C(8)-C(7)	-179.9(9)
C(9)-C(8)-C(7)-C(12)	0.4(17)
C(9)-C(8)-C(7)-C(2)	179.5(11)
C(8)-C(7)-C(12)-C(11)	-1.8(16)
C(2)-C(7)-C(12)-C(11)	179.1(11)
O(4)-C(10)-C(11)-C(12)	178.2(11)
C(9)-C(10)-C(11)-C(12)	-0.9(17)
C(7)-C(12)-C(11)-C(10)	2.1(17)
Br(3)-C(15)-C(14)-O(3)	-61.2(13)
Br(2)-C(15)-C(14)-O(3)	59.2(14)
Br(3)-C(15)-C(14)-C(2)	116.5(9)
Br(2)-C(15)-C(14)-C(2)	-123.2(9)
O(3)-C(14)-C(2)-C(3)	-5.8(16)
C(15)-C(14)-C(2)-C(3)	176.6(9)
O(3)-C(14)-C(2)-C(7)	121.1(13)
C(15)-C(14)-C(2)-C(7)	-56.5(13)
O(3)-C(14)-C(2)-C(1)	-117.4(13)
C(15)-C(14)-C(2)-C(1)	65.0(11)
C(12)-C(7)-C(2)-C(14)	108.5(12)
C(8)-C(7)-C(2)-C(14)	-70.6(13)
C(12)-C(7)-C(2)-C(3)	-126.8(12)
C(8)-C(7)-C(2)-C(3)	54.2(14)
C(12)-C(7)-C(2)-C(1)	-12.5(15)
C(8)-C(7)-C(2)-C(1)	168.4(10)
C(4)-O(1)-C(1)-O(2)	-177.5(10)
C(4)-O(1)-C(1)-C(2)	4.7(12)
C(14)-C(2)-C(1)-O(2)	-45.6(14)
C(3)-C(2)-C(1)-O(2)	-163.8(11)
C(7)-C(2)-C(1)-O(2)	73.6(14)
C(14)-C(2)-C(1)-O(1)	132.2(9)
C(3)-C(2)-C(1)-O(1)	14.0(11)
C(7)-C(2)-C(1)-O(1)	-108.7(10)
C(1)-O(1)-C(4)-C(5)	99.8(11)

C(1)-O(1)-C(4)-C(6)	-138.8(9)
C(1)-O(1)-C(4)-C(3)	-20.9(11)
C(14)-C(2)-C(3)-C(4)	-143.8(9)
C(7)-C(2)-C(3)-C(4)	93.6(11)
C(1)-C(2)-C(3)-C(4)	-26.4(10)
C(5)-C(4)-C(3)-C(2)	-88.1(13)
O(1)-C(4)-C(3)-C(2)	28.8(10)
C(6)-C(4)-C(3)-C(2)	139.9(11)

Chapter 2

Catalytic Enantioselective Construction of β-Dicarbonyls Bearing Quaternary Stereocenters via Intermolecular C-Acylation of Acyclic Silyl Ketene Acetals: Evidence for a Stereoconvergent Acylation Process.

Part A. Introduction to Stereoselective Methods for Enolate Generation and Stereoconvergent Enolate Processes.

The use of prochiral enolates as building blocks is invaluable for the construction of compounds of synthetic or biological interest. Stereochemical control of the enolization for ketone- and carboxylic acid-derived enolates has been thoroughly investigated. In 1976, Ireland proposed a model for enolization that invoked a Zimmerman-Traxler transition state.[39] He proposed that the interaction of a carbonyl compound and a base such as lithium diisopropyl amide leads to the assembly of a six-membered transition state, which accounts for stereoselective enolization of the carbonyl.[40] As illustrated for carbonyl **2.11** undergoing enolization (Figure 2A.1), two interconverting chair-like transition states **2.14** and **2.15** lead to the formation of (*Z*)-enolate **2.12** and (*E*)-enolate **2.13**, respectively. This model explains why ketones and amides furnish (*Z*)-enolates, whereas (*E*)-enolates are produced from esters. Arguments for this selectivity involve developing (1,3)-diaxial interactions that disfavor **2.14** (leading to (*E*)-enolate formation) and gauche interactions between R and R^1 that disfavor **2.15** (leading to (*Z*)-enolate formation). While this model is a useful predictive tool for carbonyl compounds when $R^2 = H$, it generally fails when $R^2 \neq H$. Efforts to address the stereoselective generation of disubstituted enolates have not been met with significant success.

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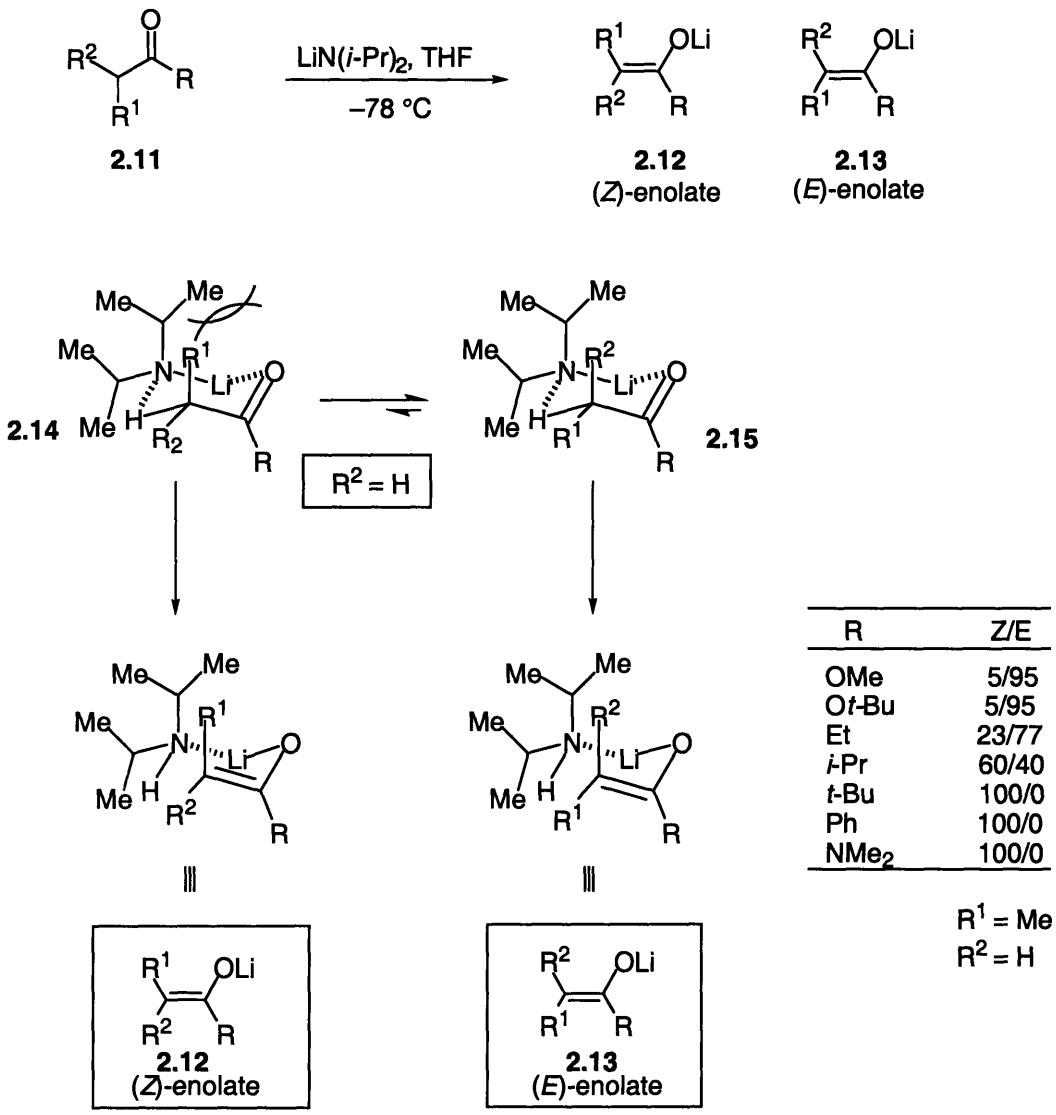
[39] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[40] For leading references on stereoselective enolization processes, see: (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081. (c) Masamune, S.; Ellingoe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *204*, 5526-5528. (d) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571-9574.

Figure 2A.1. Ireland Model for the Stereoselective Enolation of Ketones, Esters and Amides



The inability to stereoselectively generate disubstituted enolates has necessitated the development of processes that react in a stereoconvergent manner. While accounts of such processes are not common, they have been reported for certain aldol reactions of

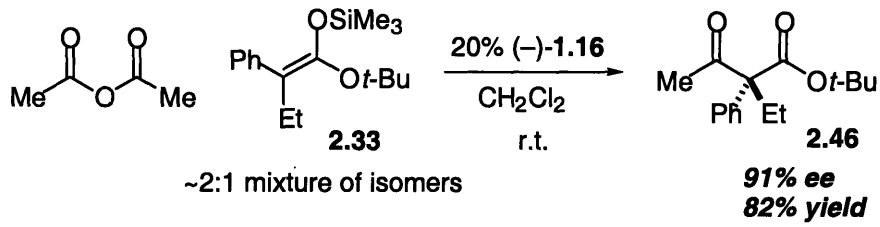
monosubstituted enol silanes.[41] The authors invoke open transition state models to rationalize the origin of stereoselectivity for the transformation being explored. In this chapter, we describe the catalytic enantioselective C-acylation of acyclic silyl ketene acetals, including the first stereoconvergent reaction of disubstituted enolates.

[41] For recent examples of catalytic asymmetric aldol reactions exhibiting enolate stereoconvergence, see: (a) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405-13407. (b) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292-3302.

Part B. Results and Discussion

In chapter one, we addressed the catalytic enantioselective C-acylation of cyclic silyl ketene acetals, and we described the high level of enantioselectivity by which that process occurred. In the development of that transformation, we restricted ourselves to lactone-derived silyl ketene acetals to avoid the complication of (*E*)- and (*Z*)-enolate mixtures. Having established the fundamental reactivity and elucidated the key features that were mechanistically relevant to the C-acylation process, we addressed the possibility of employing acyclic substrates.

With the lack of methods available to effectively generate highly (*E*)- or (*Z*)-enriched disubstituted ester enolates, we chose to explore the use of a mixture of enolate isomers. Although we were concerned that a mixture of enolates might result in poor enantioselectivities, a ~2:1 mixture of acyclic silyl ketene acetals was subjected to the catalytic C-acylation process described in chapter 1 (2B.1). We were pleased to observe both high enantioselectivity and high yield, suggesting that both isomers were selectively converted into β-ketoester **2.46**. In addition, in situ ^{1}H NMR analysis of this reaction showed that the minor isomer of **2.33** was more reactive than the major isomer.

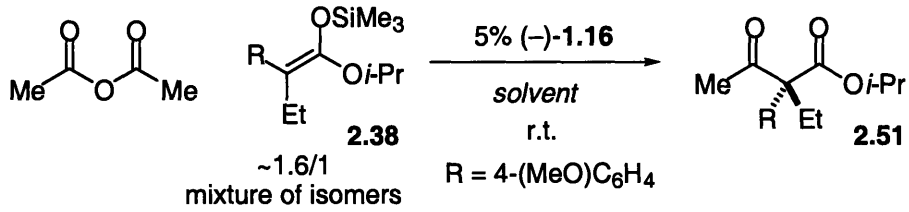


(2B.1)

A survey of solvent and reaction concentration was conducted first, with the hope of accelerating the reaction rate while maintaining high enantioselectivity. Using a ~1.6/1 isomeric mixture of silyl ketene acetal **2.38** as our test substrate, we screened several common solvents, as shown in Table 2B.2. Although the highest

enantioselectivities were obtained by use of EtOAc, Et_2O, and toluene, these solvents led to very poor conversions (Table 2B.2, entries 3, 4, and 5). In contrast, dichloromethane and THF led to rapid, but less selective formation of product **2.51** (Table 2B.2, entries 1 and 2). In order to maximize both rate and selectivity, we decided to examine binary solvent systems.

Table 2B.2. Enantioselectivity as a Function of Solvent.



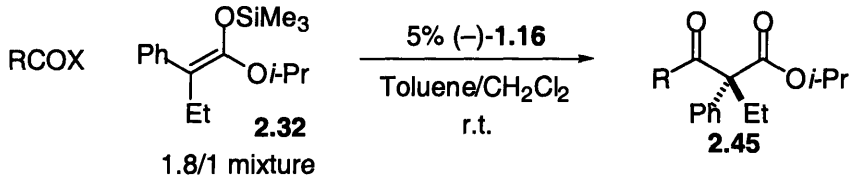
entry	solvent	% ee
1	CH_2Cl_2	84
2	THF	86
3	EtOAc	90
4	Et_2O	94
5	toluene	96

Unfortunately, reactions were sluggish in mixed solvent systems such as THF/toluene, dichloromethane/toluene, dichloromethane/Et_2O, and THF/Et_2O. When the concentration was raised to 1 M, however, conversion to product **2.51** was complete in 24 hours with 88% ee, employing a mixture of toluene/dichloromethane (2:1). In addition, this high concentration allowed reactions to be monitored colorimetrically. Upon addition of Ac_2O to a solution of silyl ketene acetal **2.38** and 5% catalyst (–)-**1.16**, a bright-red color was observed. When the reaction was complete, we observed the reaction become the magenta color characteristic of the catalyst.

Under these conditions, we surveyed a variety of acylating agents for this process. As illustrated in Table 2B.3, anhydrides were very effective (Table 2B.3, entries 2-4), with acetic anhydride providing excellent yields and stereoselectivity for the asymmetric

C-acylation of substrate **2.32**. Rate suffered with increased steric demand of the anhydride, however. Propionic anhydride, led to a 59% yield (Table 2B.3, entry 3), while no product was obtained with isobutyric anhydride (Table 2B.3 entry 5). Acid chlorides were very ineffective in this process (Table 2B.3, entry 1).

Table 2B.3. Variation of the Acylating Agent.



entry	RCOX	product	% ee	% yield
1	AcCl	**2.45**	5	11
2	Ac_2O	**2.45**	85	92
3	Bz_2O	**2.57**	54	83
4	$(EtCO)_2O$	**2.58**	89	59
5	$(i\text{-}PrCO)_2O$	**2.59**	–	–

The steric demand of the alkoxy moiety on the silyl ketene acetal had a large effect on enantioselectivity. When a *t*-butyl ester-derived silyl ketene acetal was employed, 93% ee was obtained (Table 2B.4, entry 3). Neopentyl substrate **2.34** was less selective (Table 2B.4, entry 4), and methoxy substrate **2.31** reacted with a disappointing 70% ee. Also notable in this survey was the reduction in rate associated with the increased steric demand of this moiety (Table 2B4, entry 3).[42] In order to realize an optimal combination of rate and selectivity, the isopropyl substrate was selected for further study.

Table 2B.4. Enantioselectivity as a Function of the Ester Moiety.

entry	R	substrate	isomer ratio	product	% ee	% yield
1	Me	**2.31**	1.5/1	**2.44**	70	87
2	*i*-Pr	**2.32**	1.8/1	**2.45**	85	92
3	*t*-Bu	**2.33**	1.5/1	**2.46**	93	47
4	CH_2CMe_3	**2.34**	1.1/1	**2.47**	79	75

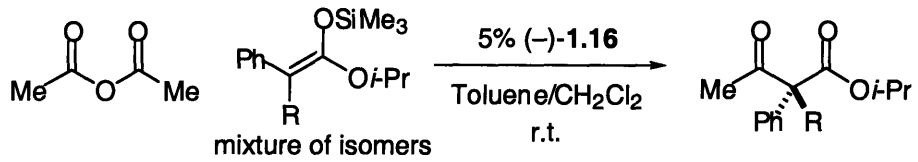
After establishing the effect of the alkoxy substituent, we looked at differences in rate and enantioselectivity imparted by variance of the α-alkyl substituent (Table 2B.5). Smaller alkyl groups, such as a methyl group in substrate **2.35**, furnished modest selectivities (69% ee, Table 2B.5, entry 1).[43] Incorporation of an isopropyl substituent, as evident in silyl ketene acetal **2.36**, afforded a dramatic enhancement in enantioselectivity to 97% ee (Table 2B.5, entry 3), although some O-acylation was observed. The formation of this undesired regioisomer was attributed to the significantly increased steric demand of substrate **2.36**.[44] The moderately demanding isobutyl substrate **2.37** furnished 85% ee (Table 2B.5, entry 4).

[42] Substrate **2.33** achieved higher conversions at longer reaction times ($t > 24$ h.).

[43] The low yield for the acylation of **2.34** was addressed with longer reaction times and increased catalyst loading, resulting in a negligible change in conversion.

[44] The product derived from O-acylation of **2.36** did not rearrange to C-acylated product **2.49**, even under forcing conditions.

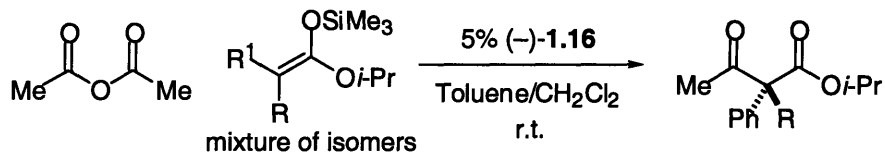
Table 2B.5. Enantioselectivity as a Function of the α-Substituent.



entry	R	substrate	isomer ratio	product	% ee	% yield
1	Me	**2.35**	1.8/1	**2.48**	69	54
2	Et	**2.32**	1.8/1	**2.45**	85	92
3	*i*-Pr	**2.36**	1.7/1	**2.49**	97	46
4	CH_2CMe_2	**2.37**	3.3/1	**2.50**	85	82

In analogy to the study of cyclic silyl ketene acetals conducted previously, we next examined variation of the aromatic substituent.[45,46] High enantioselectivities and yields were observed for many of the silyl ketene acetals listed in Table 2B.6. We were

Table 2B.6. Enantioselectivity as a Function of the Aromatic Substituent.



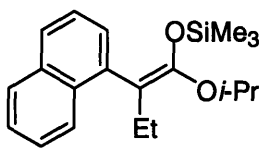
entry	R^1	R	substrate	isomer ratio	product	% ee	% yield
1	Ph	Et	**2.32**	**1.8/1**	**2.45**	85	92
2	4-(MeO)C_6H_4	Et	**2.38**	**1.5/1**	**2.51**	90	83
3	4-(F_3C)C_6H_4	Et	**2.39**	**2.1/1**	**2.52**	92	96
4	6-(MeO)-2-naphthyl	Me	**2.40**	**1.5/1**	**2.53**	90	92
5	2-thienyl[7]	Et	**2.41**	**10.0/1**	**2.54**	72	66
6	(1,1)-indanyl	Et	**2.42**	**1.4/1**	**2.55**	81	82
7	(*E*)-styrenyl[8]	Et	**2.43**	**1.1/1**	**2.56**	54	81

[45] For 2-thienyl substrate **2.41** (Table 2B.6, entry 5), the TBS analog was used. Use of a TMS group led to mixtures of C- and O-silylation products during substrate preparation.

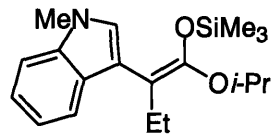
[46] Refer to Table 1C.6 for the corresponding variance in aromatic group for cyclic silyl ketene acetals.

especially pleased that this process accommodated indane-derived silyl ketene acetal **2.42**, furnishing respectable stereoselectivity and yield (Table 2B.6, entry 6).[47] (*E*)-Styrenyl-substituted silyl ketene acetal **2.43** also participated in this C-acylation process, affording product **2.56** in good yield with a modest 54% ee (Table 2B.6, entry 7). Exclusive α-acylation was observed with substrate **2.43**, with no isomerization of the double bond or erosion of the (*E*)-olefin configuration.

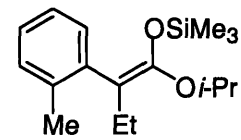
Some substrates provided less desirable results (2B.7). In the case of the 1-naphthyl substituent, O-acylation was the dominant product, although the minor C-acylation product was obtained in 82% ee. The trace amount of product obtained from reaction of 3-(*N*-methylindole)-substituted silyl ketene acetal **2.62** was shown to be racemic.[48] Under the conditions outlined in Table 2B.6, no product was obtained



2.61
~1.4/1
mixture of isomers



2.62
~7.3/1
mixture of isomers



2.63
~1.3/1
mixture of isomers

(2B.7)

with *o*-tolyl substrate **2.63**.[49] The failure of these substrates was surprising, since their cyclic analogs performed well.[50]

As mentioned earlier in this section, the minor isomer was observed to be the more reactive species in C-acylation reactions, as elucidated by initial experiments with

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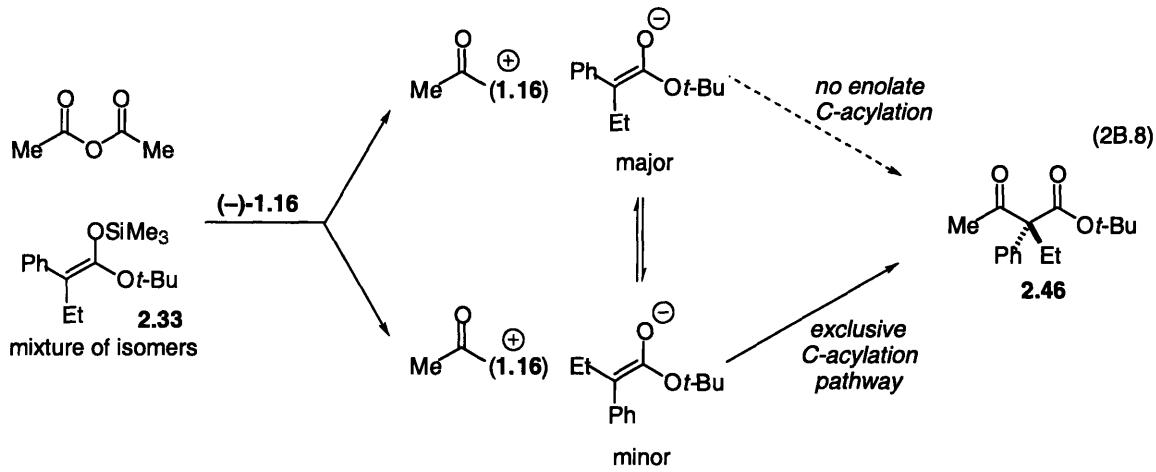
[47] The acylation of **2.42** was conducted in dichloromethane to achieve the yield listed in Table 2B.6. Reaction of that substrate in Toluene/CH_2Cl_2 led to a low conversion.

[48] The low yield for 3(*N*-methylindole) substrate **2.62** could imply that an achiral impurity, possibly one generated from the decomposition of catalyst, may have led to the observed racemic product.

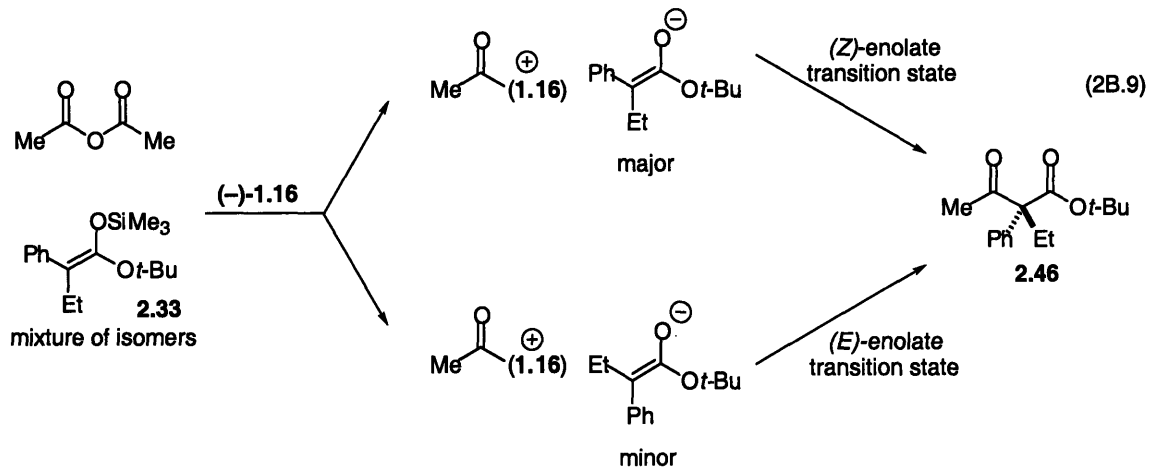
[49] Substrate **2.63**, when reacted in dichloromethane, afforded a 34% yield of product which was shown to have 14% ee.

[50] See chapter 1, Table 1C.6 for comparison.

substrate **2.33**. Unfortunately, the inability to independently synthesize these isomeric forms substantially limited our mechanistic analysis. Nonetheless, we sought to determine whether the major isomer enolate could equilibrate to the minor isomer enolate, allowing the C-acylation event to take place via a single transition state (2B.8).

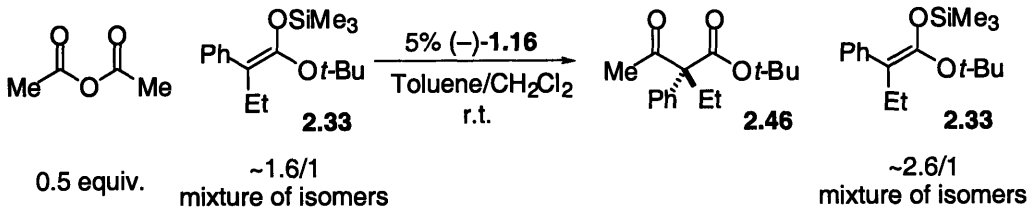


Alternatively, the reaction may occur through two stereoconvergent transition states (2B.9). To address the issue of enolate equilibration, various separate mixtures of silyl ketene acetals were subjected to 5 mol% $Me_4N[OAc]$ in the absence of acetic anhydride. Under these conditions, we expected the reversible formation of a tetramethylammonium enolate and Me_3SiOAc. Since the mixtures have different isomeric ratios, equilibration of each mixture should yield the same ratio of isomers.



(2B.9)

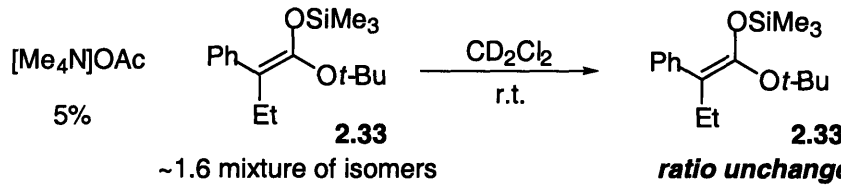
In order to investigate this mechanistic hypothesis, two different isomeric mixtures of silyl ketene acetal **2.33** were synthesized. Enolization with LDA followed by a TMSCl quench at –78 °C afforded a ~1.6/1 isomeric ratio of the silyl ketene acetal. Unfortunately, addition of HMPA led to no observable difference in this ratio. Treatment of **2.33** with TMSOTf and triethylamine at reduced temperature led primarily to cleavage of the *t*-butyl ester. We ultimately solved this problem by exploiting the difference in reactivity between the two isomers. By executing a catalytic enantioselective C-acylation of substrate **2.33** with 0.5 equivalents of Ac_2O, we were able to consume a significant amount of the minor silyl ketene acetal isomer of **2.33**. Recovery of the starting material afforded a ~2.6/1 isomer ratio of the silyl ketene acetal (2B.10).



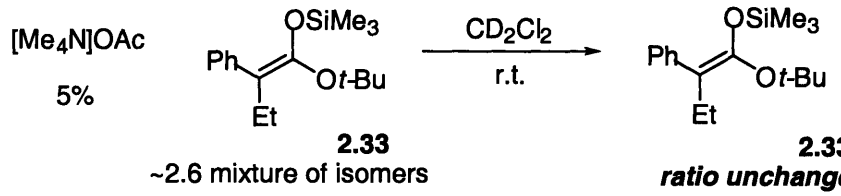
(2B.10)

Subjection of each mixture to 5% $Me_4N[OAc]$ resulted in no change in the isomeric ratios in either case after 60 hours at room temperature (2B.11 and 2B.12).

While these data do not fully discredit an equilibration mechanism, this pathway appears to be unlikely.



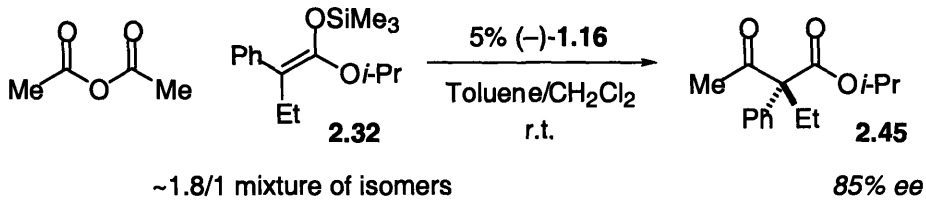
(2B.11)



(2B.12)

Construction of a transition state model that correctly rationalized the enantioselectivity for both geometrical enolate isomers was a challenging problem. Mechanistic discussion of silyl ketene acetal additions to various carbonyl compounds (i.e., aldehydes, ketones, and acetals) in the literature usually invokes an open transition state model.[51] Furthermore, an open transition state more readily rationalizes stereoconvergent behavior (e.g., isomeric mixtures of substrates that lead to a single product).

Our analysis is divided into two sets of open transition state models: those with an acyl group in the plane of the catalyst (the more stable conformation due to resonance effects), and those with the acyl group skewed from the top ring (the more reactive conformation due to lack of resonance effects). Keeping in mind that the pro-(*R*) enantioface of **2.32** leads to the indicated stereochemistry in **2.45** (2B.13), we correspondingly developed a series of transition state models.

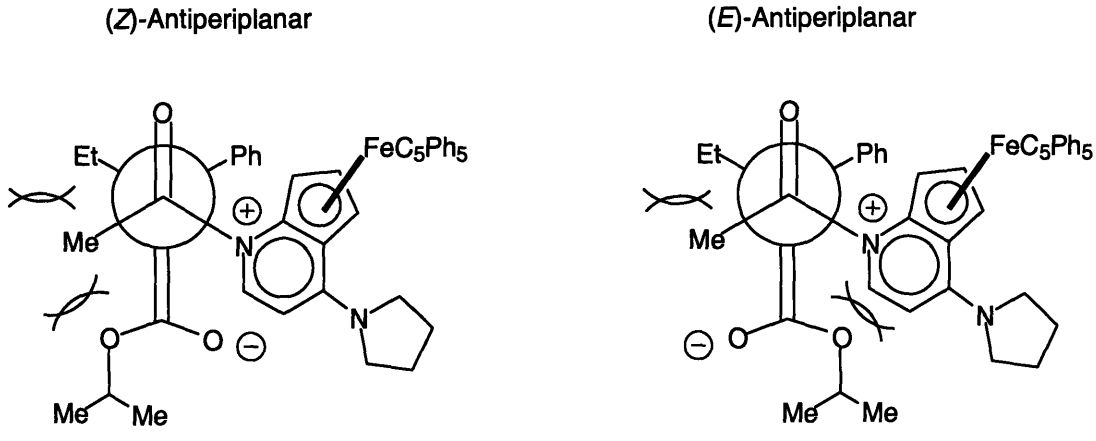


(2B.13)

Assumption 1: Coplanar Arrangement of Catalyst Top-Ring and Acyl Group.

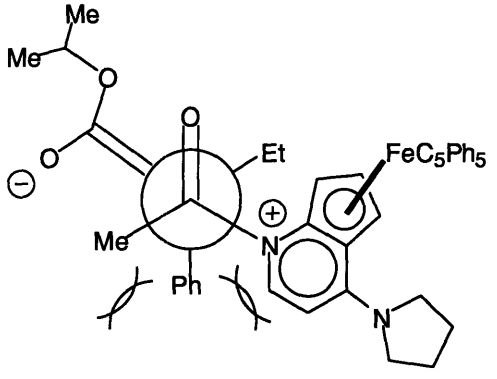
With a coplanar arrangement of the catalyst and the acetyl moiety, six staggered transition states, consisting of antiperiplanar and synclinal approaches, are possible, leading to reaction at the favored pro-(*R*) enantioface (Figure 2B.14). An important consideration to note is that the transition states describing reactivity of the (*Z*)-isomer do not have to coincide with the (*E*)-isomer. Different approaches may be involved for the (*E*)- and (*Z*)-isomers of **2.32**.

Figure 2B.14. Transition State Models–Coplanar Arrangement of Acetyl Group.



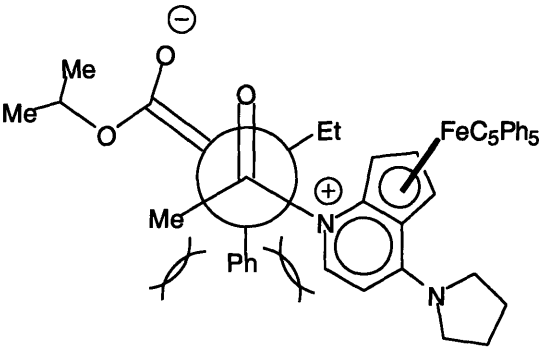
[51] While open transition states are frequently invoked for silyl ketene acetal additions to carbonyl compounds, closed transition states have also been postulated for such processes. For example, see:

(*Z*)-Synclinal 1



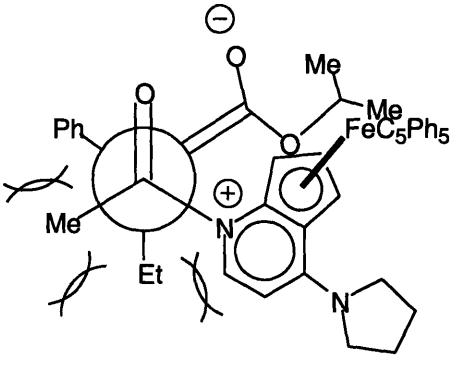
2.63

(*E*)-Synclinal 1



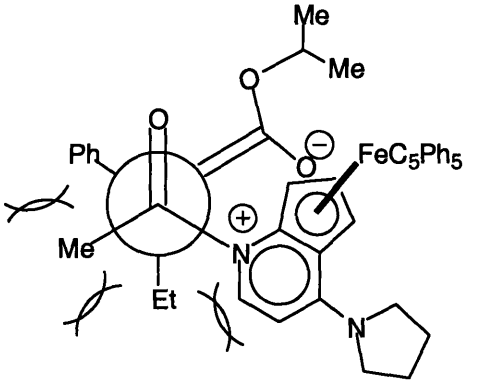
2.64

(*Z*)-Synclinal 2



2.65

(*E*)-Synclinal 2



2.66

While unfavorable steric and electronic interactions are present in all of these models, they are more pronounced in transition states **2.62**, **2.63**, **2.64**, and **2.65**. For example, model (*Z*)-synclinal 2 (**2.65**) suffers from severe steric interactions between the catalyst and the isopropyl ester moiety, and is therefore disfavored. The same argument can be made against model (*E*)-antiperiplanar (**2.62**). Models **2.62** and **2.65** are further disfavored by the fact that their respective pro-(*S*) enantiofaces would have less steric

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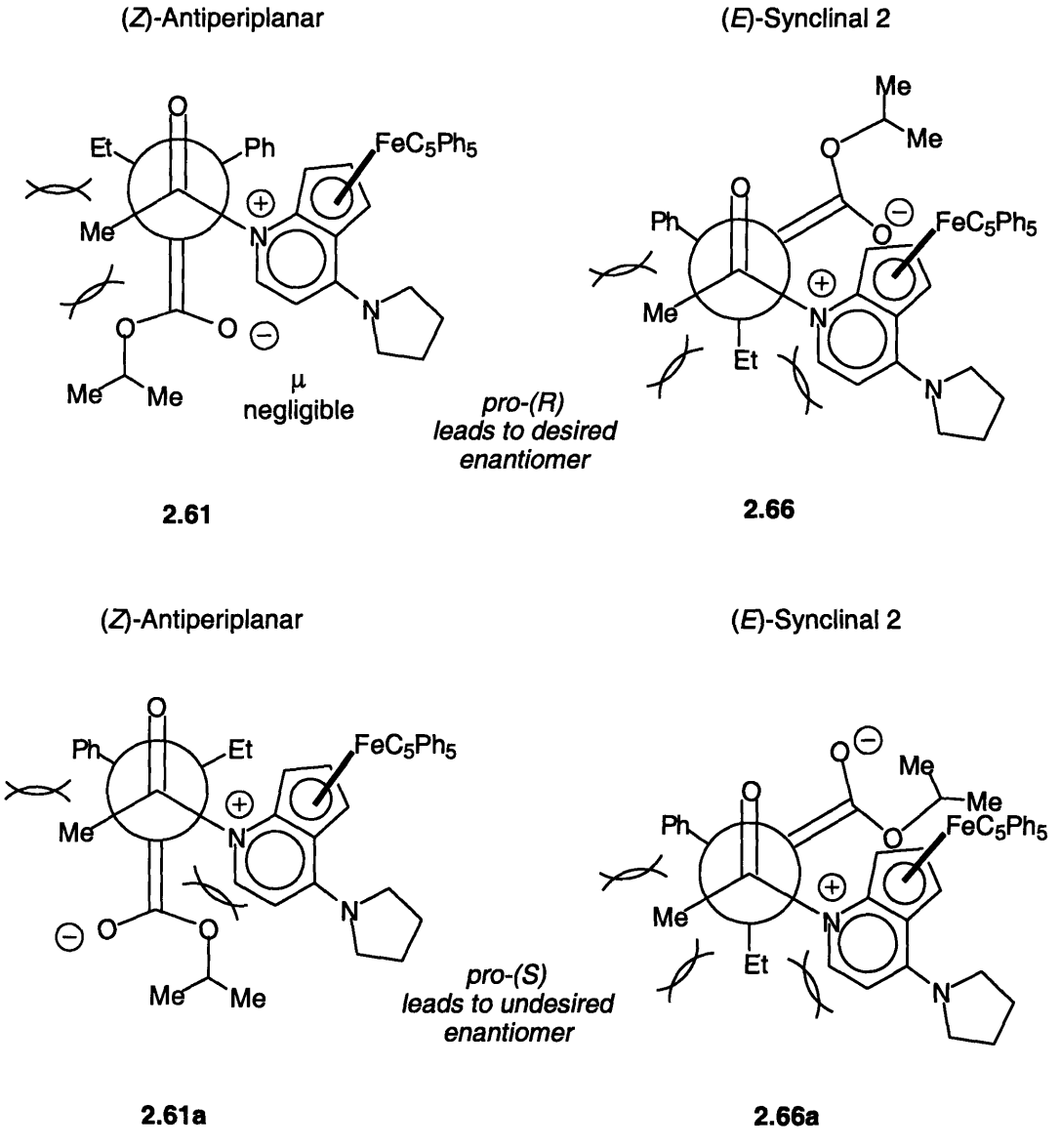
interactions with the catalyst than the pro-(*R*) enantioface, leading to a reduction enantioselectivity. In addition, a larger α-alkyl group should decrease the selectivity according to models **2.62** and **2.65**, because gauche interactions would be amplified.

Models (*Z*)-synclinal 1 (**2.63**) and (*E*)-synclinal 1 (**2.64**) are disfavored for more subtle reasons. Both of these models lead to developing gauche interactions between the phenyl and ethyl substituents on the silyl ketene acetal and catalyst (–)-**1.16**. They also have significant charge separation. Moreover, the size of the ester substituent should have little effect on the enantioselectivity, according to these models. Increased steric demand of the α-alkyl substituent would lead to increased steric repulsion with the catalyst for both models **2.63** and **2.64**, thus at odds with empirical results.

The remaining models, (*Z*)-antiperiplanar (**2.61**) and (*E*)-synclinal 2 (**2.66**), involve the least number of disfavored gauche interactions and are the most congruent with the empirical enantioselectivity data. These models accommodate minimal (**2.61**) or no (**2.66**) steric repulsion with increased ester size, which allows reactivity to be maintained. With larger alkoxy groups, the disfavored pro-(*S*) faces of **2.32** for these models do encounter severe steric repulsion with the catalyst for both of these models, leading to suppression of the minor enantiomer. As the size of the α-alkyl substituent is increased, the disfavored pro-(*S*) enantioface of **2.32** encounters destabilizing steric interactions with the catalyst for model **2.61**, and amplified gauche interactions with other substituents in model **2.66** (Figure 2B.15). Furthermore, models **2.61** and **2.66** involve minimal separation of charge.

Figure 2B.15. Comparison of pro-(*R*) and pro-(*S*) Faces of 2.32.



Assumption 2: Non-Coplanar Arrangement of Catalyst Top-Ring and Acyl Group.

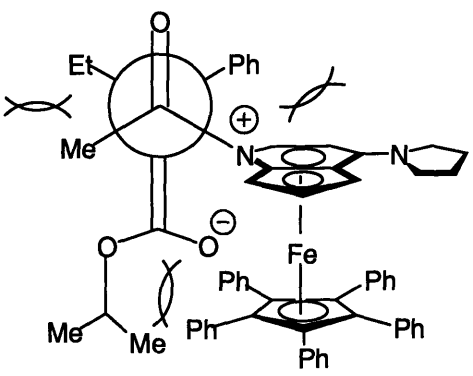
While ground state arguments do not favor rotation of the acyl group such that it is perpendicular (or not in conjugation with) to the top-ring of the catalyst, accessing such a conformation during the course of the reaction cannot be ruled out. Analysis of this set of models leads to conclusions analogous to those outlined for models **2.61-2.66**. One

systematic disadvantage of the skewed model, however, is that the pentaphenyl-cyclopentadienyl moiety may exacerbate certain steric interactions, disfavoring transition states **2.67**-**2.72** in comparison to **2.61**-**2.66**. If this factor is disregarded, (Z)-antiperiplanar (**2.67**) and (E)-synclinal 2 (**2.72**) appear to be the most reasonable transition states for this acyl group conformation (Figure 2B.16).

An overall comparison of all transition state models suggests that if an open transition state model is involved, models **2.61** and **2.66** best support the sense and level of stereoselection for the catalytic asymmetric C-acylation of **2.32** with catalyst (–)-**1.16** and acetic anhydride.

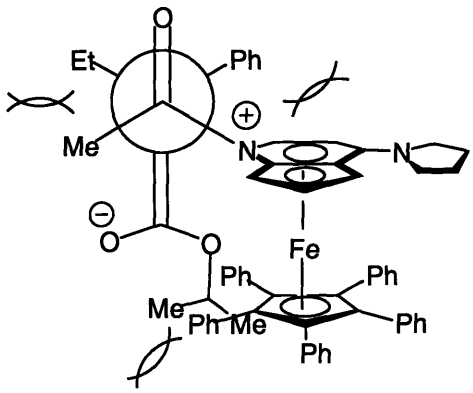
Figure 2B.14. Transition State Models–Non-Coplanar Arrangement of Acetyl Group.

(*Z*)-Antiperiplanar



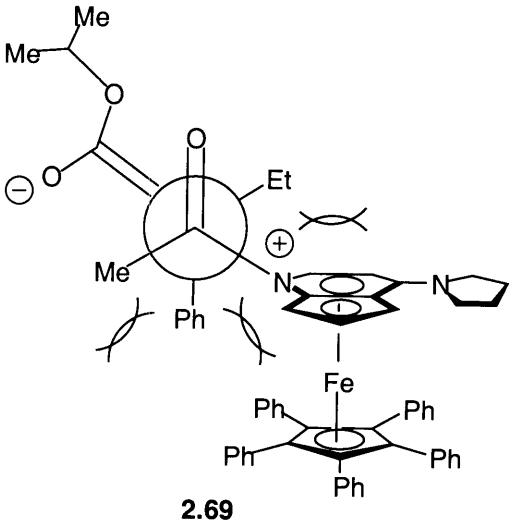
2.67

(*E*)-Antiperiplanar



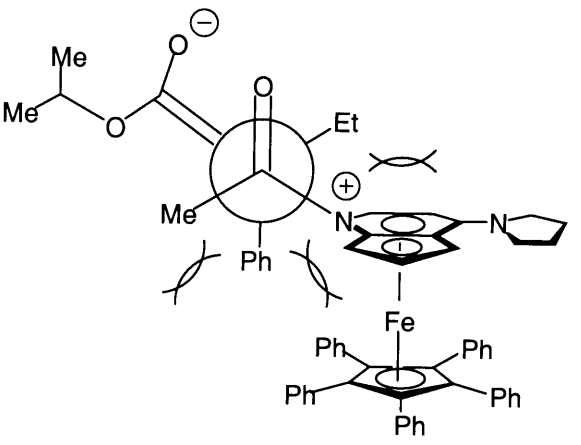
2.68

(*Z*)-Synclinal 1



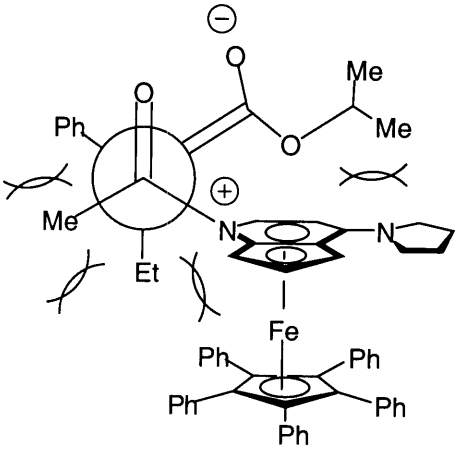
2.69

(*E*)-Synclinal 1



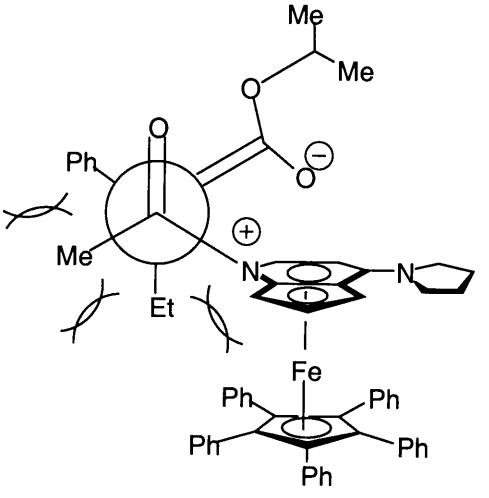
2.70

(*Z*)-Synclinal 2



2.71

(*E*)-Synclinal 2



2.72

Conclusions

In chapter one, we established a novel catalytic enantioselective C-acylation process for cyclic silyl ketene acetals, highlighting a dual activation concept. The results presented in this chapter demonstrate an extension of this process to acyclic substrates. Importantly, subjection of (*E*)- and (*Z*)-silyl ketene acetals to this C-acylation process leads to efficient conversion to highly enantiomerically enriched β-ketoesters. The minor isomer of the silyl ketene acetal serves as the more reactive species.

We learned that as the steric demand of the ester and the α-alkyl substituent of the silyl ketene acetal increase, a corresponding rise in enantioselectivity is observed. Novel substrates, such as styrenyl-substituted silyl ketene acetals or silyl ketene acetals with an indane-derived substructure, also participate in this process, furnishing moderate to good enantioselectivities. In addition, the catalyst can be recovered in almost quantitative yield at the end of the reaction.

No equilibration of silyl ketene acetal mixtures is observed in the presence of $Me_4N[OAc]$, suggesting that the enolate isomers react in a stereoconvergent manner. Open transition state models which are in accord with the experimental data were presented to account for the stereoselection.

Experimental

General

THF, Toluene, and CH_2Cl_2 were purified by passage through a neutral alumina column. Ac_2O and $(EtCO)_2O$ were distilled from phosphorus pentoxide. Benzoic anhydride was recrystallized from Et_2O. $[Me_4N]OAc$ (Alfa Aesar) was purified by recrystallization from 2:1 CH_3CN/CH_2Cl_2 and dried under vacuum at 150 °C.*n*-BuLi (Alfa Aesar) was titrated with diphenylacetic acid (Aldrich) prior to each use. Methylene chloride-d_2 (Cambridge Isotope Laboratories) was distilled from CaH_2. 2-Phenylbutyric acid (Aldrich), 4-methoxyphenylacetic acid (Avocado), 4-trifluoromethylphenylacetic acid (Avocado), (*E*)-styrylacetic acid (Aldrich), naphthalene-1-acetic acid (Avocado), thiophene-2-acetic acid (Avocado), (*S*)-(+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid (TCI), thiophene-3-acetic acid (Aldrich), 3-oxo-1-indancarboxylic acid (Aldrich), bromoethane (Alfa Aesar), iodomethane (Alfa Aesar), iodoethane (Alfa Aesar), 2-bromopropane (Avocado), 1-bromo-2-methylpropane (Aldrich), diisopropylamine (Aldrich), 1,4-dioxane (Aldrich), Me_3SiCl (Avocado), *t*-$BuMe_2SiCl$ (Pfizer), Et_2O (Mallinckrodt), pentane (Burdick & Jackson), hydrochloric acid (Fisher), sulfuric acid (Fisher), magnesium sulfate (Fisher), 2-propanol (Fluka), $AgSbF_6$ (Strem), oxalyl chloride (Aldrich), 2-methyl-2-propanol (Aldrich), 2,2-dimethylpropanol (Avocado), NEt_3 (EM Science), *N,N*-dimethylformamide (Aldrich), zinc dust (Mallinckrodt), mercury (II) chloride (Alfa Aesar), acetonitrile (Aldrich), MeOH (Mallinckrodt), were used as received.

Analytical thin layer chromatography was performed making use of EM Reagents 0.25 mm silica gel 60 plates, and visualization was achieved with ultraviolet light and/or

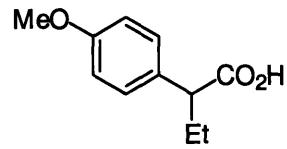
ceric ammonium nitrate or potassium permanganate stains. Flash chromatography was performed making use of Sorbent Technologies silica gel 60 (230-400 mesh).

Optical rotations were acquired with a Jasco-1010 polarimeter. Infrared spectra were obtained on a Perkin-Elmer Series 2000 FT-IR spectrophotometer. Melting points (uncorrected) were acquired on a Thomas Hoover Unimelt capillary melting point apparatus.

^{1}H and ^{13}C nuclear magnetic resonance spectra were obtained on a Varian Unity 300, Varian Mercury 300, or Varian VXR 500 spectrometer at room temperature. ^{1}H NMR data are reported using the following notation: chemical shift in parts per million downfield from tetramethylsilane (δ scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, and app t = apparent triplet), integration, and coupling constant (Hz). ^{13}C chemical shifts are recorded in ppm downfield with respect to tetramethylsilane (δ scale), and were acquired with full proton decoupling.

All experiments were conducted under an argon or nitrogen atmosphere in oven-dried glassware with magnetic stirring, unless otherwise specified.

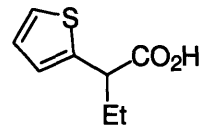
Preparation of Acids



2-(4-methoxyphenyl)butyric acid [29644–99–3]. A solution of *n*-BuLi (2.67 M in hexanes; 24.8 mL, 66.2 mmol) was added via syringe to a –78 °C solution of 4-methoxyphenyl-acetic acid (5.00 g, 30.1 mmol) in THF (80 mL). The resulting mixture was warmed to room temperature over 45 minutes after which neat bromoethane (9.00 mL, 120 mmol) was then added. The resulting solution stirred for 12 hours. The reaction

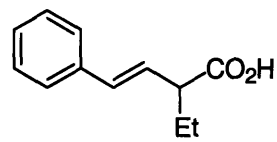
mixture was quenched by addition of 1N HCl (100 mL), extracted with Et_2O (3 x 100 mL), dried (Na_2SO_4), and concentrated to a yellow oil (5.07 g, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (ddd, 2H, J=8.4, J=3.0, J=1.8), 6.87 (ddd, 2H, J=8.7, J=3.0, J=2.1), 3.80 (s, 3H), 3.41 (dd, 1H, J=7.8, J=7.5), 2.09 (dq, 1H, J=13.8, J=7.5), 1.79 (dq, 1H, J=13.5, J=7.8), 0.90 (app t, 3H, J=7.2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.9, 159.1, 130.6, 129.3, 114.2, 55.4, 52.6, 26.5, 12.3.



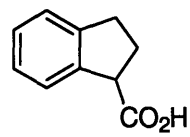
2-thienylbutyric acid [54955-40-7]. Made via the procedure of Doyle.[52]

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.0 (s, 1H), 7.26 (m, 1H), 7.01 (m, 2H), 3.83 (app t, 1H, J=7.5), 2.17 (m, 1H), 1.92 (m, 1H), 1.01 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 127.3, 127.0, 125.4, 48.6, 27.8, 12.1.



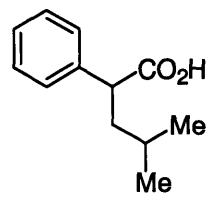
(*E*)-4-phenyl-2-ethyl-3-butenic acid [52216-97-4]. A solution of *n*-BuLi (2.90 M in hexanes; 14.2 mL, 41.1 mmol) was added via syringe to a –78 °C solution of trans-styrylacetic acid (3.03 g, 18.7 mmol) in THF (50 mL). After 40 minutes of stirring at –78°C, neat bromoethane (4.20 mL, 56.1 mmol) was added via syringe, and the resulting solution was stirred for 12 hours. The reaction mixture was quenched by addition of saturated NH_4Cl (100 mL), extracted with Et_2O (3 x 100 mL), washed with saturated NaCl (2 x 50 mL), dried (Na_2SO_4), and concentrated to a yellow solid (3.36 g, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.40 (m, 5H), 6.50 (d, 1H, J=15.9), 6.19 (dd, 1H, J=15.9, J=9.0), 3.11 (m, 1H), 1.91 (m, 1H), 1.71 (m, 1H), 0.99 (dd, 3H, J=7.80, J=7.20). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6, 136.9, 133.0, 128.7, 127.8, 126.9, 126.5, 51.2, 26.0, 11.8.



Indan-1-carboxylic acid [14381-42-1]. Mercury (II) chloride (0.192g, 0.709 mmol) was added to a solution of zinc dust (7.52g, 115 mmol) in water (5.0 mL). Hydrochloric acid (0.3 mL) was added, after which the slurry was stirred for 15 minutes, then filtered and washed with water. This solid was added to a flask containing 3-oxo-indan-1-carboxylic acid (2.50 g, 14.2 mmol) dissolved in 2.5/1 solution of toluene/water (20 mL). Concentrated hydrochloric acid (10 mL) was added, after which the reaction was refluxed for 12 hours. The reaction was cooled to room temperature, extracted with ether (3 x 100 mL), dried ($MgSO_4$), and concentrated to a yellow oil (2.13 g, 93%).

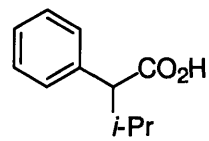
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 1H), 7.18-7.29 (m, 3H), 4.10 (dd, 1H, J=8.4, J=6.3), 3.11 (m, 1H), 2.94 (m, 1H), 2.30-2.52 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 144.9, 140.7, 128.5, 127.3, 125.7, 125.4, 50.7, 32.4, 29.4.



[52] Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669-8680.

4-methyl-2-phenylpentanoic acid [14320-58-2]. Made via the procedure of Doyle.[14]

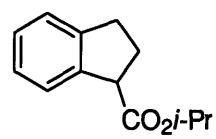
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H), 3.67 (app t, 1H, J=8.0), 1.96 (ddd, 1H, J=14.0, J=8.0, J=6.0), 1.71 (ddd, 1H, J=14.0, J=7.5, J=6.5), 1.50 (app sept, 1H, J=6.5), 0.92 (app d, 6H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.9, 138.8, 128.9, 128.3, 127.7, 49.7, 42.2, 26.0, 22.8, 22.4.



3-methyl-2-phenylbutyric acid [3508-94-9]. Made via the procedure of Mosher[53] et al using phenylacetic acid (11.3 g, 83.1 mmol) and 2-bromopropane (11.5 mL, 122 mmol) to furnish the product as a tan solid (14.5 g, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.0 (s, 1H), 7.26-7.36 (m, 5H), 3.15 (d, 1H, J=10.5), 2.34 (m, 1H), 1.09 (d, 3H, J=6.5), 0.72 (d, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6, 137.9, 128.8, 128.7, 127.7, 60.2, 31.7, 21.7, 20.3.

Preparation of Esters



Isopropyl indan-1-carboxylate [214461-31-1]. Isopropanol (20 mL), concentrated sulfuric acid (6 drops), and magnesium sulfate (3 scoops) were added to indan-1-

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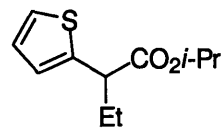
[14] Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669-8680.

[53] Aaron, C.; Dull D.; Schmiegel, J. L.; Jaeger, D., Ohashi, Y.; Mosher, H. S. *J. Org. Chem.* **1967**, *32*, 2797-2802.

carboxylic acid (2.13 g, 13.1 mmol). The reaction was refluxed for 12 hours, after which it was quenched by addition of saturated $NaHCO_3$ (100 mL), extracted with ether (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 100 mL), dried (Na2SO4), and concentrated to an orange oil. Purification by flash chromatography (5% Et_2O/95% pentane) provided a clear, colorless oil (1.91 g, 71%).

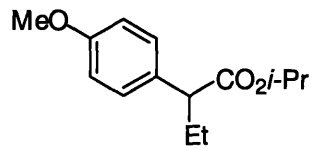
^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, 1H, J=7.0), 7.21-7.29 (m, 3H), 5.11 (app sept, 1H, J=6.0), 4.05 (dd, 1H, J=8.0, J=7.0), 3.15 (m, 1H), 2.96 (m, 1H), 2.49 (m, 1H), 2.36 (m, 1H), 1.32 (d, 3H, J=6.5), 1.31 (d, 3H, J=6.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 144.3, 141.2, 127.6, 126.5, 124.8 (plus isochronous peak), 68.2, 50.5, 31.9, 28.7, 22.1, 22.0.



Isopropyl thiophene-2-butyrate. Isopropanol (35 mL), concentrated sulfuric acid (6 drops) and magnesium sulfate (3 scoops) were added to thiophene-2-butyric acid (4.12 g, 24.2 mmol). The reaction was refluxed for 12 hours after which it was quenched by addition of saturated $NaHCO_3$ (50 mL), extracted with Et_2O (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 100 mL), dried (Na_2SO_4), and concentrated to a brown oil. Purification by flash chromatography (8% Et_2O/92% pentane → 12% Et_2O/88% pentane) afforded the pure product (1.47 g, 29%). Several later fractions that were contaminated with a close running impurity were discarded.

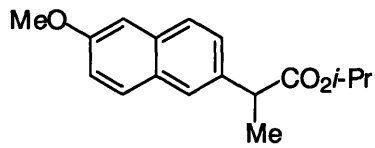
^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (dd, 1H, J=4.0, J=2.5), 6.94 (m, 2H), 5.04 (app sept, 1H, J=6.0), 3.74 (dd, 1H, J=7.5, J=8.0), 2.10 (d app q, 1H, J=15.0, J=7.5), 1.86 (d app q, 1H, J=14.5, J=7.5), 1.25 (d, 3H, J=6.5), 1.22 (d, 3H, J=6.0), 0.96 (app t, 3H,

J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 141.8, 126.5, 125.2, 124.4, 68.4, 49.1, 28.2, 21.8, 21.7, 12.1. FTIR (thin film) 3108, 3073, 2979, 2935, 2877, 1732, 1457, 1375, 1259, 1179, 1108, 957, 827 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{11}H_{16}O_2S$ $(M+Na)^+$ 212.0866, found 212.0861.



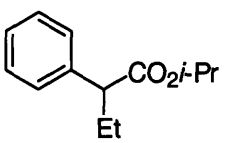
Isopropyl 4-methoxyphenylbutyrate. Isopropanol (10 mL), concentrated sulfuric acid (5 drops), toluene (10 mL), and magnesium sulfate (3 scoops) were added to 4-methoxyphenylbutyric acid (1.02 g, 5.25 mmol). The reaction was refluxed for 12 hours, after which it was quenched by addition of saturated $NaHCO_3$ (100 mL), extracted with ether (3 x 75 mL), washed successively with saturated $NaHCO_3$ (2 x 100 mL) and saturated NaCl (2x 100 mL), dried ($MgSO_4$), and concentrated to a yellow oil (0.875 g, 71%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (ddd, 2H, J=9.0, J=3.0, J=2.1), 6.85 (ddd, 2H, J=9.0, J=3.0, J=2.1), 4.99 (app sept, 1H, J=6.3), 3.79 (s, 3H), 3.35 (app t, 1H, J=7.5), 2.05 (d app q, 1H, J=15.0, J=7.5), 1.74 (d app q, 1H, J=14.7, J=7.2), 1.22 (d, 3H, J=6.3), 1.14 (d, 3H, J=6.3), 0.89 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, C_6D_6) δ 173.8, 159.6, 132.3, 129.6, 114.6, 67.9, 55.0, 53.6, 27.7, 22.1, 21.9, 12.7. FTIR (thin film) 2967, 2936, 2876, 1728, 1611, 1513, 1465, 1374, 1303, 1251, 1172, 1108, 1037, 831 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{14}H_{20}O_3$ (M^+) 236.1407, found 236.1412.



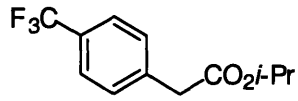
Isopropyl 6-methoxy-naphthalene-2-propionate [68641-85-0]. Isopropanol (15 mL), concentrated sulfuric acid (6 drops), and magnesium sulfate (3 scoops) were added to 6-methoxy-naphthalene-2-propionic acid (1.92 g, 8.34 mmol). The reaction was refluxed for 12 hours, after which it was quenched by addition of saturated $NaHCO_3$ (100 mL), extracted with ether (3 x 100 mL), washed successively with saturated $NaHCO_3$ (2 x 100 mL) and saturated NaCl (2 x 100 mL), dried (Na_2SO_4), and concentrated to a white solid (2.05 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, 2H, J=9.0, J=4.5), 7.67 (d, 1H, J=1.0), 7.42 (dd, 1H, J=8.5, J=2.0), 7.14 (dt, 2H, J=9.0, J=2.5), 5.01 (app sept, 1H, J=6.0), 3.92 (s, 3H), 3.81 (q, 1H, J=7.0), 1.57 (d, 3H, J=7.0), 1.23 (d, 3H, J=6.5), 1.13 (d, 3H, J=6.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 158.3, 136.7, 134.3, 130.0, 129.6, 127.7, 127.0, 126.6, 119.6, 106.2, 68.7, 56.0, 46.3, 22.5, 22.3, 19.3.



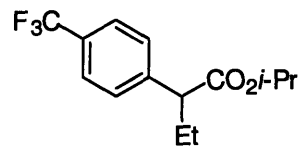
Isopropyl 2-phenylbutyrate [135806-11-0]. Isopropanol (5 mL), concentrated sulfuric acid (4 drops), toluene (25 mL), and magnesium sulfate (3 scoops) were added to 2-phenylbutyric acid (10.0 g, 60.9 mmol). The reaction was refluxed for 12 hours, after which it was quenched by addition of saturated $NaHCO_3$ (100 mL), extracted with ether (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 100 mL), dried ($MgSO_4$), and concentrated to a light yellow oil (6.19 g, 49%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 4H), 7.27 (m, 1H), 5.04 (app sept, 1H, J=6.5), 3.44 (dd, 1H, J=7.5, J=7.0), 2.13 (d app q, 1H, J=14.5, J=7.0), 1.81 (d app q, 1H, J=15.0, J=8.0), 1.26 (d, 3H, J=6.5), 1.17 (d, 3H, J=6.5), 0.94 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 140.1, 129.2, 128.6, 127.7, 68.5, 54.5, 27.6, 22.5, 22.3, 12.9.



Isopropyl 4-trifluoromethylphenylacetate. Isopropanol (15 mL), sulfuric acid (5 drops), and magnesium sulfate (3 scoops) were added to 4-trifluoromethylphenylacetic acid (3.00 g, 12.9 mmol) in a Schlenk tube. After heating for 36 hours at 100 °C, the reaction was quenched by addition of saturated $NaHCO_3$, extracted with Et_2O (3 x 100 mL), washed successively with saturated $NaHCO_3$ (2 x 100 mL) and water (2 x 100 mL), dried (Na_2SO_4), and concentrated to a white crystalline solid (2.72 g, 86%).

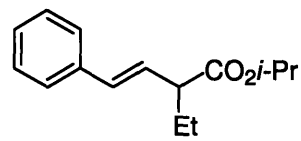
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, 2H, J=8.1), 7.40 (d, 2H, J=8.1), 5.02 (sept, 1H, J=6.3), 3.64 (s, 2H), 1.23 (d, 6H, J=6.3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 139.0, 130.3, 130.0 (q, J=32.2), 126.1 (q, J=4.0), 124.9 (q, J=272), 69.3, 42.1, 22.4. FTIR (thin film) 2988, 1719, 1559, 1457, 1327, 1230, 1180, 1109, 1070, 1021, 905, 835 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{12}H_{13}F_3O_2$ $(M+Na)^+$ 269.0760, found 269.0768. mp = 33-34°C.



Isopropyl 4-trifluoromethylphenylbutyrate. A solution of *n*-BuLi (2.73 M in hexanes; 3.12 mL, 8.53 mmol) was added via syringe to a –78 °C solution of diisopropylamine (1.20 mL, 8.53 mmol) in THF (10 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of isopropyl 4-trifluoromethylphenylacetate (2.00 g, 8.12 mmol) in THF (20 mL) was added via cannula. The mixture was stirred for 45 minutes at –78 °C, after which iodoethane (0.715 g, 8.93 mmol) was added. The reaction was warmed to room temperature and stirred for 12 hours. The reaction was quenched by

addition of 1M HCl (50 mL), extracted with Et_2O (3 x 100 mL), washed successively with 1M HCl (1 x 50 mL), saturated $NaHCO_3$ (2 x 50 mL), and water (2 x 50 mL), dried ($MgSO_4$), and concentrated to a dark orange oil. Purification by flash chromatography (10% Et_2O/90% pentane) provided a clear, colorless oil (1.86 g, 83%).

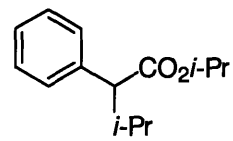
^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, 2H, J=8.0), 7.44 (d, 2H, J=8.0), 5.01 (app sept, 1H, J=6.0), 3.48 (app t, 1H, J=7.5), 2.11 (d app q, 1H, J=14.5, J=7.0), 1.79 (d app q, 1H, J=14.5, J=7.0), 1.24 (d, 3H, J=6.5), 1.15 (d, 3H, J=6.5), 0.91 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 144.0, 130.0 (q, J=32.2), 129.0, 126.1 (q, J=3.5), 124.9 (q, J=272), 68.9, 54.2, 27.5, 22.4, 22.2, 12.7. FTIR (thin film) 2981, 2939, 2880, 1731, 1619, 1459, 1376, 1327, 1170, 1126, 1069, 1020, 841 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{14}H_{17}F_3O_2$ (M^+) 274.1175, found 274.1177.



Isopropyl (*E*)-4-phenyl-2-ethyl-3-butyrate. Isopropanol (28 mL), concentrated sulfuric acid (10 drops), and magnesium sulfate (4 scoops) were added to (*E*)-4-phenyl-2-ethyl-3-butyric acid (2.85 g, 15.0 mmol), and the resulting mixture was refluxed for 12 hours. After cooling to room temperature, the reaction was quenched by addition of saturated $NaHCO_3$ (100 mL), extracted with Et_2O (3 x 125 mL), washed with saturated $NaHCO_3$ (2 x 100 mL), dried (Na_2SO_4) and concentrated to a gold-colored oil. Purification by flash chromatography (5% Et_2O/95% pentane) provided a light yellow oil (1.74 g, 50%).

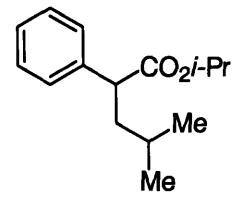
^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.32 (td, 2H, J=8.5, J=2.0), 7.24 (tt, 1H, J=7.0, J=2.0), 6.48 (d, 1H, J=15.5), 6.22 (dd, 1H, J=16.0, J=9.0), 5.05 (app sept, 1H, J=6.0), 3.03 (m, 1H), 1.88 (dq, 1H, J=14.5, J=7.0), 1.66 (dq, 1H, J=15.0, J=7.5), 1.27 (d,

3H, J=7.0), 1.25 (d, 3H, J=6.5), 0.96 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 137.7, 132.7, 129.2, 128.5, 128.2, 127.0, 68.5, 52.2, 26.8, 22.6, 22.5, 12.4. FTIR (thin film) 2978, 2935, 2877, 1728, 1452, 1374, 1264, 1176, 1107, 967, 744, 695 cm^{-1} .HRMS (EI, *m/z*) calcd. for $C_{15}H_{20}O_2$ (M^+) 232.1458, found 232.1457.



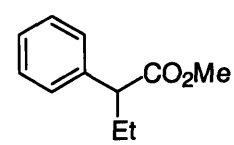
Isopropyl 3-methyl-2-phenylbutyate [13027-70-8]. Oxalyl chloride (2.09 mL, 24.0 mmol) was added over 5 minutes to a –78 °C solution of 3-methyl-2-phenylbutyric acid (1.71 g, 9.59 mmol) and *N,N*-dimethylformamide (2 drops) in CH_2Cl_2 (20 mL). The resulting mixture was stirred at –78 °C for 2 hours, and then it was warmed to room temperature and concentrated. CH_2Cl_2 (10 mL) was then added to the unpurified acid chloride, and the resulting solution was cooled to 0 °C. To this solution was added 2-methyl-2-propanol (10 mL) and then NEt_3 (2.67 mL). The reaction mixture was slowly warmed to room temperature and then stirred for 12 hours. Saturated $NaHCO_3$ (50 mL) was added, and then the reaction mixture was extracted with Et_2O (3 x 75 mL), washed with saturated $NaHCO_3$ (2 x 75 mL), dried (Na_2SO_4), filtered, and concentrated, to yield a light yellow oil (1.80 g, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.31 (td, 2H, J=7.0, J=2.0), 7.25 (tt, 1H, J=7.0, J=1.5), 5.00 (app sept, 1H, J=6.5), 3.11 (d, 1H, J=11.0), 2.35 (m, 1H), 1.24 (d, 3H, J=6.0), 1.16 (d, 3H, J=6.0), 1.07 (d, 3H, J=6.5), 0.72 (d, 3H, J=6.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 138.8, 128.7, 128.6, 127.3, 68.0, 60.7, 32.2, 22.1, 21.8, 21.6, 20.5.



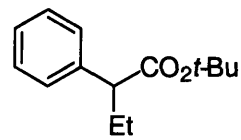
Isopropyl 4-methyl-2-phenylpentanoate [124888-45-5]. Oxalyl chloride (2.84 mL, 32.5 mmol) was added over 5 minutes to a –78 °C solution of 4-methyl-2-phenylpentanoic acid (2.50 g, 13.0 mmol) and *N,N*-dimethylformamide (2 drops) in CH_2Cl_2 (35 mL). The resulting mixture was stirred at –78 °C for 2.5 hours, and then it was warmed to room temperature and concentrated. CH_2Cl_2 (20 mL) was then added to the unpurified acid chloride, and the resulting solution was cooled to 0 °C. To this solution was added 2-methyl-2-propanol (20 mL) and then NEt_3 (2.2 mL). The reaction mixture was slowly warmed to room temperature and then stirred for 12 hours. Saturated NH_4Cl (50 mL) was added, and then the reaction mixture was extracted with Et_2O (3 x 100 mL), washed successively with saturated $NaHCO_3$ (2 x 100 mL) and saturated NaCl (2 x 50 mL), dried (Na_2SO_4), filtered, and concentrated, to a light yellow oil. Purification by flash chromatography (5% Et_2O/95% pentane) provided a clear, colorless oil (1.90 g, 62%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.35 (m, 5H), 4.99 (app sept, 1H, J=6.3), 3.61 (dd, 1H, J=7.5, J=7.2), 1.97 (ddd, 1H, J=13.5, J=9.0, J=6.3), 1.65 (dt, J=13.8, J=6.9), 1.48 (m, 1H), 1.22 (d, 3H, J=6.3), 1.13 (d, 3H, J=6.6), 0.92 (app d, 6H, J=6.6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 139.8, 128.7, 128.1, 127.2, 68.0, 50.1, 42.7, 26.1, 22.8, 22.6, 22.0, 21.8.



Methyl 2-phenylbutyrate [2294-71-5]. Methanol (123 mL) and sulfuric acid (0.81 mL, 15.2 mmol) were added to a solution of 2-phenylbutyric acid (25.0 g, 152 mmol) in benzene (300 mL). After refluxing for 14 hours, the reaction was cooled to room temperature, diluted with water (200 mL), extracted with Et_2O (3 x 200 mL), washed successively with saturated $NaHCO_3$ (2 x 200 mL) and saturated NaCl solution (2 x 200 mL), dried ($MgSO_4$), and concentrated to a yellow liquid. Purification by vacuum distillation (118 °C, 1 mm Hg) furnished a clear, colorless liquid (23.0 g, 85%).

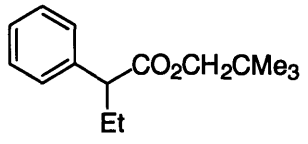
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.35 (m, 5H), 3.67 (s, 3H), 3.50 (app t, 1H, J=8.0), 2.15 (d app q, 1H, J=15.5, J=8.0), 1.84 (d app q, 1H, J=14.5, J=7.0), 0.93 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 139.4, 128.8, 128.2, 127.5, 53.6, 52.1, 27.0, 12.4.



2,2-Dimethylethyl 2-phenylbutyrate. Oxalyl chloride (10.6 mL, 122 mmol) was added over 5 minutes to a –78 °C solution of 2-phenylbutyric acid (8.00 g, 48.7 mmol) and *N,N* -dimethylformamide (3 drops) in CH_2Cl_2 (40 mL). The resulting mixture was stirred at –78 °C for 2 hours, and then it was warmed to room temperature and concentrated. CH_2Cl_2 (40 mL) was then added to the unpurified acid chloride, and the resulting solution was cooled to 0 °C. To this solution was added 2-methyl-2-propanol (5.13 mL, 53.6 mmol) and then NEt_3 (3 mL). The reaction mixture was slowly warmed to room temperature and then stirred for 15 hours. Saturated NH_4Cl (50 mL) was added, and then the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL), washed successively with saturated $NaHCO_3$ (2 x 100 mL) and water (2 x 50 mL), dried ($MgSO_4$), filtered, and

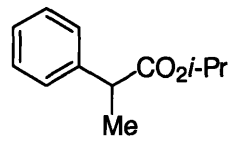
concentrated, to yield an orange oil. Purification by vacuum distillation (83–85 °C, 1 mm Hg) furnished the product as a clear, colorless liquid (6.06 g, 52%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.32 (dd, 2H, J=6.0, J=0.5), 7.13 (m, 2H), 7.04 (tt, 1H, J=7.5, J=1.5), 3.35 (app t, 1H, J= 7.5), 2.12 (d app t, 1H, J=13.5, J=7.5), 1.70 (d app t, 1H, J=13.5, J=7.5), 1.29 (s, 9H), 0.83 (app t, 3H J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 139.9, 128.5, 128.0, 127.0, 80.6, 54.6, 28.1, 27.0, 12.4. FTIR (thin film) 3030, 2969, 2933, 2876, 1729, 1454, 1148, 1078, 749, 698 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{14}H_{20}O_2$ (M^+) 220.1457, found 220.1458.



2,2-Dimethylpropyl 2-phenylbutyrate. 2,2-dimethylpropanol (9.9 mL, 91.4 mmol), concentrated sulfuric acid (6 drops), and magnesium sulfate (3 scoops) were added to a solution of 2-phenylbutyric acid (5.00 g, 30.5 mmol) in toluene (30 mL). After refluxing for 12 hours, the reaction was quenched by addition of saturated $NaHCO_3$ (100 mL), extracted with Et_2O (2 x 100 mL), dried ($MgSO_4$), and concentrated to a yellow oil (6.54 g , 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19-7.38 (m, 5H), 3.83 (d, 1H, J=11.0), 3.79 (d, 1H, J=10.5), 3.52 (app t, 1H, J=7.5), 2.18 (m, 1H), 1.87 (m, 1H), 0.95 (app t, 3H, J=7.5), 0.90 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 139.5, 128.7, 128.3, 127.4, 74.0, 31.7, 26.7, 26.6, 12.5. FTIR (thin film) 3031, 2963, 2875, 1735, 1455, 1368, 1164, 995, 698 cm^{-1} .HRMS (EI, *m/z*) calcd. for $C_{15}H_{22}O_2$ (M^+) 234.1614, found 234.1613.

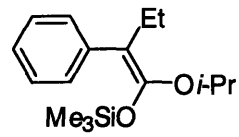


Isopropyl 2-phenylpropionate [65757-64-4]. Isopropanol (25 mL), sulfuric acid (6 drops), and magnesium sulfate (3 scoops) were added to 2-phenylpropionic acid (5.00 g, 33.3 mmol). After 72 hours of refluxing, the reaction was cooled to room temperature and quenched by addition of saturated $NaHCO_3$, extracted with Et_2O (3 x 100 mL), washed successively with saturated $NaHCO_3$ (2 x 50 mL) and water (2 x 50 mL), dried (Na_2SO_4), and concentrated to a clear, colorless oil (4.95 g, 77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.32 (m, 5H), 5.00 (app sept, 1H, J=6.0), 3.67 (q, 1H, J=7.2), 1.49 (d, 3H, J=7.2), 1.22 (d, 3H, J=6.0), 1.14 (d, 3H, J=6.3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 141.5, 129.2, 128.1, 127.7, 68.6, 46.4, 22.5, 22.2, 19.3.

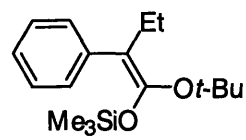
Preparation of Acyclic Silyl Ketene Acetals

General procedure. A solution of *n*-BuLi (1.05 equiv.) was added via syringe to a –78 °C solution of diisopropylamine (1.05 equiv) in THF. The mixture was stirred at –78 °C for 30 minutes, and then a solution of the ester (1.0 equiv.) in THF was added via cannula. The mixture was stirred at –78 °C for 60 minutes, and then Me_3SiCl (1.1 equiv) was added, resulting in a clear, light-yellow solution which was warmed to room temperature and stirred for 3 hours. The THF was then removed, and the residue was taken up in pentane and filtered. The solvent was removed, and unless indicated, the resulting oil was used without further purification (no impurities by ^{1}H NMR).



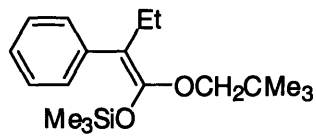
(**2.32**). The general procedure was followed, using *n*-BuLi (2.74 M in hexanes; 6.50 mL, 17.8 mmol), diisopropylamine (2.49 mL, 17.8 mmol, in 20 mL THF), ester (3.50 g, 17.0 mmol, in 10 mL THF), and Me_3SiCl (3.50 g, 17.0 mmol). Product **2.32**, a light yellow liquid, was purified by fractional distillation (132 °C, 2mm mm Hg) to afford a clear, colorless liquid as a 1.6/1 mixture of isomers (2.81 g, 59%).

^1H (300 MHz, C_6D_6) NMR δ 6.99-7.49 (m, 10H, major, minor), 4.34 (sept, 1H, J=6.3, major), 4.06 (sept, 1H, J=6.0, minor), 2.61 (q, 2H, J=7.5, major), 2.53 (q, 2H, J=7.2, minor), 1.16 (d, 6H, J=6.3, major), 0.91 (d, 6H, J=6.0, minor), 1.04 (m, 6H, major, minor), 0.21 (s, 9H, minor), –0.067 (s, 9H, major). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 149.1, 140.8, 140.4, 130.2, 130.0, 128.4 (isochronous with other isomer), 126.0, 125.9, 106.0, 105.2, 71.7, 69.7, 24.6, 23.9, 22.4, 22.2, 14.5, 14.1, 0.65, 0.27. FTIR (neat) 3056, 2958, 2870, 1660, 1599, 1364, 1253, 1197, 1134, 1013, 963, 847, 761, 698 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{16}H_{26}O_2Si$ (M^+) 278.1697, found 278.1691.



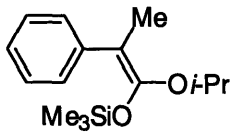
(**2.33**). The general procedure was followed, using *n*-BuLi (2.56 M in hexanes; 4.41 mL, 11.3 mmol), diisopropylamine (1.58 mL, 11.3 mmol, in 20 mL THF), ester (2.50 g, 11.3 mmol, in 20 mL THF), and Me_3SiCl (1.43 mL, 11.3 mmol). Product **2.33**, a light yellow liquid, was purified by fractional distillation (88-91 °C, 1.0 mm Hg) to afford product as a clear, colorless liquid a 1.5/1 mixture of isomers (1.80 g, 55%).

^{1}H NMR (500 MHz, C_6D_6) δ 6.99-7.47 (m, 10H, major, minor), 2.56 (q, 2H, J=7.5, major), 2.52 (q, 2H, J=7.5, minor), 1.36 (s, 9H, major), 1.04 (s, 9H, minor), 1.03 (t, 3H, J=7.2, minor), 0.99 (t, 3H, J=7.5, major), 0.24 (s, 9H, minor), –0.92 (s, 9H, major). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 149.1, 140.9, 140.3, 130.4, 130.3, 126.1, 125.9, 109.7, 108.7, 80.5, 79.0, 55.7, 55.2, 29.8, 29.5, 24.6 (isochronous with other isomer), 14.0 (isochronous with other isomer), 1.0, 0.6. FTIR (CH_2Cl_2) 2967, 2876, 1658, 1642, 1598, 1367, 1218, 1148, 1093, 987 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{17}H_{28}O_2$ Si (M-C_4H_8)$^+$ 236.1227, found 236.1222.



(**2.34**). The general procedure was followed, using *n*-BuLi (2.83 M in hexanes; 4.73 mL, 13.4 mmol), diisopropylamine (1.88 mL, 13.4 mmol, in 12 mL THF), ester (3.00 g, 12.8 mmol, in 10 mL THF), and Me_3SiCl (1.79 mL, 14.1 mmol). Purification by chromatography on alumina adsorption (pentane) inside a glovebox afforded a 1.1/1 mixture of isomers of product **2.34** as a clear, colorless oil (1.92 g, 49%).

^{1}H NMR (300 MHz, C_6D_6) δ 6.99-7.47 (m, 10H, major, minor), 3.50 (s, 2H, major), 3.32 (s, 2H, minor), 2.60 (q, 2H, J=7.5, major), 2.49 (q, 2H, J=7.5, minor), 1.10 (t, 3H, J=7.5, major), 1.02 (t, 3H, J=7.5, minor), 0.95 (s, 9H, major), 0.70 (s, 9H, minor), 0.22 (s, 9H, minor), -0.06 (s, 9H, major). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 151.4, 140.9, 139.9, 130.3, 130.1, 128.4, 128.3, 126.1, 126.0, 104.5, 103.2, 80.5, 79.3, 32.4, 32.2, 27.1, 27.0, 24.6, 24.1, 14.9, 14.0, 0.62, 0.33. FTIR (neat) 3056, 2958, 2870, 1660, 1599, 1364, 1197, 1134, 1013, 963, 847, 761, 698 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{18}H_{30}O_2Si$ (M)$^+$ 306.2010, found 306.2004.



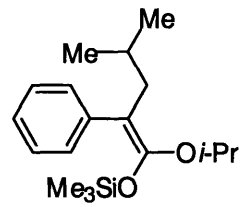
(**2.35**). The general procedure was followed, using *n*-BuLi (2.62 M in hexanes; 6.26 mL, 16.4 mmol), diisopropylamine (2.30 mL, 16.4 mmol, in 20 mL THF), ester (3.00 g, 15.6 mmol, in 15 mL THF), and Me_3SiCl (2.18 mL, 17.2 mmol). Product **2.35**, a light yellow oil, was isolated as a 1.8/1 mixture of isomers (3.74 g, 91%), for which purification was not necessary.

^1H NMR (500 MHz, C_6D_6) δ 7.61 (m, 2H, minor), 7.52 (m, 2H, major), 7.21 (m, 3H, major), 7.03 (m, 3H, minor), 4.34 (sept, 1H, J=6.0, major), 4.15 (sept, 1H, J=6.5, minor), 2.08 (s, 3H, major), 2.03 (s, 3H, minor), 1.14 (d, 6H, J=6.0, major), 0.97 (d, 6H, J=6.0, minor), 0.20 (s, 9H, minor), -0.03 (s, 9H, major). ^{13}C NMR (125 MHz, C_6D_6) δ 150.4, 149.5, 142.0, 141.5, 129.4, 129.2, 128.3, 128.2, 125.8, 125.7, 98.8, 98.4, 71.5, 70.3, 22.3, 22.2, 17.2, 16.6, 0.58, 0.30. FTIR (neat) 3055, 2975, 2930, 1661, 1599, 1494, 1443, 1382, 1373, 1253, 1206, 1134, 1107, 1067, 1027, 957, 900, 848, 762 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{15}H_{24}O_2Si$ (M^+) 264.1540, found 264.1539.

(**2.36**). The general procedure was followed, using *n*-BuLi (2.56 M in hexanes; 2.05 mL, 5.24 mmol), diisopropylamine (0.734 mL, 5.24 mmol, in 10 mL THF), ester (1.10 g, 4.99 mmol, in 10 mL THF), and Me_3SiCl (0.697 mL, 5.49 mmol). Product **2.36**, a light yellow oil, was isolated as a 1.3/1 mixture of isomers (1.39 g, 95%), for which purification was not necessary.

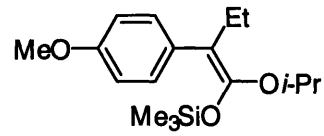
^1H NMR (500 MHz, C_6D_6) δ 7.10-7.30 (m, 10, major, minor), 4.38 (sept, 1H, J=6.5, major), 4.05 (sept, 1H, J=6.5, minor), 3.34 (sept, 1H, J=7.0, major), 3.17 (sept, 1H,

J=7.0, minor), 1.20 (d, 6H, J=6.0, major), 1.14 (d, 6H, J=7.0, minor), 1.14 (d, 6H, J=7.0, major), 0.93 (d, 6H, J=6.5, minor), 0.27 (s, 9H, minor), -0.056 (s, 9H, major). ^{13}C NMR (125 MHz, C_6D_6) δ 149.2, 148.4, 139.3, 138.9, 132.1, 132.0, 128.2, 128.0, 126.6, 126.5, 110.2, 109.7, 71.3, 69.4, 29.6, 29.0, 22.8, 22.5, 22.3, 22.2, 0.64, 0.19. FTIR (neat) 3055, 2962, 2931, 2871, 1665, 1494, 1466, 1382, 1360, 1253, 1207, 1107, 1062, 972, 906, 848, 753, 701 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{17}H_{28}O_2Si$ (M^+) 292.1853, found 292.1852.



(**2.37**). The general procedure was followed, using *n*-BuLi (2.93 M in hexanes; 2.30 mL, 6.73 mmol), diisopropylamine (0.943 mL, 6.73 mmol, in 10 mL THF), ester (1.50 g, 6.40 mmol, in 10 mL THF), and Me_3SiCl (0.893 mL, 7.04 mmol). Product **2.37**, a light yellow oil, was isolated as a 3.3/1 mixture of isomers (1.82 g, 93%), for which purification was not necessary.

^{1}H NMR (500 MHz, C_6D_6) δ 7.44-7.54 (m, 4H, major, minor), 7.19-7.30 (m, 4H, major, minor), 7.06-7.13 (m, 2H, major, minor), 4.45 (sept, 1H, J=6.3), 4.11 (sept, 1H, J=6.0, major), 2.59 (d, 2H, J=7.2, J=1.8, major), 2.52 (d, 2H, J=7.2, minor), 1.80 (m, 2H, major, minor), 1.26 (d, 6H, J=6.0, minor), 1.02 (d, 6H, J=6.3, major), 1.01 (d, 6H, J=6.9, major), 1.00 (d, 6H, J=6.5, minor), 0.32 (s, 9H, major), 0.010 (s, 9H, minor). ^{13}C NMR (125 MHz, C_6D_6) δ 151.1, 150.1, 141.4, 141.0, 130.5, 130.1, 128.7, 128.4, 126.0, 125.9, 103.2, 102.4, 71.8, 69.7, 40.5, 39.5, 27.9, 27.8, 23.3, 23.2, 22.5, 22.3, 0.91, 0.33. FTIR (neat) 3056, 2956, 2868, 1654, 1465, 1383, 1372, 1253, 1206, 1133, 1105, 1005, 994, 882, 848, 757 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{18}H_{30}O_2Si$ (M^+) 306.2010, found 306.2013.

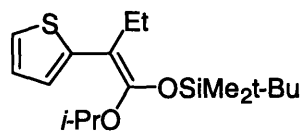


(**2.38**). The general procedure was followed, using *n*-BuLi (2.76 M in hexanes; 1.61 mL, 4.44 mmol), diisopropylamine (0.622 mL, 4.44 mmol, in 20 mL THF), ester (1.00 g, 4.23 mmol, in 10 mL THF), and Me_3SiCl (0.591 mL, 4.65 mmol). Product **2.38**, a light yellow oil, was isolated as a1.5/1 mixture of isomers (1.98 g, 75%), for which purification was not necessary.

^1H NMR (300 MHz, C_6D_6) δ 7.44 (m, 4H, major, minor), 6.87 (m, 4H, major, minor), 4.40 (sept, 1H, J=6.3, minor), 4.14 (sept, 1H, J=6.3, major), 3.36 (s, 6H, major, minor), 2.67 (q, 2H, J=7.5, minor), 2.60 (q, 2H, J=7.5, major), 1.22 (d, 6H, J=6.0, minor), 1.13 (t, 6H, J=7.5, major, minor), 1.01 (d, 6H, J=6.3, major), 0.28 (s, 9H, major), 0.025 (s, 9H, minor). ^{13}C NMR (125 MHz, C_6D_6) δ 158.4, 158.3, 149.6, 148.7, 132.9, 132.6, 131.2, 131.0, 113.9 (isochronous with other isomer), 105.5, 104.8 , 71.5, 69.7, 55.1, 55.0, 24.7, 24.0, 22.4, 22.3, 14.5, 14.2, 0.69, 0.35. FTIR (neat) 3036, 2967, 2933, 2874, 1661, 1610, 1512, 1465, 1383, 1287, 1253, 1203, 1178, 1132, 1106, 1040, 989, 848 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{17}H_{28}O_3Si$ (M^+) 308.1802, found 308.1809.

(**2.39**). The general procedure was followed, using *n*-BuLi (2.66 M in hexanes; 1.58 mL, 4.21 mmol), diisopropylamine (0.590 mL, 4.21 mmol, in 15 mL THF), ester (1.10 g, 4.01 mmol, in 10 mL THF), and Me_3SiCl (0.559 mL, 4.41 mmol). Product **2.39**, an orange oil, was isolated as a 1.6/1 mixture of isomers (1.07 g, 62%), for which purification was not necessary.

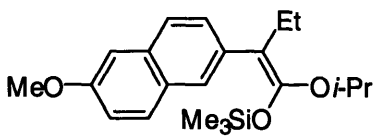
^{1}H NMR (300 MHz, C_6D_6) δ 7.24-7.43 (m, 8H, major, minor), 4.29 (sept, 6H, J=6.3, minor), 4.03 (sept, 6H, J=6.3, major), 2.49 (q, 2H, J=7.2, minor), 2.41 (q, 2H, J=7.2, major), 1.10 (d, 6H, J=6.0, minor), 0.95 (t, 6H, J=7.5, major, minor), 0.85 (d, 6H, J=6.3, major), 0.17 (s, 9H, major), -0.15 (s, 9H, minor). ^{13}C NMR (125 MHz, C_6D_6) δ 150.8, 150.1, 144.8, 144.3, 130.1, 129.8, 129.0, 128.6, 127.6, 127.4, 125.2 (q, J=4.0), 125.1 (q, J=4.0), 104.7 (q, coupling indeterminate), 104.0 (q, coupling indeterminate), 71.8, 70.1, 23.9, 23.3, 22.2, 22.0, 14.3, 14.0, 0.44, 0.70. FTIR (neat) 2964, 2929, 2874, 1657, 1649, 1613, 1384, 1327, 1254, 1213, 1165, 1125, 1068, 990, 844 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{17}H_{25}F_3O_2Si$ (M^+) 346.1570, found 346.1571.



(**2.40**). A solution of *n*-BuLi (2.50 M in hexanes; 1.98 mL, 4.95 mmol) was added via syringe to a –78 °C solution of diisopropylamine (0.694 mL, 4.95 mmol) in THF (10 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of the ester (1.00 g, 4.71 mmol) in THF (10 mL) was added via cannula. The mixture was stirred at –78 °C for 45 minutes, and then a solution of *t*-$BuMe_2SiCl$ (0.851g, 5.65 mmol) in THF (5 mL) was added, resulting in a clear, light-yellow solution which was warmed to room temperature and stirred for 3 hours. The THF was then removed, and the residue was taken up in pentane and filtered. Purification by chromatography on Alumina Adsorption (pentane) inside a glove box afforded **2.40** as a clear, colorless oil (1.06 g, 69%) as a 10/1 mixture of isomers.

^{1}H NMR (500 MHz, C_6D_6) δ 7.02 (ddd, 1H, J=3.5, J=1.5, J=0.5, minor), 6.99 (ddd, 1H, J=3.5, J=1.0, J=0.5, major), 6.94 (dd, 1H, J=5.5, J=1.5, major), 6.92 (m, 1H, minor), 6.89 (ddd, 1H, J=5.0, J=3.5, J=0.5, major), 6.86 (ddd, 1H, J=5.0, J=3.5, J=0.5,

minor), 4.39 (sept, 1H, J=6.0, major), 4.35 (sept, 1H, J=6.0, minor), 2.64 (q, 2H, J=7.5), 2.59 (q, 2H, J=7.5, minor), 1.24 (d, 6H, J=6.0, major), 1.23 (t, 3H, J=7.5, major), 1.19 (t, 3H, J=7.5, minor), 1.12 (d, 6H, J=6.0, minor), 0.98 (s, 6H, minor), 0.97 (s, 6H, major), 0.14 (s, 9H, major), 0.12 (s, 9H, minor). ^{13}C NMR (125 MHz, C_6D_6) δ 149.7, 149.3, 142.8, 142.5, 126.8, 126.5, 124.8, 124.4, 123.3, 122.9, 102.5, 101.5, 72.1, 71.2, 27.0, 26.5, 26.1, 23.4, 22.1, 21.5, 18.6, 14.3, -3.7, -4.1. FTIR (neat) 2960, 2931, 2859, 1646, 1463, 1373, 1255, 1235, 1200, 1128, 1104, 1050, 975, 915, 831, 783, 685 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{17}H_{30}O_2SSi$ (M^+) 326.1730 , found 326.1728.



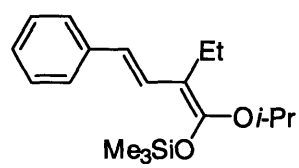
(**2.41**). The general procedure was followed, using *n*-BuLi (2.45 M in hexanes; 2.36 mL, 5.78 mmol), diisopropylamine (0.810 mL, 5.78 mmol, in 20 mL THF), ester (1.50 g, 5.51 mmol, in 15 mL THF), and Me_3SiCl (0.769 mL, 6.06 mmol). Product **2.41**, a white solid, was isolated as a 1.5/1 mixture of isomers (1.45 g, 76%), for which purification was not necessary.

^{1}H NMR (300 MHz, C_6D_6) δ 7.01-8.05 (m, 12H, major, minor), 4.49 (sept, 1H, J=6.0, major), 4.26 (sept, 1H, J=6.0, minor), 3.46 (s, 6H, major, minor isochronous peaks), 2.29 (s, 3H, major), 2.24 (s, 3H, minor), 1.29 (d, 6H, J=6.6, major), 1.07 (d, 6H, J=6.0, minor), 0.33 (s, 9H, minor), 0.053 (s, 9H, major). ^{13}C NMR (125 MHz, C_6D_6) δ 158.2, 158.1, 150.6, 149.8, 137.3, 136.9, 133.6 (isochronous with other isomer), 130.0 (isochronous with other isomer), 129.9, 129.1, 128.9, 128.7, 127.4, 127.0, 126.5, 126.4, 119.4, 119.3, 106.3, 106.2, 98.9, 98.4, 71.8, 70.4, 55.1 (isochronous with other isomer), 22.3 (isochronous with other isomer), 17.4, 16.7, 0.67, 0.35. FTIR (thin film) 2972,

2930, 1653, 1604, 1485, 1464, 1373, 1254, 1199, 1121, 1065, 1035, 895 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{20}H_{28}O_3Si$ (M^+) 344.1808, found 344.1821. mp = 51-54°C.

(**2.42**). The general procedure was followed, using *n*-BuLi (2.66 M in hexanes; 3.67 mL, 9.77 mmol), diisopropylamine (1.37 mL, 9.77 mmol, in 20 mL THF), ester (1.90 g, 9.30 mmol, in 15 mL THF), and Me_3SiCl (1.29 mL, 10.2 mmol). Product **2.42**, a light yellow oil, was isolated as a 1.4/1 mixture of isomers (2.05 g, 80%), for which purification was not necessary.

^1H NMR (300 MHz, C_6D_6) δ 8.90 (d, 1H, J=7.8, minor), 7.93 (d, 1H, J=8.1, major), 6.98-7.22 (m, 6H, major, minor), 4.37 (sept, 1H, J=6.0, minor), 4.28 (sept, 1H, J=6.3, major), 2.66-2.82 (m, 8H, major, minor), 1.15 (d, 6H, J=6.0, minor), 1.09 (d, 6H, J=6.0, major), 0.20 (s, 9H, major), 0.15 (s, 9H, minor). ^{13}C NMR (125 MHz, C_6D_6) δ 147.7, 147.6, 145.6, 145.1, 141.6, 141.5, 127.0 (isochronous with other isomer), 125.9, 125.7, 125.3, 125.2, 124.2, 123.8, 107.1, 106.7, 71.2, 70.7, 30.9, 30.8, 28.2, 28.0, 22.4, 22.2, 0.75, 0.70. FTIR (neat) 3066, 3019, 2974, 2932, 2850, 1679, 1599, 1460, 1383, 1372, 1286, 1253, 1205, 1140, 1109, 1003, 862, 848, 754 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{16}H_{24}O_2Si$ (M^+) 276.1540, found 276.1543.



(**2.43**). The general procedure was followed, using *n*-BuLi (2.84 M in hexanes; 1.37 mL, 3.89 mmol), diisopropylamine (0.545 mL, 3.89 mmol, in 10 mL THF), ester (0.861 g,

3.71 mmol, in 10 mL THF), and Me_3SiCl (0.518 mL, 4.08 mmol). The product, a light yellow oil, was isolated as a 1.1/1 mixture of isomers (0.870 g, 77%), for which purification was not necessary.

^1H NMR (300 MHz, C_6D_6) δ 7.54 (d, 1H, J=16.2, minor), 7.37 (d, 1H, J=16.2, major), 7.44 (m, 3H, major, minor), 7.13 (m, 6H, major, minor), 6.97 (m, 1H, major), 6.48 (d, 1H, J=16.2, minor), 6.47 (d, 1H, J=16.2, major), 4.32 (sept, 1H, J=6.3, major), 4.23 (sept, 1H, J=6.3, minor), 2.52 (q, 2H, J=7.2, major), 2.43 (q, 2H, J=7.5, minor), 1.21 (t, 3H, J=7.50, major), 1.19 (t, 3H, J=7.80, minor), 1.07 (d, 6H, J=6.3, minor), 1.06 (d, 6H, J=6.0, major), 0.14 (s, 9H, major), 0.13 (s, 9H, minor). ^{13}C NMR (125 MHz, C_6D_6) δ 152.1, 152.0, 140.2 (isochronous with other isomer), 129.3 (isochronous with other isomer), 128.7, 127.1 (isochronous with other isomer), 126.7, 125.4, 126.4, 123.5, 123.3, 106.8, 105.2, 71.8, 70.2, 22.3, 22.2, 19.9, 19.5, 14.4, 14.2, 0.55, 0.38. FTIR (neat) 3079, 3039, 2974, 2933, 2874, 1630, 1596, 1494, 1452, 1373, 1332, 1254, 1195, 1120, 1038, 967, 866, 848, 750, 692 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{18}H_{28}O_2Si$ (M^+) 304.1853, found 304.1850.

Catalytic Enantioselective Intermolecular C-Acylation of Acyclic Silyl Ketene Acetals

General. Although some of the silyl ketene acetals were purified by chromatography on Alumina Adsorption inside a glove box, this level of purity is not essential for catalytic enantioselective C-acylations–we have used unpurified silyl ketene acetals, and they furnish the same ee. However, we routinely purify the silyl ketene acetals in order to accurately determine the yields of the acylation reactions.

Unless otherwise specified, all reactions are the average of two runs (one run with each enantiomer of the catalyst). The majority of acylations were set up in a glove box.

due to the moisture sensitivity of the trimethylsilyl ketene acetals, which results in lower yields when reactions are set up without a glove box. For certain silyl ketene acetals, the second run was performed outside of the glove box to demonstrate that under dry conditions and Argon, the yields and enantioselectivities can be replicated.

General Procedure A. A solution of catalyst (0.05 equiv) in Toluene/CH_2Cl_2 (2:1) was added to a 4-mL vial containing the silyl ketene acetal (1.0 equiv). The resulting solution was stirred for 5 minutes at room temperature, after which the acylating agent (1.3 equiv) was added. The vial was capped and removed from the glove box, and the reaction mixture was stirred for 24 hours at room temperature. The product was then purified directly by flash chromatography (Et_2O/pentane). The catalyst was recovered by eluting with 3 volumes of CH_2Cl_2, followed by 10% Et_3N/90% EtOAc. The ee of the product was determined either by chiral HPLC or by chiral GC.

General Procedure B. The catalyst (0.05 equiv) was added to a 4-mL vial (with a puncturable teflon fitted cap) containing a solution of the silyl ketene acetal (1.0 equiv) in Toluene/CH_2Cl_2 (2:1). The resulting solution was stirred for 5 minutes at room temperature, after which the acylating agent (1.3 equiv) was added. The reaction mixture was stirred for 24-36 hours at room temperature. The product was then purified directly by flash chromatography (Et_2O/pentane). The catalyst was recovered by eluting with 3 volumes of CH_2Cl_2, followed by 10% Et_3N/90% EtOAc. The ee of the product was determined either by chiral HPLC or by chiral GC.

Variation of the Acylating Agent (Table 2B.3)

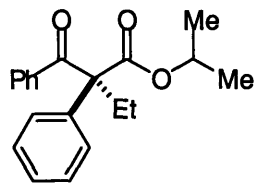


Table 2B.3, entry 3. General procedure A was followed, using silyl ketene acetal **2.32** (0.150 g, 0.539 mmol), Bz_2O (0.159 g, 0.701 mmol), (+)-**1.16** (0.0185 g, 0.0270 mmol), and 0.539 mL of Toluene/CH_2Cl_2 (2:1) to produce 83% (0.139 g, 0.448 mmol) of **2.57** as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 99:1, 1.0 mL/min, retention times of enantiomers: 10.2 min (major), 11.4 min (minor)) to have 55% ee.

^{1}H NMR (500 MHz, C_6D_6) δ 7.98 (ddd, 2H, J=7.5, J=2.0, J=1.5), 7.94 (ddd, 2H, J=7.5, J=2.0, J=1.5), 7.09 (app t, 2H, J=8.0), 6.99 (m, 1H), 6.90 (tt, 1H, J=7.0, J=1.0), 6.84 (m, 2H), 4.92 (app sept, 1H, J=6.0), 2.64 (dq, 1H, J=15.0, J=7.5), 2.47 (dq, J=15.5, J=7.5), 0.93 (app t, 3H, J=7.5), 0.87 (d, 3H, J=6.5), 0.54 (d, 3H, J=6.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 170.9, 139.1, 136.8, 132.2, 129.7, 128.8, 128.4, 128.2, 127.4, 68.5, 65.7, 33.4, 21.3, 20.6, 9.1. FTIR (neat) 3027, 3060, 2980, 2937, 2880, 1734, 1688, 1599, 1580, 1495, 1447, 1385, 1375, 1238, 1177, 1104, 758, 700. HRMS (ESI, *m/z*) calcd. for $C_{20}H_{22}O_3$ $(M+Na)^+$ 333.1461 found 333.1457. $[\alpha]^{22}_D = -51°$ (c=0.19, CH_2Cl_2; for product with 55% ee).

For run 2, general procedure A was followed with silyl ketene acetal **2.32** (0.150 g, 0.539 mmol), Bz_2O (0.159 g, 0.701 mmol), and (–)-**1.16** (0.0185 g, 0.0270 mmol) in 0.539 mL Toluene/CH_2Cl_2 (2:1) which furnished 82% of product **2.57** (0.137 g, 0.441 mmol), which was shown by chiral HPLC to have 52% ee.

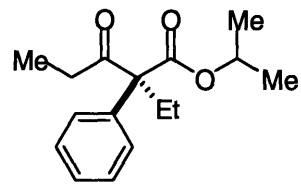


Table 2B.3, entry 4. General procedure A was followed, using silyl ketene acetal **2.32** (0.100 g, 0.359 mmol), $(EtCO)_2O$ (0.0608 mL, 0.467 mmol), (+)-**1.16** (0.0123 g, 0.0180 mmol), and 0.359 mL of Toluene/CH_2Cl_2 (2:1) to produce 57% (0.0536 g, 0.204 mmol) of **2.58** as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 7.7 min (major), 14.1 min (minor)) to have 88% ee.

^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.37 (m, 5H), 5.18 (app sept, 1H, J=6.0), 2.10-2.51 (m, 4H), 1.29 (d, 3H, J=5.1), 1.27 (d, 3H, J=5.4), 0.96 (app t, 3H, J=7.2), 0.84 (app t, 3H, J=7.2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 170.8, 137.4, 128.7, 128.3, 127.6, 69.2, 69.0, 33.5, 28.5, 21.9, 21.8, 9.5, 9.1. FTIR (neat) 3061, 2980, 2939, 2882, 1739, 1715, 1496, 1462, 1385, 1376, 1231, 1103, 1034, 967, 835. HRMS (ESI, *m/z*) calcd. for $C_{16}H_{22}O_3$ $(M+Na)^+$ 285.1461 found 285.1465. $[\alpha]^{22}_D = -54°$ (c=0.21, CH_2Cl_2; for product with 89% ee).

For run 2, general procedure B was followed with silyl ketene acetal **2.32** (0.100 g, 0.359 mmol), $(EtCO)_2O$ (0.0600 mL, 0.467 mmol), and (–)-**1.16** (0.0123 g, 0.0180 mmol) in 0.359 mL Toluene/CH_2Cl_2 (2:1) which furnished 60% of product **2.58** (0.0561 g, 0.241 mmol), which was shown by chiral GC to have 89% ee.

Enantioselectivity as a Function of the Ester Moiety (Table 2B.6)

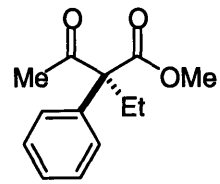


Table 2B.4, entry 1. General procedure A was followed, using silyl ketene acetal **2.31** (0.150 g, 0.599 mmol), Ac_2O (0.0735 mL, 0.779 mmol), (+)-**1.16** (0.0205 g, 0.0300 mmol), and 0.600 mL of Toluene/CH_2Cl_2 (2:1) to produce 89% (0.118 g, 0.536 mmol) of **2.44** as a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 110 °C, 1.0 mL/min, retention times of enantiomers: 18.6 min (minor), 19.7 min (major)) to have 70% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.38 (m, 5H), 3.81 (s, 3H), 2.38 (m, 1H), 2.19 (m, 1H), 2.08 (s, 3H), 0.86 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 171.9, 137.2, 128.9, 128.2, 127.9, 69.4, 52.6, 28.3, 27.9, 9.8. FTIR (neat) 3061, 2953, 2883, 1715, 1496, 1438, 1435, 1355, 1234, 1204, 1127, 700 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{13}H_{16}O_3$ $(M+Na)^+$ 243.0992 found 243.0988. $[\alpha]^{23}_D = -66°$ (c=0.35, CH_2Cl_2; for product with 70% ee).

For run 2, general procedure B was followed with silyl ketene acetal **2.31** (0.153 g, 0.613 mmol), Ac_2O (0.0752 mL, 0.797 mmol), and (–)-**1.16** (0.0210 g, 0.0306 mmol) in 0.613 mL Toluene/CH_2Cl_2 (2:1) which furnished 85% of product **2.44** (0.115 g, 0.522 mmol), which was shown by chiral GC to have 70% ee.

Table 2B.4, Entry 2. See Table 2B.6, entry 1, for experimental and characterization data.

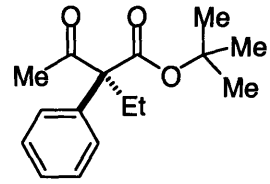


Table 2B.4, entry 3. General procedure A was followed, using silyl ketene acetal **2.33** (0.150 g, 0.513 mmol), Ac_2O (0.0629 mL, 0.667 mmol), (+)-**1.16** (0.0176 g, 0.0257 mmol), and 0.513 mL of Toluene/CH_2Cl_2 (2:1) to produce 44% (0.0590 g, 0.225 mmol) of **2.46** as a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 110 °C, 1.0 mL/min, retention times of enantiomers: 24.5 min (minor), 25.5 min (major)) to have 93% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.38 (m, 5H), 2.33 (dq, 1H, J=14.0, J=7.5), 2.13 (dq, 1H, J=14.0, J=7.5), 2.08 (s, 3H), 1.51 (s, 9H), 0.86 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 170.2, 137.4, 128.7, 128.3, 127.6, 82.6, 69.7, 28.5, 28.1, 27.9, 9.5. FTIR (thin film) 2978, 1737, 1713, 1495, 1370, 1248, 1156, 1126, 841, 700 cm^{-1}. $[\alpha]^{20}_D = -70°$ (c=0.70, $CHCl_3$; for product with 91% ee).

For run 2, general procedure B was followed with silyl ketene acetal **2.33** (0.152 g, 0.519 mmol), Ac_2O (0.0640 mL, 0.678 mmol), and (–)-**1.16** (0.0179 g, 0.0260 mmol) in 0.519 mL Toluene/CH_2Cl_2 (2:1) which furnished 49% of product **2.46** (0.0670 g, 0.255 mmol), which was shown by chiral GC to have 92% ee.

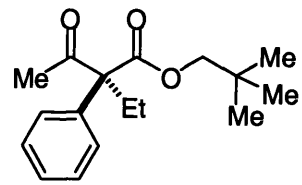


Table 2B.4, entry 4. General procedure A was followed, using silyl ketene acetal **2.34** (0.150 g, 0.489 mmol), Ac_2O (0.0600 mL, 0.636 mmol), (+)-**1.16** (0.0168 g, 0.0245 mmol), and 0.489 mL of Toluene/CH_2Cl_2 (2:1) to produce 72% (0.0975 g, 0.353 mmol)

of **2.47** as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 9.5 min (major), 7.4 min (minor)) to have 79% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 3.90 (d, 1H, J=10.5), 3.86 (d, 1H, J=10.5), 2.38 (m, 1H), 2.21 (m, 1H), 2.08 (s, 3H), 0.92 (s, 9H), 0.86 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 171.4, 137.4, 128.8, 128.2, 127.8, 75.2, 69.5, 31.5, 28.4, 28.0, 26.7, 9.8. FTIR (neat) 2962, 2883, 1715 (br), 1496, 1465, 1368, 1232, 1127, 986, 755, 700 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{17}H_{24}O_3$ $(M+Na)^+$ 299.1618 found 299.1616. $[\alpha]^{22}_D = -54°$ (c=0.59, CH_2Cl_2; for product with 79% ee).

For run 2, general procedure B was followed with silyl ketene acetal **2.34** (0.150 g, 0.489 mmol), Ac_2O (0.0600 mL, 0.636 mmol), and (–)-**1.16** (0.0168 g, 0.0245 mmol) in 0.489 mL Toluene/CH_2Cl_2 (2:1) which furnished 77% of product **2.47** (0.104 g, 0.376 mmol), which was shown by chiral HPLC to have 79% ee.

Enantioselectivity as a Function of the α-Substituent (Table 2B.5)

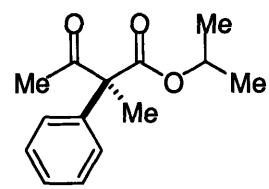


Table 2B.5, entry 1. General procedure A was followed, using silyl ketene acetal **2.35** (0.150 g, 0.567 mmol), Ac_2O (0.0700 mL, 0.737 mmol), (+)-**1.16** (0.0195 g, 0.0284 mmol), and 0.567 mL of Toluene/CH_2Cl_2 (2:1) to produce 54% (0.0720 g, 0.307 mmol) of **2.48** as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 17.1 min (major), 21.9 min (minor)) to have 69% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.38 (m, 5H), 5.13 (app sept, 1H, J=6.3), 2.10 (s, 3H), 1.74 (s, 3H), 1.27 (d, 3H, J=6.6), 1.25 (d, 3H, J=6.3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 172.1, 139.4, 129.3, 128.3, 128.0, 70.0, 65.4, 28.1, 22.3, 22.2, 22.1. FTIR (neat) 3062, 2983, 2936, 1734, 1716, 1600, 1497, 1457, 1448, 1375, 1355, 1256, 1101, 1076, 1031, 929, 887 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{18}O_3$ $(M+Na)^+$ 257.1148 found 257.1155. $[\alpha]^{23}_D = -47.1°$ (c=0.70, $CHCl_3$; for product with 69% ee).

For run 2, general procedure A was followed with the silyl ketene acetal (0.138 g, 0.520 mmol), Ac_2O (0.0638 mL, 0.676 mmol), and (–)-**4** (0.0179 g, 0.0260 mmol) in 0.520 mL Toluene/CH_2Cl_2 (2:1) which furnished 53% of the product (0.064 g, 0.273 mmol), which was shown by chiral HPLC to have 69% ee.

Table 2B.5, entry 2. See Table 2B.6, entry 1, for experimental and characterization data.

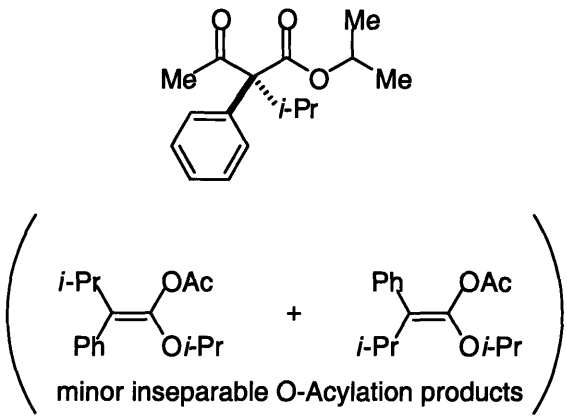


Table 2B.5, entry 3. General procedure A was followed, using silyl ketene acetal **2.36** (0.162 g, 0.553 mmol), Ac_2O (0.0678 mL, 0.719 mmol), (+)-**1.16** (0.0190 g, 0.0277 mmol), and 0.553 mL of Toluene/CH_2Cl_2 (2:1) to produce 46% (0.0682 g, 0.260 mmol) of **2.49** as a clear, colorless oil, as a 12:1 mixture of C-acyl:O-acyl isomers which was

shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 105 °C, 1.0 mL/min, retention times of enantiomers: 37.7 min (minor), 39.8 min (major)) to have 97% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06-7.37 (m, 5H), 5.25 (app sept, 1H, J=6.5), 2.90 (app sept, 1H, J=6.5), 1.99 (s, 3H), 1.33 (app t, 6H, J=6.5), 1.00 (d, 3H, J=7.0), 0.75 (d, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 170.0, 136.5, 128.7, 128.6, 127.6, 72.7, 69.3, 32.8, 28.7, 22.1, 22.0, 19.7, 18.5. FTIR (neat) 3063, 3031, 2969, 2938, 2877, 1734, 1710, 1653, 1540, 1457, 1387, 1236, 1199, 1167, 1104, 700 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{16}H_{22}O_3$ $(M+Na)^+$ 285.1461 found 285.1459. $[\alpha]^{21}_D = -75°$ (c=0.45, CH_2Cl_2; for product with 97% ee).

For run 2, general procedure B was followed with silyl ketene acetal **2.36** (0.160 g, 0.547 mmol), Ac_2O (0.0671 mL, 0.711 mmol), and (–)-**1.16** (0.0188 g, 0.0274 mmol) in 0.547 mL Toluene/CH_2Cl_2 (2:1) which furnished 52% of product **2.49** (0.0750 g, 0.286 mmol) as a 12:1 mixture of C-acyl:O-acyl isomers, which was shown by chiral GC to have 97% ee.

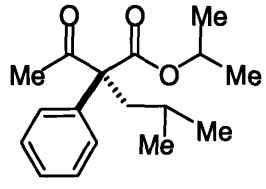


Table 2B.5, entry 4. General procedure A was followed, using silyl ketene acetal **2.37** (0.130 g, 0.424 mmol), Ac_2O (0.0520 mL, 0.551 mmol), (+)-**1.16** (0.0146 g, 0.0272 mmol), and 0.424 mL of Toluene/CH_2Cl_2 (2:1) to produce 79% (0.0921 g, 0.333 mmol) of **2.50** as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 99:1, 0.7 mL/min, retention times of enantiomers: 7.1 min (minor), 7.9 min (major)) to have 85% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.34 (m, 2H), 7.27 (tt, 1H, J=6.5, J=1.5), 5.18 (app sept, 1H, J=6.5), 2.27 (dd, 1H, J=14.5, J=6.5), 2.09 (dd, 1H, J=14.5, J=6.0), 2.05 (s, 3H), 1.49 (app sept, 1H, J=6.5), 1.30 (d, 3H, J=6.0), 1.28 (d, 3H, J=6.5), 0.86 (d, 3H, J=7.0), 0.70 (d, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 170.8, 137.6, 128.7, 128.4, 127.6, 69.2, 68.4, 43.9, 27.5, 25.2, 24.3, 23.9, 21.8, 21.7. FTIR (neat) 2959, 2872, 1714, 1497, 1375, 1218, 1104, 701, 575 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{17}H_{24}O_3$ $(M+Na)^+$ 299.1618 found 299.1616. $[\alpha]^{23}_D = -63°$ (c=0.25, CH_2Cl_2; for product with 85% ee).

For run 2, general procedure A was followed with silyl ketene acetal **2.37** (0.130 g, 0.539 mmol), Ac_2O (0.0520 mL, 0.551 mmol), and (–)-**1.16** (0.0146 g, 0.0272 mmol) in 0.424 mL Toluene/CH_2Cl_2 (2:1) which furnished 85% of product **2.50** (0.0994 g, 0.360 mmol), which was shown by chiral HPLC to have 84% ee.

Enantioselectivity as a Function of the Aromatic Substituent (Table 2B.6)

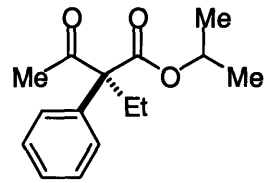
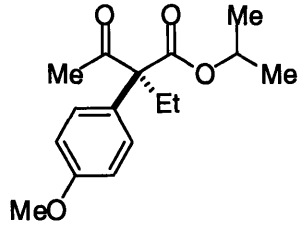


Table 2B.6, entry 1. General procedure A was followed, using silyl ketene acetal **2.32** (0.150 g, 0.539 mmol), Ac_2O (0.0661 mL, 0.701 mmol), (+)-**1.16** (0.0185 g, 0.0269 mmol), and 0.539 mL of Toluene/CH_2Cl_2 (2:1) to produce 90% (0.120 g, 0.483 mmol) of **2.45** as a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 110 °C, 1.0 mL/min, retention times of enantiomers: 21.2 min (major), 20.0 min (minor)) to have 84% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H), 5.18 (app sept, 1H, J=6.5), 2.35 (m, 1H), 2.15 (m, 1H), 2.06 (s, 3H), 1.28 (d, 3H, J=6.0), 1.27 (d, 3H, J=6.0), 0.84 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.9, 170.8, 158.9, 129.4, 128.9, 114.0, 69.1, 68.5, 55.4, 28.2, 27.6, 21.8, 21.7, 9.5. FTIR (neat) 3061, 2981, 2939, 2883, 1734, 1714, 1497, 1448, 1386, 1354, 1234, 1103, 833, 700 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{20}O_3$ $(M+Na)^+$ 271.1305, found 271.1309. $[\alpha]^{22}_D = -69°$ (c=0.58, CH_2Cl_2; for product with 84% ee).

For run 2, general procedure B was followed with silyl ketene acetal **2.32** (0.150 g, 0.539 mmol), Ac_2O (0.0661 mL, 0.701 mmol), and (–)-**1.16** (0.0185 g, 0.0269 mmol) in 0.539 mL of Toluene/CH_2Cl_2 (2:1) which furnished 94% of product **2.45** (0.126 g, 0.507 mmol), which was shown by chiral GC to have 86% ee.



(Table 2B6, entry 2). General procedure A was followed, using silyl ketene acetal **2.38** (0.150 g, 0.486 mmol), Ac_2O (0.0596 mL, 0.632 mmol), (+)-**1.16** (0.0167 g, 0.0243 mmol), and 0.486 mL of Toluene/CH_2Cl_2 (2:1) to produce 86% (0.116 g, 0.417 mmol) of **2.51** as a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 120 °C, 1.0 mL/min, retention times of enantiomers: 105.5 min (major), 99.7 min (minor)) to have 90% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (ddd, 2H, J=9.0, J=5.0, J=3.0), 6.88 (ddd, 2H, J=9.0, J=5.0, J=3.0), 5.17 (app sept, 1H, J=6.5), 3.80 (s, 3H), 2.32 (m, 1H), 2.14 (m, 1H), 2.05 (s, 3H), 1.28 (d, 3H, J=6.0), 1.26 (d, 3H, J=6.5), 0.83 (app t, 3H, J=7.5). ^{13}C NMR

(125 MHz, $CDCl_3$) δ 203.9, 170.8, 158.9, 129.4, 128.9, 114.0, 69.1, 68.4, 55.3, 28.1, 27.6, 21.8, 21.7, 9.4. FTIR (neat) 2980, 2938, 2839, 1734, 1712, 1610, 1514, 1465, 1375, 1254, 1234, 1186, 1102, 1035, 828 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{16}H_{22}O_4$ $(M+Na)^+$ 301.1410, found 301.1406. $[\alpha]^{22}_D = -89°$ (c=0.99, CH_2Cl_2; for product with 90% ee).

For run 2, general procedure B was followed with the silyl ketene acetal **2.38** (0.150 g, 0.486 mmol), Ac_2O (0.0596 mL, 0.632 mmol), and (–)-**1.16** (0.0167 g, 0.0243 mmol) in 0.486 mL of Toluene/CH_2Cl_2 (2:1) which furnished an 80% yield of product **2.51** (0.108 g, 0.388 mmol), which was shown by chiral GC to have 89% ee.

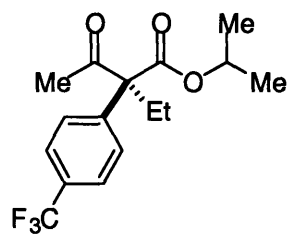
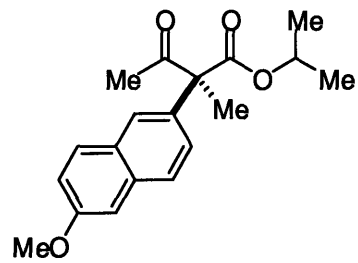


Table 2B.6, entry 3. General procedure A was followed, using silyl ketene acetal **2.39** (0.130 g, 0.375 mmol), Ac_2O (0.0567 mL, 0.601 mmol), (+)-**1.16** (0.0159 g, 0.0231 mmol), and 0.462 mL of Toluene/CH_2Cl_2 (2:1) to produce 96% (0.114 g, 0.360 mmol) of **2.52** as a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 130 °C, 1.0 mL/min, retention times of enantiomers: 11.2 min (major), 10.5 min (minor)) to have 92% ee.

^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, 2H, J=9.0), 7.53 (d, 2H, J=9.0), 5.19 (app sept, 1H, J=6.5), 2.38 (m, 1H), 2.18 (m, 1H), 2.10 (s, 3H), 1.31 (d, 3H, J=6.5), 1.28 (d, 3H, J=6.5), 0.84 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 170.1, 141.0, 129.9 (q, J=32.6), 125.6 (q, J=4.0), 124.1 (q, J=271), 69.7, 69.1, 28.4, 27.8, 21.8, 21.7, 9.3. FTIR (neat) 2983, 2940, 1734, 1716, 1653, 1617, 1540, 1457, 1386, 1328, 1235,

1168, 1127, 1102, 1071, 1018, 832 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{16}H_{19}F_3O_3$ $(M+Na)^+$ 339.1179 found 339.1166. $[\alpha]^{22}_D = -43°$ (c=0.41, CH_2Cl_2; for product with 92% ee).

For run 2, general procedure A was followed with silyl ketene acetal **2.39** (0.131 g, 0.378 mmol), Ac_2O (0.0567 mL, 0.601 mmol), and (–)-**1.16** (0.0159g, 0.0231 mmol) in 0.462 mL Toluene/CH_2Cl_2 (2:1) which furnished 96% of product **2.52** (0.115 g, 0.364 mmol), which was shown by chiral GC to have 91% ee.



(Table 2B.6, entry 4). General procedure A was followed, using silyl ketene acetal **2.40** (0.150 g, 0.435 mmol), Ac_2O (0.0534 mL, 0.566 mmol), (+)-**1.16** (0.0149 g, 0.0218 mmol), and 0.435 mL of Toluene/CH_2Cl_2 (2:1) to produce 93% (0.127 g, 0.403 mmol) of **2.53** as a white solid, which was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 22.3 min (major), 28.8 min (minor)) to have 91% ee.

^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (app t, 3H, J=9.0), 7.38 (dd, 1H, J=8.5, J=1.5), 7.17 (dd, 1H, J=9.0, J=2.5), 7.14 (d, 1H, J=2.5), 5.19 (app sept, 1H, J=6.5), 3.92 (s, 3H), 2.15 (s, 3H), 1.86 (s, 3H), 1.31 (d, 3H, J=6.0), 1.29 (d, 3H, J=6.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 171.7, 158.2, 133.9, 133.8, 129.8, 128.8, 127.2, 126.3, 126.1, 119.3, 105.5, 69.5, 64.6, 55.5, 27.5, 21.8, 21.7, 21.6. FTIR (thin film) 2983, 2938, 1734, 1716, 1653, 1636, 1607, 1559, 1540, 1506, 1457, 1387, 1375, 1255, 1199, 1101, 1032,

922 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{19}H_{22}O_4$ $(M+Na)^+$ 337.1410, found 337.1400. $[\alpha]^{22}_D = -49°$ (c=0.29, CH_2Cl_2; for product with 91% ee). mp = 63-64°C.

For run 2, general procedure B was followed with the silyl ketene acetal **2.40** (0.168 g, 0.488 mmol), Ac_2O (0.0596 mL, 0.634 mmol), and (–)-**1.16** (0.0168 g, 0.0244 mmol) in 0.488 mL of Toluene/CH_2Cl_2 (2:1) which furnished 88% of product **2.53** (0.137 g, 0.436 mmol), which was shown by chiral GC to have 88% ee.

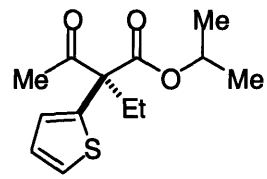


Table 2B.6, entry 5. General procedure A was followed, using silyl ketene acetal **2.41** (0.155 g, 0.475 mmol), Ac_2O (0.0582 mL, 0.617 mmol), (+)-**1.16** (0.0163 g, 0.0238 mmol), and 0.475 mL of Toluene/CH_2Cl_2 (2:1) to produce 66% (0.0787 g, 0.309 mmol) of **2.54** as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 6.9 min (major), 12.3 min (minor)) to have 72% ee (note that reaction time was 36 hours).

^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, 1H, J=5.0, J=1.5), 7.0 (dd, 1H, J=5.5, J=4.0), 6.95 (dd, 1H, J=7.0, J=1.0), 5.19 (app sept, 1H, J=6.5), 2.33 (m, 1H), 2.22 (m, 1H), 2.07 (s, 3H), 1.30 (d, 3H, J=6.0), 1.28 (d, 3H, J=6.5), 0.80 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 170.0, 138.9, 126.7, 126.6, 126.5, 69.9, 66.9, 30.5, 26.6, 21.8, 21.6, 9.1. FTIR (neat) 3108, 2980, 2938, 2880, 1741, 1716, 1457, 1375, 1355, 1233, 1103, 832, 703 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{13}H_{18}O_3S$ $(M+Na)^+$ 277.0869 found 277.0867. $[\alpha]^{22}_D = -77°$ (c=0.23, CH_2Cl_2; for product with 72% ee).

For run 2, general procedure B was followed with silyl ketene acetal **2.41** (0.155 g, 0.475 mmol), Ac_2O (0.0582 mL, 0.617 mmol), and (–)-**1.16** (0.0163 g, 0.0238 mmol) in 0.475 mL Toluene/CH_2Cl_2 (2:1) which furnished 54% of product **2.54** (0.0650 g, 0.255 mmol), which was shown by chiral HPLC to have 73% ee (note that reaction time was 36 hours).

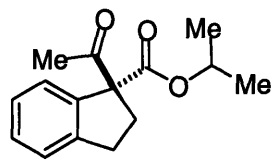


Table 2B.6, entry 6. General procedure A was followed, using silyl ketene acetal **2.42** (0.150 g, 0.543 mmol), Ac_2O (0.0666 mL, 0.706 mmol), (+)-**1.16** (0.0186 g, 0.0271 mmol), and 0.543 mL of CH_2Cl_2 to produce 82% (0.110 g, 0.447 mmol) of product **2.55** as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 8.1 min (major), 9.6 min (minor)) to have 82% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.23-7.30 (m, 3H), 5.09 (app sept, 1H, J=6.5), 2.95-3.07 (m, 2H), 2.73 (ddd, 1H, J=15.5, J=8.5, J=7.0), 2.55 (ddd, 1H, J=13.0, J=8.0, J=4.5), 2.21 (s, 3H), 1.29 (d, 3H, J=6.5), 1.25 (d, 3H, J=6.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 170.7, 144.9, 139.4, 128.7, 126.8, 126.6, 125.0, 72.6, 69.5, 33.2, 31.0, 26.6, 21.8, 21.7. FTIR (thin film) 3071, 2982, 2935, 2854, 1734, 1716, 1603, 1458, 1386, 1375, 1356, 1233, 1106, 1074, 830, 766 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{18}O_3$ $(M+Na)^+$ 269.1148 found 269.1140. $[\alpha]^{22}_D = -35°$ (c=0.29, CH_2Cl_2; for product with 82% ee).

For run 2, general procedure B was followed with silyl ketene acetal **2.42** (0.155 g, 0.561 mmol), Ac_2O (0.0688 mL, 0.728 mmol), and (–)-**1.16** (0.0193g, 0.0281 mmol)

in 0.561 mL CH_2Cl_2 which furnished 82% of product **2.55** (0.113 g, 0.459 mmol), which was shown by chiral GC to have 80% ee.

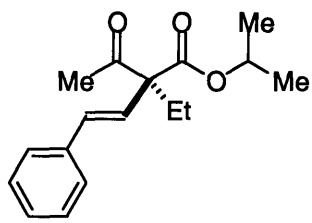


Table 2B.6, entry 7. General procedure A was followed, using silyl ketene acetal **2.43** (0.130 g, 0.427 mmol), Ac_2O (0.0524 mL, 0.555 mmol), (+)-**1.16** (0.0147 g, 0.0214 mmol), and 0.427 mL of Toluene/CH_2Cl_2 (2:1) to produce 80% (0.0938 g, 0.342 mmol) of **2.56** as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALPAK AD, 4.6 mm x 25 cm, hexane/isopropanol 99:1, 0.7 mL/min, retention times of enantiomers: 10.0 min (minor), 10.6 min (major)) to have 54% ee (note that reaction time was 80 hours).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.34 (m, 2H), 7.27 (m, 1H), 6.81 (d, 1H, J=17.0), 6.38 (d, 1H, J=16.5), 5.16 (app sept, 1H, J=6.0), 2.15-2.20 (m, 4H), 2.04-2.11 (m, 1H), 1.28 (app t, 6H, J=6.5), 0.85 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 171.0, 136.8, 132.4, 128.8, 128.2, 126.7, 126.0, 69.4, 66.5, 28.5, 27.3, 21.8, 21.7, 8.9. FTIR (neat) 3027, 2974, 2938, 1734, 1713, 1457, 1449, 1375, 1234, 1103, 972, 748 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{17}H_{22}O_3$ (M^+) 274.1563, found 274.1572. $[\alpha]^{22}_D = -12°$ (c=0.21, CH_2Cl_2; for product with 54% ee).

For run 2, general procedure A was followed with silyl ketene acetal **2.43** (0.130 g, 0.427 mmol), Ac_2O (0.0524 mL, 0.555 mmol), and (–)-**1.16** (0.0147 g, 0.0214 mmol) in 0.427 mL Toluene/CH_2Cl_2 (2:1) which furnished 81% of product **2.56** (0.0944 g, 0.344 mmol), which was shown by chiral HPLC to have 53% ee.

Mechanistic Studies (2B.11 and 2B.12)

Note that these NMR reactions were stored inside a glove box when NMR spectra was not actively being taken to minimize the stereorandom hydrolysis of the silyl ketene acetals.

Eq. 2B.11. A solution of the silyl ketene acetal **2.33** (16.8 mg, 0.0574 mmol) in CD_2Cl_2 (0.70 mL) was added to a J-Young NMR tube. The isomer ratio was determined to be 1.6/1, after which solid $[Me_4N]OAc$ (0.4 mg, 0.003 mmol) was added. The NMR tube was vigorously shaken and NMR spectra were taken after 10 minutes, 30 minutes, 2 hours, 18 hours, and 60 hours. These spectra indicate no deviation (within NMR error) from the starting 1.6/1 isomer ratio.

Eq. 2B.12. A solution of the silyl ketene acetal **2.33** (30.0 mg, 0.103 mmol) and (+)-**1.16** in CD_2Cl_2 (0.70 mL) was added to a screwcap NMR tube after which the isomer ratio was found to be 1.6/1 (NMR parameters: ss=0, d1=5 seconds). Acetic Anhydride (0.0048 mL, 0.051 mmol) was added. The reaction was monitored by ^1H NMR spectroscopy after reaction times of 15 minutes, 40 hours, and 72 hours. The reaction was had reached completion at 72 hours, after which the new isomeric ratio for the remaining silyl ketene acetal was determined to be 2.6/1. To this reaction mixture, solid $[Me_4N]OAc$ (0.4 mg, 0.005 mmol was added). The NMR tube was vigorously shaken and NMR spectra were taken after 10 minutes, 30 minutes, 2 hours, 18 hours, and 60 hours, which indicate very little deviation (within NMR error) from the initially established 2.6/1 isomer ratio.

Chapter 3

Generation of Quaternary Stereocenters via Catalytic Enantioselective C-Acylations of Silyl Ketene Imines.

Part A. Ketene Imines: Structure, Preparation, and Fundamental Reactivity.

Background

In 1921, Staudinger reported that, in the presence of triaryliminophosphoranes or trialkyliminophosphoranes, diphenylketene reacts to form a class of compounds called ketene imines.[54] Owing largely to the utility of these compounds in organic synthesis,[55] a number of accounts have addressed the synthesis of ketene imines, both concerning substituent pattern and ease of synthesis.[56] One of the most noteworthy improvements was the development of routes that provided access to ketene imines bearing alkyl, rather than aryl, substituents. Due to the difficulty of separating the product away from reaction mixtures, in conjunction with its inherent moisture sensitivity, this class of ketene imines has become a significant synthetic challenge.

Three major resonance forms of ketene imines have been postulated, each of which expain reactivity patterns and spectroscopic properties. Aside from neutral form **3.11**, a major contributing resonance structure is **3.12**, which places a net negative charge on the β-carbon. Resonance form **3.13** simultaneously places anionic character on the nitrogen with cationic character on the α-carbon.

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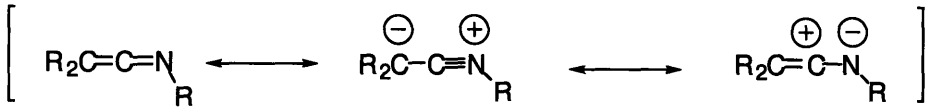
[54] Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 887-896.

[55] For reviews on the chemistry of ketene imines see: (a) Krow, G. R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 435-449. (b) Barker, M. W.; McHenry, W. E. *The Chemistry of Ketenes, Allenes and Related Compounds, Part 2*; John Wiley: New York, 1980; Chapter 17. For other references, see: (c) Schmittel, M.; Steffen, J.; Ángel, M. Á. W.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1562-1564. (d) Alajarín, M.; Molina, P.; Vidal, A.; Tovar, F. *Tetrahedron* **1997**, *53*, 13449-13472. (e) Wolf, R.; Wong, M. W.; Kennard, C. H. L.; Wentrup, C. *J. Am. Chem. Soc.* **1995**, *117*, 6789-6790. (f) Molina, P.; Alajarín, M.; Vidal, A. *J. Org. Chem.* **1991**, *56*, 4008-4016. (g) Saimoto, H.; Houge, C.; Hesbain-Frisque, A.; Mockel, A.; Ghosez, L. *Tetrahedron Lett.* **1983**, *24*, 2251-2254. (h) Minami, T.; Takimoto, F.; Agawa, T. *Bull. Chim. Soc. Japan* **1975**, *48*, 3259-3261.

[56] For an example, see: Lee, K.; Singer, A. *J. Org. Chem.* **1974**, *39*, 3780-3781.



3.11 **3.12** **3.13**

As indicated by resonance forms **3.12** and **3.13,** ketene imines, being ambident nucleophiles, may react with electrophiles at either carbon or nitrogen.[57] Furthermore, ketene imines act as electrophiles at the α-carbon. ^{13}C NMR chemical shifts for the α and β carbons are consistent with these observations.[58] The α-carbon is strongly deshielded, having chemical shifts ranging from 186-195 ppm, while the strongly shielded β-carbon falls in the 36-78 ppm chemical shift range. An electron-poor α-carbon is prone to react with a nucleophilic species, while the electron-rich β-carbon is expected to react as a nucleophile.

Ketene imines are structurally similar to allenes in that they possess an element of axial chirality. Unlike allenes, however, ketene imines are prone to racemization at nitrogen by an inversion mechanism involving a nitrilium-like species. This is accelerated by electron-withdrawing substituents at the β-carbon, as supported by resonance structure **3.12**. The racemization barrier for an *N*-phenyl ketene imine has been quantified to be 9.1 kcal/mol,[59] indicating that inversion occurs rapidly at room temperature. While substituents have a large effect on this barrier,[60] ketene imines are known to rapidly racemize at room temperature and cannot be isolated in enantioenriched form.

Methods available for the preparation of ketene imines fall into three main categories: linear dehydration of amides and imino chlorides, fragmentation of heterocyclic intermediates, and alkylation reactions of unsubstituted nitriles via nitrile

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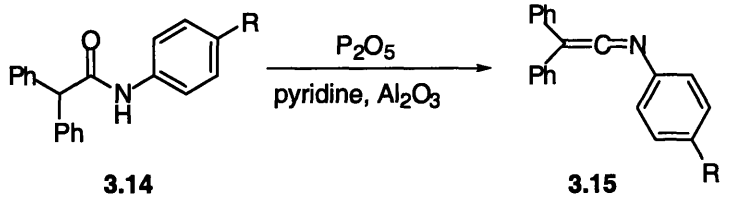
[57] Clarke, L. F.; Hegarty, A. F. *J. Org. Chem.* **1992**, *57*, 1940-1942.
[58] Firl, J.; Runge, W.; Hartman, W.; Utikal, H. *Chem. Lett.* **1975**, 51-54.
[59] Jochims, J. C.; Anet, F. A. L. *J. Am. Chem. Soc.* **1970**, *92*, 5524-5525.

anions. Dehydration routes developed by Stevens and coworkers, as illustrated by the transformation of **3.14** into **3.15**, have been shown to furnish respectable yields of ketene imines from aryl amides (3A.1).[61,62]

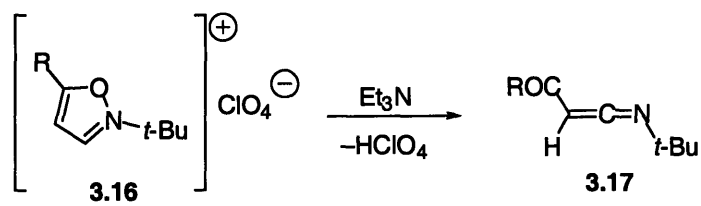


3.14 **3.15**

R	yield (%)
Me	87
Br	69
OMe	69
SMe	75
NO_2	84
SO_2Me	67

(3A.1)

Ketene imines can also be accessed via fragmentation of certain heterocycles. Woodward reported the use of 1,3-oxazolium perchlorate salts (**3.16**) as viable precursors for ketene imines (3A.2). Treatment of oxazolium **3.16** with a mild base yields β-acyl ketene imine **3.17** (3A.2).[63] Photolytic cleavage of 3,4,5-triphenylisoxazoles (3A.3) provides a similar route to ketene imines.[64] The mechanism for the formation of ketene imine **3.19** from the isoxazole involves fragmentation of the weak N–O bond and concomitant [1,2]-aryl migration.



3.16 **3.17**

R= Ph, 60%
R= Me, 70-80%

(3A.2)

---

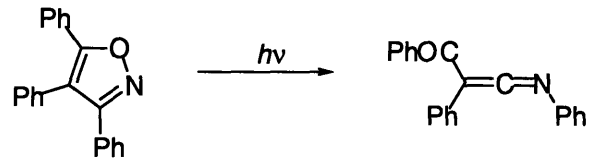
[60] (a) Tahmassebi, D. *Magn. Reson. Chem.* **2003**, *41*, 273-277. (b) Sung, K. *J. Chem. Soc., Perkin Trans. 2*, **1999**, 1169-1173.

[61] (a) Stevens, C. L.; Singhal, G. H. *J. Org. Chem.* **1964**, *29*, 34-37. (b) Stevens, C. L.; French, J. C. *J. Am. Chem. Soc.* **1954**, *76*, 4398-4402.

[62] Subsequent work showed that ketene imines can also be obtained by treatment of *N*-aryl amides with PCl_5, in a Vilsmeier-type fashion, to form an imino chloride, which, can lose HCl to furnish the ketene imine.

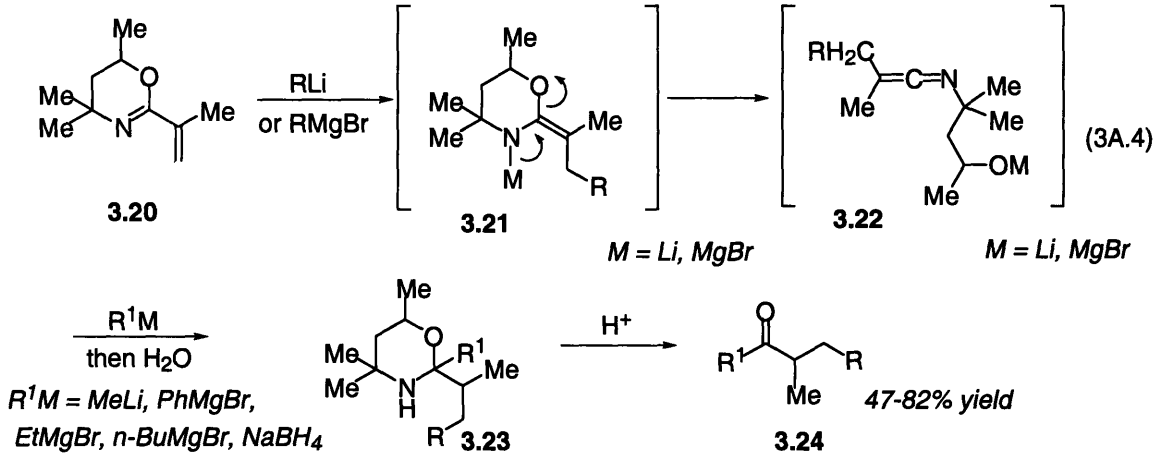
[63] Woodward, R. B.; Woodman, D. J. *J. Am. Chem. Soc.* **1966**, *88*, 3169-3170.

[64] Kurtz, D. W.; Shechter, H. *Chem. Commun.* **1966**, 689-690.



3.18 **3.19** (3A.3)

Meyers exploited a key ketene imine intermediate to synthesize unsymmetrical diketones (3A.4).[65] The authors postulate that ketene imine **3.22**, generated from the addition of alkylithium or alkyl Grignard reagents to **3.20**, is susceptible to nucleophilic attack at the α-carbon. This adduct may be quenched to furnish isolable 1,3-oxazine **3.23**. Aminal intermediate **3.23** is later hydrolyzed to liberate the desired unsymmetrical ketone **3.24**.



3.20 **3.21** **3.22** **3.23** **3.24** (3A.4)

Nitriles can be converted to ketene imines by α-deprotonation and subsequent *N*-selective reaction with an electrophile (e.g., alkylation). This method provides access to a wide array of functionalized ketene imines, because unfunctionalized nitriles can be first elaborated and then converted to the substituted ketene imine.[66] In addition to *N*-alkyl ketene imines, synthetically valuable organotin, organosilicon, and organoboron

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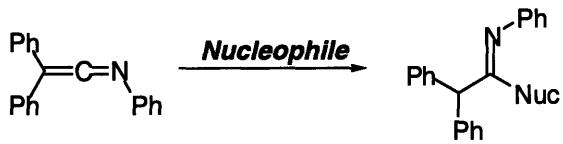
[65] Meyers, A. I.; Kovelesky, A. C. *J. Am. Chem. Soc.* **1969**, *91*, 5887-5888.

[66] For representative examples of ketene imine anions reacting at nitrogen with alkyl halides, see: (a) Newman, M. S.; Fukunaga, T.; Miwa, T. *J. Am. Chem. Soc.* **1960**, *82*, 873-875. (b) Parker, C. O.; Emmons, W. D.; Pagano, A. S.; Rolewicz, H. A.; McCallum, K. S. *Tetrahedron* **1962**, *17*, 89-104.

species are accessible via this method. Facile cleavage of these groups allows the compounds to act as latent nitrile anion equivalents.[67]

Ketene imines are reactive towards a variety of nucleophiles at the α-carbon. Ketene imine **3.25** can be converted into adduct **3.26** with nucleophiles such as aniline, chloride (in the form of HCl), H_2S, water, and various alcohols. Carbon-based nucleophiles, such as the anion of diethyl malonate, sulfur ylides, Grignard reagents, alkyllithiums, and electron-rich arenes such as resorcinol, have also been shown to participate in this addition process (3A.5).[68]



3.25 **3.26**

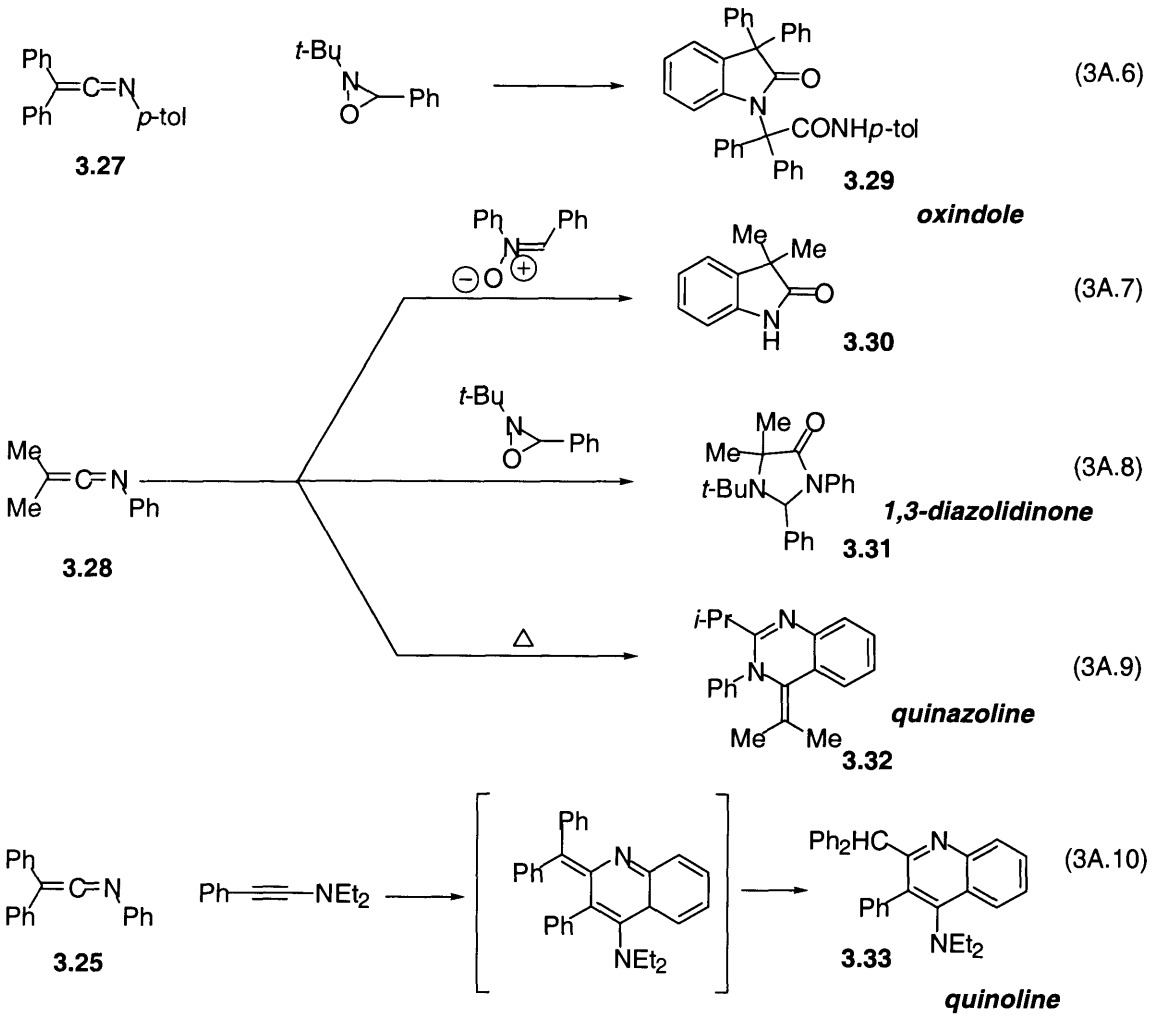
Nucleophiles	
$PhNH_2$	$\ominus CH(COOEt)_2$
HCl	CH_2SMe_2
H_2S	PhMgBr
H_2O	MesLi
MeOH	resorcinol

(3A.5)

Ketene imines are also useful for the construction of various nitrogen-containing heterocycles such as oxindoles, 1,3-diazolidines, quinolines, and quinazolines. As seen in transformations 3A.6-3A.10, dialkyl ketene imine **3.28** is capable of forming a more diverse array of heterocycles, such as oxindole **3.30**, 1,3-diazolidinone **3.31**, and quinazoline **3.32**, by varying the conditions and reagents. Aryl ketene imines are more stable, but still react to form oxindole **3.29** from **3.27** and quinoline **3.33** from **3.25**.

[67] See part B for a discussion of nitrile anions as precursors to silyl ketene imines.

[68] (a) Stevens, C. L.; Freeman, R.; Noll, K. *J. Org. Chem.* **1965**, *30*, 3718-3720. (b) Stevens, C. L.; French, J. C. *J. Am. Chem. Soc.* **1953**, *75*, 657-6. (c) Ichimura, K.; Ohta, M. *Bull. Chem. Soc. Japan* **1967**, *40*, 2135-2139.


Ph
Ph
C=N
p-tol
3.27
t-Bu
N
O
Ph
Ph
Ph
O
N
CONHp-tol
Ph
Ph
3.29
oxindole
(3A.6)
Ph
N
O
Ph
Me
Me
O
N
H
3.30
(3A.7)
t-Bu
N
O
Ph
Me
C=N
Me
Ph
3.28
Me
O
Me
t-BuN
NPh
Ph
3.31
1,3-diazolidinone
(3A.8)
i-Pr
N
Ph
N
Me
Me
3.32
quinazoline
(3A.9)
Δ
Ph
Ph
C=N
Ph
3.25
Ph—≡—NEt2
Ph
Ph
N
Ph
NEt2
Ph2HC
N
Ph
NEt2
3.33
quinoline
(3A.10)

Part B. Silyl Ketene Imines: Preparation and Reactivity Towards Electrophiles

Background

While nitrile anions are readily accessible intermediates for the formation of various ketene imines, they are more likely to react at the β-carbon than at nitrogen when treated with most electrophiles.[69] Nonetheless, for select hard electrophiles such as organotin, organoboron, and organosilicon reagents, reaction at nitrogen is observed.[70] In addition to the electronic considerations, the steric demand of both the nitrile anion and the electrophile greatly influence the regiochemical outcome of nitrile anion attack.

Organosilicon species are attractive electrophiles due to their increased availability, ease of handling, and low toxicity. The reaction of a nitrile anion with a wide variety of sterically diverse silylating agents leads to predominant *N*-silylation. Only when the sterics of the silyl group are dramatically reduced and the groups on the β-carbon of the ketene imine are small does C-silylation can occur.[71] To date, relatively few accounts of silyl ketene imines have been reported. Unlike *N*-alkyl or *N*-aryl ketene imines, most silyl ketene imines are stable and isolable, providing convenient starting material for a subsequent reaction. Nonetheless, very few electrophiles have been demonstrated to react with this class of compounds.

In the presence of HgI_2, silyl ketene imines such as **3.34** have been shown to participate in [1,2]- and [1,4]-additions to certain aldehydes (Table 3B.1). Aromatic

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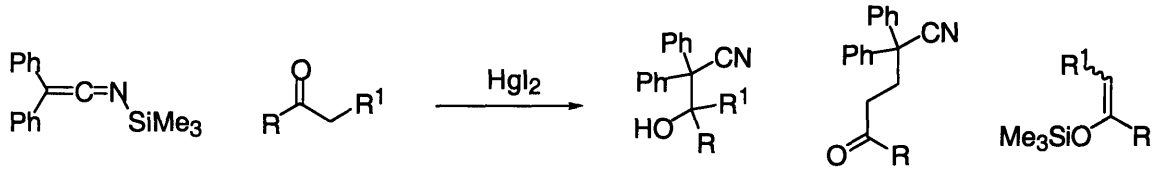
[69] For accounts of physical properties and reactivity of nitrile anions, see: (a) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885-2888. (b) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1-23. (c) Kraus, G. A.; Dneprovskaia, E. *Tetrahedron Lett.* **2000**, *41*, 21-24. (d) Enders, D.; Kirchhoff, J.; Gerdes, P; Mannes, D.; Raabe, G.; Runsink, J.; Gernot, B.; Marsch, M; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, 63-72. (e) Ros, F.; de la Rosa, J.; Enfedaque, J. *J. Org. Chem.* **1995**, *60*, 5419-5424. (f) Strzalko, T.; Seyden-Penne, J.; Wartski, L. *Tetrahedron Lett.* **1994**, *35*, 3935-3936. (g) Assithianakis, P.; Stamm, H. *Chem. Ber.* **1987**, *120*, 855-857. (h) Cariou, M. *Bull. Soc. Chim. Fr.* **1969**, *1*, 198-205.

[70] Abel, E. W.; Crow, J. P.; Wingfield, J. N. *Chem. Commun.* **1969**, 967-968.

substitution adjacent to the reacting carbonyl has been shown to favor [1,2]-addition product **3.35**. When ketones are employed, however, the reaction furnishes a mixture of [1,2]-addition (**3.35**), [1,4]-addition (**3.36**), and transenolization-silylation products (**3.37**).[72]

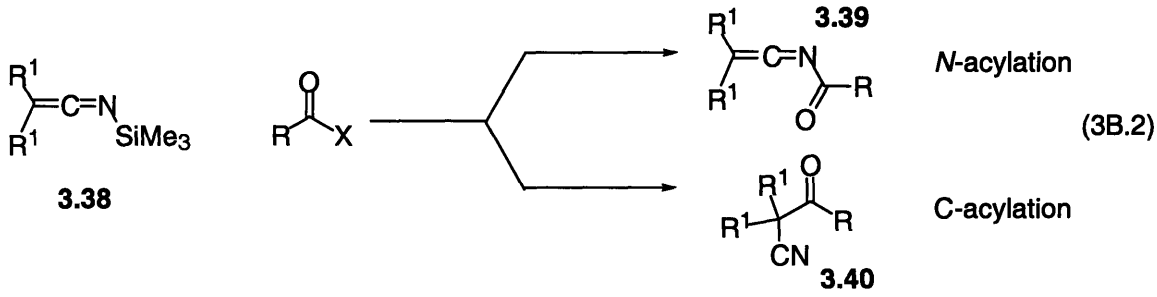
Table 3B.1. HgI_2-Catalyzed Silyl Ketene Imine Additions to Carbonyls.



3.34 **3.35** **3.36** **3.37**

$RCOR^1$	[1,2]-adduct	[1,4]-adduct	enolization/silyl transfer
PhCHO	100	0	–
crotonaldeyde	0	100	–
cinnamaldehyde	37	63	–
$PhCOCH_3$	100	–	0
CH_3COCH_3	90	–	10
$BnCOCH_3$	75	–	15
t-BuCOMe	11	–	89
cyclohexanone	0	–	100

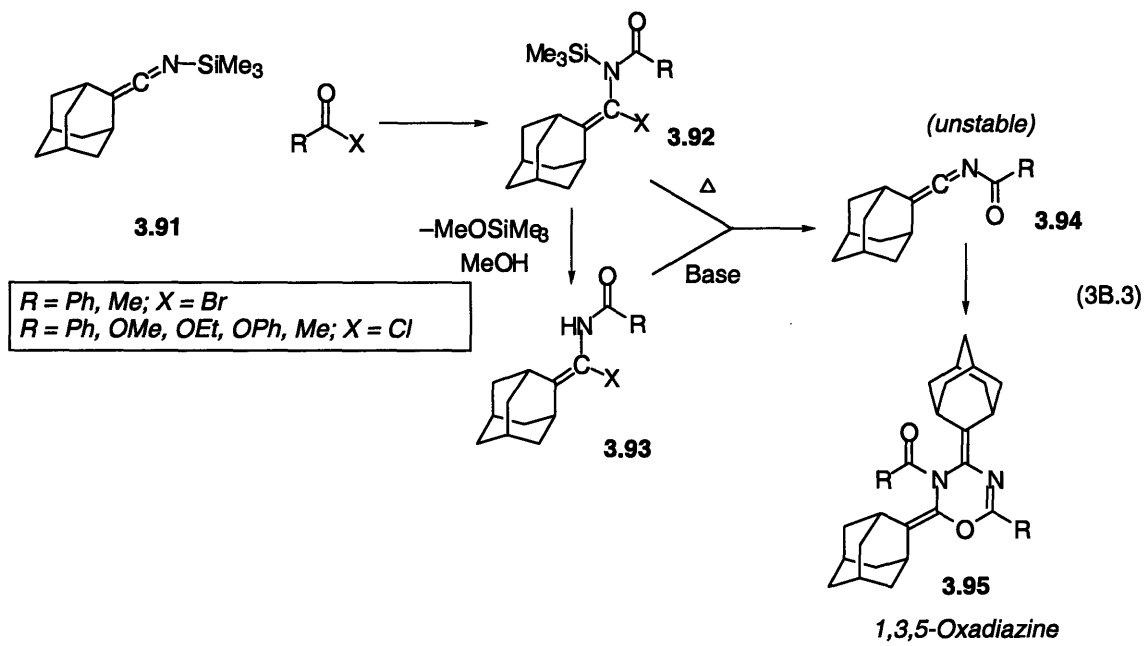
Addition to acylating agents affords either *N*-acyl ketene imine **3.39** or α-cyanocarbonyl **3.40**, depending on the steric demand of the ketene imine and on the identity of the X group (3B.2). It is generally observed that bulky substituents at the β-carbon promote *N*-acylation (R^1=Ph, *t*-Bu, 2-adamantyl). With acid fluorides, C-acylation product **3.39** is observed.



3.38 (3B.2)

[71] Watt, D. *Synth. Commun.* **1974**, *4*, 127-132. West, R.; Gornowicz, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 1714-1720.

Despite apparent trends based on the electronic nature of the acylating agent and the steric demand of the ketene imine, prediction of regiochemistry is often inaccurate. For example, the subjection of adamantyl-substituted silyl ketene imine **3.91** to acylating agents such as acid chlorides, chloroformates, and acid bromides, leads to dimerization via the process outlined in 3B.3. This dimerization pathway is frequently encountered when unstable *N*-acyl-ketene imines would result.[73]



(3B.3)

With ready access to many isolable silyl ketene imines, this class of nucleophiles can be easily incorporated into catalytic asymmetric processes. To the best of our knowledge, there have been no reports of such catalytic, enantioselective processes using silyl ketene imines.[74] This fueled our interest to explore the chemistry of this substrate

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[72] Cazeau, P; Llonch, J.-P.; Simonin-Dabescat, F.; Frainnet, E. *J. Organomet. Chem.* **1976**, *105*, 145-156.

[73] (a) Meier, S; Würthwein, E. *Chem. Ber.* **1990**, 2339-2347. (b) Cazeau, P; Llonch, J.-P.; Simonin-Dabescat, F.; Frainnet, E. *J. Organomet. Chem.* **1976**, *105*, 157-160.

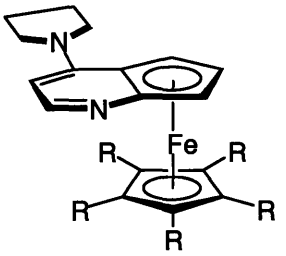
[74] For examples of catalytic asymmetric methods for the synthesis of cyano-substituted, all-carbon quaternary stereocenters, see: (a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295-8296. (b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204-11205.

class in the context of our previously reported nucleophile-catalyzed enantioselective C-acylation processes.[75]

[75] The use of a siloxy-nitrile anion intermediate has been reported to react with acylating agents in a Lewis-catalyzed process starting from acylsilylanes. A silyl ketene imine is not observed in this process, see:

Part C. Results and Discussion

Our initial efforts were focused on the development of a catalytic system that furnished the desired product with a favorable degree of stereocontrol. Keeping in mind the factors that were essential for catalytic activity for silyl ketene acetals, we designed a test system to probe the efficacy of several catalysts that have been developed in our group. Accordingly, silyl ketene imine **3.51** was treated with propionic anhydride in the presence of a series of planar-chiral catalysts (3C.1).



R= Me	**(–)-1.12**
R= Ph	**(–)-1.16**
R= 4-MeC_6H_4	**(–)-3.41**
R= 4-(O*i*-Pr)C_6H_4	**(–)-3.42**
R= 3,5-$Me_2C_6H_4$	**(–)-3.43**

This survey quickly illustrated that the substructure of the lower ring was critical to obtaining good enantioselectivity. In addition, the rate of this reaction was highly dependent on the top-ring amino group. DMAP-derived catalysts did not furnish any appreciable amount of product, while catalysts derived from PPY were much more competent. As a result, we limited our subsequent screening to catalysts possessing the PPY top-ring substructure.

Moreover, we observed that catalysts bearing a Cp* lower ring (Table 3C.1, entry 1) lead to almost racemic product mixtures. In contrast, we found that pentaphenylcyclopentadienyl lower rings were very effective in this process (Table 3C.1, entries 2-4). When the steric demand of the lower ring was even greater (Table 3C.1, entry 5), the reaction afforded products with poor enantioselectivity. Minor steric changes and electronic changes from catalyst **(–)-1.16** did not lead to enhanced selectivity

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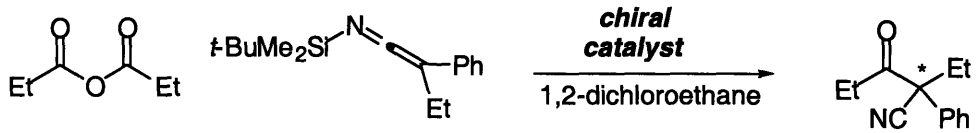
Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2652-2655.

(Table 3C.1, entries 3 and 4). It was also observed that catalyst **(–)-1.12** quickly decomposed when subjected to this catalytic process. The inferior selectivity observed in entry 1 may be in part due to a competitive, non-enantioselective acylation event catalyzed by a species resulting from the decomposition of **(–)-1.12**. As a result, we selected **(–)-1.16** as the catalyst of choice for this process.

Table 3C.1. Enantioselectivity as a Function of Catalyst.



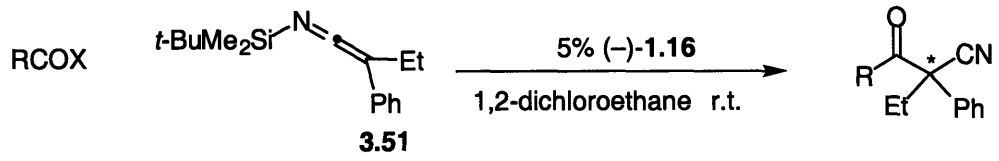
3.51 **3.61**

Entry	chiral catalyst	ee
1	**(–)-1.12**	8
2	**(–)-1.16**	81
3	**(–)-3.41**	69
4	**(–)-3.42**	64
5	**(–)-3.43**	15

Upon selection of the appropriate catalyst, we varied the acylating agent. Sterically non-demanding anhydrides (Table 3C.2, entries 1 and 2) were very effective in this catalytic transformation, furnishing good levels of enantioselectivity and chemical yield.[76] Bulkier anhydrides yielded no desired product, even under forcing conditions (Table 3C.2, entry 3). Cyanoformates and chloroformates afforded products with negligible enantioselectivity (Table 3C.2, entries 4 and 5). The respectable chemical yields coupled with poor enantioselectivities associated with the use of cyanoformates anc chloroformates entries could indicate that some achiral species, possibly an achiral fragment generated by the decomposition of catalyst (–)-**1.16**, may be catalyzing these processes. Based on these results, propionic anhydride was selected for further studies.

[76] The product derived from reaction with acetic anhydride is unstable and readily decomposes to 2-phenylbutyronitrile.

Table 3C.2. Enantioselectivity as a Function of the Acylating Agent.

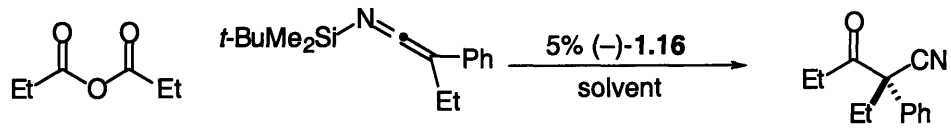


3.51

entry	RCOX	Product	% ee	% yield
1	Ac_2O	**3.44**	72	64
2	$(EtCO)_2O$	**3.61**	81	85
3	$(i\text{-}PrCO)_2O$	**3.46**	NR	NR
4	$NCCO_2Me$	**3.47**	3	81
5	$ClCO_2CH_2CMe_3$	**3.48**	7	61

A survey of solvent revealed that 1,2-dichloroethane was very effective for the enantioselective acylation of **3.51** (Table 3C.3, entry 8). While chloroform was also an effective solvent for this transformation (Table 3C.3, entry 9), the potential for acid in this solvent, which would lead to substrate hydrolysis, deterred us from using it. Interestingly, the poor selectivity observed in THF (3C.3, entry 1) is in direct contrast to the enantioselectivities observed for the acylation of silyl ketene acetals.[77]

Table 3C.3. Enantioselectivity as a Function of Solvent.



3.51 **3.61**

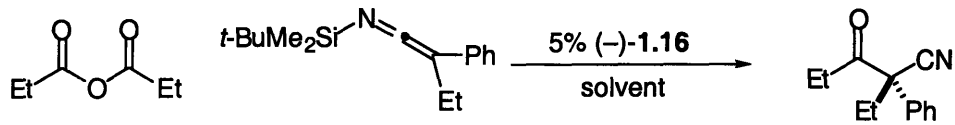
entry	solvent	% ee
1	THF	18
2	$PhCF_3$	42
3	EtOAc	64
4	Et_2O	70
5	PhCl	72
6	CH_2Cl_2	74
7	Toluene	75
8	**1,2-dichloroethane**	**80**
9	$CHCl_3$	80

[77] See Table 1C.3 (entry 9) and Table 2B.2 (entry 2) for direct comparisons.

After selection of an appropriate solvent, we conducted further experiments to determine the optimal temperature and substrate concentration for this process. When the reaction was heated to 50 °C, a 78% ee was observed, but catalyst decomposition became significant. A reduction in temperature to 0 °C led to a significantly slower rate, although enantioselectivity was relatively unchanged (74% ee). At –20 °C, however, a precipitous drop in enantioselectivity occurred (32% ee). In addition, significant amounts of starting material were recovered. Conveniently, room temperature was best suited for this transformation.

Upon screening substrate concentrations from 50 mM to 1M, we observed that enantioselectivity leveled off at 100-275 mM (Table 3C.4, entries 2-4). More dilute reaction conditions led to a minor reduction in enantioselectivity (Table 3C.4, entry 1), while concentrations of **3.51** ≥ 500 mM led to significant erosion of enantioselectivity (Table 3C.4, entries 5 and 6). Accordingly, a concentration of 275 mM was chosen for further study.

Table 3C.4. Enantioselectivity as a Silyl Ketene Imine Concentration.

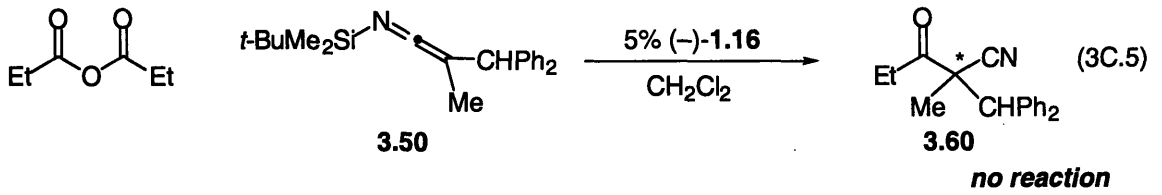


3.51 **3.61**

entry	[3.51] mM	% ee
1	50	74
2	100	79
3	200	80
4	275	80
5	500	60
6	1000	60

After optimization of the reaction conditions, we next examined the substrate scope. Our initial goal was to test whether aromatic substitution on the reacting β-carbon of the ketene imine was a necessary feature for C-acylation. While many alkyl/alkyl substrates could be envisioned, sufficient steric differentiation between the two

substituents was critical for analytical purposes. We therefore selected substrate **3.50**, a silyl ketene imine bearing diphenylmethyl and methyl subsitutents (3C.5).



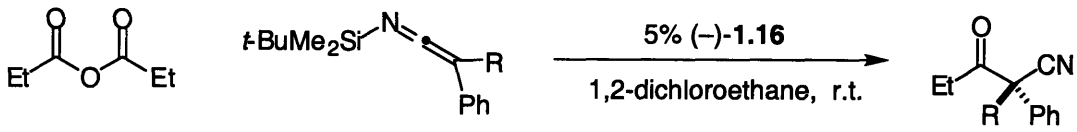
(3C.5)

After subjecting **3.50** to multiple reaction conditions,[78] we concluded that the transformation of **3.50** into **3.60,** and thus all substrates that have an alkyl/alkyl substitution pattern, would not be viable with this catalyst system. The unwillingness of **3.50** to participate in this catalytic process was not altogether surprising, as we believe that the active species involved in this transformation is a silicon-free nitrile anion, the formation of which may require a stabilizing substituent, as will be discussed later in this chapter.

In light of the result in 3C.5, substrates that contained an aromatic substituent were pursued. We first studied variation of the alkyl moiety, holding the aromatic group fixed as a phenyl group. For primary alkyl substituents, little variation in enantioselectivity was observed (Table 3C.6, entries 1,2,4, and 5). In contrast, the incorporation of a secondary substituent led to a significant loss of rate and enantioselectivity, presumably due to the increased steric demand of this substrate (Table 3C.6, entry 3).[79] Hindered substrate **3.59** displayed similar enantioselectivity, although the yield was lower.

[78] Increased temperature, catalyst loading (10%), and longer reaction times (up to one week) were tried.

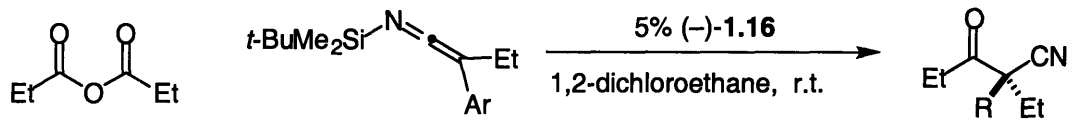
Table 3C.6. Variance of the Alkyl Substituent.



entry	substrate	R	Product	% ee	% yield
1	**3.56**	Me	**3.66**	81	89
2	**3.51**	Et	**3.61**	81	85
3	**3.57**	Cyclopentyl	**3.67**	69	53
4	**3.58**	CH_2CHMe_2	**3.68**	83	93
5	**3.59**	CH_2CMe_3	**3.69**	81	52

Variation of the aryl group provided more consistent results, except for the case of electron-poor substrate **3.53**.[80] It may be the case that the desilylation of ketene imine **3.53** affords a stable ion pair, sequestering the catalyst. With a longer-lived ion pair, non-reactive conformations resulting in further stabilization (such as π-interactions) may be accessed, leading to an erosion in enantioselectivity. However, this explanation remains speculative. Other aryl groups, including 3-thienyl substrate **3.55** (Table 3C.7, entry 5), reacted with the similar enantioselectivity to phenyl substrate **3.51** (Table 3C.7, entry 1).

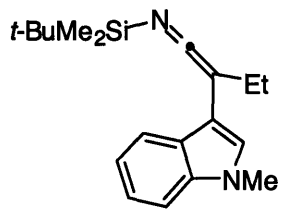
Table 3C.7. Variance of the Aryl Substituent.



entry	substrate	Ar	Product	% ee	% yield
1	**3.51**	Ph	**3.61**	**81**	**85**
2	**3.52**	4-(MeO)C_6H_4	**3.62**	**81**	**65**
3	**3.53**	4-(F_3C)C_6H_4	**3.63**	**53**	**50**
4	**3.54**	1-naphthyl	**3.64**	**80**	**78**
5	**3.55**	3-thienyl	**3.65**	**77**	**72**

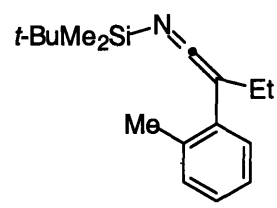
[80] For **3.53**, longer reaction times (up to two weeks) and increased catalyst loading (10%) led to little improvement in yield.

Some substrates were problematic, including indole-derived silyl ketene imine **3.82** and *o*-tolyl substituted substrate **3.83**. While good conversion was obtained with substrate **3.82**, the product was racemic. This result was somewhat surprising, since the cyclic silyl ketene acetal variant of this substrate reacted with excellent enantioselectivity. In contrast, substrate **3.83** furnished the product in moderate yield with 80% ee. Unfortunately, purification of the product was not possible.[81]



3.82

racemic product obtained



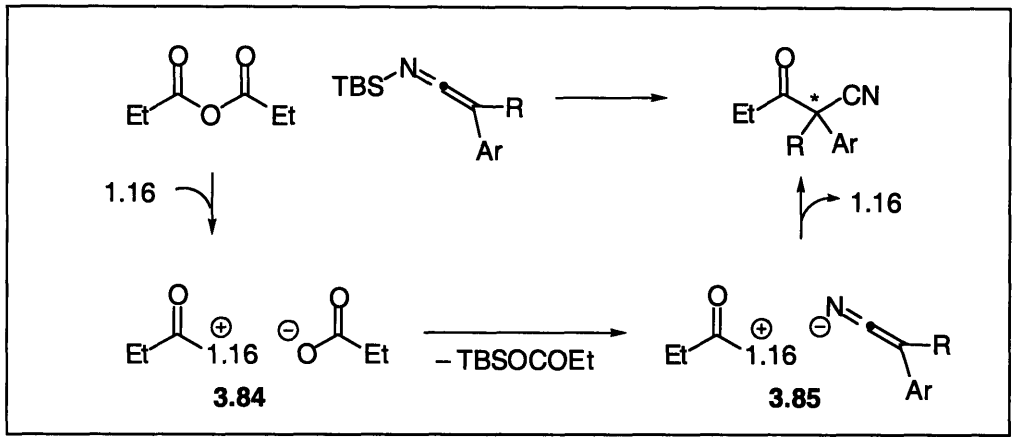
3.83

product inseparable from protodesilylated material

In analogy with mechanistic results obtained for the C-acylation of silyl ketene acetals, we believe that the C-acylation of silyl ketene imines follows a similar pathway (Scheme 3C.8). First, propionic anhydride is converted to ion pair **3.84** via attack of catalyst **1.16**. The propionate counterion then complexes to the Lewis-acidic silicon moiety to furnish ion pair **3.85**. Combination of ion pair **3.85** yields the desired product with concomitant liberation of catalyst **1.16**.

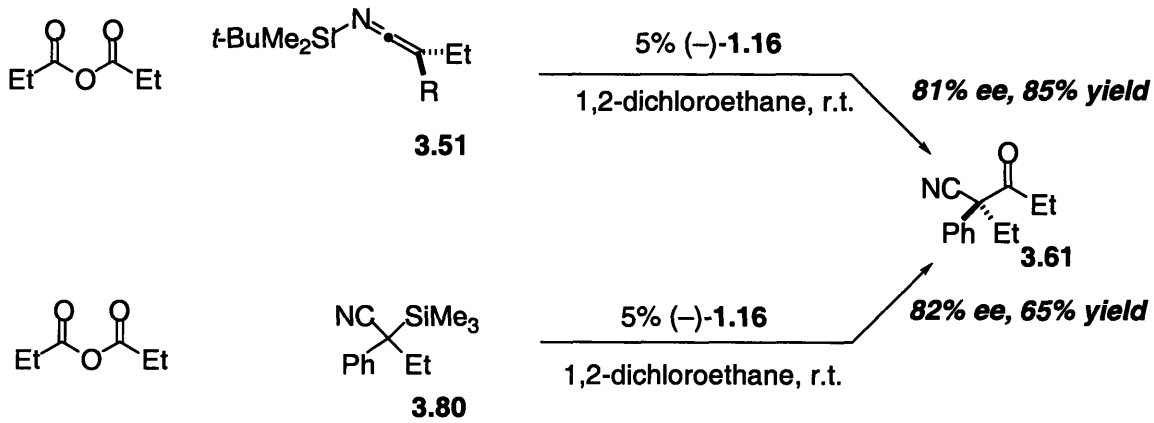
[81] The unreacted silyl ketene imine, which hydrolyzed upon workup to the parent nitrile, was inseparable from the C-acylation product obtained from **3.83**.

Scheme 3C.8. Proposed Mechanism for the C-Acylation Catalyzed by 1.16.



Elucidation of the mechanism presented in Scheme 3C.8 was achieved by comparing the catalytic reaction of silyl ketene imine **3.51** with that of C-silylated analog **3.80** (Scheme 3C.9). If ion pair **3.85** is accessed in the reaction mechanism, then the initial location and the steric demand of the silicon should not affect the enantioselectivity of the transformation.[82] Our observations indicate that substrates **3.51** and **3.80**[83] furnish the same ee value and same sense of asymmetric induction for product **3.61**. The ee data are consistent with the intermediacy of ion pair **3.85** in the catalytic process outlined in Scheme 3C.8.

Scheme 3C.9. Comparison of N-Silyl and C-Silyl Variants of Starting Material.



[82] This is assuming that TBSOCOEt is innocuous under the reaction conditions.

Conclusions

We have presented the catalytic asymmetric transformation of silyl ketene imines to α-cyanoketones with our PPY-derived planar-chiral heterocycles. While acetic anhydride is effective for the acylation of certain silyl ketene acetals, propionic anhydride was a more effective acylating agent, furnishing a more stable α-cyanoketone product. The optimized reaction conditions involve 1,2-dichloroethane as the solvent at ambient temperature. This transformation is somewhat sensitive to reaction concentrations, with reduced enantioselectivities observed for substrate concentrations of 0.5 M and higher.

Consistent with our observations for the C-acylation of silyl ketene acetals, we found that the reaction of silyl ketene imines catalyzed by **(–)-1.16** occurs for substrates bearing an aromatic group on the β-carbon. Variation of the alkyl group leads to minor changes in enantioselectivity, with the exception of a secondary alkyl. In addition, when electron-poor aromatic rings are introduced as part of the silyl ketene imine, a decrease in rate and enantioselectivity is observed.

The proposed mechanistic pathway parallels the mechanism elucidated for the acylation of silyl ketene acetals. We believe that initial formation of acylpyridinium ion pair **3.84** occurs, followed by desilylation of the ketene imine to form a new nitrile anion/acyl pyridinium ion pair **3.85**. The stereoconvergent reactivity of C-silylated and N-silylated substrates provides additional support for the involvement of a silicon-free intermediate in the stereochemistry-determining step.

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[83] The reaction of **3.80** was conducted over a one week period, leading to an 81% isolated yield.

Experimental

General

THF, CH_2Cl_2, and Et_2O were purified by passage through a neutral alumina column. Hexafluorobenzene (Avocado) and 1,2-dichloroethane (J.T. Baker) were distilled over CaH_2. Methylene chloride-d_2 and benzene-d_6 (Cambridge Isotope Laboratories) were distilled from CaH_2.

Methyl cyanoformate (Aldrich) was distilled over magnesium sulfate. neopentyl chloroformate (Avocado) was distilled over PCl_5. Ac_2O (Mallinckrodt), $(EtCO)_2O$ (Aldrich), and $(i\text{-}PrCO)_2O$ (Aldrich)were distilled from phosphorus pentoxide. *n*-BuLi (Alfa Aesar) was titrated with diphenylacetic acid (Aldrich) prior to each use.

2-Phenylbutyronitrile (Aldrich), 4-methoxyphenylacetonitrile (Aldrich), 4-trifluoromethylphenylacetonitrile (Avocado), naphthalene-1-acetonitrile (Avocado), thiophene-3-acetontirile (Aldrich), *o*-tolylacetonitrile (Avocado), indole-3-acetonitrile (Aldrich), α-methylphenylacetonitrile (Avocado), benzyl cyanide (Aldrich), 3,4-dimethoxyphenylacetonitrile, bromoethane (Alfa Aesar), iodoethane (Alfa Aesar), iodomethane (Alfa Aesar), benzophenone (Aldrich), diethylcyanomethylphosphonate (Aldrich), 2-bromopropane (Avocado), cyclopentyl bromide (Avocado), 1-bromo-2-methylpropane (Aldrich), neopentyl iodide (Aldrich), 2-(2-bromoethyl)-1,3-dioxolane (Aldrich), diisopropylamine (Aldrich), sodium hydride (Aldrich), methylmagnesium bromide (Aldrich), Martin's sulfurane (Aldrich), palladium on Carbon/10% wt. (Aldrich), sodium triacetoxyborohydride (Aldrich), *N*-methylhomoveratrylamine hydrochloride (Aldrich), Me_3SiCl (Alfa Aesar), *t*-$BuMe_2SiCl$ (Pfizer), pentane (Burdick & Jackson), magnesium sulfate (Fisher), ethanol (Pharmco), oxalic acid dihydrate (Aldrich), NEt_3

(EM Science), acetone (Aldrich), chloroform (Mallinckrodt), and methanol (Fisher) were used as received. Catalysts **1-4** were prepared as previously reported.[84]

Analytical thin layer chromatography was performed with EM Reagents 0.25 mm silica gel 60 plates, and visualization was achieved with ultraviolet light and/or ceric ammonium nitrate or potassium permanganate stains. Flash chromatography was performed with Sorbent Technologies silica gel 60 (230-400 mesh).

Optical rotations were acquired with a Jasco-1010 polarimeter. Infrared spectra were obtained on a Perkin-Elmer Series 2000 FT-IR spectrophotometer. Melting points (uncorrected) were acquired on a Thomas Hoover Unimelt capillary melting point apparatus.

^{1}H and ^{13}C nuclear magnetic resonance spectra were obtained on a Varian Unity 300, Varian Mercury 300, or Varian VXR 500 spectrometer at room temperature. ^{1}H NMR data are reported using the following notation: chemical shift in parts per million downfield from tetramethylsilane (δ scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, and app t = apparent triplet), integration, and coupling constant (Hz). ^{13}C chemical shifts are recorded in ppm downfield with respect to tetramethylsilane (δ scale), and were acquired with full proton decoupling.

All experiments were conducted under an argon or nitrogen atmosphere in oven-dried glassware with magnetic stirring, unless otherwise specified.

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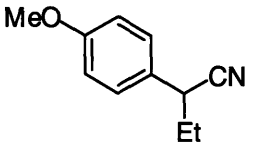
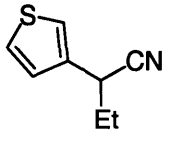
[84] (84) (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230-7231. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493. (c) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**,

Preparation of Nitriles



2-(4-methoxyphenyl)butyronitrile [39066-09-6]. A solution of *n*-BuLi (2.80 M in hexanes; 17.9 mL, 49.9 mmol) was added via syringe to a –78 °C solution of diisopropylamine (6.99 mL, 49.9 mmol) in THF (100 mL). The mixture was stirred at –78 °C for 40 minutes, and then a solution of 4-methoxyphenylacetonitrile (7.00 g, 47.6 mmol) in THF (17 mL) was added via cannula. The solution was stirred at -78 °C for 90 minutes after which neat iodoethane (4.19 mL, 120 mmol) was added via syringe. The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of 1N HCl (50 mL), extracted with Et_2O (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 100 mL), saturated NaCl (2 x 100 mL), dried ($MgSO_4$), and concentrated to a dark orange oil. Purification by flash chromatography (5% Et_2O/95% hexanes → 10% Et_2O/90% hexanes) provided an off while solid (6.08 g, 73%).

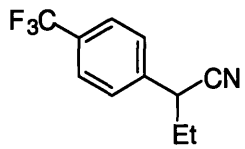
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (ddd, 2H, J=9.0, J=3.0, J=2.0), 6.91 (ddd, 2H, J=8.5, J=3.0, J=2.0), 3.81 (s, 3H), 3.69 (app t, 1H, J=6.5), 1.92 (m, 2H), 1.06 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 128.5, 127.9, 121.2, 114.5, 55.4, 38.2, 29.4, 11.6.



120, 11532-11533. (d) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091-5092.

2-(3-thienyl)butyronitrile. A solution of *n*-BuLi (2.65 M in hexanes; 14.5 mL, 38.4 mmol) was added via syringe to a –78 °C solution of diisopropylamine (5.38 mL, 38.4 mmol) in THF (30 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of 3-thiopheneacetonitrile (4.50 g, 36.5 mmol) in THF (10 mL) was added via cannula. The orange solution was stirred at -78 °C for 60 minutes, after which neat iodoethane (3.07 mL, 38.4 mmol) was added via syringe. The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of saturated NH_4Cl (50 mL), extracted with Et_2O (3 x 75 mL), washed with saturated $NaHCO_3$ (3 x 50 mL), saturated NaCl (3 x 50 mL), dried (Na_2SO_4), and concentrated to a brown oil. Purification by flash chromatography (12% Et_2O/88% hexanes → 25% Et_2O/75% hexanes) provided a clear, light yellow oil (3.25 g, 59%).

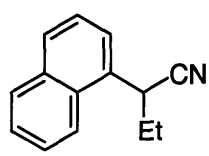
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, 1H, J=5.0, J=3.5), 7.24 (m, 1H), 7.03 (dd, 1H, J-5.0, J=1.5), 3.85 (app t, 1H, J=7.0), 1.95 (m, 2H), 1.07 (app t, 3H, J=8.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 127.0, 126.3, 122.4, 120.6, 34.1, 28.1, 11.4. FTIR (neat) 3111, 2973, 2936, 2879, 2242, 1460, 1385, 1236, 1087, 1039, 937, 834, 703 cm^{-1}. HRMS (ESI, *m/z*) calcd. for C_8H_9S $(M+Na)^+$ 174.0348, found 174.0347.



2-(4-trifluoromethylphenyl)butyronitrile. A solution of *n*-BuLi (2.80 M in hexanes; 7.20 mL, 19.8 mmol) was added via syringe to a –78 °C solution of diisopropylamine (2.78 mL, 19.8 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of 4-trifluoromethylphenylacetonitrile (3.50 g, 18.9 mmol) in THF (10 mL) was added via cannula. The cherry-red solution was stirred at -78 °C for

45 minutes after which neat iodoethane (1.66 mL, 20.8 mmol) was added via syringe. The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of 1N HCl (20 mL), extracted with Et_2O (3 x 75 mL), washed with saturated $NaHCO_3$ (2 x 75 mL), saturated NaCl (2 x 75 mL), dried (Na_2SO_4), and concentrated to a deep-red oil. Purification by flash chromatography (5% Et_2O/95% pentane) provided a clear, colorless oil (1.91 g, 47%).

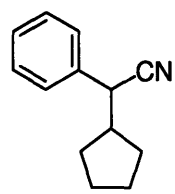
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, 2H, J=7.5), 7.46 (d, 2H, J=8.0), 3.83 (app t, 1H, J=7.5), 1.93 (m, 2H), 1.06 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 130.5 (q, J=33.9), 127.8, 126.0 (q, J=3.4), 124.0 (q, J=272.2), 120.1, 38.7, 29.1, 11.3. FTIR (thin film) 3076, 2976, 2941, 2882, 2244, 1620, 1462, 1422, 1387, 1327, 1168, 1128, 1069, 1020, 843, 667, 606 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{11}H_{10}F_3N$ $(M+Na)^+$ 236.0658, found 236.0659.



2-(1-naphthyl)butyronitrile [56477-48-6]. A solution of *n*-BuLi (2.85 M in hexanes; 8.81 mL, 25.1 mmol) was added via syringe to a –78 °C solution of diisopropylamine (3.52 mL, 25.1 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of 1-naphthaleneacetonitrile (4.00 g, 23.9 mmol) in THF (20 mL) was added via cannula. The dark-orange solution was stirred at -78 °C for 45 minutes after which neat iodoethane (2.10 mL, 26.3 mmol) was added via syringe. The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of 1N HCl (50 mL), extracted with Et_2O (3 x 50 mL), washed with saturated $NaHCO_3$ (2 x 50 mL), saturated NaCl (2 x 50 mL), dried

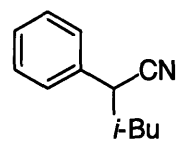
($MgSO_4$), and concentrated. Purification by flash chromatography (5% Et_2O/95% hexanes → 10% Et_2O/90% hexanes) provided a light yellow solid (3.15 g, 68%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 4H), 7.52 (m, 2H), 7.40 (dd, 1H, J=8.4, J=1.8), 3.91 (app t, 1H, J=7.2), 2.04 (m, 2H), 1.11 (app t, 3H, J=7.2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.4, 133.2, 133.0, 129.2, 128.1, 127.9, 126.9, 126.7, 126.6, 125.0, 121.0, 39.2, 29.3, 11.7.



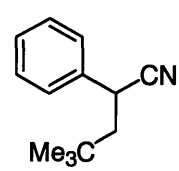
2-cyclopentylphenylacetonitrile [3753-59-1]. A solution of *n*-BuLi (2.58 M in hexanes; 13.2 mL, 34.1 mmol) was added via syringe to a –78 °C solution of diisopropylamine (4.78 mL, 34.1 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 20 minutes, and then a solution of benzyl cyanide (4.00 g, 34.1 mmol) in THF (10 mL) was added via cannula. After 45 minutes, the solution of the nitrile anion was added via cannula to a solution of bromocyclopentane (3.84 mL, 35.8 mmol) in THF (30 mL) at –78 °C. The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of 1N HCl (50 mL), extracted with Et_2O (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 75 mL), saturated NaCl (2 x 75 mL), dried (Na_2SO_4), and concentrated to an orange oil. Purification by flash chromatography (5% Et_2O/95% hexanes → 10% Et_2O/90% hexanes) provided a clear, colorless oil (3.46 g, 55%). Several early fractions enriched in the product were discarded due to a close running impurity.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.40 (m, 5H), 3.75 (m, 1H), 2.33 (m, 1H), 1.86 (m, 1H), 1.72 (m, 3H), 1.58 (m, 3H), 1.35 (m, 1H).). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 129.2, 128.2, 127.8, 120, 8, 45.5, 42.7, 31.2, 30.5, 25.1 (multiplicity 2).



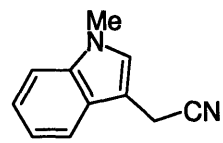
4-methyl-2-phenylpentanenitrile [5558-31-6]. A solution of *n*-BuLi (2.78 M in hexanes; 15.4 mL, 42.7 mmol) was added via syringe to a –78 °C solution of diisopropylamine (5.98 mL, 42.7 mmol) in THF (30 mL). The mixture was stirred at –78 °C for 10 minutes, and then a solution of benzyl cyanide (5.00 g, 42.7 mmol) in THF (10 mL) was added via cannula. After 45 minutes, the anion solution was added via cannula to a solution of 1-bromo-2-methylpropane (4.95 mL, 45.7 mmol) in THF (10 mL) at –78 °C. The resulting solution was stirred at –78 °C for 60 minutes, then warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of 1N HCl (50 mL), extracted with Et_2O (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 75 mL), saturated NaCl (2 x 75 mL), dried (Na_2SO_4), and concentrated to yellow oil. Purification by flash chromatography (5% Et_2O/95% hexanes → 10% Et_2O/90% hexanes) provided a clear, colorless oil (4.23 g, 57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.41 (m, 5H), 3.83 (dd, 1H, J=9.5, J=6.0), 1.81-1.95 (m, 2H), 1.65 (ddd, 1H, J=13.5, J=8.5, J=7.5), 1.00 (app t, 6H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 129.2, 128.1, 127.3, 121.2, 45.1, 35.6, 26.2, 22.7, 21.7.



2,2-dimethyl-4-phenylpentanenitrile [61066-90-8]. A solution of *n*-BuLi (2.73 M in hexanes; 7.95 mL, 21.7 mmol) was added via syringe to a –78 °C solution of diisopropylamine (3.04 mL, 21.6 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of benzyl cyanide (2.53 g, 21.6 mmol) in THF (20 mL) was added via cannula. The dark orange solution was stirred at –78 °C for 30 minutes after which neat neopentyl iodide (3.01 mL, 22.7 mmol) was added via syringe. The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of 1N HCl (50 mL), extracted with Et_2O (3 x 75 mL), washed with saturated $NaHCO_3$ (2 x 75 mL), saturated NaCl (2 x 75 mL), dried (Na_2SO_4), and concentrated to an orange oil. Purification by flash chromatography (5% Et_2O/95% pentane) provided a clear, colorless oil (2.05 g, 50%).

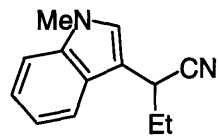
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.41 (m, 5H), 3.77 (dd, 1H, J=10.5, J=4.0), 2.06 (m, 1H), 1.67 (dd, 1H, J=14.5, J=3.5), 1.07 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 129.3, 128.0, 127.3, 122.3, 50.5, 33.4, 31.3, 29.5.



2-(3-*N*-methylindole)acetonitrile [51584-17-9]. A solution of indole-3-acetonitrile (4.50 g, 28.8 mmol) in THF (20 mL) was added to a 0 °C sluury of sodium hydride (0.725 g, 30.2 mmol) in THF (50 mL). After stirring for 45 minutes at 0 °C, neat iodomethane (1.70 mL, 28.8 mmol) was added, and the reaction was warmed to room temperature and stirred for 6 hours. The reaction was quenched by addition of 1N HCl (5 mL), followed by extraction with Et_2O (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 75 mL), saturated NaCl (2 x 75 mL), dried (Na_2SO_4), and concentrated to a brown

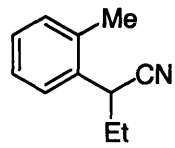
residue. Purification by flash chromatography (25% Et_2O/75% pentane → 40% Et_2O/60% pentane) provided a clear, colorless oil (3.70 g, 76%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dt, 1H, J=8.0, J=1.0), 7.36 (m, 2H), 7.23 (m, 1H), 7.09 (s, 1H), 3.83 (d, 2H, J=1.0), 3.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 127.5, 126.5, 122.5, 119.8, 118.5, 118.3, 109.8, 103.0, 32.9, 14.4.



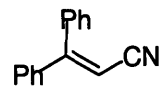
2-(3-*N*-methylindole)butyronitrile [176688-65-6]. A solution of *n*-BuLi (2.74 M in hexanes; 4.82 mL, 13.2 mmol) was added via syringe to a –78 °C solution of diisopropylamine (1.85 mL, 13.2 mmol) in THF (30 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of 2-(3-*N*-methylindole)acetonitrile (2.25 g, 13.2 mmol) in THF (20 mL) was added via cannula. The solution was stirred at -78 °C for 90 minutes after which neat iodoethane (1.06 mL, 13.2 mmol) was then added via syringe. The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of 1N HCl (5 mL), diluted with water (25 mL), extracted with Et_2O (3 x 75 mL), washed with saturated $NaHCO_3$ (2 x 75 mL), saturated NaCl (2 x 75 mL), dried ($MgSO_4$), and concentrated to a dark brown oil. Purification by flash chromatography (10% Et_2O/90% pentane → 25% Et_2O/75% pentane) provided a viscous yellow oil (2.10 g, 80%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, 1H, J=8.0), 7.36 (d, 1H, J=8.0), 7.31 (td, 1H, J=7.0, J=1.5), 7.19 (td, 1H, J=7.0, J=1.5), 7.11 (s, 1H), 4.05 (app t, 1H, J=6.5), 3.79 (s, 3H), 2.08 (m, 2H), 1.15 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 127.1, 125.9, 122.4, 121.3, 119.7, 118.7, 109.9, 109.1, 33.0, 30.5, 27.6, 11.8.



2-(2-methylphenyl)buytronitrile. A solution of *n*-BuLi (2.88 M in hexanes; 9.27 mL, 26.7 mmol) was added via syringe to a –78 °C solution of diisopropylamine (3.74 mL, 26.7 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 15 minutes, and then a solution of *o*-tolylacetonitrile (3.50 g, 26.7 mmol) in THF (10 mL) was added via cannula. The solution was stirred at -78 °C for 90 minutes after which neat iodoethane (2.24 mL, 28.0 mmol) was added via syringe. The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of 1N HCl (5 mL) and diluted with water (25 mL), extracted with Et_2O (3 x 75 mL), washed with saturated $NaHCO_3$ (2 x 75 mL), saturated NaCl (2 x 75 mL), dried (Na_2SO_4), and concentrated to a yellow oil. Purification by flash chromatography (10% Et_2O/90% pentane → 25% Et_2O/75% pentane) provided a yellow oil (1.96 g, 46%).

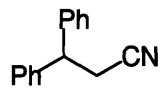
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, 1H, J=7.0, J=2.0), 7.19-7.28 (m, 3H), 3.91 (dd, 1H, J=6.0, J=6.0), 2.36 (s, 3H), 1.91 (m, 2H), 1.14 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 134.3, 131.1, 128.2, 127.6, 126.9, 121.2, 35.9, 28.0, 19.3, 12.0.



3,3-diphenyl-cyanopropene [3531-24-6]. Neat diethylcyanomethylphosphonate (20.4 mL, 125.7 mmol) was added to a 0 °C solution of sodium metal (2.89 g, 125.7 mmol) in absolute ethanol (100 mL). After stirring for 10 minutes at 0 °C, solid benzophenone (20.8 g, 113.1 mmol) was added. The reaction was heated to 60 °C for one hour then cooled to room temperature. The solvent was removed, and the resulting white residue

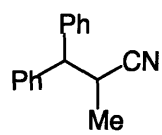
was extracted with Et_2O (3 x 100 mL), dried (Na_2SO_4), and concentrated to a yellow oil. Purification by vacuum distillation (130 °C, 1 mm Hg) afforded a clear colorless liquid (4.03 g, 17%). Approximately 19g of material was left over, which was enriched in product, but contained an close-boiling impurity.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 6H), 7.39 (m, 2H), 7.31 (m, 2H), 5.76 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 139.2, 137.3, 130.7, 130.3, 129.8, 128.9, 128.8 (isochronous with another peak), 118.2, 95.1.



3,3-diphenylcyanopropane [2286-54-6]. Palladium on carbon (0.573 g, 5% wt) was added to a solution of 3,3-diphenyl-cyanopropene (1.49g, 7.26 mmol) in absolute ethanol (25 mL). A balloon containing hydrogen gas (1 atm) was affixed, and the reaction was stirred at room temperature for 24 hours. The reaction mixture was filtered through a pad of celite and concentrated to an off white solid (0.633 g, 42%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.40 (m, 10H), 4.39 (t, 2H, J=7.5), 3.08 (d, 1H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 129.6, 128.2, 128.1, 119.1, 47.8, 25.0.



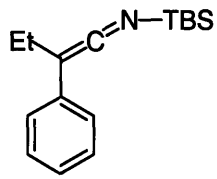
2-methyl-3,3-diphenylcyanopropane [92962-30-6]. A solution of *n*-BuLi (2.80 M in hexanes; 0.900 mL, 2.53 mmol) was added via syringe to a –78 °C solution of diisopropylamine (0.355 mL, 2.53 mmol) in THF (10 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of 3,3-diphenylcyanopropane (0.500 g, 2.41

mmol) in THF (10 mL) was added via cannula. The solution was stirred at -78 °C for 90 minutes after which neat iodomethane (0.165 mL, 2.65 mmol) was added via syringe. The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of water (25 mL), extracted with Et_2O (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 50 mL), saturated NaCl (2 x 50 mL), dried ($MgSO_4$), and concentrated to a yellow oil. Purification by flash chromatography (5% EtOAc/95% hexanes → 8% EtOAc/92% hexanes) provided a clear, colorless oil (0.311 g, 58%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.40 (m, 10H), 4.02 (d, 1H, J=7.0), 3.39 (m, 1H), 1.29 (d, 3H, J=7.0).

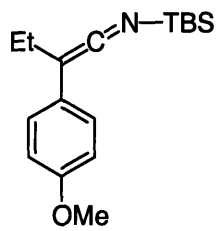
Preparation of Silyl Ketene Imines

General procedure. A solution of *n*-BuLi (2.56–2.90 M in hexanes; 1.05 equiv.) was added via syringe to a –78 °C solution of diisopropylamine (1.05 equiv.) in THF. The mixture was stirred at –78 °C for 15 minutes, and then a solution of the nitrile (1.00 equiv.) in THF was added via cannula. The mixture was stirred at –78 °C for 5 minutes, and then *t*-$BuMe_2SiCl$ (1.20–2.10 equiv.) was added in THF, resulting in a clear, bright yellow solution. The reaction mixture was warmed to room temperature and stirred for 1.5 hours. The THF was then removed, and the residue was taken up in pentane and filtered inside a glove box. The solvent was removed, and the yellow oil was used in acylation reaction without further purification (essentially no impurities detectable by ^{1}H NMR).



1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-phenyl-1-butenylidene)-silanamine [51965-62-9], **(3.51).** The general procedure was followed, using *n*-BuLi (2.90 M in hexanes; 7.48 mL, 21.7 mmol), diisopropylamine (3.04 mL, 21.7 mmol, in 30 mL THF), nitrile (3.00 g, 20.7 mmol, in 10 mL THF), and *t*-$BuMe_2SiCl$ (3.27 g, 24.8 mmol, in 10 mL THF). The product was isolated as a bright yellow oil (5.15 g, 96%), for which purification was not necessary.

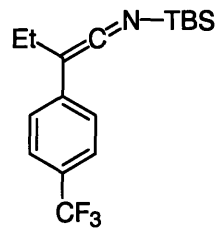
^1H NMR (300 MHz, C_6D_6) δ 7.12-7.24 (m, 4H), 6.90 (m, 1H), 2.26 (app q, 2H, J=7.5), 1.11 (app t, 3H, J=7.5), 0.87 (s, 9H), 0.057 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 186.9, 139.1, 129.4, 123.6, 123.0, 56.6, 25.9, 19.6, 18.1, 13.9, -4.4.



1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-(4-methoxyphenyl)-1-butenylidene)-silanamine (3.52). The general procedure was followed, using *n*-BuLi (2.80 M in hexanes; 4.29 mL, 12.0 mmol), diisopropylamine (1.68 mL, 12.0 mmol, in 20 mL THF), nitrile (2.00 g, 11.4 mmol, in 10 mL THF), and *t*-$BuMe_2SiCl$ (3.62 g, 24.0 mmol, in 10 mL THF). The product was isolated as a bright yellow oil (3.30 g, 100%), for which purification was not necessary.

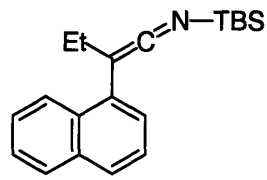
^1H NMR (300 MHz, C_6D_6) δ 7.05 (ddd, 2H, J=8.4, J=2.4, J=0.9), 6.84 (ddd, 2H, J=8.4, J=2.4, J=0.6), 3.34 (s, 3H), 2.27 (app q, 2H, J=7.5), 1.13 (app t, 3H, J=7.5), 0.89

(s, 9H), 0.087 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 189.9, 156.7, 130.6, 124.7, 115.2, 56.1, 55.2, 26.0, 19.9, 18.1, 13.9, -4.4. FTIR (neat) 2954, 2932, 2858, 2278, 1679, 1606, 1513, 1464, 1441, 1254, 1180, 1034, 837 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{17}H_{27}NOSi$ $(M)^+$ 289.1862, found 289.1860.



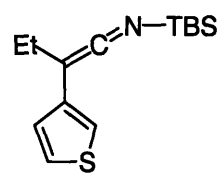
1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-(4-trifluoromethylphenyl)-1-butenylidene)-silanamine (3.53). A solution of *n*-BuLi (2.73 M in hexanes; 2.89 mL, 7.88 mmol) was added via syringe to a –78 °C solution of diisopropylamine (1.10 mL, 7.88 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 15 minutes, and then a solution of *t*-$BuMe_2SiCl$ (1.36 g, 9.00 mmol) was added in THF (15 mL). After 5 minutes, the nitrile (1.60 g, 7.50 mmol) in THF (12 mL) was added via cannula. The mixture was stirred at –78 °C for 30 minutes, resulting in an orange solution which was warmed to room temperature and stirred for 1.5 hours. The THF was then removed, and the residue was taken up in pentane and filtered inside a glove box. The solvent was removed, and the remaining orange residue (2.44 g, 99%) was used without the need of purification. [Reverse order of addition is necessary for this substrate, other polymerization results.]

^1H NMR (500 MHz, CD_2Cl_2) δ 7.48 (dd, 2H, J=9.0, J=1.0), 7.10 (dd, 2H, J=9.0, J=1.0), 2.37 (app q, 2H, J=7.5), 1.22 (app t, 3H, J=7.5), 1.04 (s, 9H), 0.35 (s, 6H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 180.2, 144.5, 127.6 (q, J=231), 125.9 (q, J=3.4), 123.2 (q, J=32.2), 122.6, 56.1, 25.8, 19.2, 18.2, 13.6, -4.3. FTIR (neat) 2932, 2885, 2858, 2044, 1608, 1517, 1464, 1422, 1256, 1167, 1129, 1069, 1019, 835, 784 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{17}H_{24}F_3NSi$ $(M)^+$ 327.1625, found 327.1626.



1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-(1-naphthyl)-1-butenylidene)-silanamine (3.54). The general procedure was followed, using *n*-BuLi (2.77 M in hexanes; 2.33 mL, 6.46 mmol), diisopropylamine (0.910 mL, 6.46 mmol, in 10 mL THF), nitrile (1.20 g, 6.15 mmol, in 10 mL THF), and *t*-BuMe$_2$SiCl (1.95 g, 12.9 mmol, in 8 mL THF). The product was isolated as a bright yellow oil (1.86 g, 98%), for which purification was not necessary.

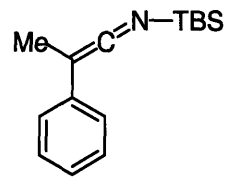
^{1}H NMR (300 MHz, C_6D_6) δ 7.60 (m, 3H), 7.42 (m, 2H), 7.27 (ddd, 1H, J=6.9, J=6.9, J=1.5), 7.17 (ddd, 1H, J=6.9, J=6.9, J=1.5), 2.35 (app q, 2H, J=7.5), 1.17 (app t, 3H, J=7.5), 0.89 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 186.2, 136.7, 135.6, 131.3, 128.7, 128.4, 127.6, 126.7, 124.5, 124.4, 119.4, 57.6, 25.9, 19.6, 18.2, 13.7, -4.4. FTIR (neat) 3058, 2955, 2931, 2883, 2857, 2277, 1681, 1628, 1600, 1508, 1470, 1434, 1254, 1127, 1019, 837 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{20}H_{27}NSi$ $(M+H)^+$ 310.1986, found 310.1993.



1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-(3-thienyl)-1-butenylidene)-silanamine (3.55). The general procedure was followed, using *n*-BuLi (2.62 M in hexanes; 3.58 mL, 9.37 mmol), diisopropylamine (1.31 mL, 9.37 mmol, in 20 mL THF), nitrile (1.35 g, 8.93 mmol, in 10 mL THF), and *t*-BuMe$_2$SiCl (1.61 g, 10.7 mmol, in 10 mL THF). The

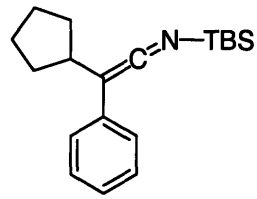
product was isolated as a bright yellow oil (2.17 g, 92%), for which purification was not necessary.

^{1}H NMR (500 MHz, C_6D_6) δ 6.98 (dd, 1H, J=5.0, J=2.5), 6.91 (dd, 1H, J=5.0, J=1.5), 6.40 (dd, 1H, J=2.5, J=1.5), 2.20 (app q, 2H, J=7.5), 1.10 (app t, 3H, J=7.5), 0.87 (s, 9H), 0.053 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 186.3, 138.7, 129.4, 124.1, 122.9, 62.7, 26.0, 25.1, 23.2, 18.1, -4.4. FTIR (neat) 3107, 2957, 2931, 2884, 2859, 2038, 1828, 1681, 1533, 1471, 1384, 1253, 1084, 825 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{14}H_{23}NSSi$ $(M)^+$ 265.1320, found 265.1320.



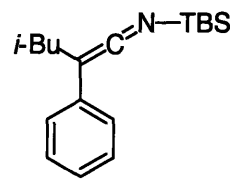
1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-phenyl-1-propenylidene)-silanamine [53097-53-3], **(3.56).** The general procedure was followed, using *n*-BuLi (2.82 M in hexanes; 9.93 mL, 28.0 mmol), diisopropylamine (3.92 mL, 28.0 mmol, in 20 mL THF), nitrile (3.50 g, 26.7 mmol, in 10 mL THF), and *t*-$BuMe_2SiCl$ (4.82 g, 32.0 mmol, in 10 mL THF). The product was isolated as a bright orange oil (5.01 g, 76%), for which purification was not necessary.

^{1}H NMR (500 MHz, C_6D_6) δ 7.21 (dddd, 2H, J=7.5, J=7.0, J=2.0, J=1.5), 7.13 (ddd, 2H, J=7.5, J=2.0, J=1.5), 6.89 (tt, 1H, J=7.0, J=1.5), 1.84 (s, 3H), 0.86 (s, 9H), 0.056 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6) δ 186.4, 139.1, 128.8, 122.9, 122.4, 48.0, 25.4, 17.6, 11.6, -4.9.



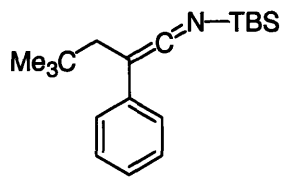
1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-cyclopentyl-2-phenyl-1-ethenylidene)-silanamine (3.57). The general procedure was followed, using *n*-BuLi (2.56 M in hexanes; 4.41 mL, 11.3 mmol), diisopropylamine (1.58 mL, 11.3 mmol, in 20 mL THF), nitrile (2.00 g, 10.8 mmol, in 10 mL THF), and *t*-$BuMe_2SiCl$ (2.03 g, 13.5 mmol, in 10 mL THF). The product was isolated as a bright yellow oil (3.23 g, 100%), for which purification was not necessary.

^1H NMR (500 MHz, C_6D_6) δ 7.24 (m, 4H), 6.91 (m, 1H), 2.77 (m, 1H), 1.96 (m, 2H), 1.64 (m, 2H), 1.53 (m, 4H), 0.89 (s, 9H), 0.080 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 186.3, 139.4, 129.3, 124.2, 122.9, 60.5, 36.5, 33.5, 26.0, 25.5, 18.1, -4.3. FTIR (neat) 3024, 2955, 2860, 2034, 1596, 1495, 1450, 1252, 1076, 823 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{19}H_{29}NSi$ $(M+H)^+$ 300.2142, found 300.2146.



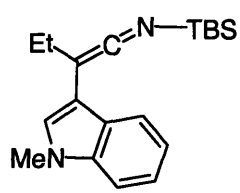
1-(1,1-dimethylethyl)-1,1-dimethyl-N-(4-methyl-2-phenyl-1-pentenylidene)-silanamine (3.58). The general procedure was followed, using *n*-BuLi (2.82 M in hexanes; 1.35 mL, 3.80 mmol), diisopropylamine (0.533 mL, 3.80 mmol, in 10 mL THF), nitrile (0.627 g, 3.62 mmol, in 10 mL THF), and *t*-$BuMe_2SiCl$ (0.655 g, 4.34 mmol, in 10 mL THF). The product was isolated as a bright yellow oil (0.970 g, 93%), for which purification was not necessary.

^{1}H NMR (500 MHz, C_6D_6) δ 7.21 (m, 4H), 6.90 (m, 1H), 2.23 (d, 2H, J=7.0), 1.87 (m, 1H), 0.95 (d, 6H, J=7.0), 0.88 (s, 9H), 0.081 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 186.2, 139.1, 129.4, 128.7, 123.8, 122.9, 52.9, 36.5, 28.1, 25.9, 23.3, 18.0, -4.3. FTIR (neat) 3025, 2954, 2930, 2860, 2040, 1597, 1496, 1464, 1253, 841, 785, 690 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{18}H_{29}NSi$ $(M)^+$ 287.2069, found 287.2062.



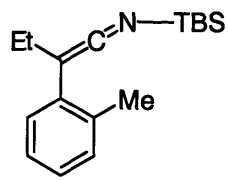
1-(1,1-dimethylethyl)-1,1-dimethyl-N-(4,4-dimethyl-2-phenyl-1-pentenylidene)-silanamine (3.59). The general procedure was followed, using *n*-BuLi (2.58 M in hexanes; 3.26 mL, 8.41 mmol), diisopropylamine (1.18 mL, 8.41 mmol, in 15 mL THF), nitrile (1.50 g, 8.01 mmol, in 10 mL THF), and *t*-$BuMe_2SiCl$ (1.45 g, 9.61 mmol, in 10 mL THF). The product was isolated as a bright yellow oil (2.40 g, 100%), for which purification was not necessary.

^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (m, 2H), 7.20 (m, 2H), 6.88 (tt, 1H, J=7.0, J=1.0), 2.30 (s, 2H), 0.98 (s, 9H), 0.88 (s, 9H), 0.075 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 185.8, 139.9, 129.2, 124.1, 122.8, 51.4, 40.1, 34.6, 30.3, 25.9, 18.0, -4.3. FTIR (neat) 3082, 3056, 3024, 2954, 2932, 2860, 2041, 1596, 1496, 1472, 1363, 1254, 1076, 1005, 990, 841 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{19}H_{31}NSi$ $(M+H)^+$ 302.2299, found 302.2298.



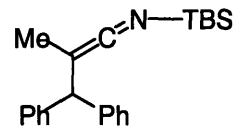
1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-(3-N-methylindole)-1-butenylidene)-silanamine (3.82). The general procedure was followed, using *n*-BuLi (in hexanes; 0.890 mL, 2.49 mmol), diisopropylamine (0.349 mL, 2.49 mmol, in 10 mL THF), nitrile (0.469 g, 2.37 mmol, in 10 mL THF), and *t*-$BuMe_2SiCl$ (0.428 g, 2.84 mmol, in 10 mL THF). The product was isolated as an orange oil (0.737 g, 99%), for which purification was not necessary.

^1H NMR (500 MHz, C_6D_6) δ 8.17 (dt, 1H, J=8.0, J=1.5), 7.21 (m, 2H), 7.00 (dt, 1H, J=8.0, J=1.0), 6.36 (s, 1H), 2.44 (app q, 2H, J=7.5), 1.28 (app t, 3H, J=7.5), 0.95 (s, 9H), 0.17 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 194.3, 138.3, 126.9, 122.7, 122.4, 120.8, 118.9, 110.7, 109.8, 50.4, 32.3, 26.1, 22.1, 18.3, 14.0.



1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-(2-methylphenyl)-1-butenylidene)-silanamine (3.83). The general procedure was followed, using *n*-BuLi (in hexanes; 2.52 mL, 6.59 mmol), diisopropylamine (0.924 mL, 6.59 mmol, in 15 mL THF), nitrile (1.00 g, 6.28 mmol, in 10 mL THF), and *t*-$BuMe_2SiCl$ (1.14 g, 7.54 mmol, in 8 mL THF). The product was isolated as a bright yellow oil (1.58 g, 92%), for which purification was not necessary.

^1H NMR (300 MHz, C_6D_6) δ 6.77-7.30 (m, 4H), 2.38 (m, 5H), 1.09 (app t, 3H, J=7.5), 0.83 (s, 9H), 0.018 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 185.5, 136.7, 135.4, 131.3, 126.8, 126.5, 124.9, 53.7, 25.9, 23.1, 22.3, 18.1, 14.3, -4.7.



1-(1,1-dimethylethyl)-1,1-dimethyl-N-(2-(2,2-diphenylmethyl)1-propenylidene)-silanamine (3.50). The general procedure was followed, using *n*-BuLi (in hexanes; 0.420 mL, 1.19 mmol), diisopropylamine (0.167 mL, 1.19 mmol, in 10 mL THF), nitrile (0.250 g, 1.13 mmol, in 5 mL THF), and *t*-$BuMe_2SiCl$ (0.357 g, 2.37 mmol, in 5 mL THF). The product was isolated as a bright yellow oil (0.371 g, 98%), for which purification was not necessary.

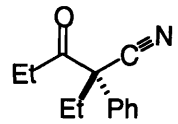
^1H NMR (500 MHz, C_6D_6) δ 7.25 (m, 4H), 7.10 (m, 4H), 6.99 (m, 2H), 4.45 (s, 1H), 1.63 (s, 3H), 0.79 (s, 9H), -0.11 (s, 6H).

Catalytic Asymmetric Acylations of Silyl Ketene Imines

Unless otherwise specified, all reactions are the average of two runs, one run with each enantiomer of the catalyst.

General Procedure . A solution of **(–)-1.16** (0.050 equiv) in 1,2-dichloroethane was added to a 20-mL vial containing the silyl ketene imine (1.0 equiv). The resulting solution was stirred for 5 minutes at room temperature, after which $(EtCO)_2O$ (1.3 equiv) was added. The vial was capped and removed from the glove box, and the reaction mixture was stirred for 36 hours at room temperature. The product was then purified directly by flash chromatography (4% Et_2O/96% hexanes → 9% Et_2O/91% hexanes). The catalyst was recovered by eluting with CH_2Cl_2, followed by 10% Et_3N/90% EtOAc. The ee of the product was determined either by chiral HPLC or by chiral GC.

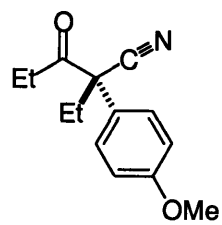
If a glove box was not used, lower yields were obtained, due to the moisture sensitivity of silyl ketene imines.



2-phenyl-2-propionylbutyronitrile (3.61). The general procedure was followed, using silyl ketene imine **3.51** (0.183 g, 0.704 mmol), $(EtCO)_2O$ (0.117 mL, 0.915 mmol), **(–)-1.16** (0.0242 g, 0.0352 mmol), and 2.6 mL of 1,2-dichloroethane to produce 87% (0.124 g, 0.612 mmol) of a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 100 °C, 1.0 mL/min, retention times of enantiomers: 27.9 min (minor), 29.3 min (major)) to have 80% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.44 (m, 5H), 2.82 (dq, 1H, J=18.0, J=7.5), 2.53 (dq, 1H, J=18.5, J=8.0), 2.33 (dq, 1H, J=14.0, J=7.5), 2.11 (dq, 1H, J=14.5, J=7.5), 1.01 (app t, 3H, J=7.5), 0.96 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 134.1, 129.6, 129.0, 126.5, 119.6, 60.6, 33.2, 30.1, 9.8, 8.3. FTIR (neat) 3064, 3032, 2977, 2940, 2881, 2239, 1734, 1549, 1494, 1450, 1407, 1383, 1344, 1122, 1033, 755, 699 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{13}H_{15}NO$ $(M+Na)^+$ 224.1046, found 224.1041. $[\alpha]^{23}_D = +47°$ (c=0.53, CH_2Cl_2; for product with 80% ee).

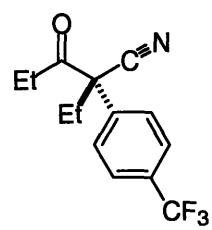
For run 2, the general procedure was followed with the silyl ketene imine **3.51** (0.183 g, 0.704 mmol), $(EtCO)_2O$ (0.117 mL, 0.915 mmol), and **(+)-1.16** (0.0242 g, 0.0352 mmol) in 2.6 mL of 1,2-dichloroethane which furnished 82% of the product (0.116 g, 0.577 mmol), which was shown by chiral GC to have 81% ee. A 97% catalyst recovery was obtained for this substrate.



2-(4-methoxyphenyl)-2-propionylbutyronitrile (3.62). The general procedure was followed, using silyl ketene imine **3.52** (0.175 g, 0.605 mmol), $(EtCO)_2O$ (0.101 mL, 0.786 mmol), **(–)-1.16** (0.0208 g, 0.0302 mmol), and 2.2 mL of 1,2-dichloroethane to produce 64% (0.0900 g, 0.387 mmol) of a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 7.96 min (major), 9.04 min (minor)) to have 82% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, 2H, J=9.0, J=2.5), 6.92 (dd, 2H, J=9.0, J=2.5), 3.81 (s, 3H), 2.78 (dq, 1H, J=18.5, J=7.5), 2.53 (dq, 1H, J=18.5, J=8.0), 2.29 (dq, 1H, J=14.0, J=7.5), 2.06 (dq, 1H, J=14.0, J=7.0), 0.99 (app t, 3H, J=7.5), 0.96 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 160.0, 127.7, 125.9, 119.8, 114.8, 59.8, 55.5, 32.9, 29.9, 9.7, 8.3. FTIR (neat) 2977, 2940, 2840, 2237, 1731, 1609, 1582, 1512, 1462, 1409, 1304, 1256, 1186, 1121, 1033, 829 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{17}NO_2$ $(M+Na)^+$ 254.1151, found 254.1146. $[\alpha]^{23}_D = +88°$ (c=0.23, CH_2Cl_2; for product with 82% ee).

For run 2, the general procedure was followed with the silyl ketene imine **3.52** (0.175 g, 0.605mmol), $(EtCO)_2O$ (0.101 mL, 0.786 mmol), and **(+)-1.16** (0.0208 g, 0.0302 mmol) in 2.2 mL of 1,2-dichloroethane which furnished 65% of the product (0.0913 g, 0.393 mmol), which was shown by chiral HPLC to have 80% ee.

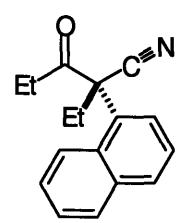


2-(4-trifluoromethylphenyl)-2-propionylbutyronitrile (3.63). The general procedure was followed, using silyl ketene imine **3.53** (0.170 g, 0.520 mmol), $(EtCO)_2O$ (0.0867

mL, 0.676 mmol), **(–)-1.16** (0.0179 g, 0.0260 mmol), and 1.9 mL of 1,2-dichloroethane to produce 50% (0.0701 g, 0.260 mmol) of a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 120 °C, 1.0 mL/min, retention times of enantiomers: 8.21 min (minor), 8.94 min (major)) to have 54% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, 2H, J=8.0), 7.59 (d, 2H, J=8.5), 2.89 (dq, 1H, J=19.0, J=7.0), 2.54 (dq, 1H, J=18.5, J=7.5), 2.37 (dq, 1H, J=14.0, J=7.5), 2.12 (dq, 1H, J=14.0, J=7.5), 1.03 (app t, 3H, J=7.5), 0.96 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 138.1, 131.4 (q, J=33.4), 127.1, 126.6 (q, J=3.4), 123.9 (q, J=272.2), 119.1, 60.5, 33.7, 30.6, 9.8, 8.2. FTIR (neat) 3078, 2983, 2944, 2885, 2240, 1730, 1619, , 1462, 1385, 1327, 1171, 1130, 1070, 1019, 958, 833, 611 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{14}F_3NO$ $(M+Na)^+$ 292.0920, found 292.0929. $[\alpha]^{23}_D$ = +35° (c=0.32, CH_2Cl_2; for product with 54% ee).

For run 2, the general procedure was followed with the silyl ketene imine **3.53** (0.170 g, 0.520 mmol), $(EtCO)_2O$ (0.0867 mL, 0.676 mmol), and **(+)-1.16** (0.0179 g, 0.0260 mmol) in 1.9 mL of 1,2-dichloroethane which furnished 50% of the product (0.0703 g, 0.261 mmol), which was shown by chiral GC to have 52% ee. A 95% catalyst recovery was obtained for this substrate.

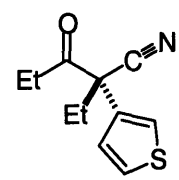


2-(1-naphthalenyl)-2-propionylbutyronitrile (3.64). The general procedure was followed, using silyl ketene imine (0.172 g, 0.557 mmol), $(EtCO)_2O$ (0.0928 mL, 0.724 mmol), **(–)-1.16** (0.0191 g, 0.0279 mmol), and 2.0 mL of 1,2-dichloroethane to produce 80% (0.112 g, 0.446 mmol) of a clear, colorless oil, which was shown by chiral HPLC

(Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 7.18 min (major), 8.46 min (minor)) to have 80% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, 1H, J=1.5), 7.90 (m, 3H), 7.56 (m, 2H), 7.40 (dd, 1H, J=8.5, J=2.0), 2.88 (dq, 1H, J=18.5, J=7.5), 2.56 (dq, 1H, J=18.5, J=7.0), 2.42 (dq, 1H, J=14.5, J=7.0), 2.23 (dq, 1H, J=14.0, J=7.5), 1.01 (app t, 3H, J=7.0), 0.99 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 133.4, 133.2, 131.3, 129.7, 128.4, 127.8, 127.3, 127.2, 126.5, 123.0, 119.7, 60.8, 33.2, 29.9, 9.8, 8.3. FTIR (neat) 3060, 2978, 2940, 2881, 2237, 1732, 1633, 1598, 1507, 1460, 1407, 1381, 1345, 1275, 1120, 1037, 963, 856, 818 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{17}H_{17}NO$ $(M+Na)^+$ 274.1202, found 274.1195. $[\alpha]^{23}_D$ = +89° (c=0.28, CH_2Cl_2; for product with 80% ee).

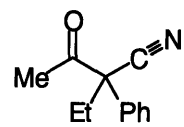
For run 2, the general procedure was followed with the silyl ketene imine **3.54** (0.172 g, 0.557 mmol), $(EtCO)_2O$ (0.0928 mL, 0.724 mmol), and **(+)-1.16** (0.0191 g, 0.0279 mmol) in 2.0 mL of 1,2-dichloroethane which furnished 76% of the product (0.106 g, 0.422 mmol), which was shown by chiral HPLC to have 80% ee.



2-(3-thienyl)-2-propionylbutyronitrile (3.65). The general procedure was followed, using silyl ketene imine **3.55** (0.179 g, 0.674 mmol), $(EtCO)_2O$ (0.112 mL, 0.876 mmol), **(–)-1.16** (0.0231 g, 0.0337 mmol), and 2.5 mL of 1,2-dichloroethane to produce 69% (0.0960 g, 0.462 mmol) of a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 120 °C, 1.0 mL/min, retention times of enantiomers: 8.04 min (minor), 8.39 min (major)) to have 78% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, 1H, J=3.5, J=1.5), 7.37 (m, 1H), 7.00 (dd, 1H, J=5.0, J=1.5), 2.83 (dq, 1H, J=19.0, J=8.0), 2.65 (dq, 1H, J=18.5, J=7.0), 2.30 (dq, 1H, J=14.5, J=7.0), 2.23 (dq, 1H, J=14.0, J=7.5), 1.03 (app t, 3H, J=7.5), 0.99 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 135.1, 127.9, 125.4, 123.6, 119.8, 57.3, 33.1, 30.1, 9.8, 8.1. FTIR (neat) 3108, 2979, 2940, 2881, 2239, 1731, 1460, 1406, 1379, 1346, 1230, 1121, 1096, 847, 784 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{11}H_{13}NOS$ $(M+Na)^+$ 230.0610, found 230.0605. $[\alpha]^{23}_D$ = +66° (c=0.37, CH_2Cl_2; for product with 78% ee).

For run 2, the general procedure was followed with the silyl ketene imine **3.55** (0.179 g, 0.674 mmol), $(EtCO)_2O$ (0.112 mL, 0.876 mmol), and **(+)-1.16** (0.0231 g, 0.0337 mmol) in 2.5 mL of 1,2-dichloroethane which furnished 74% of the product (0.103 g, 0.496 mmol), which was shown by chiral GC to have 76% ee.

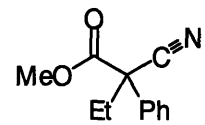


2-acetyl-2-phenylbutyronitrile (3.44). The general procedure was followed, using silyl ketene imine **3.51** (0.160 g, 0.617 mmol), Ac_2O (0.0756 mL, 0.802 mmol), **(–)-1.16** (0.0211 g, 0.0309 mmol), and 2.2 mL of 1,2-dichloroethane to produce 63% (0.0730 g, 0.390 mmol) of **3.44** as a clear, colorless oil, which was an inseparable mixture (3:1 product:2-phenylbutyronitrile) and shown by chiral HPLC (Daicel CHIRALCEL OJ-H, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 7.98 min (minor), 8.70 min (major)) to have 71% ee for the desired product (yield determined by ^{1}H NMR ratios and weight of product mixture).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.42 (m, 5H), 2.32 (dq, 1H, J=14.5, J=7.0), 2.28 (s, 3H), 2.10 (dq, 1H, J=15.0, J=7.5), 0.98 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz,

$CDCl_3$) δ 199.0, 133.8, 129.7, 129.1, 126.5, 119.4, 61.0, 29.8, 27.2, 9.8. FTIR (neat) 3064, 2977, 2940, 2882, 2239, 1728, 1599, 1494, 1450, 1359, 1174, 1034, 756, 699. . HRMS (ESI, m/z) calcd. for $C_{12}H_{13}NO$ $(M+Na)^+$ 210.0889, found 210.0888. $[\alpha]^{23}_D$ = +52° (c=0.33, CH_2Cl_2; for product with 71% ee).

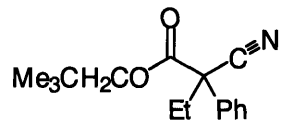
For run 2, the general procedure was followed with the silyl ketene imine **3.51** (0.180 g, 0.694 mmol), Ac_2O (0.0851 mL, 0.902 mmol), and **(+)-1.16** (0.0238 g, 0.0347 mmol) in 2.5 mL of 1,2-dichloroethane which furnished 64% of product **3.44** (0.0835 g, 0.446 mmol), which was shown by chiral HPLC to have 73% ee (3:1 mixture with 2-phenylbutyronitrile).



2-(methoxy carbonyl)-2-phenylbutyronitrile (3.47). The general procedure was followed, using silyl ketene imine **3.51** (0.140 g, 0.540 mmol), methyl cyanoformate (0.0557 mL, 0.702 mmol), **(–)-1.16** (0.0185 g, 0.0270 mmol), and 2.0 mL of 1,2-dichloroethane to produce 80% (0.0885 g, 0.435 mmol) of **3.47** as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OD-H, 4.6 mm x 25 cm, hexane/isopropanol 99:1, 1.0 mL/min, retention times of enantiomers: 6.12 min. and 6.44 min.) to be racemic.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dt, 2H, J=7.0, J=1.5), 7.41 (m, 3H), 3.79 (s, 3H), 2.44 (dq, 1H, J=14.5, J=7.5), 2.19 (dq, 1H, J=15.0, J=7.5), 1.07 (app t, 3H, J=7.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 134.4, 129.3, 129.1, 126.3, 118.4, 55.1, 54.1, 31.9, 10.0. FTIR (neat) 3064, 2980, 2883, 2245, 1749, 1494, 1494, 1451, 1436, 1386, 1239, 1147, 1013, 809, 760, 731, 697 cm-1. HRMS (ESI, *m/z*) calcd. for $C_{12}H_{13}NO_2$ $(M+Na)^+$ 226.0838, found 226.0833.

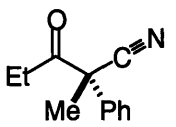
For run 2, the general procedure was followed with the silyl ketene imine **3.51** (0.140 g, 0.540 mmol), methyl cyanoformate (0.0557 mL, 0.702 mmol), and **(+)-1.16** (0.0185 g, 0.0270 mmol) in 2.0 mL of 1,2-dichloroethane which furnished 82% of product **3.47** (0.0899 g, 0.442 mmol), which was shown by chiral HPLC to be racemic.



2-(2,2-dimethypropyloxy carbonyl)-2-phenylbutyronitrile (3.48). The general procedure was followed, using silyl ketene imine **3.51** (0.100 g, 0.387 mmol), neopentyl chloroformate (0.0757 mL, 0.504 mmol), (–)-**1.16** (0.0133 g, 0.0194 mmol), and 1.4 mL of 1,2-dichloroethane, which furnished a 63% yield (0.0627 g, 0.242 mmol) as a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRACEL OD-H, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 3.84 min (minor) and 4.26 min (major)) to have 8% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (ddd, 2H, J=7.5, J=2.5, J=1.0), 7.40 (m, 3H), 3.92 (d, 1H, J=11.0), 3.81 (d, 1H, J=10.0), 2.46 (dq, 1H, J=15.0, J=7.5), 2.21 (dq, 1H, J=15.0, J=8.0), 1.09 (app t, 3H, J=7.5), 0.88 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 134.7, 129.3, 129.0, 126.4, 118.5, 76.1, 55.4, 31.9, 31.5, 26.3, 10.1. FTIR (neat) 3065, 2964, 2884, 2245, 1747, 1600, 1480, 1369, 1237, 1147, 1009, 936, 841, 759 cm^{-1}. HRMS (ESI, *m/z*) submitted.

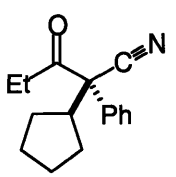
For run 2, the general procedure was followed, using silyl ketene imine **3.51** (0.100 g, 0.387 mmol), neopentyl chloroformate (0.0757 mL, 0.504 mmol), and (+)-**1.16** (0.0133 g, 0.0194 mmol) in 1.4 mL of 1,2-dichloroethane, which furnished an 58% yield of the product (0.0581 g, 0.224 mmol), which was shown by chiral HPLC to have 6 % ee.



2-phenyl-2-propionylpropionitrile (3.66). The general procedure was followed, using silyl ketene imine **3.56** (0.186 g, 0.757 mmol), $(EtCO)_2O$ (0.126 mL, 0.984 mmol), **(–)-1.16** (0.0260 g, 0.0379 mmol), and 2.8 mL of 1,2-dichloroethane to produce 91% (0.129 g, 0.688 mmol) of a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 105 °C, 0.7 mL/min, retention times of enantiomers: 17.6 min (minor), 18.1 min (major)) to have 82% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.45 (m, 5H), 2.82 (dq, 1H, J=18.5, J=7.0), 2.51 (dq, 1H, J=18.5, J=7.0), 1.83 (s, 3H), 1.02 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 135.7, 129.7, 129.1, 126.1, 120.6, 54.0, 32.3, 23.9, 8.4. FTIR (neat) 3064, 2986, 2942, 2910, 2881, 2240, 1733, 1600, 1495, 1449, 1379, 1345, 1138, 1081, 1030, 967, 758 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{12}H_{13}NO$ $(M+Na)^+$ 210.0889, found 288.0883. $[\alpha]^{23}_D = +60°$ (c=0.91, CH_2Cl_2; for product with 82% ee).

For run 2, the general procedure was followed with the silyl ketene imine **3.56** (0.180 g, 0.733 mmol), $(EtCO)_2O$ (0.122 mL, 0.953 mmol), and **(+)-1.16** (0.0252 g, 0.0367 mmol) in 2.7 mL of 1,2-dichloroethane which furnished 87% of the product (0.119 g, 0.634 mmol), which was shown by chiral GC to have 80% ee.

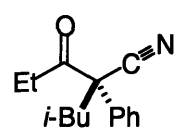


2-cyclopentyl-2-phenyl-2-propionylacetonitrile (3.67). The general procedure was followed, using silyl ketene imine **3.57** (0.174 g, 0.581 mmol), $(EtCO)_2O$ (0.0965 mL,

0.753 mmol), **(–)-1.16** (0.0199 g, 0.0290 mmol), and 2.1 mL of 1,2-dichloroethane to produce 55% (0.0771 g, 0.320 mmol) of a clear, colorless oil, which was shown by chiral HPLC (Daicel CHIRALCEL OJ-H, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 9.3 min (major), 10.3 min (minor)) to have 70% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.49 (m, 5H), 2.97 (app pent., 1H, J=8.0), 2.82 (dq, 1H, J=18.5, J=7.0), 2.56 (dq, 1H, J=18.5, J=7.0), 1.97 (m, 1H), 1.59-178 (m, 3H), 1.20-1.50 (m, 4H), 0.99 (app t, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 134.4, 129.5, 128.9, 126.6, 119.3, 65.2, 45.7, 33.6, 29.9, 28.8, 25.8, 25.1, 8.2. FTIR (neat) 3063, 3027, 2960, 2871, 2238, 1732, 1598, 1495, 1450, 1407, 1344, 1118, 1034, 752, 700 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{16}H_{19}NO$ $(M+Na)^+$ 264.1359, found 264.1355. $[\alpha]^{23}_D$ = +63° (c=0.28, CH_2Cl_2; for product with 70% ee).

For run 2, the general procedure was followed with the silyl ketene imine **3.57** (0.223 g, 0.744 mmol), $(EtCO)_2O$ (0.124 mL, 0.968 mmol), and **(+)-1.16** (0.0256 g, 0.0373 mmol) in 2.7 mL of 1,2-dichloroethane which furnished 50% of the product (0.0897 g, 0.371 mmol), which was shown by chiral HPLC to have 68% ee. The catalyst recovery for this substrate was shown to be 45%.

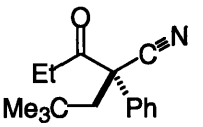


4-methyl-2-phenyl-2-propionylvaleronitrile (3.68). The general procedure was followed, using silyl ketene imine **3.58** (0.178 g, 0.620 mmol), $(EtCO)_2O$ (0.103 mL, 0.805 mmol), **(–)-1.16** (0.0213 g, 0.0310 mmol), and 2.3 mL of 1,2-dichloroethane to produce 94% (0.134 g, 0.584 mmol) of a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 120 °C, 0.7 mL/min, retention times of

enantiomers: 11.7 min (minor), 12.4 min (major)) to have 84% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.47 (m, 5H), 2.88 (dq, 1H, J=18.5, J=7.0), 2.54 (dq, 1H, J=18.5, J=7.5), 2.28 (dd, 1H, J=14.0, J=7.5), 2.04 (dd, 1H, J=14.0, J=5.5), 1.75 (app sept, 1H, J=6.5), 1.00 (app t, 3H, J=7.5), 0.95 (d, 3H, J=7.0), 0.82 (d, 3H, J=6.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 135.3, 130.0, 129.4, 127.0, 120.6, 59.3, 44.8, 33.3, 26.7, 24.3, 23.6, 8.9. FTIR (neat) 3064, 3033, 2960, 2939, 2874, 2238, 1733, 1599, 1495, 1450, 1370, 1109, 1032, 754, 699 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{19}NO$ $(M+Na)^+$ 252.1359, found 252.1361. $[\alpha]^{23}_D = +63°$ (c=0.27, CH_2Cl_2; for product with 84% ee).

For run 2, the general procedure was followed with the silyl ketene imine **3.58** (0.165 g, 0.574 mmol), $(EtCO)_2O$ (0.0958 mL, 0.747 mmol), and **(+)-1.16** (0.0197 g, 0.0287 mmol) in 2.1 mL of 1,2-dichloroethane which furnished 92% of the product (0.122 g, 0.532 mmol), which was shown by chiral GC to have 82% ee.



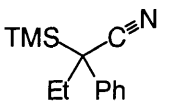
4,4-dimethyl-2-phenyl-2-propionylvaleronitrile (3.69). The general procedure was followed, using silyl ketene imine **3.59** (0.173 g, 0.574 mmol), $(EtCO)_2O$ (0.0958 mL, 0.748 mmol), **(–)-1.16** (0.0197 g, 0.0288 mmol), and 2.1 mL of 1,2-dichloroethane to produce 53% (0.0730 g, 0.300 mmol) of a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 120 °C, 0.7 mL/min, retention times of enantiomers: 14.2 min (minor), 14.9 min (major)) to have 82% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.38 (m, 3H), 2.91 (dq, 1H, J=18.5, J=7.0), 2.52 (dq, 1H, J=18.5, J=7.5), 2.49 (d, 1H, J=14.5), 2.04 (d, 1H, J=15.0), 0.99 (app t, 3H, J=7.0), 0.93 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 135.1, 129.5, 128.8,

126.7, 120.9, 56.8, 48.3, 32.6, 31.4, 30.8, 8.6. FTIR (neat) 3064, 2958, 2877, 2238, 1734, 1598, 1494, 1450, 1369, 1249, 1107, 1033, 761, 700 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{16}H_{21}NO$ $(M+Na)^+$ 266.1515, found 266.1513. $[\alpha]^{23}_D = +58°$ (c=0.28, CH_2Cl_2; for product with 82% ee).

For run 2, the general procedure was followed with the silyl ketene imine **3.59** (0.223 g, 0.739 mmol), $(EtCO)_2O$ (0.123 mL, 0.960 mmol), and **(+)-1.16** (0.0254 g, 0.0370 mmol) in 2.7 mL of 1,2-dichloroethane which furnished 50% of the product (0.0899 g, 0.369 mmol), which was shown by chiral GC to have 80% ee.

Evidence for Acylation via a Nitrile Anion



2-phenyl-2-trimethylsilylbutyronitrile [49538-90-1], **(3.80)**. The general procedure was followed, using *n*-BuLi (2.69 Min hexanes; 10.7 mL, 28.9 mmol), diisopropylamine (4.05 mL, 28.9 mmol, in 20 mL THF), nitrile (4.00 g, 27.5 mmol, in 10 mL THF), and Me_3SiCl (5.23 mL, 41.3 mmol). The product was isolated as a white crystalline solid (4.95 g, 83%), for which purification was not necessary.

^1H NMR (500 MHz, C_6D_6) δ 7.14 (m, 2H), 7.02 (m, 2H), 6.92 (m, 1H), 1.67 (m, 2H), 0.84 (app t, 3H, J=7.5), -0.12 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6) δ 136.5, 129.2, 127.0, 126.7, 122.9, 38.5, 25.5, 10.5, -3.7.

2-phenyl-2-propionylbutyronitrile (3.61). The general procedure was followed, using C-trimethylsilyl nitrile **3.80** (0.145 g, 0.667 mmol), $(EtCO)_2O$ (0.111 mL, 0.867 mmol), **(–)-1.16** (0.0229 g, 0.0336 mmol), and 2.4 mL of 1,2-dichloroethane to produce 65%

(0.0877 g, 0.436 mmol) of a clear, colorless oil, which was shown by chiral GC (Chiraldex G-TA, 20 m x 0.25 mm, 100 °C, 1.0 mL/min, retention times of enantiomers: 27.9 min (minor), 29.3 min (major)) to have 82% ee.

For run 2, the general procedure was followed with C-trimethylsilyl nitrile **3.80** (0.145 g, 0.667 mmol), $(EtCO)_2O$ (0.111 mL, 0.867 mmol), and **(+)-1.16** (0.0229 g, 0.0336 mmol) in 2.4 mL of 1,2-dichloroethane which furnished 64% of the product (0.0855 g, 0.425 mmol), which was shown by chiral GC to have 81% ee.

For characterization data, see previous section for product **3.61**.

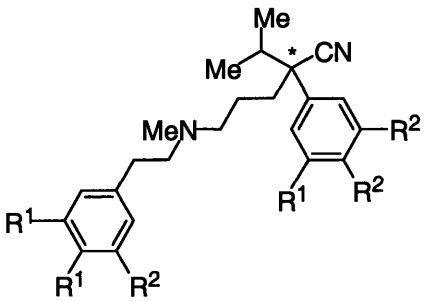
Chapter 4

Enantioselective Total Synthesis of Verapamil

Part A. Verapamil: Biological Importance and Synthetic Routes

Background

Verapamil, a member of a class of compounds possessing a biologically relevant 5-amino-2-alkyl-2-arylpentanenitrile substructure (4A.1), serves to treat a variety of cardiovascular diseases.[85] One of the major roles of verapamil is to act as a voltage-dependent calcium channel blocking agent. Of historical importance, verapamil was the first calcium channel-blocking drug approved in the United States.



R=Me; R^1=OMe; R^2=H: Verapamil **(4.11)**
R=Me; R^1, R^2 = OMe: Gallopamil **(4.12)**
R=Me; R^1, R^2 = H: Emopamil **(4.13)**
R=H; R^1, R^2 = H: Noremopamil **(4.14)**

(4A.1)

The presence of Ca^{2+} is linked to the intra- and extracellular concentrations of glutamate. In order to release glutamate from neurons, Ca^{2+} must enter presynaptic terminals that are regulated by voltage-dependent calcium channels. Glutamate release can also promote the entry of Ca^{2+} into neurons by activating postsynaptic glutamate receptors modulated by voltage-dependent calcium channels. Taken together, the release of glutatmate can lead to high concentrations of Ca^{2+} in the cell, warranting the need for agents, such as verapamil, that block these voltage-dependent calcium channels.

Although administered as a racemate, the (*S*)-enantiomer serves as a more potent calcium channel antagonist. In addition, (*S*)-verapamil has been shown to alleviate

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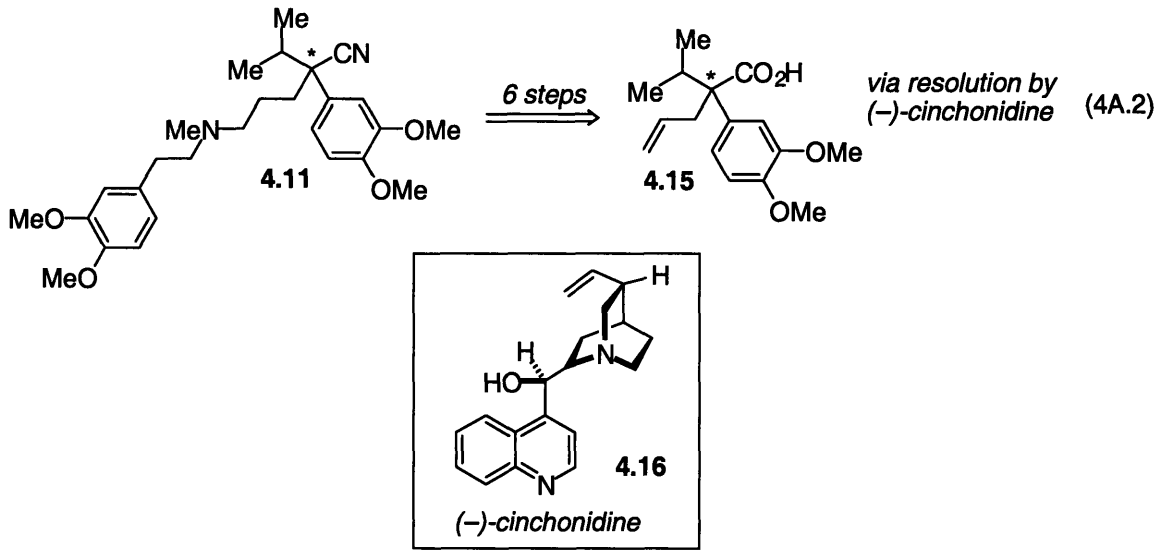
[85] For reviews of verapamil, see: (a) Prisant, L. M. *Heart Disease* **2001**, *3*, 55-62. (b) Brogden, R. N.; Benfield, P. *Drugs* **1996**, *51*, 792-819. For all other biological accounts of verapamil, see: (c) Suzuki, Y.; Yamamoto, N.; Iimura, Y.; Kawano, K.; Kimura, T.; Nagato, S.; Ito, K.; Komatsu, M.; Norimine, Y.;

cardiac arrythmia and hypertension, while the (*R*)-enantiomer is more effective for the treatment of angina. It also has been implicated that verapamil may be an agent in multidrug resistance associated with cancer chemotherapy.[86] Taking into account these significant differences in biological activity of verapamil's enantiomers, methods that address the enantioselective construction of the key quaternary stereocenter are of great importance. To date, synthetic routes toward the enantioselective synthesis of verapamil rely on the formation of diastereomeric intermediates or the generation of diastereomeric salts. To the best of our knowledge, no catalytic enantioselective methods exist for the preparation of this compound, probably due to the challenging quaternary stereocenter.[87]

In 1975, Ramuz reported the synthesis of verapamil from carboxylic acid intermediate **4.15,** which can be classically resolved with cinchonidine.[88] Elaboration of intermediate 4.15, however, required extra steps for functional groups manipulation.



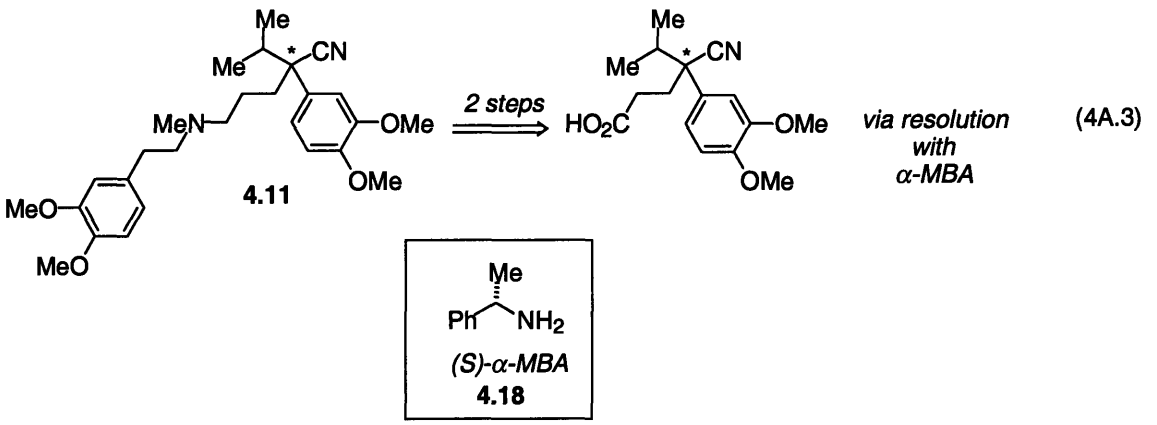
Kimura, M.; Teramoto, T.; Kaneda, Y.; Hamano, T.; Niidome, T.; Yonaga, M. *Bioorg. & Med. Chem. Lett.* **2003**, *13*, 919-922. (d) Karwatsky, J.; Lincoln, M. C.; Georges, E. *Biochem.* **2003**, *42*, 12163-12173.

[86] Robert, J.; Jarry, C. *J. Med. Chem.* **2003**, *46*, 4805-4817.

[87] (a) Mitani, K.; Sakurai, S.; Suzuki, T.; Morikawa, K.; Koshinaka, E.; Kato, H.; Ito, Y.; Fujita, T. *Chem. Pharm. Bull.* **1988**, *36*, 4103-4120. (b) Mitani, K.; Yoshida, T.; Sakurai, S.; Morikawa, K.; Iwanaga, Y.; Koshinaka, E.; Kato, H.; Ito, Y. *Chem. Pharm. Bull.* **1988**, *36*, 373-385.

[88] Ramuz, H. *Helv. Chim. Acta* **1975**, *58*, 2050-2060.

A more recent efficient route was developed by Bannister and coworkers, in which carboxylic acid **4.17** was subjected to classical resolution in the presence of α-MBA (**4.18**), (4A.3).[89] In contrast to the route by Ramuz, this synthesis required fewer chemical steps to transform the resolved carboxylic acid into enantioenriched verapamil.



In 1986, Nelson and coworkers published a stereoselective route to enantiopure verapamil from commercially available enantiopure diol **4.19** (4A.4).[90] Mesylate **4.20**, obtained from diol **4.19** in two steps, was lactonized by addition of first the dianion of 3,4-dimethoxyphenylacetic acid, and then cyclized under mildly acidic conditions to furnish **4.21** as a mixture of diastereomers. The quaternary center was constructed by diastereoselective alkylation to yield enantioenriched **4.22**. Subsequent functional group manipulation provided nitrile **4.23**, which was elaborated to *(S)*-(–)-verapamil (**4.11**) after hydroboration and homologation of the homoveratrylamine fragment. Although somewhat inefficient, this work represents the first stereoselective, high-yielding synthesis of verapamil.[91]

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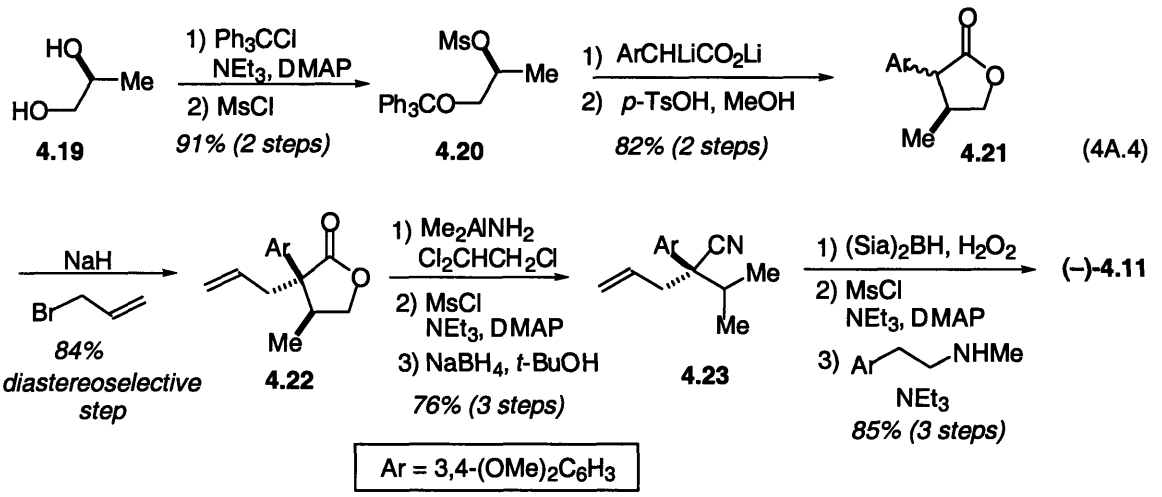
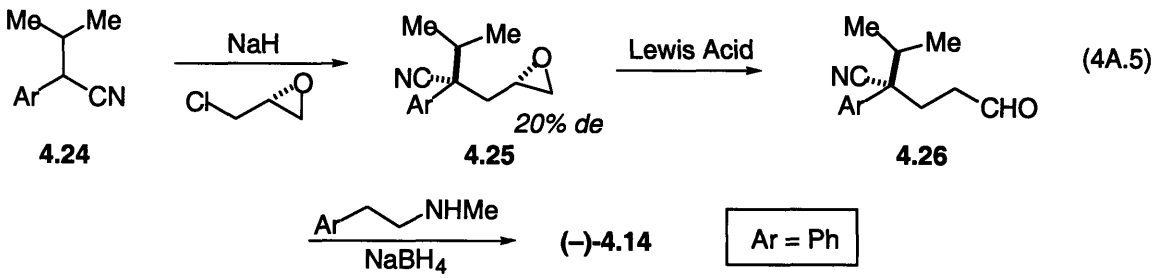
[89] Bannister, R. M.; Brookes, M. H.; Evans, G. R.; Katz, R. B.; Tyrrell, N. D. *Org. Process Res. Dev.* **2000**, *4*, 467-472.

[90] Theodore, L. J.; Nelson, W. L. *J. Org. Chem.* **1987**, *52*, 1309-1315.

[91] An overall yield of 45% is obtained of **4.11** starting from **4.19**.



An enantioselective route to Noremopamil (**4.14**) was developed by workers at Eli-Lilly (4A.5).[92] Alkylation of nitrile **4.24** with enantiopure epichlorohydrin furnished epoxide **4.25** with marginal diastereocontrol (60:40 d.r.). After chromatographic separation, the epoxide was opened with a Lewis acid,[93] leading to the formation of a transient carbocation that furnishes aldehyde **4.26** after a [1,2]-hydride shift. Reductive amination provided Noremopamil. Although the route is short and amenable to large-scale synthesis, the poor diastereoselectivity in the alkylation step makes this synthesis a less attractive route.



In light of the important biological role of verapamil, and considering the different pharmalogical activities imparted by each enantiomer, the stereoselective preparation of verapamil remains surprisingly unexplored. In this chapter, a total synthesis of verapamil will be presented, wherein the key quaternary stereocenter is

[92] Gilmore, J.; Prowse, W.; Steggles, D.; Urquhart, M.; Olkowski, J. *J. Chem. Soc., Perkin Trans. I*, **1996**, 2845-2850.

constructed via the catalytic, enantioselective C-acylation of a silyl ketene imine. Our findings represent the first catalytic enantioselective route to this molecule.

[93] The authors do not disclose the identity of the Lewis acid, presumably for patent-related issues.

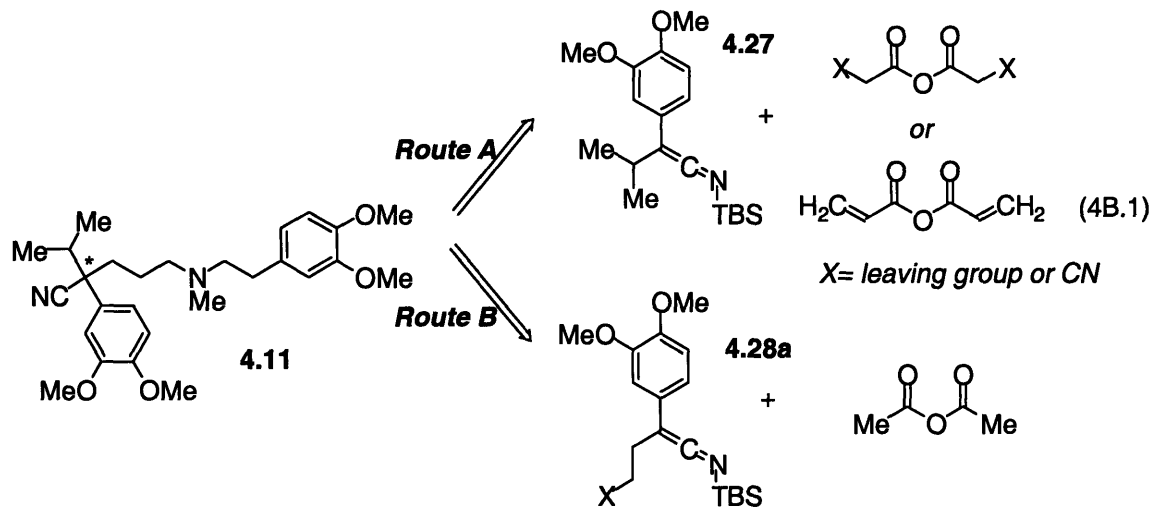
Part B. Results and Discussion

We were interested in pursuing the total synthesis of (*S*)-verapamil using our previously developed C-acylation processes. We were optimistic that the catalytic C-acylation of a silyl ketene imine would furnish the quaternary center with good enantiocontrol. Conversion of the acyl fragment into an aliphatic moiety presented a significant concern, however, given the presence of other functional groups.

The key retrosynthetic disconnection presented two options for the choice of acylating agent and silyl ketene imine (4B.1). Although both routes involved preparation of stable, isolable silyl ketene imines, we questioned which catalytic enantioselective reaction was more viable. Furthermore, strategic placement of appropriate functionalities, and their compatibility with subsequent transformations, was essential for proper construction of the target compound.

Analysis of retrosyntheses A and B presented several challenges (4B.1). In route A, an appropriately functionalized anhydride would be necessary to install the homoveratrylamine moiety. Possibilities for the anhydride partner included acrylic anhydride, cyanoacetic anhydride, or α-haloacetic anhydride. Unfortunately, acylation processes with planar-chiral heterocycles do not react efficiently with functionalized anhydrides. For example, the use of chloroacetic anhydride in the C-acylation of cyclic and acyclic silyl ketene acetals leads to poor results.[94]

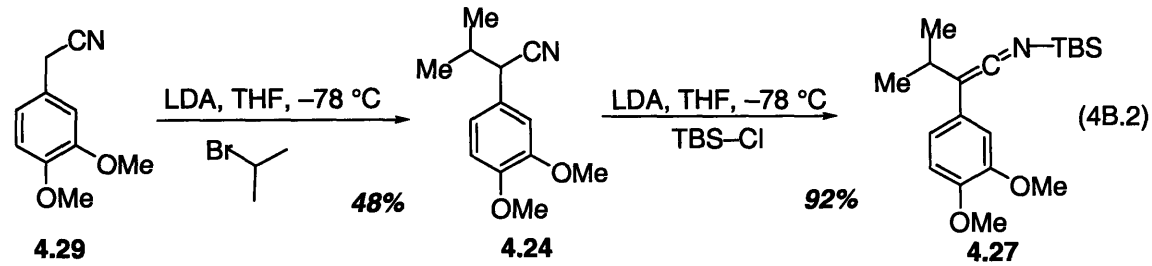
[94] See chapters 1 and 2 for more discussion on the use of chloroacetic anhydride.



In contrast, route B seemed to involve a more promising C-acylation step. We were confident that C-acylation of a silyl ketene imine with acetic anhydride would proceed smoothly, but such a route required a suitably functionalized silyl ketene imine for further elaboration. Althought we feared that a functionalized substrate might interfere with the stereoselection in the catalytic step, the route appeared promising overall. Ultimately, both routes were pursued in order to optimize the quaternary C–C bond forming process.

Route A

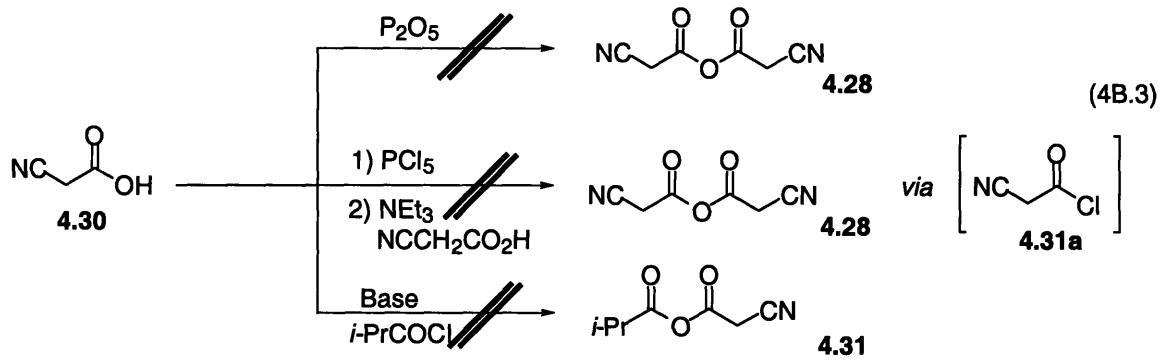
Commercially available 3,4-dimethoxyphenylacetonitrile (**4.29**) was alkylated to furnish intermediate **4.24**,[95] which was efficiently converted to silyl ketene imine **4.27**, (4B.2). The synthesis of cyanoacetic anhydride (**4.28**), however, was problematic.[96]



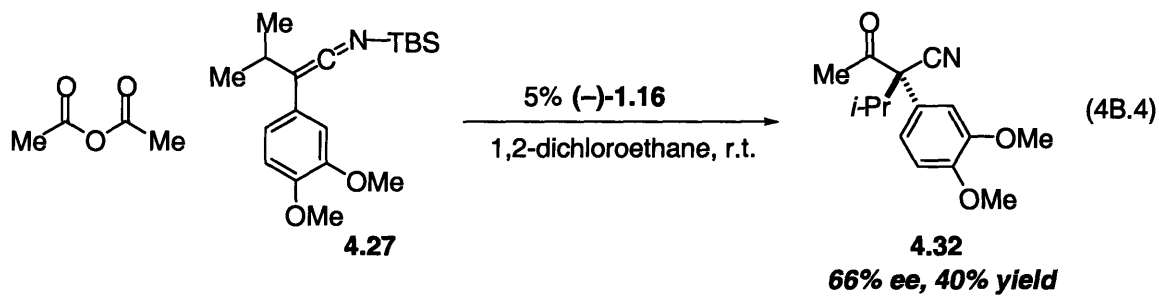
[95] Watt, D. S. *Tetrahedron Lett.* **1974**, *9*, 707-710.

[96] Preparation of this reagent was not facile, as its synthesis was not explicitly reported in the literature.

Attempts to convert cyanoacetic acid to cyanoacetic anhydride via dehydrative methods, or via generation of transient acid chloride intermediate **4.31a**, led to intractable reaction mixtures, presumably due to competing decomposition or polymerization pathways (4B.3).

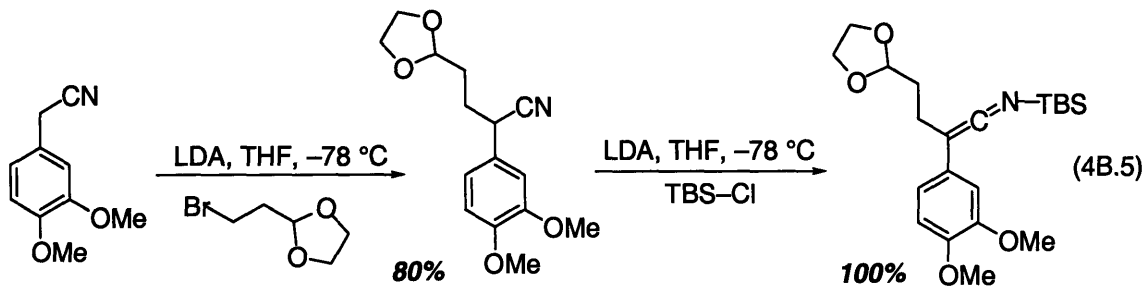


Attempts to generate mixed anhydride **4.31** also led to an inseparable mixture of products. Although the catalytic C-acylation of silyl ketene imine **4.27** occurred with a promising 66% ee, we still remained uncertain whether our functionalized anhydrides would behave similarly (4B.4). Accordingly, we focused our further efforts on route B.



Route B

Retrosynthetic route B required the preparation of a silyl ketene imine containing masked functionality to allow for convergent late-stage incorporation of the amino side chain. Our strategy involved incorporation of a pendant acetal as the alkyl moiety of the silyl ketene imine. Acetal removal in the penultimate step would furnish the primary aldehyde, allowing installation of the homoveratrylamine fragment.



4.29 4.33 4.34 (4B.5)

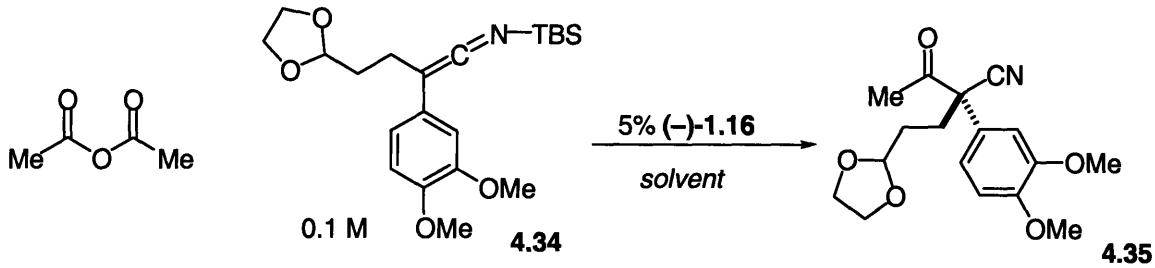
Accordingly, synthesis of nitrile **4.33** was achieved by alkylation of **4.29** with 2-(2-bromoethyl)-1,3-dioxolane in 80% yield. Conversion of **4.33** to silyl ketene imine **4.34** proceeded in quantitative yield (4B.5). Under the optimized conditions developed for the catalytic enantioselective C-acylations of silyl ketene imines, we obtained product **4.35** in 70% ee with moderate conversion.[97] In light of these promising results, we decided to abandon route A, which was still presenting us with difficulty, and fully engaged in the development of a catalytic enantioselective synthesis of **4.11** highlighting route B.

Due to the unique substitution pattern of silyl ketene imine **4.34**, we speculated that further optimization of the reaction conditions might be beneficial. For instance, the abnormally high degree of catalyst decomposition observed (~20%) could produce achiral catalyst-derived fragments that might lead to irreproducible results. Fortunately, catalyst decomposition was suppressed under more dilute reaction conditions (~100 mM).

Exhaustive examination of various solvents for the C-acylation of **4.34** revealed that hexafluorobenzene led to a significant increase in enantioselectivity (81% ee, Table 4B.6, Entry 8). The general efficacy of hexafluorobenzene as a reaction solvent for this process was evident when we revisited

[97] This process is described in chapter 3.

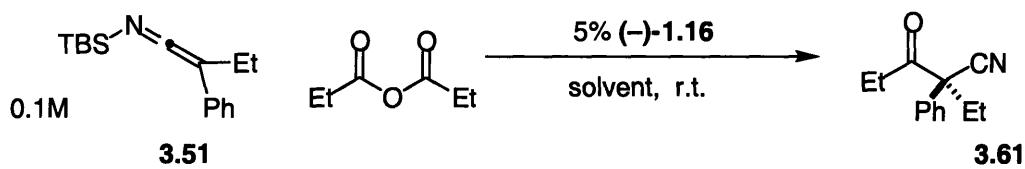
Table 4B.6. Solvent Screen for Verapamil Substrate 4.34.



entry	solvent	% ee
1	Et_2O	42
2	CCl_4	44
3	*n*-BuCl	57
4	toluene	57
5	1-chloro-3-fluorobenzene	60
6	$CHCl_3$	61
7	1,2-dichloroethane	70
8	**C_6F_6**	**81**

the C-acylation of silyl ketene imine **3.51**. A 90% ee was observed when hexafluorobenzene was employed as the reaction solvent instead of 1,2-dichloroethane.[98]

Table 4B.7. Comparison of Hexafluorobenzene and 1,2-dichloroethane.

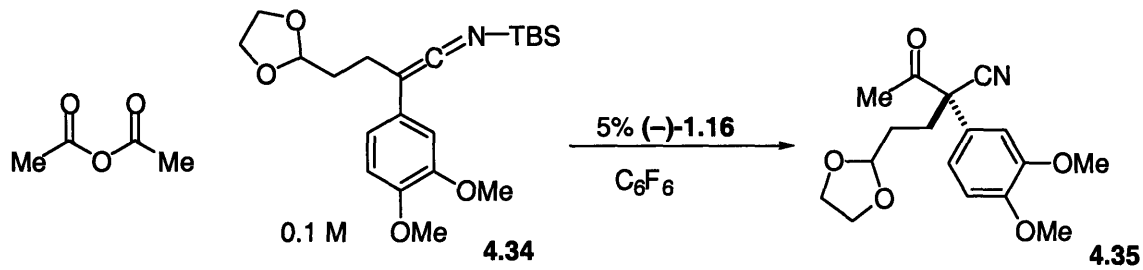


solvent	ee	yield
1,2-dichloroethane	81	85
C_6F_6	**90**	**57**

A survey of concentration effects determined that a 100 mM concentration was optimal for this reaction (Table 4B.8, Entry 4). Variation of reaction temperature had no beneficial effect, but we found it

[98] Hexafluorobenzene is significantly more expensive than 1,2-dichloroethane, making it a less attractive choice for general use.

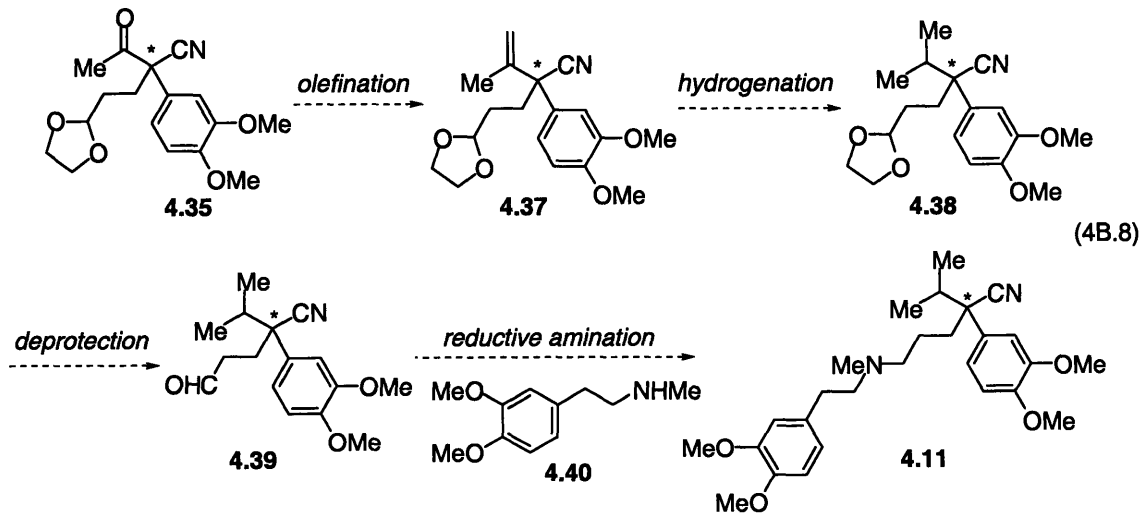
Table 4B.8. Enantioselectivity as a Function of Substrate Concentration.



entry	[4.34] (mM)	% ee
1	10	NR
2	20	80
3	50	81
4	**100**	**81**
5	150	71

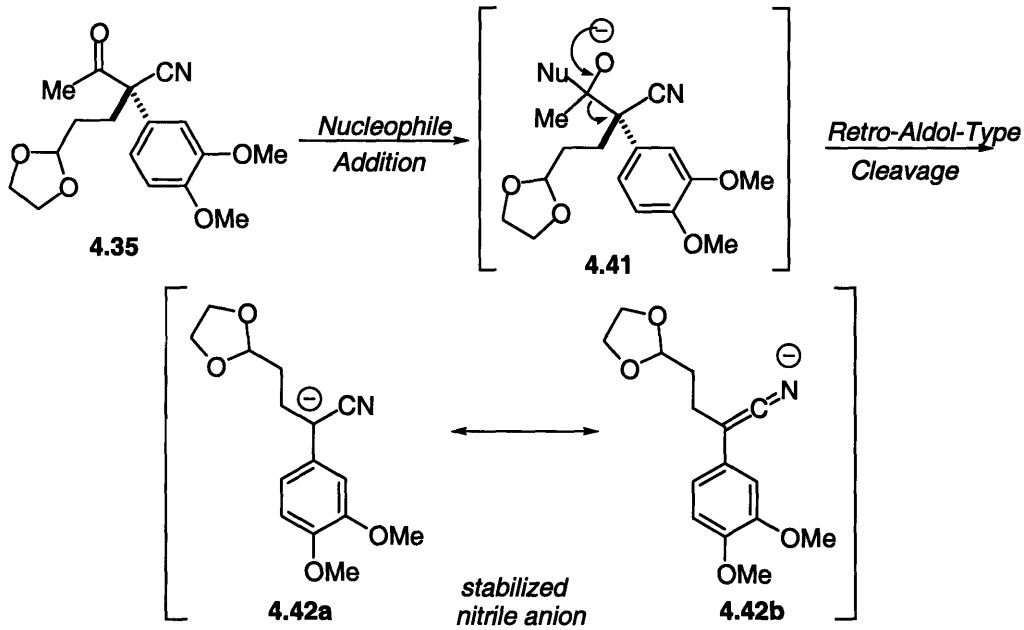
necessary to employ a 72-hour reaction time to achieve a respectable yield.

After determining the optimal reaction conditions for the asymmetric acylation of substrate **4.34**, we focused our efforts on the elaboration of acetyl intermediate **4.35**. Conversion of the acetyl group to an isopropyl group, followed by deprotection of the acetal and subsequent reductive amination with homoveratrylamine, would afford target **4.11**, as illustrated in 4B.8.



We envisioned the synthesis of isopropyl substrate **4.38** via an olefination-hydrogenation sequence. Two significant complications were anticipated in this transformation. The first concerned the steric demand of a quaternary stereocenter

adjacent to the reacting carbonyl. Equally daunting was the propensity of **4.35** towards retro-aldol-type cleavage upon generation of a tetrahedral intermediate (4B.9a). Facilitated by the veratrole moiety, as well as the nitrile group, as illustrated by resonance structures **4.42a** and **4.42b**, this undesired pathway could be detrimental to any olefination attempt, as a tetrahedral intermediate is formed in most of these processes.

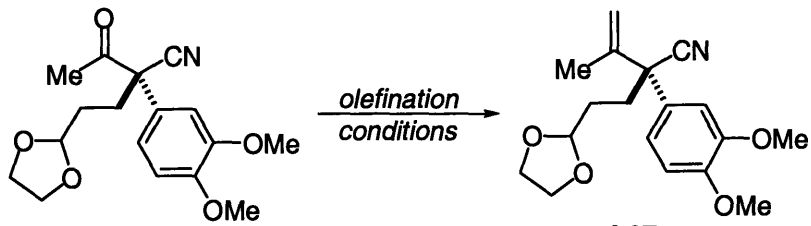


(4B.9a)

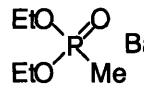
Several olefination procedures were attempted with various reagents.[99] Our results, summarized in Table 4B.9, indicated that olefination is disfavored under

[99] For hindered or retro-aldol-prone ketones,Wittig reagents have shown to be effective with DMSO additives or use of a salt-free ylide. For accounts, see: (a) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1962**, *28*, 1128-1129. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 866-867. (c) Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1978**, *43*, 1031-1040. (d) Mander, L. N.; Turner, J. V. *Tetrahedron Lett.* **1981**, *22*, 4149-4152. (e) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.;

Table 4B.9. Summary of Olefination Conditions.



4.35 **4.37**

entry	olefination conditions	result
1	$Ph_3P{=}CH_2$	*retro-aldol: major*
2	Tebbe Reagent	*retro-aldol: exclusive*
3	$TMSCH_2MgCl$	*retro-aldol: exclusive*
4		*retro-aldol: major*

standard conditions. Accordingly, we chose to access olefin **4.37** via alcohol dehydration. Surprisingly, the addition of MeMgBr to afford alcohol **4.36** proceeded with no retro-aldolization of the resulting tetrahedral intermediate.[100] In the development of this transformation, we observed that three equivalents of MeMgBr were necessary to force the reaction to go to completion, as well as reduced temperature (0 °C) during the addition and quenching steps.[101]

With the desired tertiary alcohol in hand, we examined various dehydration methods. Given that substrate **4.36** possessed an electron-rich aromatic group two carbons away from the newly established tertiary alcohol carbon, as well as an acid-labile acetal, we avoided use of strong Lewis or Brønsted acids that might effect undesired [1,2]-aryl migration and acetal deprotection. Upon treatment of the tertiary alcohol with

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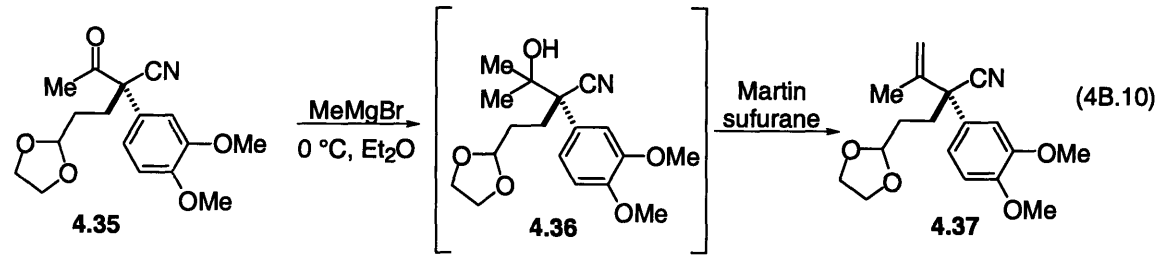
Keck, G.; Gras, J. *J. Am. Chem. Soc.* **1978**, *100*, 8031-8034. (f) Caine, D.; Deutsch, H. *J. Am. Chem. Soc.* **1978**, *100*, 8031-8032. (g) Caine, D.; Crews, E.; Salvino, J. M. *Tetrahedron Lett.* **1983**, *24*, 2083-2086.

[100] MeLi also afforded the desired alcohol **4.36**, but with significant amounts of retro-aldol product.

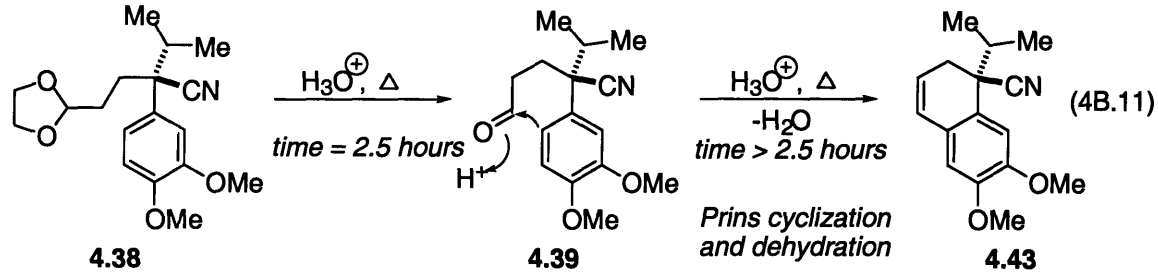
[101] The tertiary alcohol was used without purification due to its instability during purification attempts.

Martin's sulfurane ($[Ph(CF_3)_2CO]SPh_2$), a very mild dehydrating agent, we observed rapid formation of the desired olefin **4.37** in 63% overall yield for the two-step sequence (4B.10).



(4B.10)

Hydrogenation of olefin **4.35** under standard conditions (Pd/C, H_2) afforded saturated intermediate **4.38** in almost quantitative yield. With the left-hand portion of verapamil complete, we sought deprotection routes for the existing acetal moiety. Treatment of acetal **4.38** with aqueous acid effected not only deprotection, but also subsequent intramolecular Prins cyclization and dehydration to furnish **4.43** (4B.11). In order to suppress this undesired cyclization process, we surveyed various acids and reaction times. Strong acids promoted the undesired cyclization, facilitating nucleophilic attack by the electron-rich arene.



(4B.11)

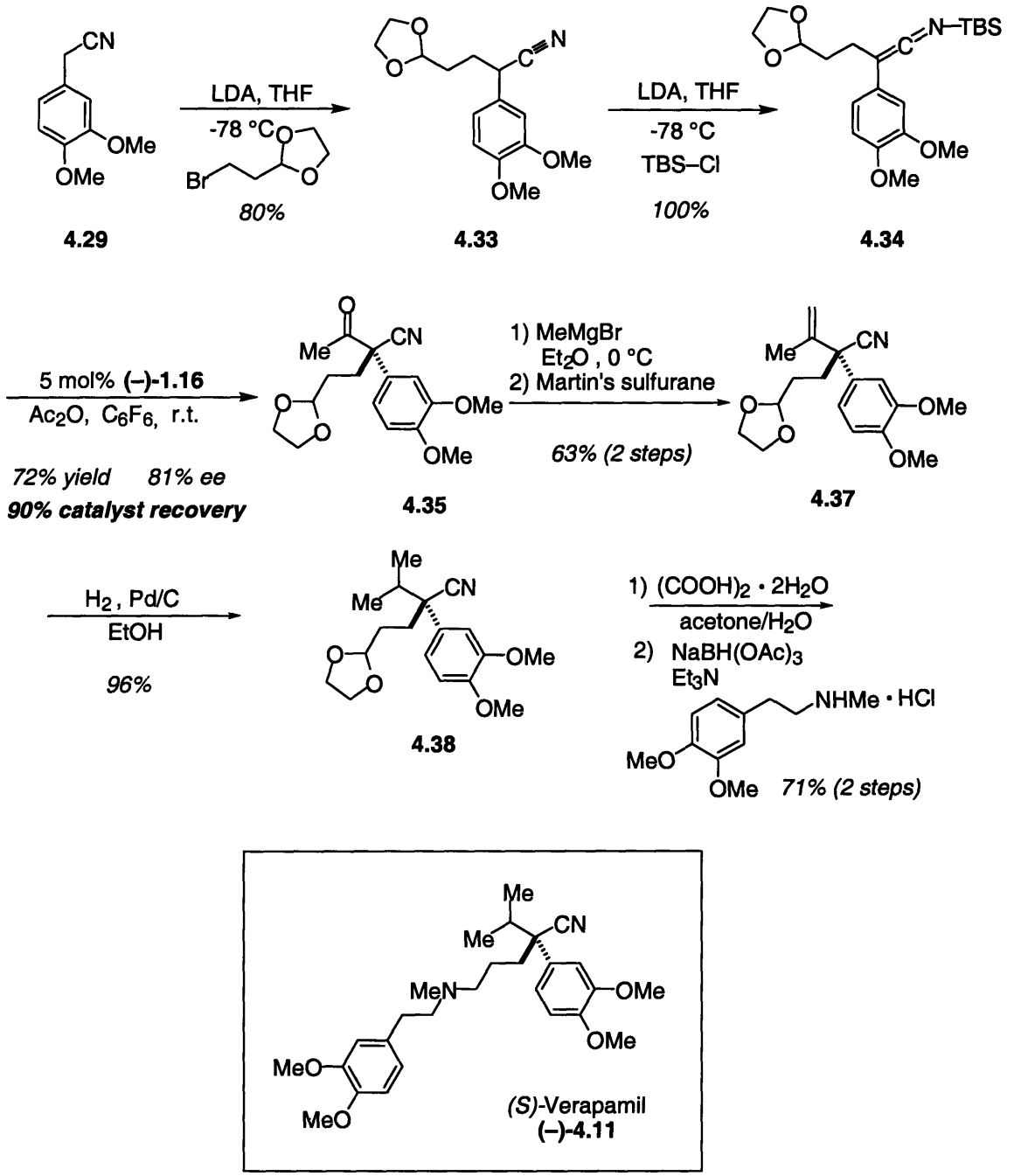
The use of oxalic acid, however, did not quickly promote the cyclization step, althought careful monitoring of reaction time was still necessary. A maximum reaction time of 2.5 hours was employed to quantitatively obtain aldehyde **4.39** without byproduct **4.43**.

Due to the sensitivity of intermediate **4.39**, we immediately subjected this material to standard reductive amination conditions with homoveratrylamine

hydrochloride, triethylamine, and sodium triacetoxyborohydride.[102] Although many borohydride-mediated aminations lead to formation of undesired byproducts (e.g., aldehyde reduction), we obtained verapamil as the exclusive product in the reductive amination of aldehyde **4.39** with amine **4.46**. A 62% overall yield was obtained for the deprotection/reductive amination sequence, completing the total synthesis summarized in scheme 4B.12 with an overall yield of 25% over 8 steps from commercially available **4.29**.

[102] Based on the procedure developed by: Abdel-Magid, A.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849-3862.

Scheme 4B.11. Enantioselective Total Synthesis of (*S*)-Verapamil, (–)-4.11.



Conclusions

We report the first catalytic enantioselective total synthesis of verapamil, highlighting the asymmetric C-acylation process developed for silyl ketene imines. Starting from commercially available 3,4-dimethoxyphenyacetonitrile, **4.29**, we selected a pendant acetal as our functional group handle for the remaining steps of the synthesis. Upon accessing the appropriate silyl ketene imine, we engaged in finding optimal conditions for this asymmetric transformation. Our most prominent change was use of hexafluorobenzene as the reaction solvent, which furnished the desired C-acylation product **4.35** in 81% ee and 72% yield. More dilute reaction conditions were also found to benefit this process by suppressing of catalyst decomposition.

We pursued direct carbonyl olefinations of **4.35** with little to no success in obtaining alkene **4.37**. However, addition of MeMgBr, followed by Martin's sulfurane, allowed us to circumvent this problematic process, and access olefin **4.37** in 63% yield from **4.35**. Hydrogenation of **4.37**, followed by careful deprotection of the acetal and reductive amination with **4.46,** furnished (*S*)-Verapamil in 25% yield from commercially available **4.29**.

Experimental

General

THF, CH_2Cl_2, and Et_2O were purified by passage through a neutral alumina column. Hexafluorobenzene (Avocado) and 1,2-dichloroethane (J.T. Baker) were distilled over CaH_2. Ac_2O and $(EtCO)_2O$ were distilled from phosphorus pentoxide. *n*-BuLi (Alfa Aesar) was titrated with diphenylacetic acid (Aldrich) prior to each use. Benzene-d_6 (Cambridge Isotope Laboratories) was distilled from CaH_2.

2-Phenylbutyronitrile (Aldrich), benzyl cyanide (Aldrich), 3,4-dimethoxyphenylacetonitrile, bromoethane (Alfa Aesar), iodoethane (Alfa Aesar), 2-bromopropane (Avocado), 2-(2-bromoethyl)-1,3-dioxolane (Aldrich), diisopropylamine (Aldrich), methylmagnesium bromide (Aldrich), Martin's sulfurane (Aldrich), palladium on Carbon/10% w.t. (Aldrich), sodium triacetoxyborohydride (Aldrich), *N*-methylhomoveratrylamine hydrochloride (Aldrich), TBS–Cl (Pfizer), Et_2O (Mallinckrodt), pentane (Burdick & Jackson), magnesium sulfate (Fisher), ethanol (Pharmco), oxalic acid dihydrate (Aldrich), NEt_3 (EM Science), acetone (Aldrich), chloroform (Mallinckrodt), and methanol (Fisher) were used as received. Catalysts **(–)-1.16** were prepared as previously reported.[103]

Analytical thin layer chromatography was performed making use of EM Reagents 0.25 mm silica gel 60 plates, and visualization was achieved with ultraviolet light and/or ceric ammonium nitrate or potassium permanganate stains. Flash chromatography was performed making use of Sorbent Technologies silica gel 60 (230-400 mesh).

Optical rotations were acquired with a Jasco-1010 polarimeter. Infrared spectra were obtained on a Perkin-Elmer Series 2000 FT-IR spectrophotometer. Melting points

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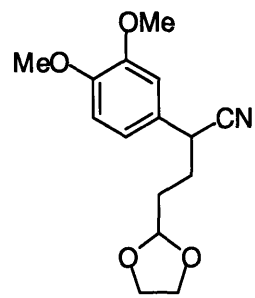
[103] Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091-5092.

(uncorrected) were acquired on a Thomas Hoover Unimelt capillary melting point apparatus.

^{1}H and ^{13}C nuclear magnetic resonance spectra were obtained on a Varian Unity 300, Varian Mercury 300, or Varian VXR 500 spectrometer at room temperature. ^{1}H NMR data are reported using the following notation: chemical shift in parts per million downfield from tetramethylsilane (δ scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, and app t = apparent triplet), integration, and coupling constant (Hz). ^{13}C chemical shifts are recorded in ppm downfield with respect to tetramethylsilane (δ scale), and were acquired with full proton decoupling.

All experiments were conducted under an argon or nitrogen atmosphere in oven-dried glassware with magnetic stirring, unless otherwise specified.

Preparation of Verapamil and Related Intermediates

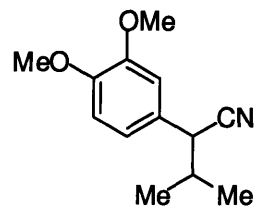


2-(3,4-dimethoxyphenyl)-4-(1,3-dioxolan-2-yl)butyronitrile (4.33). A solution of *n*-BuLi (2.57 M in hexanes; 3.30 mL, 8.47 mmol) was added via syringe to a –78 °C solution of diisopropylamine (1.19 mL, 8.47 mmol) in THF (30 mL). The mixture was stirred at –78 °C for 30 minutes, and then a solution of **4.29** (1.50 g, 8.47 mmol) in THF (20 mL) was added via cannula. The solution was stirred at -78 °C for 60 minutes after which neat 2-(2-bromoethyl)-1,3-dioxolane (1.60 g, 8.47 mmol) was then added via syringe. The resulting solution was warmed to room temperature and stirred for 12

hours. The reaction mixture was quenched by addition of water (25 mL), extracted with Et_2O (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 75 mL), saturated NaCl (2 x 75 mL), dried ($MgSO_4$), and concentrated to a yellow oil. Purification by flash chromatography (40% Et_2O/60% pentane → 70% Et_2O/30% pentane → 100% Et_2O) provided **4.33** as a bright green oil (1.90 g, 81%).

^1H NMR (500 MHz, $CDCl_3$) δ 6.63 (dd, 1H, J=8.0, J=2.0), 6.59 (d, 1H, J=2.0), 6.41 (d, 1H, J=8.5), 4.63 (app t, 1H, J=4.5), 3.26-3.43 (m, 11H), 1.68-1.95 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 148.8, 128.0, 120.9, 119.7, 111.4, 110.2, 103.4, 65.0, 64.9, 55.9 (isochronous with another peak), 36.5, 30.8, 29.9. FTIR (thin film) 2960, 2889, 2839, 2239, 1594, 1519, 1464, 1420, 1343, 1263, 1241, 1144, 1027, 945 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{19}NO_4$ $(M+Na)^+$ 300.1206, found 300.1202.

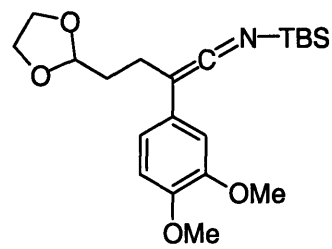
For run 2, the same procedure as above was using *n*-BuLi (2.65 M in hexanes; 5.32 mL, 14.1 mmol), diisopropylamine (1.98 mL, 14.1 mmol, in 30 mL THF), nitrile (2.50 g, 14.1 mmol, in 20 mL THF), and 2-(2-bromoethyl)-1,3-dioxolane (2.56 g, 14.1 mmol). Product **4.33** was isolated as bright green oil (3.12 g, 79%).



2-(3,4-dimethoxyphenyl)-3-methylbutyronitrile [20850-49-1] **(4.24)**. A solution of *n*-BuLi (2.69 M in hexanes; 10.5 mL, 28.2 mmol) was added via syringe to a –78 °C solution of diisopropylamine (3.95 mL, 28.2 mmol) in THF (30 mL). The mixture was stirred at –78 °C for 5 minutes, and then a solution of **4.29** (5.00 g, 28.2 mmol) in THF (15 mL) was added via cannula. After 45 minutes, a solution of the nitrile anion was added via cannula to a solution of 2-bromopropane (2.77 mL, 29.6 mmol) in THF (10

mL) at -78 °C . The resulting solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by addition of 1N HCl (10 mL), extracted with Et_2O (3 x 100 mL), washed with saturated $NaHCO_3$ (2 x 50 mL), saturated NaCl (2 x 50 mL), dried (Na_2SO_4), and concentrated to an orange oil. Purification by flash chromatography (15% Et_2O/85% hexanes → 25% Et_2O/75% hexanes) provided **4.24** as a clear, colorless oil (2.97 g, 48%). Several early fractions enriched in the product were discarded due to a close running impurity.

^1H NMR (500 MHz, C_6D_6) δ 6.68 (dd, 1H, J=8.5, J=2.5), 6.60 (d, 1H, J=2.5), 6.50 (d, 1H, J=8.5), 3.38 (s, 3H), 3.37 (s, 3H), 3.09 (d, 1H, J=6.5), 1.73 (m, 1H), 0.89 (d, 3H, J=6.5), 0.78 (d, 3H, J=7.0). ^{13}C NMR (125 MHz, C_6D_6) δ 150.6, 150.1, 120.7, 120.4, 112.4, 112.1, 55.9 (isochronous with another peak), 45.0, 34.2, 20.9, 19.3.

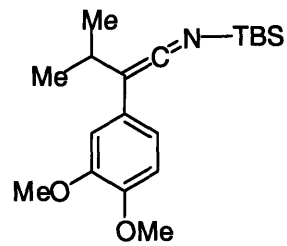


1-(1,1-dimethylethyl)-1,1-dimethyl-N-(4-(1,3-dioxolan-2-yl)-2-(3,4-dimethoxyphenyl)-1-butenylidene)silanamine (4.34). A solution of *n*-BuLi (2.61 M in hexanes; 1.74 mL, 4.54 mmol) was added via syringe to a –78 °C solution of diisopropylamine (0.636 mL, 4.54 mmol) in THF (20 mL). The mixture was stirred at –78 °C for 15 minutes, and then a solution of **4.33** in THF (10 mL) was added via cannula. The mixture was stirred at –78 °C for 5 minutes, and then TBS–Cl (0.782g, 5.19 mmol) in THF (10 mL) was added. The reaction mixture was warmed to room temperature and stirred for 1.5 hours. The THF was then removed, and the residue was taken up in pentane and filtered inside a glove box. The solvent was removed, and the

bright-orange oil (1.76 g, 100%) was used in the acylation reaction without further purification.

^{1}H NMR (500 MHz, C_6D_6) δ 6.81 (m, 2H), 6.70 (d, 1H, J=8.5), 4.97 (app t, 1H, J=5.0), 3.49-3.61 (m, 8H), 3.37 (m, 2H), 2.70 (m, 2H), 2.16 (m, 2H), 0.92 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 188.9, 151.1, 146.7, 131.1, 115.7, 114.2, 108.7, 104.6, 65.3, 56.4, 55.9, 54.0, 34.0, 26.0, 21.5, 18.1, -4.4. FTIR (neat) 2955, 2887, 2859, 2035, 1604, 1582, 1518, 1464, 1415, 1363, 1261, 1146, 1026, 994, 943, 842 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{21}H_{33}NO_4Si$ $(M)^+$ 391.2173, found 391.2178.

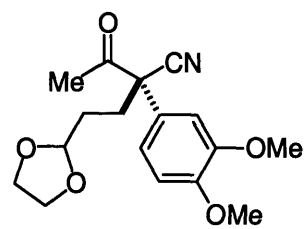
For run 2, the same procedure as above was followed, using *n*-BuLi (2.62 M in hexanes; 1.90 mL, 5.00 mmol), diisopropylamine (0.701 mL, 5.00 mmol, in 15 mL THF), 2-(3,4-dimethoxyphenyl)-4-(1,3-dioxolan-2-yl)butyronitrile (1.32 g, 4.76 mmol, in 10 mL THF), and *t*-BuMe$_2$SiCl (0.861 g, 5.71 mmol, in 10 mL THF). Product **4.34** was isolated as a bright orange residue (1.93 g, 100%), for which purification was not necessary



1-(1,1-dimethylethyl)-1,1-dimethyl-N-(4-(1,3-dioxolan-2-yl)-2-(3,4-dimethoxyphenyl)-1-butenylidene)silanamine (4.27). A solution of *n*-BuLi (2.76 M in hexanes; 3.47 mL, 9.58 mmol) was added via syringe to a –78 °C solution of diisopropylamine (1.34 mL, 9.58 mmol) in THF (20 mL) . The mixture was stirred at –78 °C for 15 minutes, and then a solution **4.24** (2.00 g, 9.12 mmol) in THF (10 mL) was added via cannula. The mixture was stirred at –78 °C for 20 minutes, and then TBS–Cl

(1.64 g, 10.9 mmol) in THF (10 mL) was added. The resulting yellow solution was warmed to room temperature and stirred for 1.5 hours. The THF was then removed, and the residue was taken up in pentane and filtered inside a glove box. The solvent was removed, and the bright yellow oil **4.27** was used in the acylation reaction without further purification (2.81 g, 92%).

^{1}H NMR (500 MHz, C_6D_6) δ 6.83 (d, 1H, J=2.0), 6.77 (m, 2H), 3.55 (s, 3H), 3.50 (s, 3H), 2.75 (app sept, 1H, J=7.0), 1.27 (d, 6H, J=7.0), 0.95 (s, 9H), 0.15 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 189.2, 151.2, 146.8, 131.0, 128.7, 116.2, 114.2, 109.5, 62.7, 56.4, 55.9, 26.0, 25.6, 23.3, 18.1, -4.4. FTIR (neat) 2956, 2932, 2859, 2027, 1823, 1515, 1464, 1240, 1211, 1142, 1029, 809, 718 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{19}H_{31}NO_2Si$ $(M+H)^+$ 334.2197, found 334.2183.

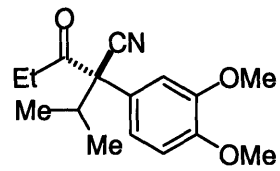


(*S*)-2-acetyl-2-(3,4-dimethoxyphenyl)-4-(1,3-dioxolan-2-yl)butyronitrile [403697-33-6], (**4.35**). A solution of catalyst **(–)-1.16** (0.0263 g, 0.0383 mmol) in hexafluorobenzene (7.6 mL) was added to a 20-mL vial containing **4.34** (0.300 g, 0.766 mmol). The resulting solution was stirred for 5 minutes at room temperature, after which Ac_2O (0.0940 mL, 0.999 mmol) was added. The vial was capped and removed from the glove box, and the reaction mixture was stirred for 72 hours at room temperature. Then, approximately two-thirds of the solvent was removed, and the product was purified directly by flash chromatography (40% Et_2O/60% hexanes → 100% Et_2O) affording 74% of **4.35** as a clear, colorless residue (0.180 g, 0.564 mmol). The product was shown by chiral HPLC (Daicel CHIRALCEL OD-H, 4.6 mm x 25 cm, hexane/isopropanol 90:10,

0.8 mL/min, retention times of enantiomers: 28.8 min (minor), 30.5 min (major)) to have 81% ee.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (dd, 1H, J=8.5, J=2.5), 6.89 (d, 1H, J=8.5), 6.84 (d, 1H, J=2.5), 4.89 (app t, 1H, J=4.5), 3.82-3.97 (m, 10H), 2.36 (dt, 1H, J=14.0, J=5.0), 2.28 (s, 3H), 2.20 (dt, 1H, J=14.0, J=4.5), 1.83 (m, 1H), 1.58 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 149.8, 149.6, 125.7, 119.4, 119.1, 111.7, 109.0, 103.4, 65.1 (isochronous with another peak), 59.1, 56.2, 56.1, 30.1, 29.7, 26.7. FTIR (thin film) 2918, 2239, 1725, 1591, 1517, 1464, 1414, 1358, 1261, 1244, 1176, 1149, 1024, 944 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{17}H_{21}NO_5$ $(M+Na)^+$ 342.1312, found 342.1303. $[\alpha]^{23}_D$ = +44° (c=0.19, CH_2Cl_2; for product with 81% ee).

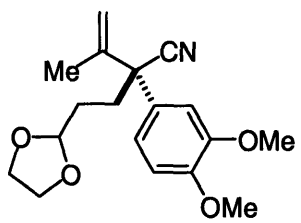
For run 2, the same procedure as above was followed with the silyl ketene imine (0.200 g, 0.511 mmol), Ac_2O (0.0626 mL, 0.664 mmol), and **(+)-1.16** (0.0176 g, 0.0256 mmol) in 5.1 mL of hexafluorobenzne which furnished 70% of product **4.35** (0.114 g, 0.357 mmol), which was shown by chiral HPLC to have 81% ee. The catalyst was recycled in 90% yield.



(*S*)-2-acetyl-2-(3,4-dimethoxyphenyl)-3-methylbutyronitrile (4.32). A solution of catalyst **(–)-1.16** (2.1 mg, 0.030 mmol) in 1,2-dichoroethane (0.24 mL) was added to a 4-mL vial containing the silyl ketene imine (20 mg, 0.060 mmol). The resulting solution was stirred for 5 minutes at room temperature, after which $(EtCO)_2O$ (0.010 mL, 0.078 mmol) was added. The vial was capped and removed from the glove box, and the reaction mixture was stirred for 24 hours at room temperature. Approximately two-thirds

of the solvent was removed and the product was then purified directly by flash chromatography (18% Et_2O/82% hexanes → 25% Et_2O/75 % hexanes) affording 40% of a clear, colorless residue (5.6 mg, 0.024 mmol). Product **4.32** was shown by chiral HPLC (Daicel CHIRALCEL OJ, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 0.8 mL/min, retention times of enantiomers: 6.9 min (minor), 7.8 min (major)) to have 66% ee.

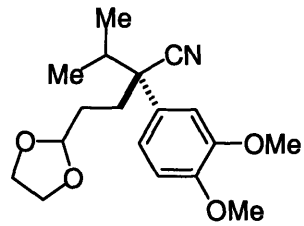
^{1}H NMR (500 MHz, C_6D_6) δ 7.08 (dd, 1H, J=8.4, J=2.4), 6.98 (d, 1H, J=2.4), 6.37 (d, 1H, J=8.7), 3.31 (s, 3H), 3.23 (s, 3H), 2.75 (m, 1H), 2.50-2.63 (dq, 1H, J=18.6, J=7.2), 2.33-2.47 (dq, 1H, J=18.6, J=7.2), 1.08 (d, 3H, J=6.3), 0.74 (app t, 3H, J=7.2), 0.69 (d, 3H, J=6.6).



(*S*)-2-(3,4-dimethoxyphenyl)-4-(1,3-dioxolan-2-yl)-2-(2-propenyl)butyronitrile (4.37). A solution of MeMgBr (3.00 M in Et_2O; 0.527 mL, 1.58 mmol) was added via syringe to a 0 °C solution of the **4.35** (0.168 g, 0.527 mmol) in Et_2O (6 mL). The reaction mixture was stirred at 0 °C for 12 hours, and then it was quenched by the addition of saturated NH_4Cl at 0 °C, extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$), and concentrated. The residue was taken up in CH_2Cl_2 (5 mL), and the Martin sulfurane, $[Ph(CF_3)_2CO]_2SPh_2$, (0.427 g, 0.632 mmol) was added. The reaction was stirred at room temperature for 12 hours, after which about half of the solvent was removed. This solution was directly purified by flash chromatography (45% Et_2O/55% hexanes → 80% Et_2O/20% hexanes), which provided a 66% yield of a clear, colorless oil (0.110 g, 0.347 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (dd, 1H, J=8.5, J=2.5), 6.87 (d, 1H, J=2.5), 6.84 (d, 1H, J=8.5), 5.36 (s, 1H), 5.13 (d, 1H, J=1.0) 4.92 (app t, 1H, J=4.5), 3.96 (m, 2H), 3.87 (m, 8H), 2.15-2.28 (m, 2H), 1.86 (m, 1H), 1.70 (m, 1H), 1.63 (d, 3H, J=1.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 149.0, 142.9, 130.1, 121.6, 119.0, 114.4, 111.2, 109.9, 103.8, 65.2 (isochronous with another peak), 56.2 (isochronous with another peak), 52.1, 30.7, 30.1, 19.5. FTIR (thin film) 2955, 2889, 2838, 2236, 1645, 1603, 1592, 1518, 1464, 1413, 1334, 1260, 1243, 1149, 1027 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{18}H_{23}NO_4$ $(M+Na)^+$ 340.1519, found 340.1508. $[\alpha]^{23}_D = -28°$ (c=0.14, CH_2Cl_2; for product with 81% ee).

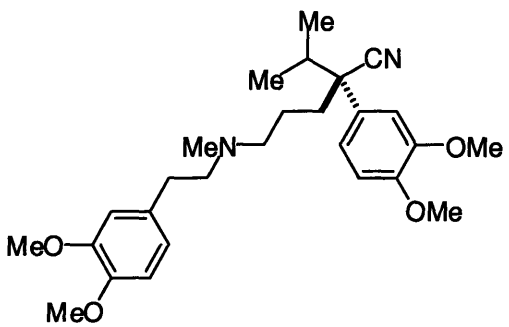
For run 2, the same procedure as above was followed, using MeMgBr (3.00 M in Et_2O; 0.416 mL, 1.24 mmol), **4.35** (0.337 g, 0.499 mmol, in 4 mL Et_2O), and Martin Sulfurane, $[Ph(CF_3)_2CO]_2SPh_2$, (1.32 g, 4.76 mmol, in 4 mL CH_2Cl_2). Product **4.37** was isolated as a clear, colorless oil (0.0788 g, 60%).



(*S*)-2-(3,4-dimethoxyphenyl)-4-(1,3-dioxolan-2-yl)-2-(2-propyl)butyronitrile (4.38). Pd/C (0.0300 g, 10 wt% on carbon) was added to a solution of olefin **4.37** (0.103 g, 0.325 mmol) in absolute EtOH (5.0 mL). A balloon filled with H_2 gas was attached to the reaction vessel. After 12 hours of stirring at room temperature, the reaction mixture was filtered through a plug of celite (Et_2O washings), and then the solvent was removed to provide a 99% yield of product **4.39** as a clear, colorless oil (0.103 g, 0.323 mmol; no impurities were evident in the ^{1}H NMR spectrum).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (dd, 1H, J=8.5, J=2.0), 6.85 (m, 2H), 4.81 (app t, 1H, J=4.5), 3.91 (m, 8H), 3.82 (m, 2H), 2.26 (m, 1H), 2.09 (m, 1H), 1.93 (m, 1H), 1.75 (m, 1H), 1.33 (m, 1H), 1.19 (d, 3H, J=6.5), 0.81 (d, 3H, J=7.0). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 148.5, 130.4, 121.4, 118.9, 111.3, 109.7, 103.8, 65.1 (isochronous with another peak), 56.2, 56.1, 53.1, 38.2, 32.0, 30.2, 19.2, 18.7. FTIR (thin film) 2965, 2935, 2877, 2233, 1605, 1591, 1518, 1464, 1413, 1391, 1259, 1146, 1026, 945 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{18}H_{25}NO_4$ $(M+Na)^+$ 342.1676, found 342.1684. $[\alpha]^{22}_D$ = –9° (c=0.10, CH_2Cl_2; for product with 81% ee).

For run 2, the same procedure was followed, using Pd/C (0.0200 g) and olefin **4.37** (0.0770 g, 0.243 mmol) in 3 mL of EtOH. Product **4.39** was isolated as a clear, colorless oil (0.0720 g, 93%), which was shown by chiral HPLC (Daicel CHIRALCEL OJ-H, 4.6 mm x 25 cm, hexane/isopropanol 90:10, 1.0 mL/min, retention times of enantiomers: 13.5 min (major), 17.0 min (minor)) to have 81% ee.



(*S*)-(–)-Verapamil [36622-29-4], **(–)-(4.11)**. Oxalic acid dihydrate (0.0594 g, 0.471 mmol) was added to a solution of acetal **4.39** (0.0500 g, 0.157 mmol) in acetone (2 mL) and water (2 mL). After 2.5 hours of stirring at 80 °C, the reaction mixture was cooled to room temperature, quenched with K_2CO_3, extracted with Et_2O (3 x 15 mL), dried (Na_2SO_4), filtered, and concentrated, affording the aldehyde as an off-white residue, which was used in the next step without further purification.

Homoveratrylamine hydrochloride (0.0364 g, 0.157 mmol), NEt_3 (0.0438 mL, 0.314 mmol), and $NaBH(OAc)_3$ (0.0466 g, 0.220 mmol) were added to a solution of the unpurified aldehyde (0.0432 g, 0.157 mmol) in 1,2-dichloroethane (5.0 mL). The reaction mixture was stirred at room temperature for 12 hours, after which it was quenched by the addition of 1 N HCl (0.5 mL), extracted with EtOAc (3 x 15 mL), washed with 6 N NaOH (3 x 15 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography (3% MeOH/97% $CHCl_3$) provided a 72% yield of the product as a clear, colorless oil (0.0516 mmol, 0.114 mmol).

^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (dd, 1H, J=8.5, J=2.0), 6.85 (d, 1H, J=2.0), 6.83 (d, 1H, J=8.5), 6.79 (d, 1H, J=8.5), 6.70 (m, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.67 (m, 2H), 2.50 (m, 2H), 2.36 (m, 2H), 2.19 (s, 3H), 2.07 (m, 2H), 1.83 (m, 1H), 1.56 (m, 1H), 1.13-1.22 (m, 4H), 0.80 (d, 3H, J=6.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 149.0, 148.4, 147.4, 133.2, 130.8, 121.7, 120.7, 118.8, 112.1, 111.3, 111.2, 109.7, 59.7, 57.1, 56.2, 56.1 (isochronous with another peak), 56.0, 53.6, 42.2, 38.1, 35.8, 33.4, 23.6, 19.2, 18.8. $[\alpha]^{23}_D = -10°$ (c=0.31, EtOH; for product with 81% ee).

For run 2, the same procedure as above was followed, using **4.39** (0.0589 g, 0.184 mmol, in 2 mL water and 2 mL acetone), oxalic acid dihydrate (0.0697 g, 0.553 mmol), homoveratrylamine hydrochloride (0.0426 g, 0.184 mmol, in 5 mL 1,2-dichloroethane), NEt_3 (0.0513 mL, 0.368 mmol), and sodium triacetoxyborohydride (0.0546 g, 0.258 mmol). Product **(–)-4.11** was isolated as a clear, colorless oil (0.0586 g, 70%).[104]

[104] The assignment of absolute configuration was compared to literature data using optical rotation. See, Bannister, R. M.; Brookes, M. H.; Evans, G. R.; Katz, R. B.; Tyrrell, N. D. *Org. Process Res. Dev.* **2000**, *4*, 467-472.

CURRICULUM VITAE

Education

Ph.D., Organic Chemistry, Massachusetts Institute of Technology, August 2004
Thesis Title: "Enantioselective Reactions of Silyl Ketene Acetals and Silyl Ketene Imines Catalyzed by Planar-Chiral Heterocycles"
Adviser: Professor Gregory C. Fu

B.S., College Honors, Chemistry, University of California, Los Angeles, June 1999
Undergraduate Thesis Title: "Enantioselective Epoxidations of Trans Alkenes"
Adviser: Professor Craig A. Merlic

B.S., College Honors, Applied Mathematics, University of California, Los Angeles, June 1999

Awards and Fellowships

2003 NIH Cancer Training Grant Fellow-MIT
2000 MIT-Department of Chemistry Teaching Assistant Award, Organic Chem. I & II
1999 College Honors-UCLA
V. Geissman Award for excellence in Organic Chemistry-UCLA
1998 Alumni Summer Research Fellowship in Chemistry-UCLA
V. Undergraduate Research Award-UCLA
1998 Association of Chemists and Biochemists Research Award-UCLA
1997 Pfizer Summer Undergraduate Research Fellowship-UCLA
1996 Award for Community Service (500 hours) at St. Joseph Medical Center-Convalescent Care/AIDS Hospice Unit

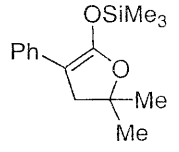
Publications

1) Mermerian, A. H.; Fu, G. C. Generation of All-Carbon Quaternary Stereocenters via Catalytic Asymmetric Acylations of Silyl Ketene Imines. Application to the Enantioselective Synthesis of Verapamil. *Angew. Chem., Int. Ed.* **2004**, *submitted.*

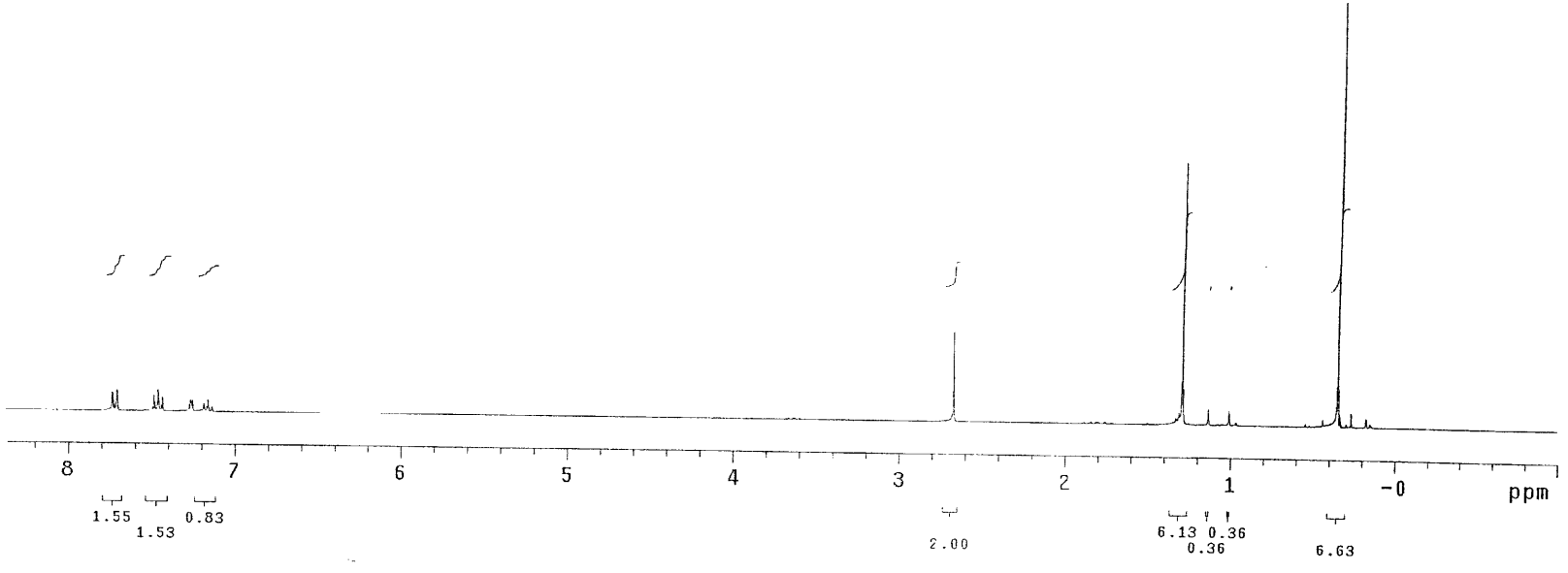
2) Mermerian, A. H.; Fu, G. C. Catalytic Enantioselective Synthesis of Quaternary Stereocenters via Intermolecular C-Acylation of Silyl Ketene Acetals: Dual Activation of the Electrophile and the Nucleophile. *J. Am. Chem. Soc.* **2003**, *125*, 4050-4051.

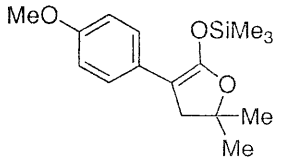
Appendix A

Selected 1H NMR Data

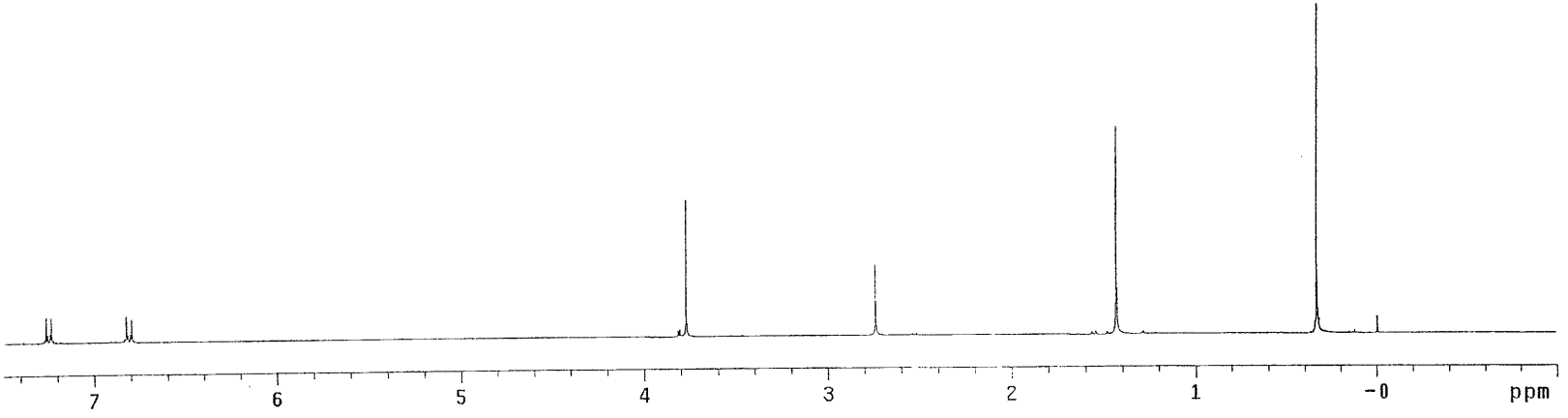


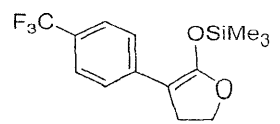
^{1}H NMR (300 MHz, C_6D_6)



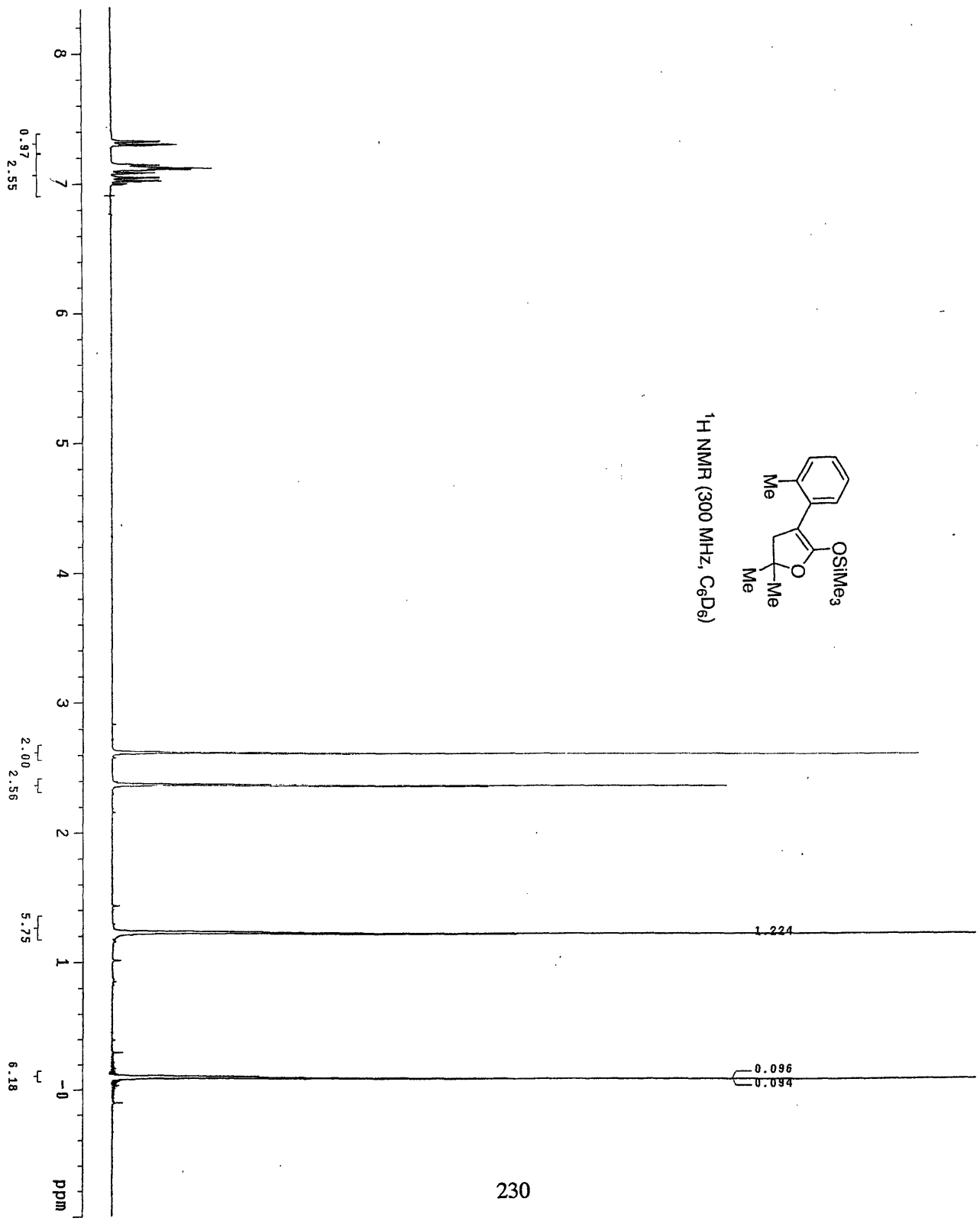


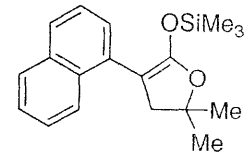
^{1}H NMR (300 MHz, C_6D_6)



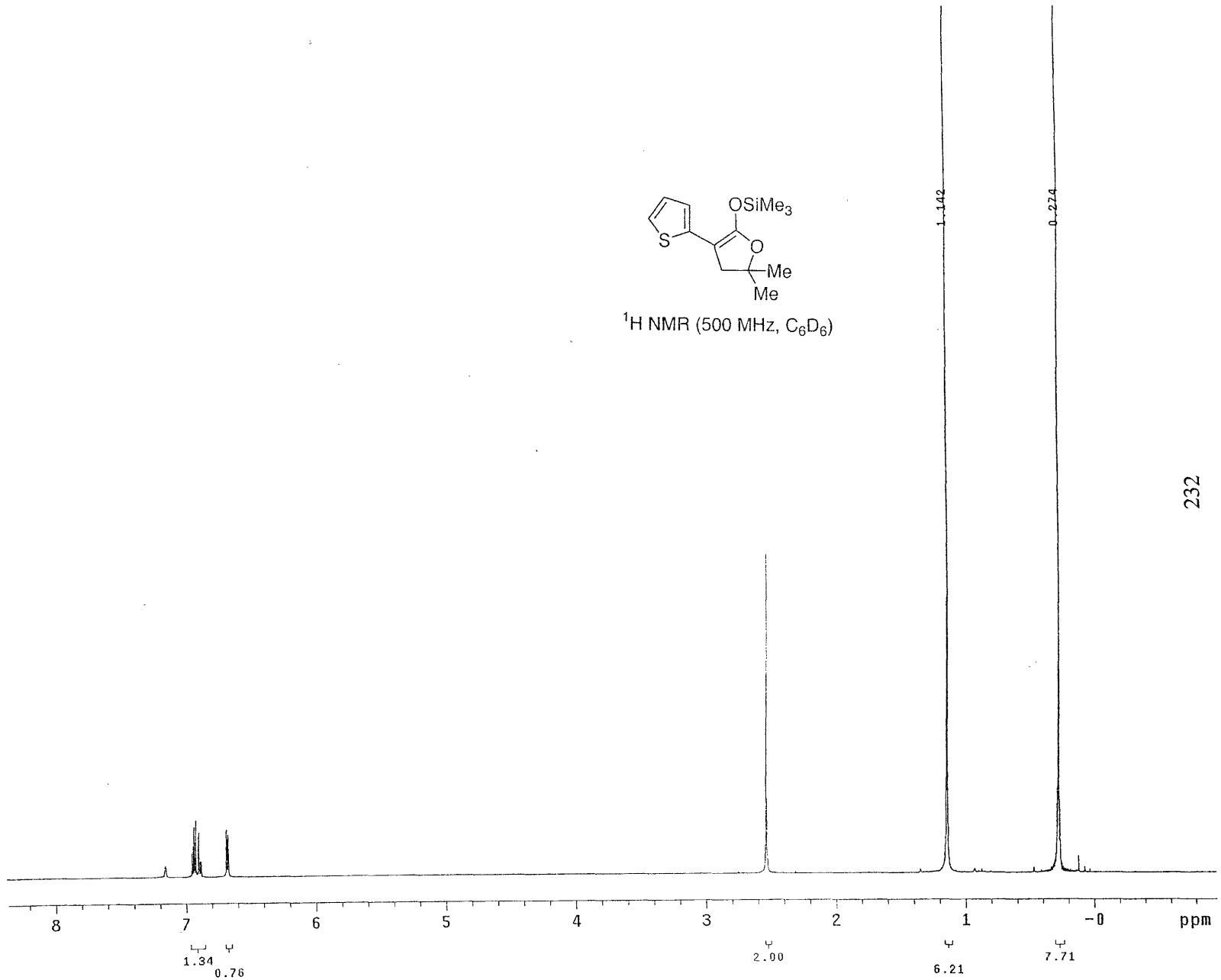


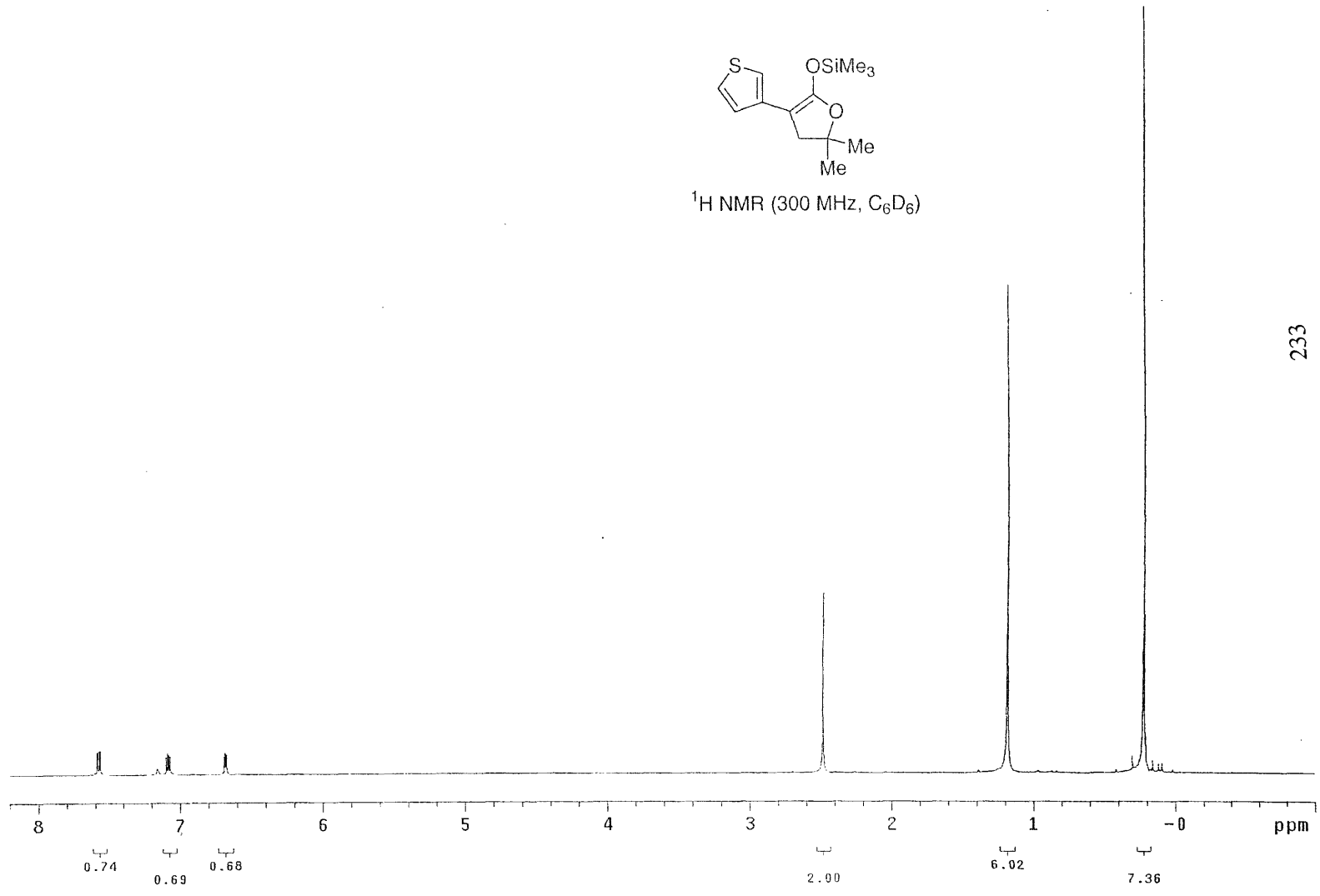
^{1}H NMR (300 MHz, C_6D_6)

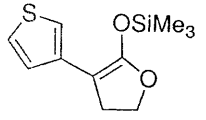

^{1}H NMR (300 MHz, C_6D_6)
Me
OSiMe$_3$
Me
Me
1.224
0.096
0.094
0.97
2.55
2.00
2.56
5.75
6.18
ppm



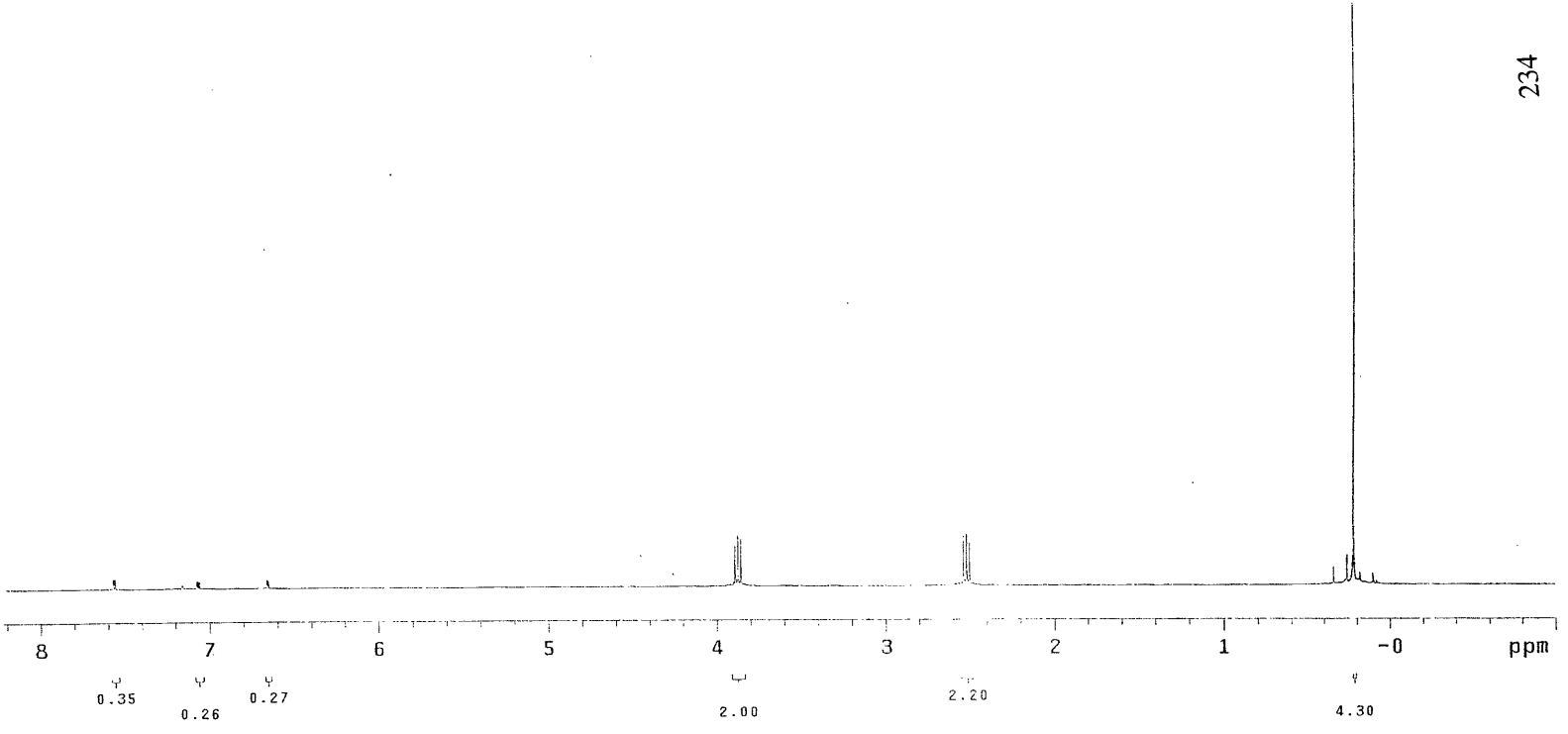
^{1}H NMR (500 MHz, CD_2Cl_2)

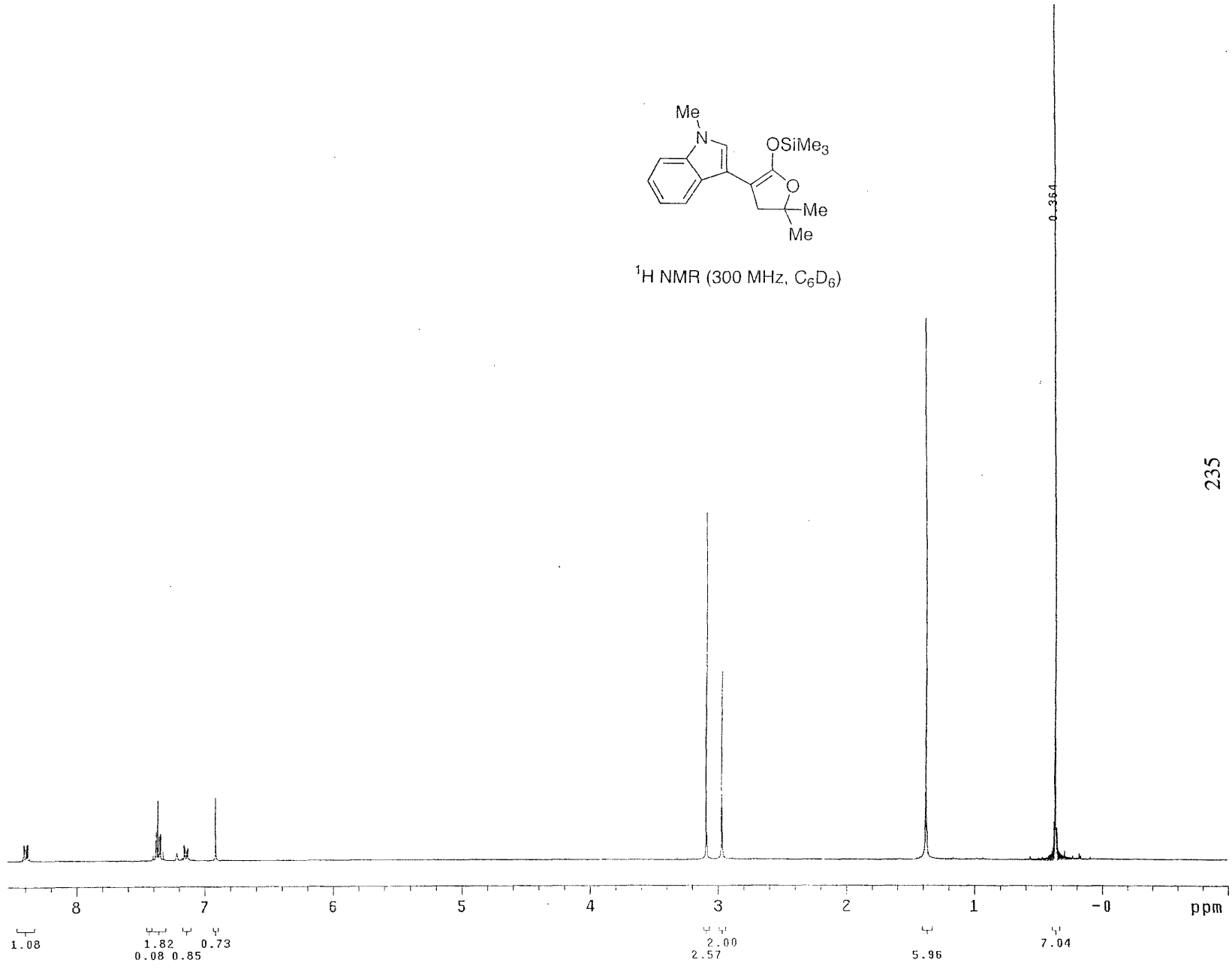

OSiMe3
S
O
Me
Me
1H NMR (500 MHz, C6D6)
1.142
0.224
8
7
6
5
4
3
2
1
-0
ppm
1.34
0.76
2.00
6.21
7.71


S
OSiMe3
O
Me
Me
1H NMR (300 MHz, C6D6)
8
7
6
5
4
3
2
1
-0
ppm
0.74
0.69
0.68
2.00
6.02
7.36

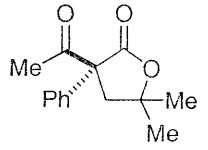


^{1}H NMR (500 MHz, C_6D_6)

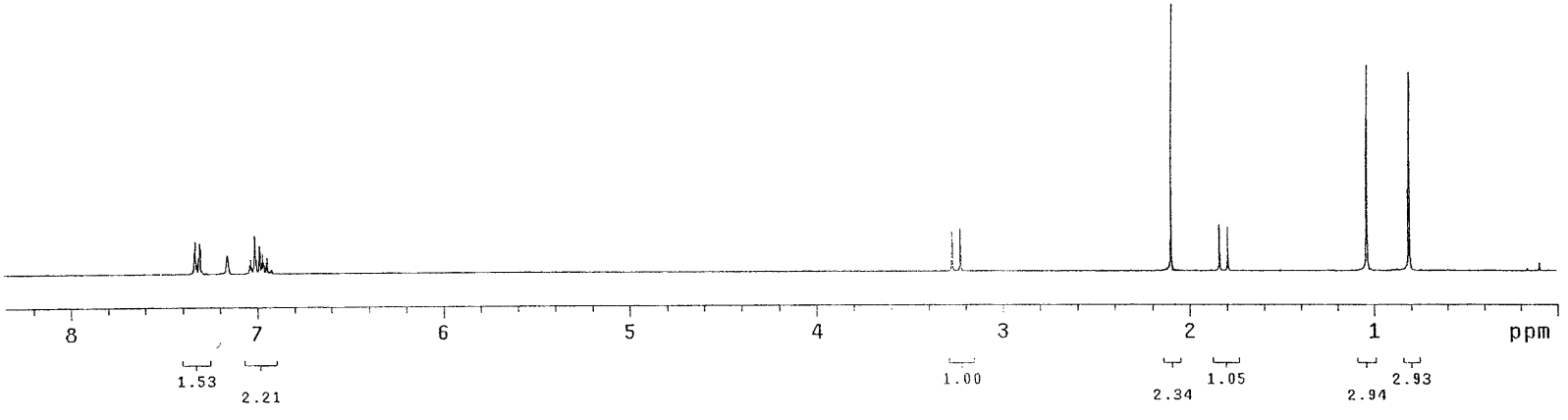


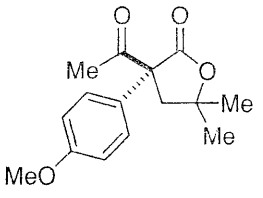


^{1}H NMR (300 MHz, C_6D_6)

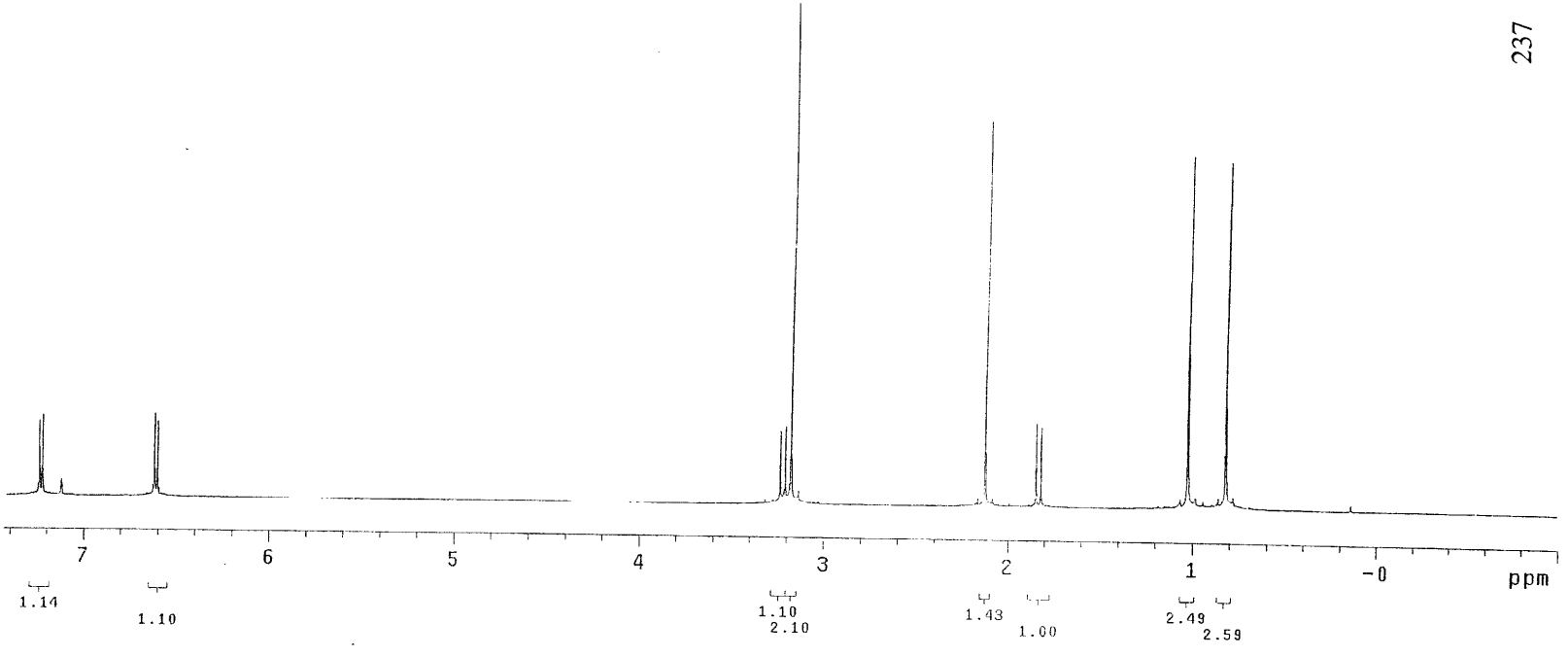


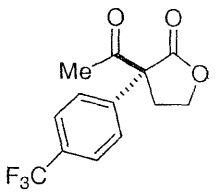
300 MHz, C_6D_6



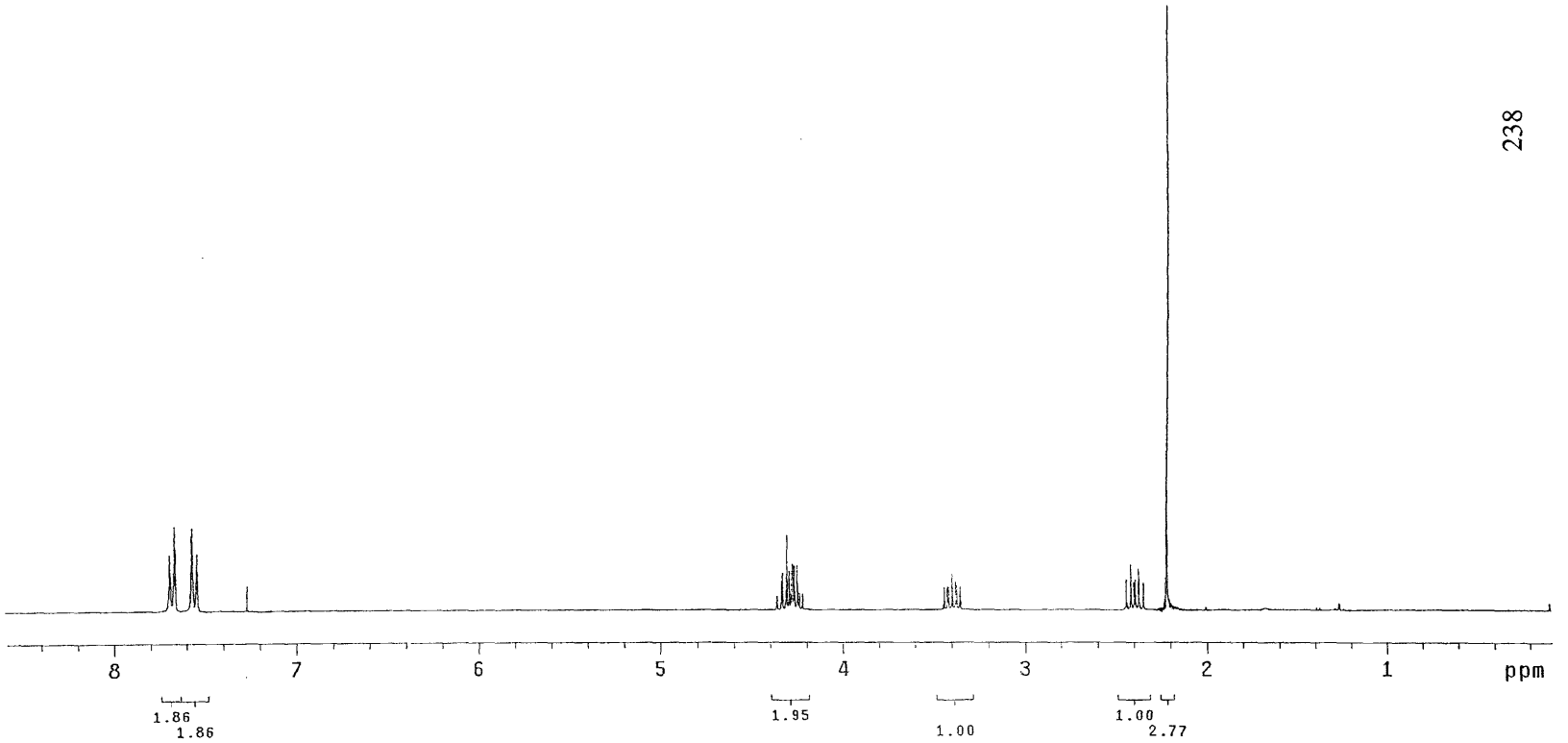


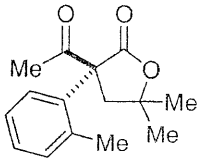
500 MHz, C_6D_6



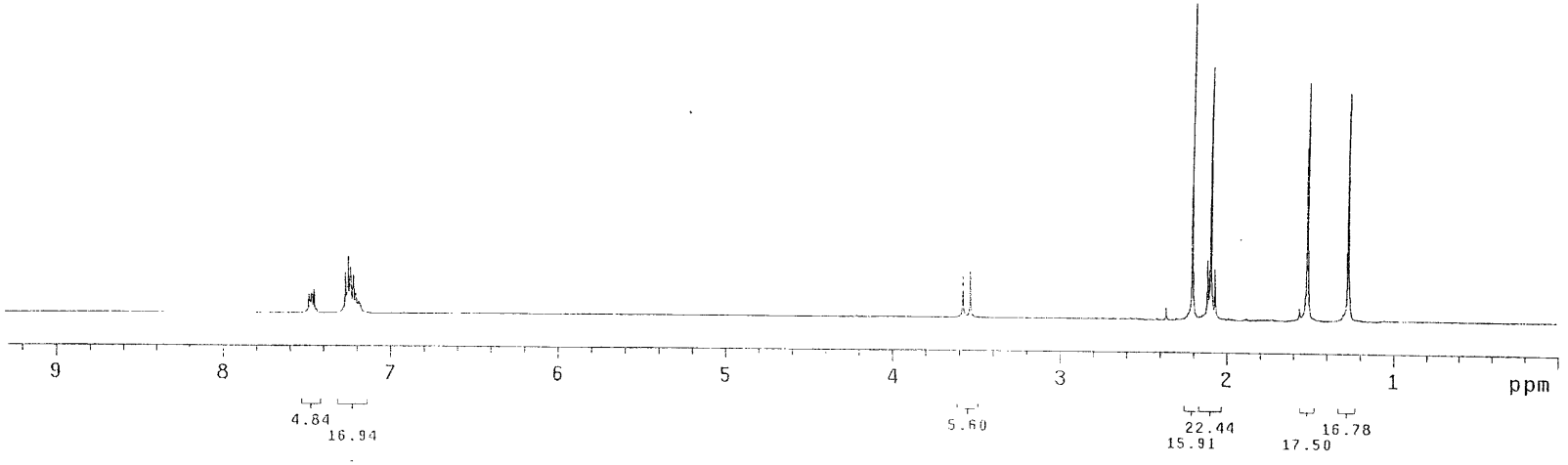


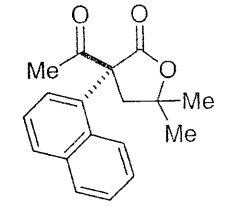
300 MHz, C_6D_6



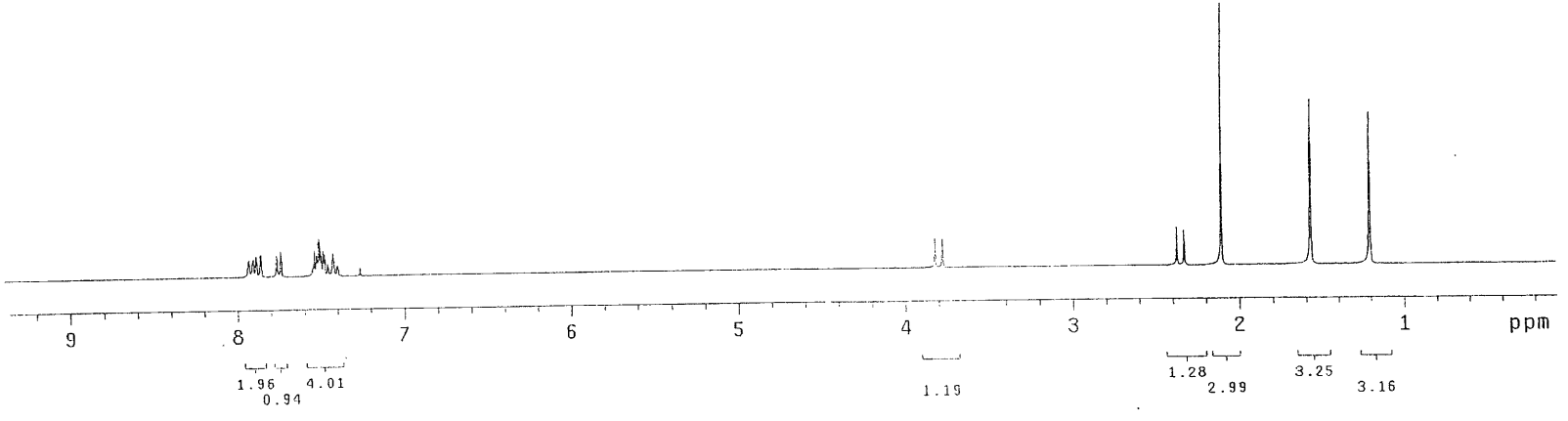


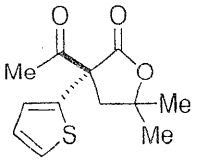
300 MHz, $CDCl_3$



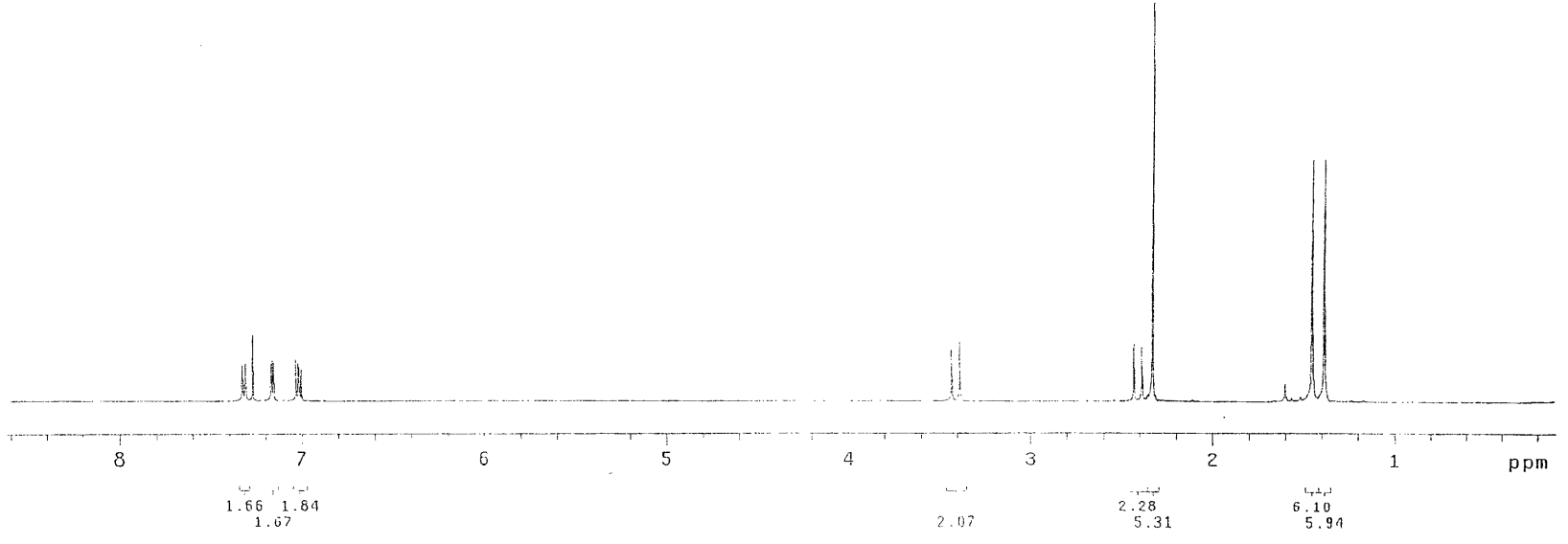


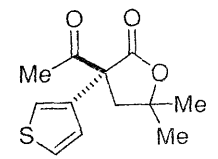
300 MHz, $CDCl_3$



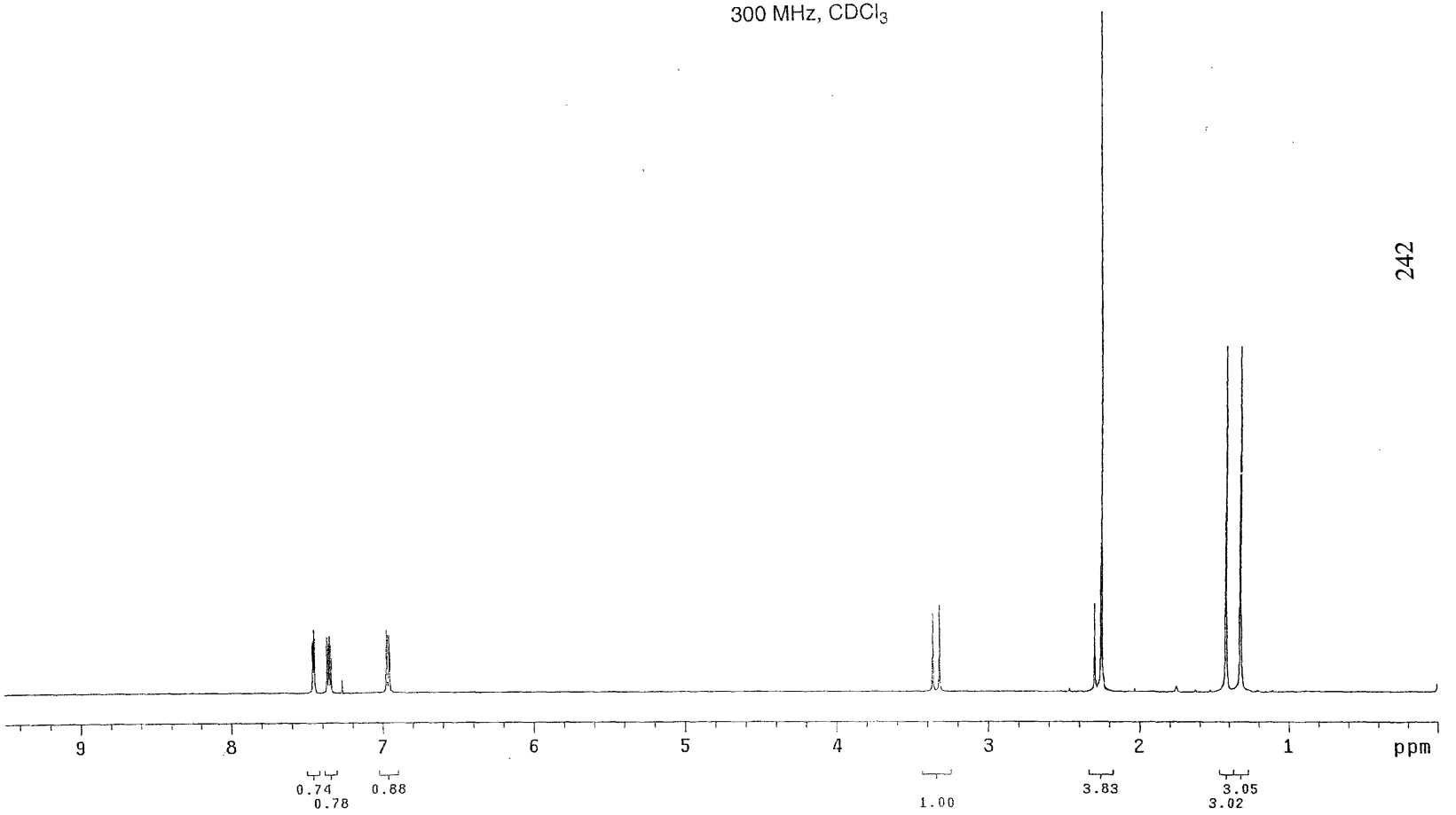


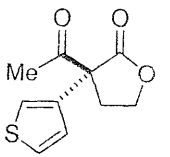
300 MHz, $CDCl_3$



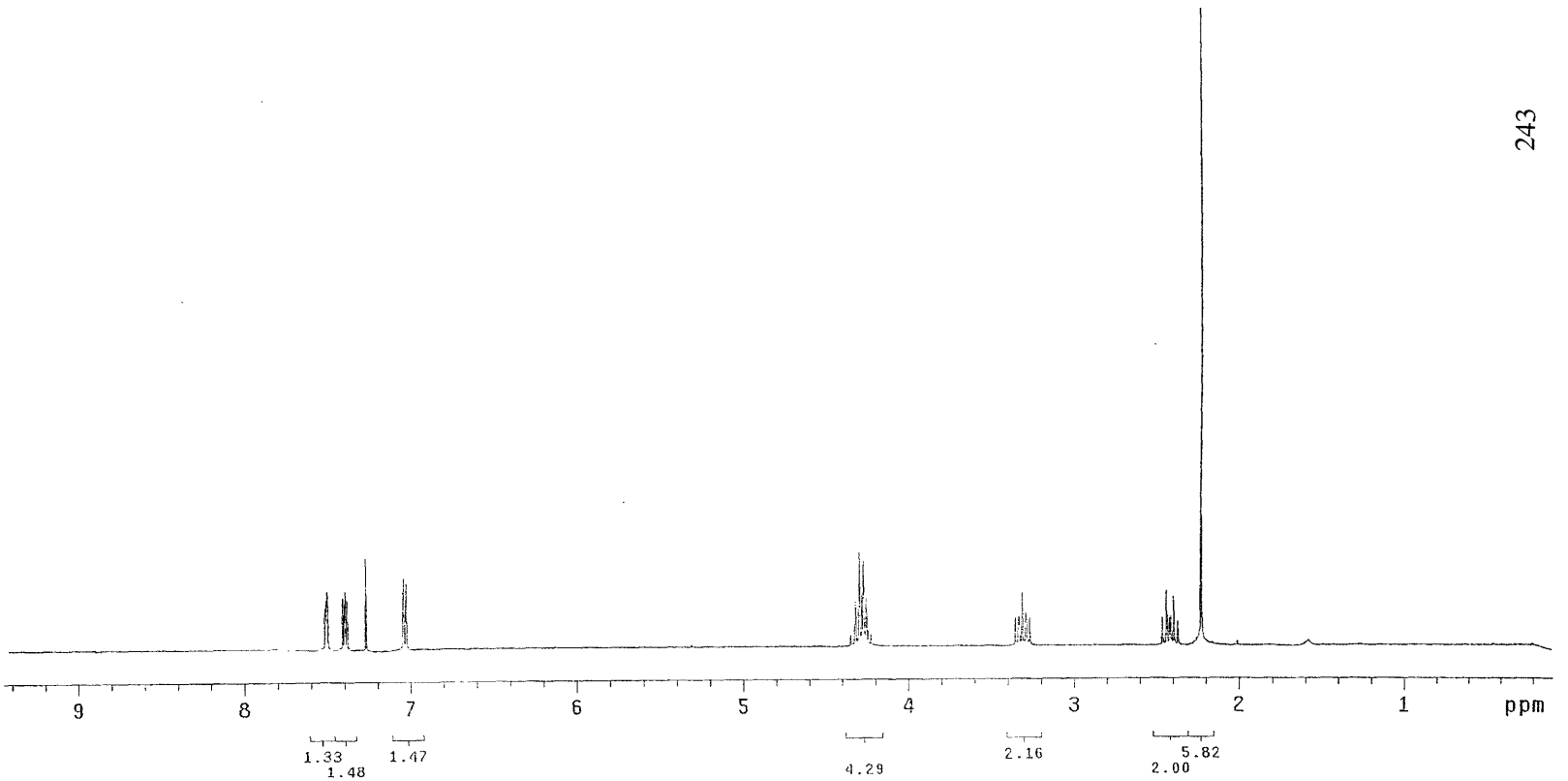


300 MHz, $CDCl_3$

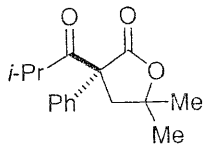




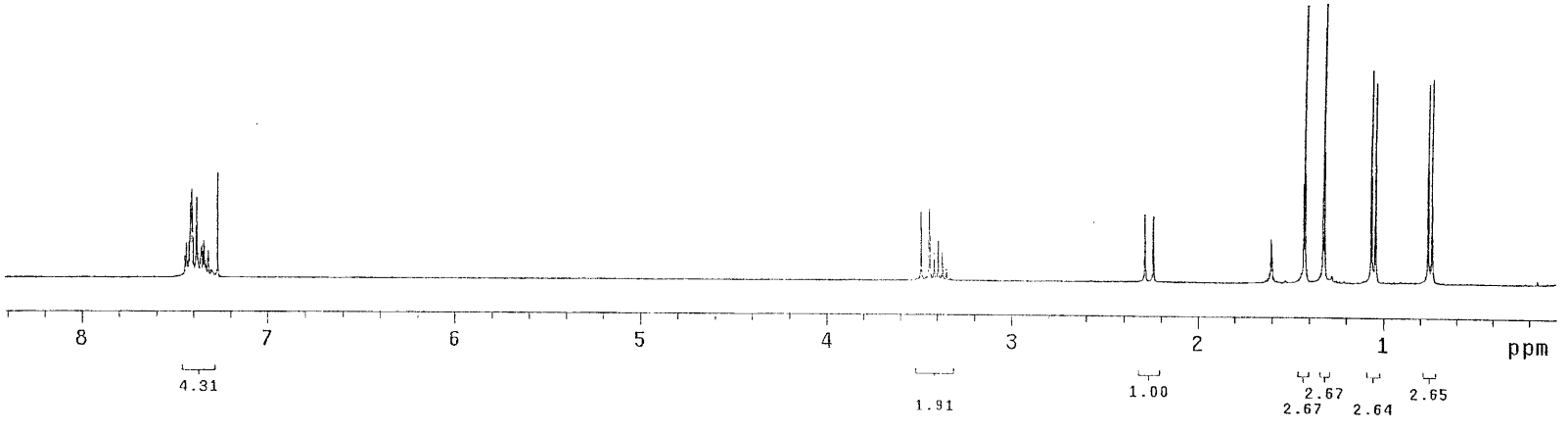
300 MHz, $CDCl_3$

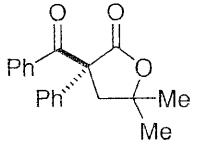


300 MHz, $CDCl_3$

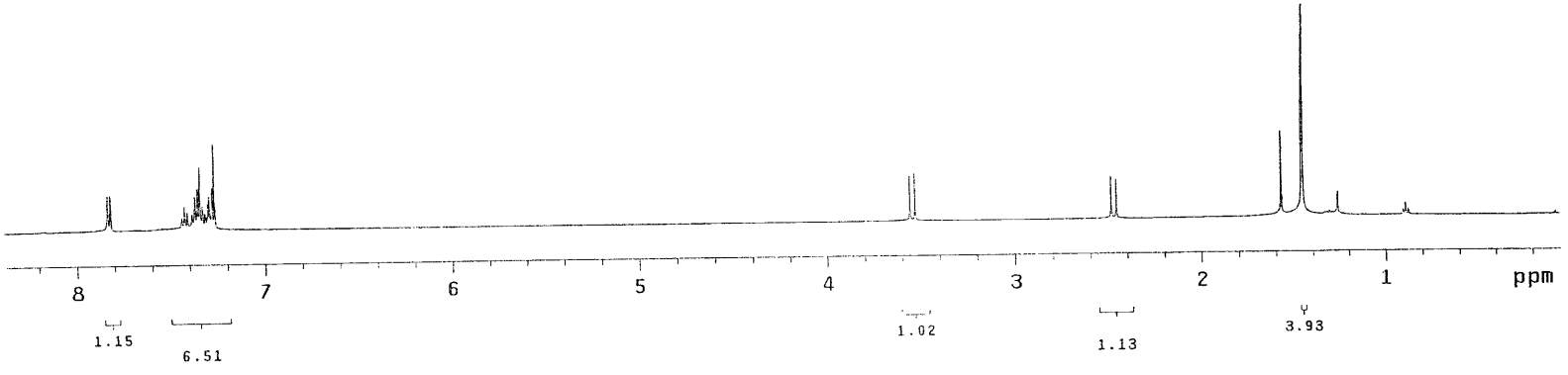


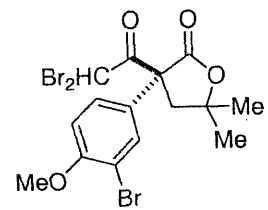
300 MHz, $CDCl_3$



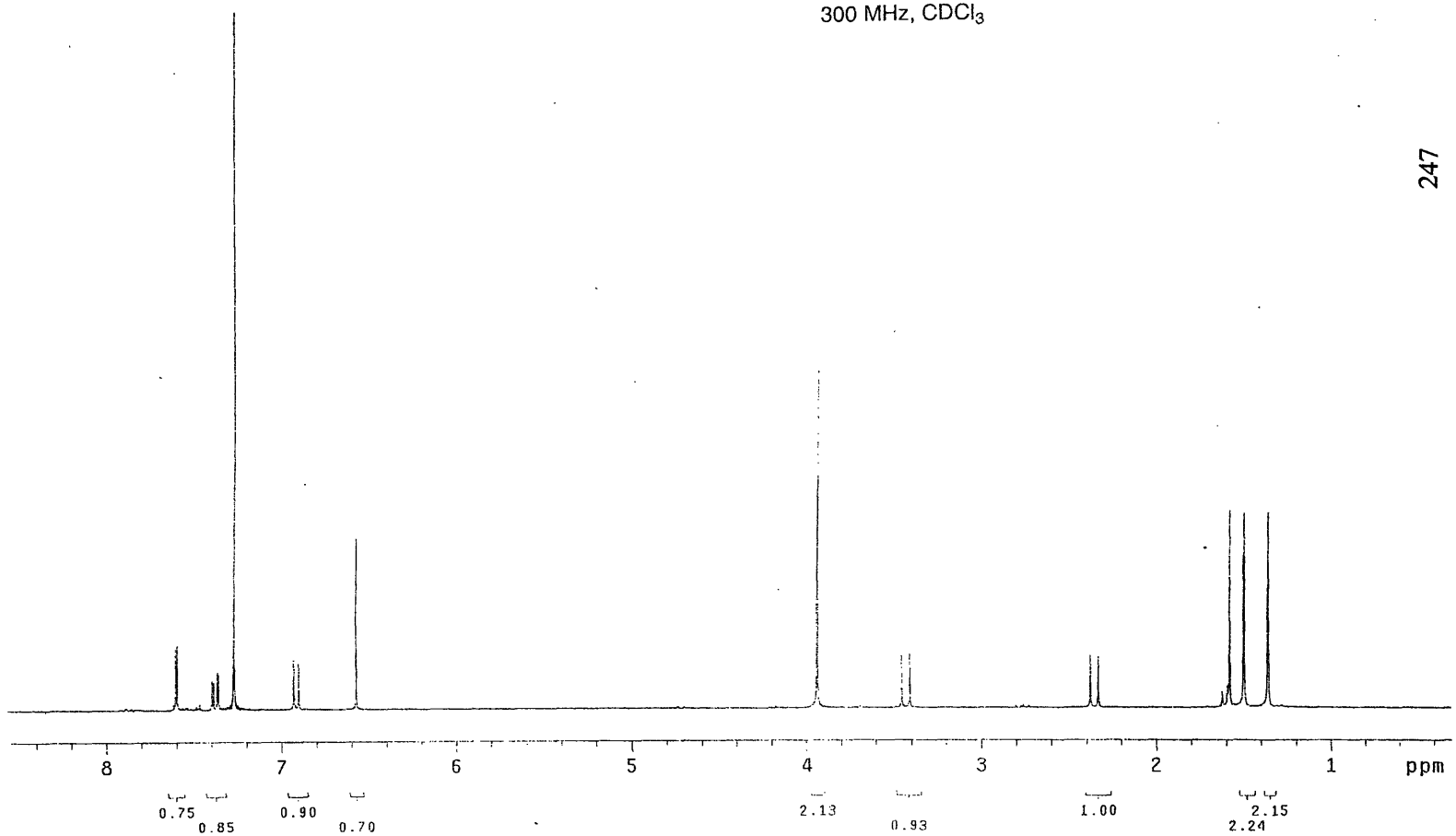


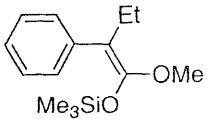
500 MHz, $CDCl_3$



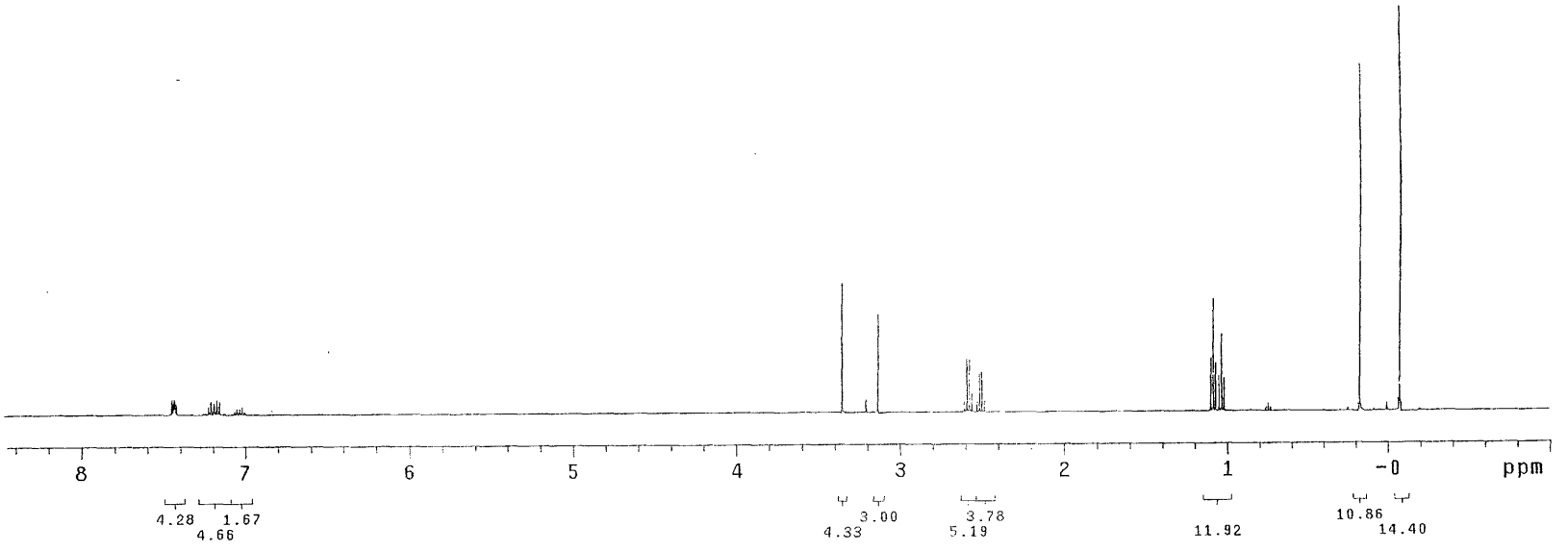


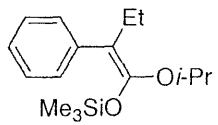
300 MHz, $CDCl_3$



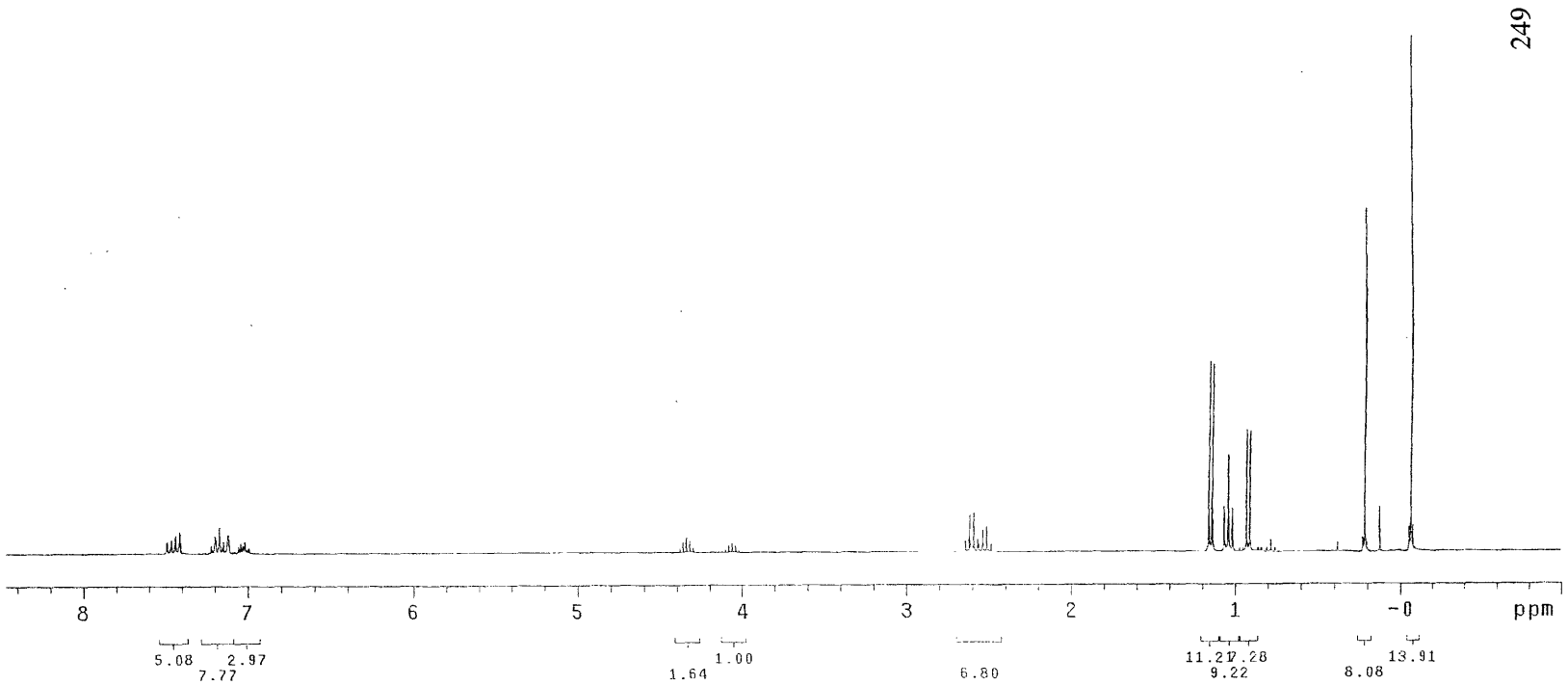


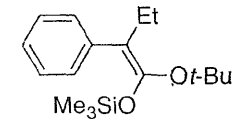
^{1}H NMR (500 MHz, C_6D_6)



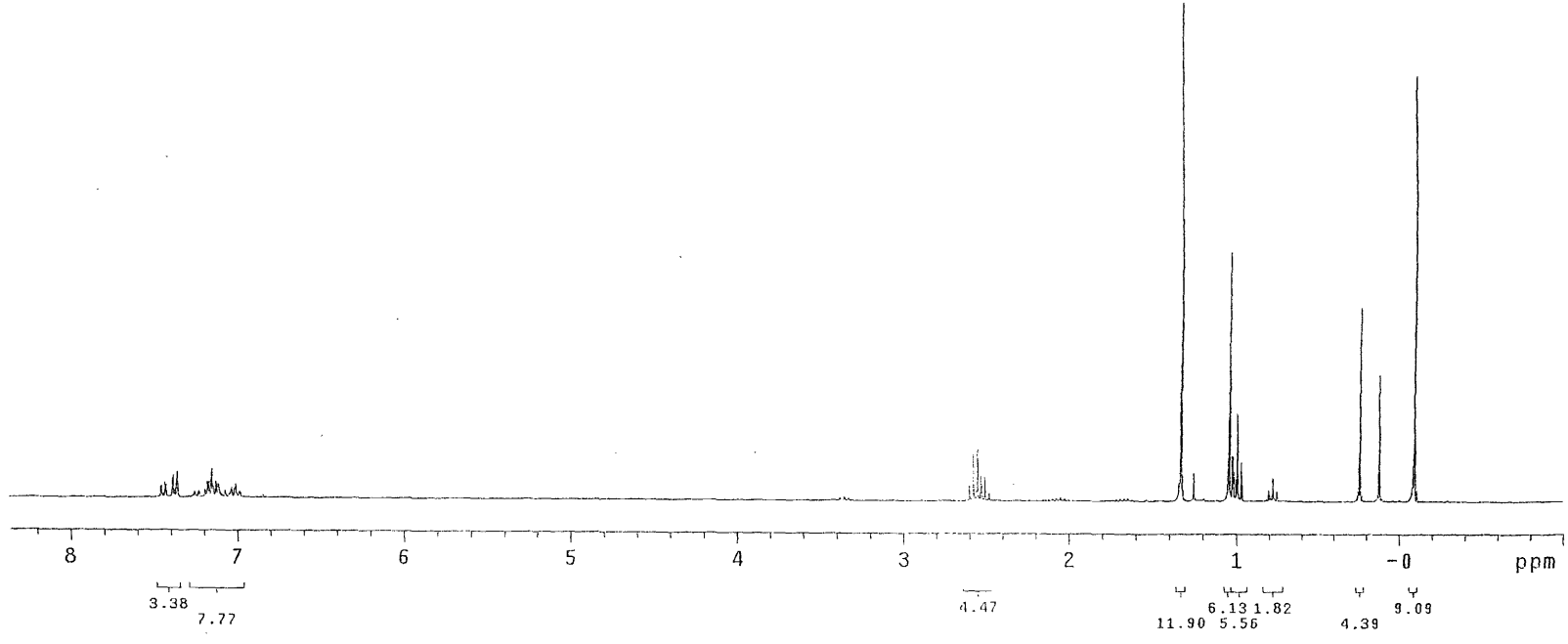


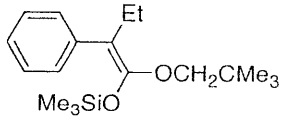
^1H NMR (300 MHz, C_6D_6)



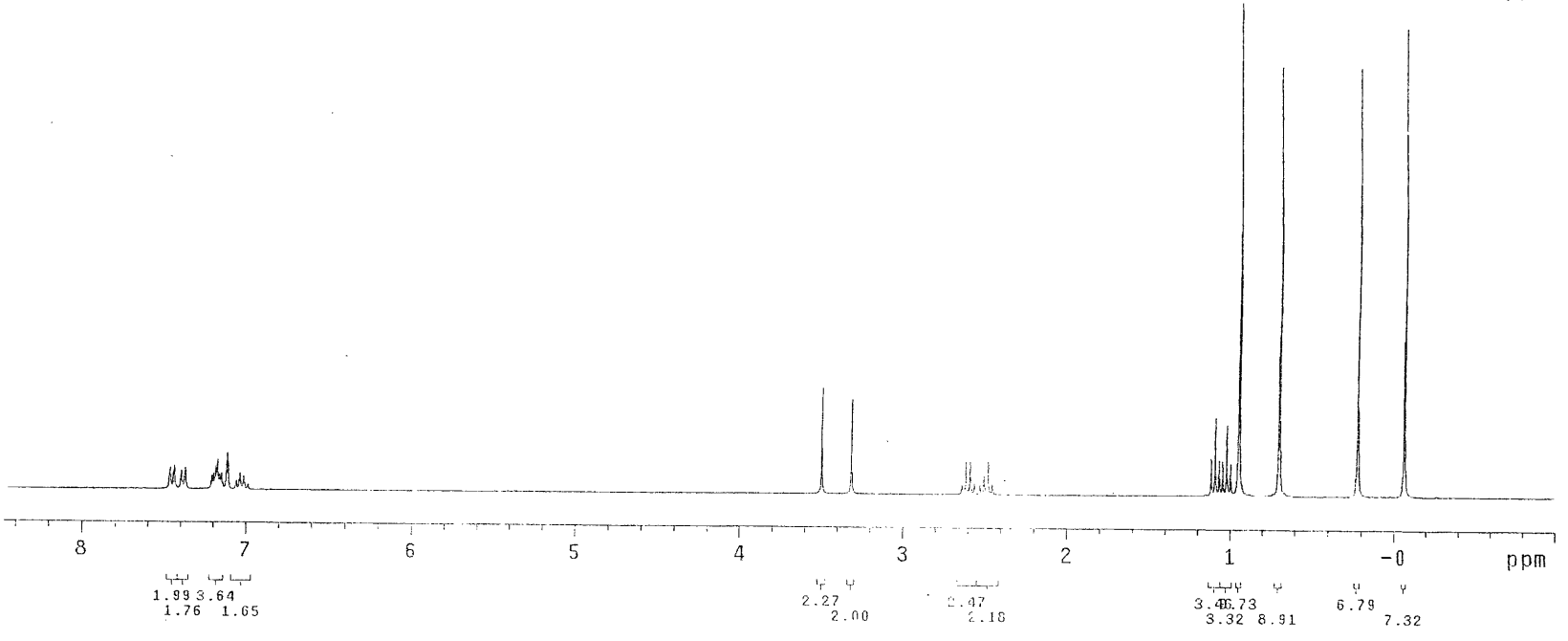


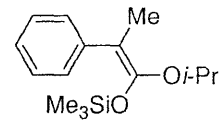
^{1}H NMR (500 MHz, C_6D_6)



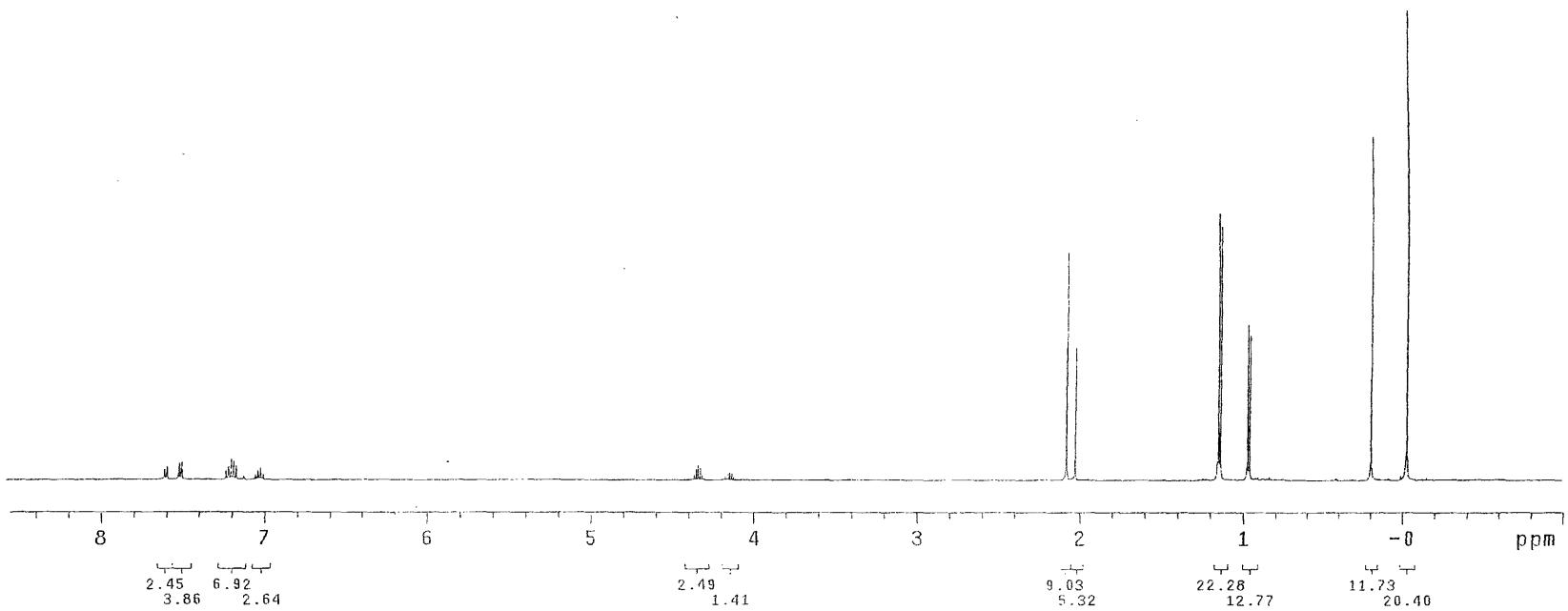


^{1}H NMR (300 MHz, C_6D_6)

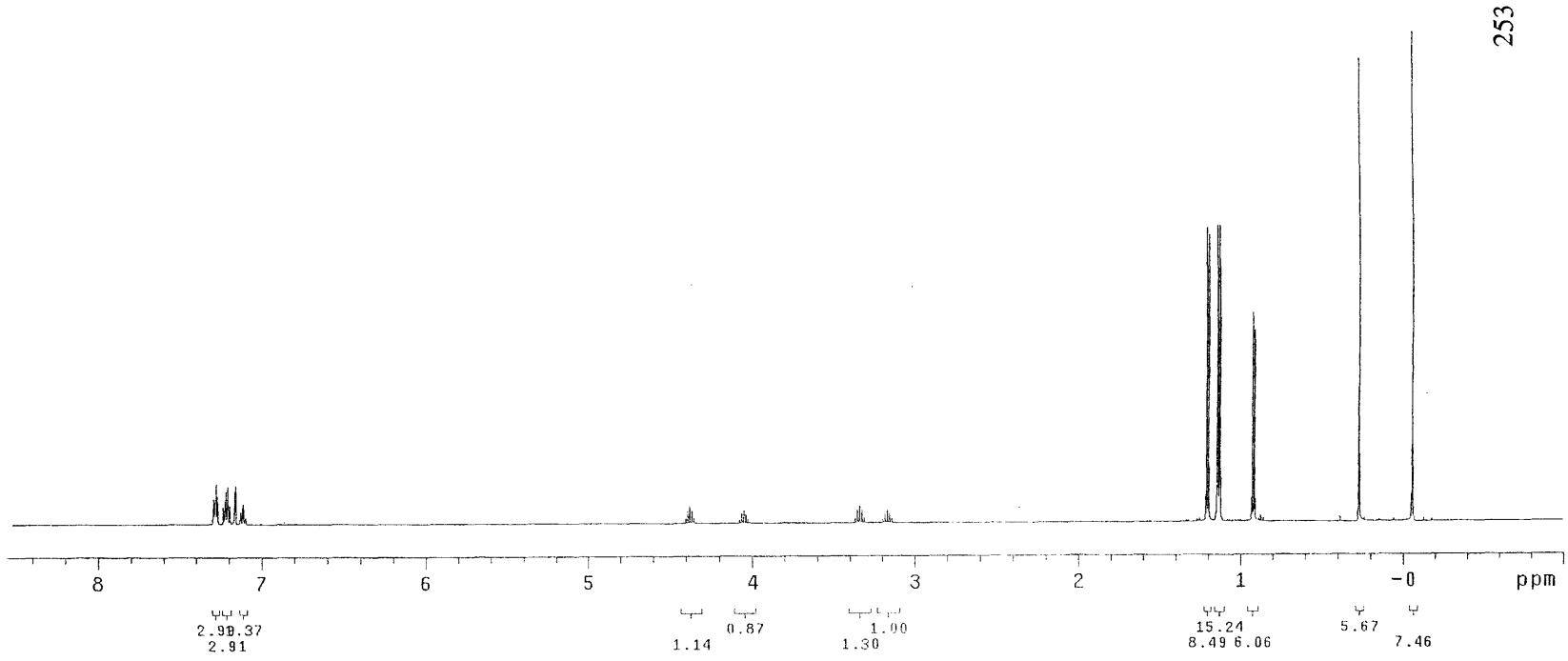


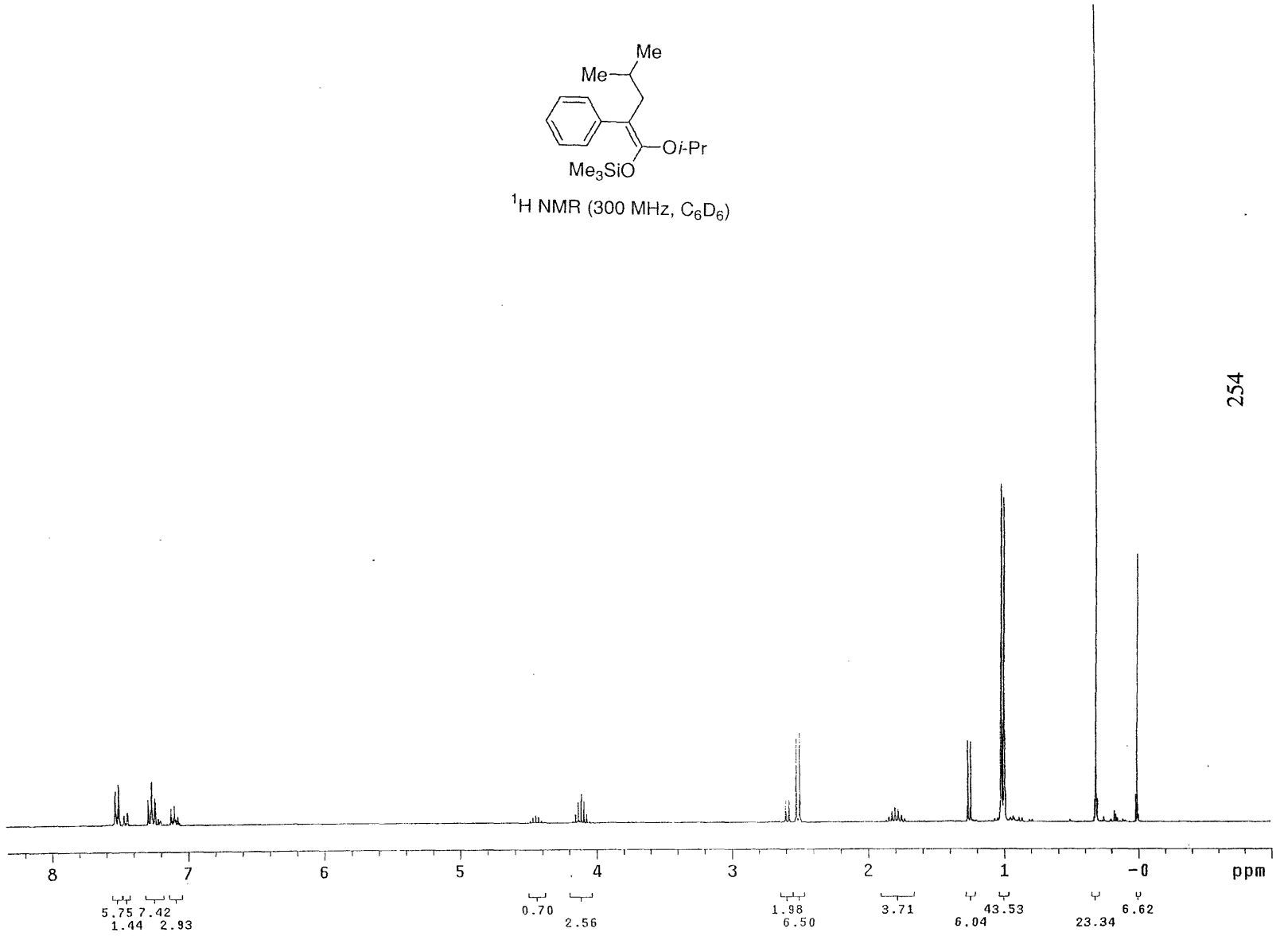


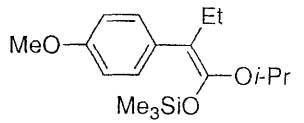
^{1}H NMR (500 MHz, C_6D_6)



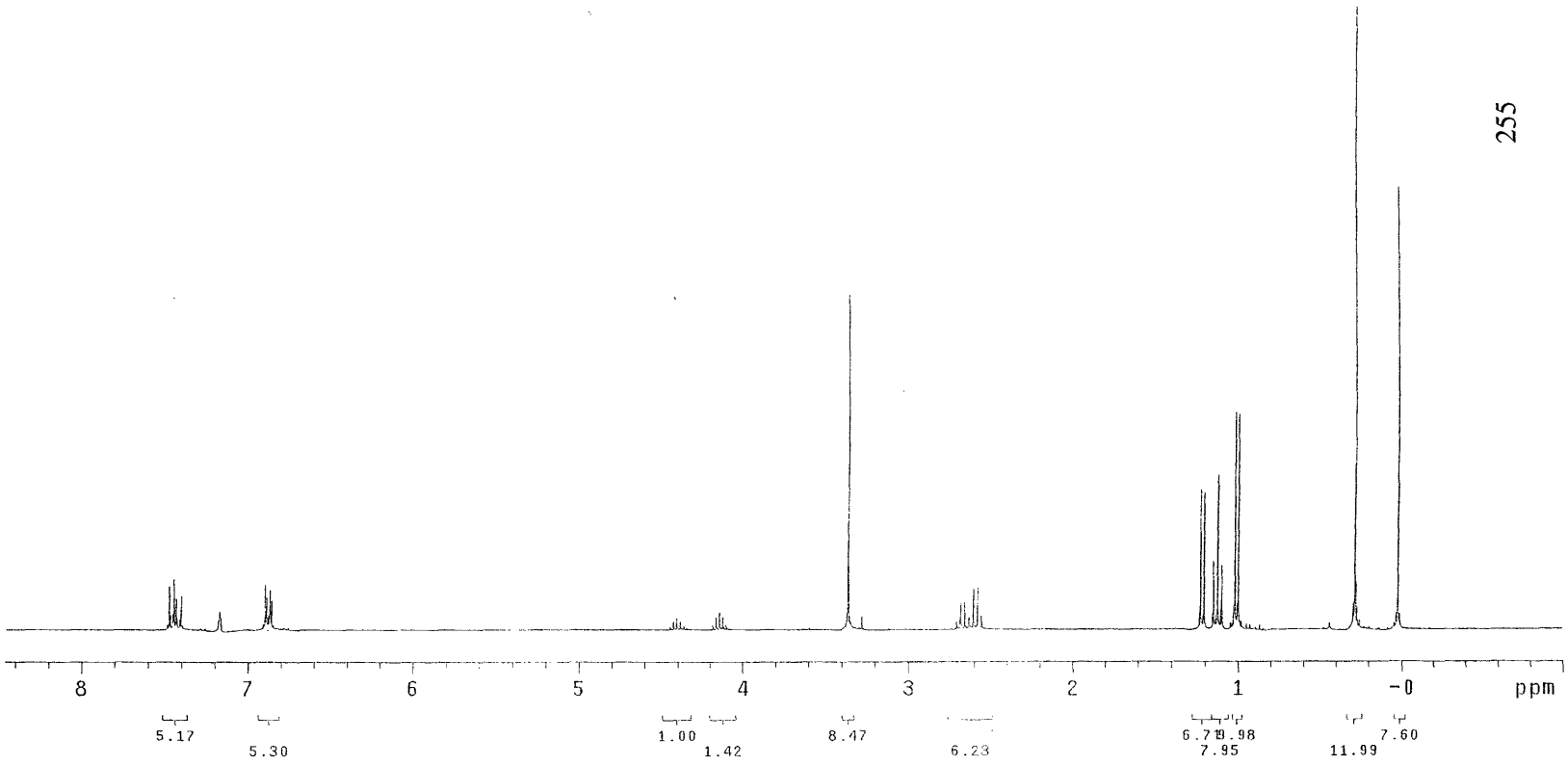
^{1}H NMR (500 MHz, C_6D_6)

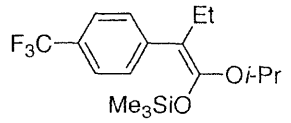



Me
Me
O*i*-Pr
Me_3SiO
^1H NMR (300 MHz, C_6D_6)
8
7
6
5
4
3
2
1
-0
ppm
5.75 7.42
1.44 2.93
0.70
2.56
1.98
6.50
3.71
6.04
43.53
23.34
6.62

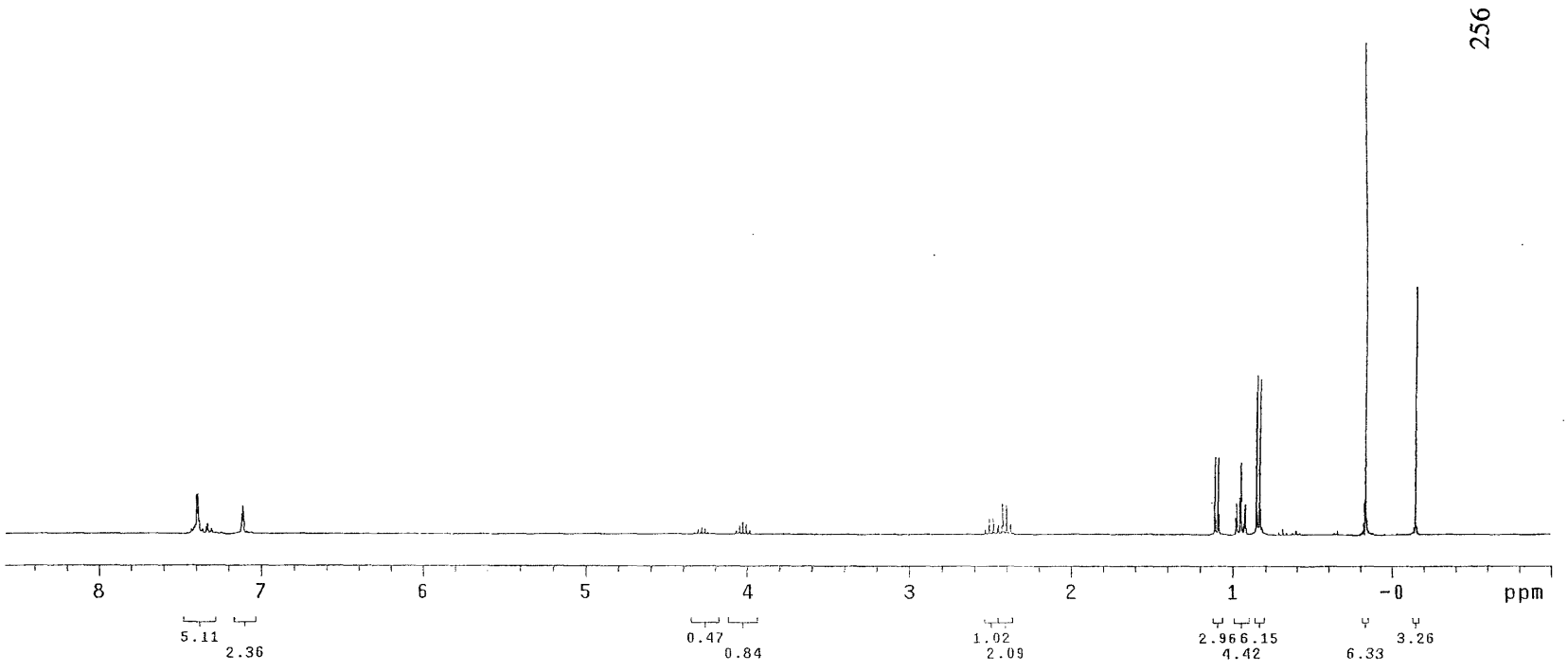


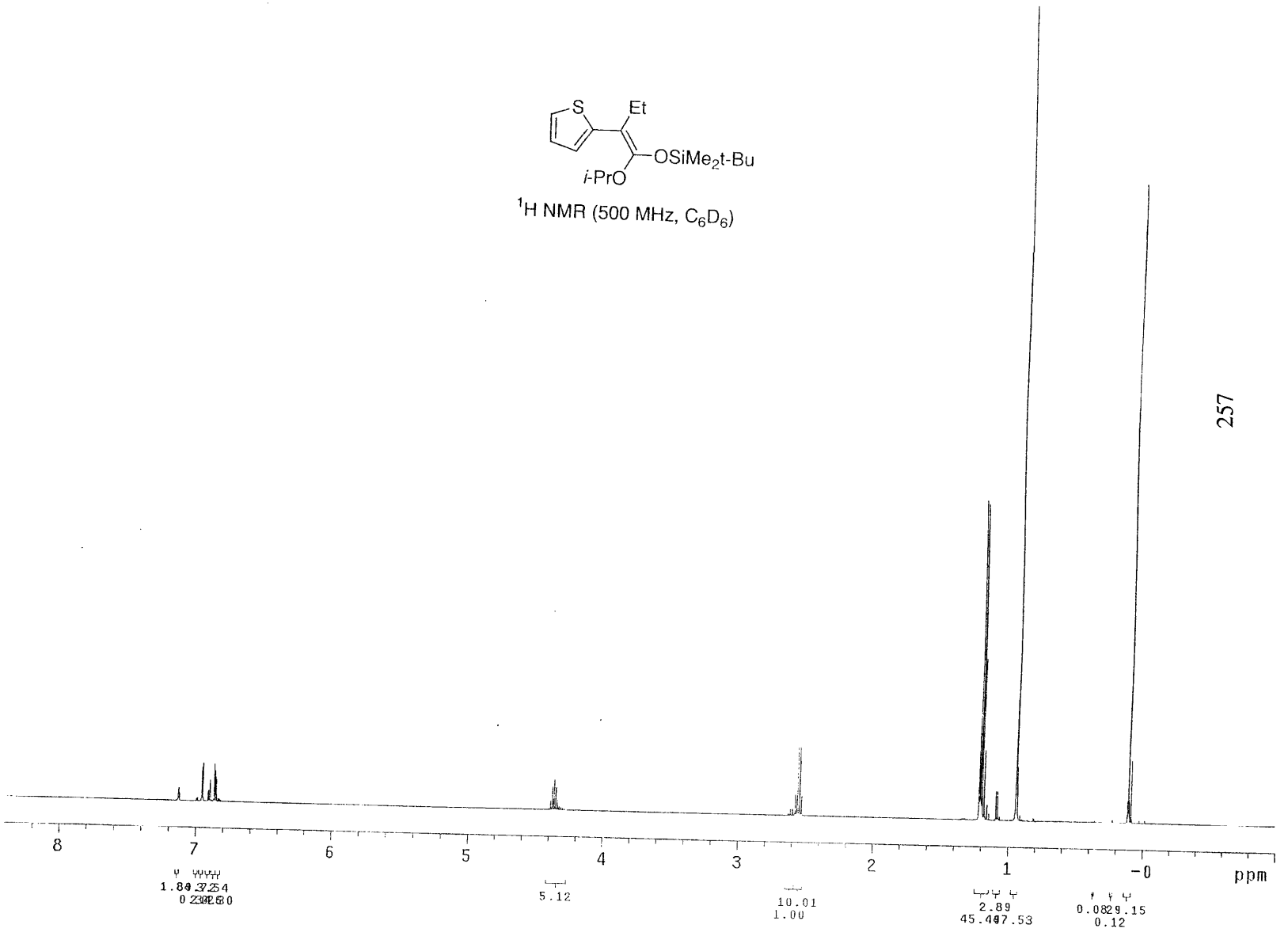
^{1}H NMR (300 MHz, C_6D_6)

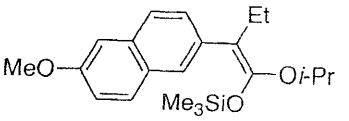




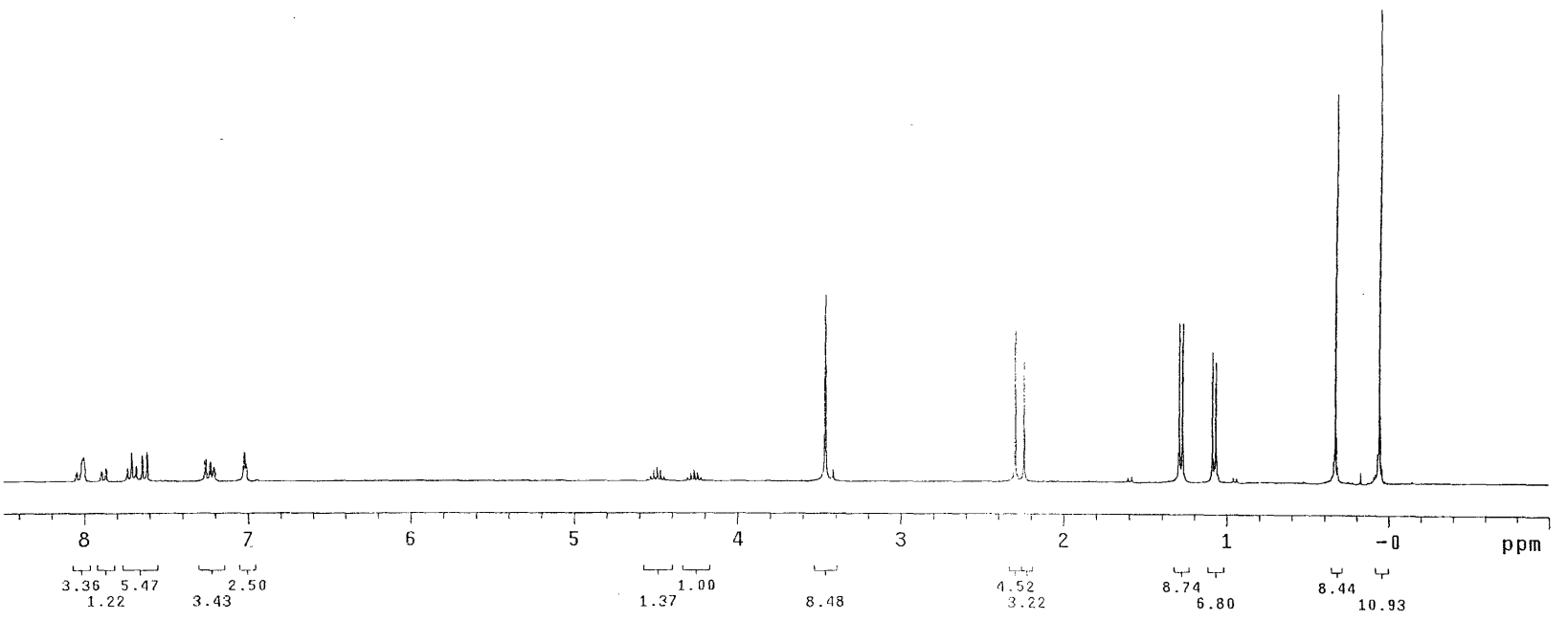
^{1}H NMR (300 MHz, C_6D_6)

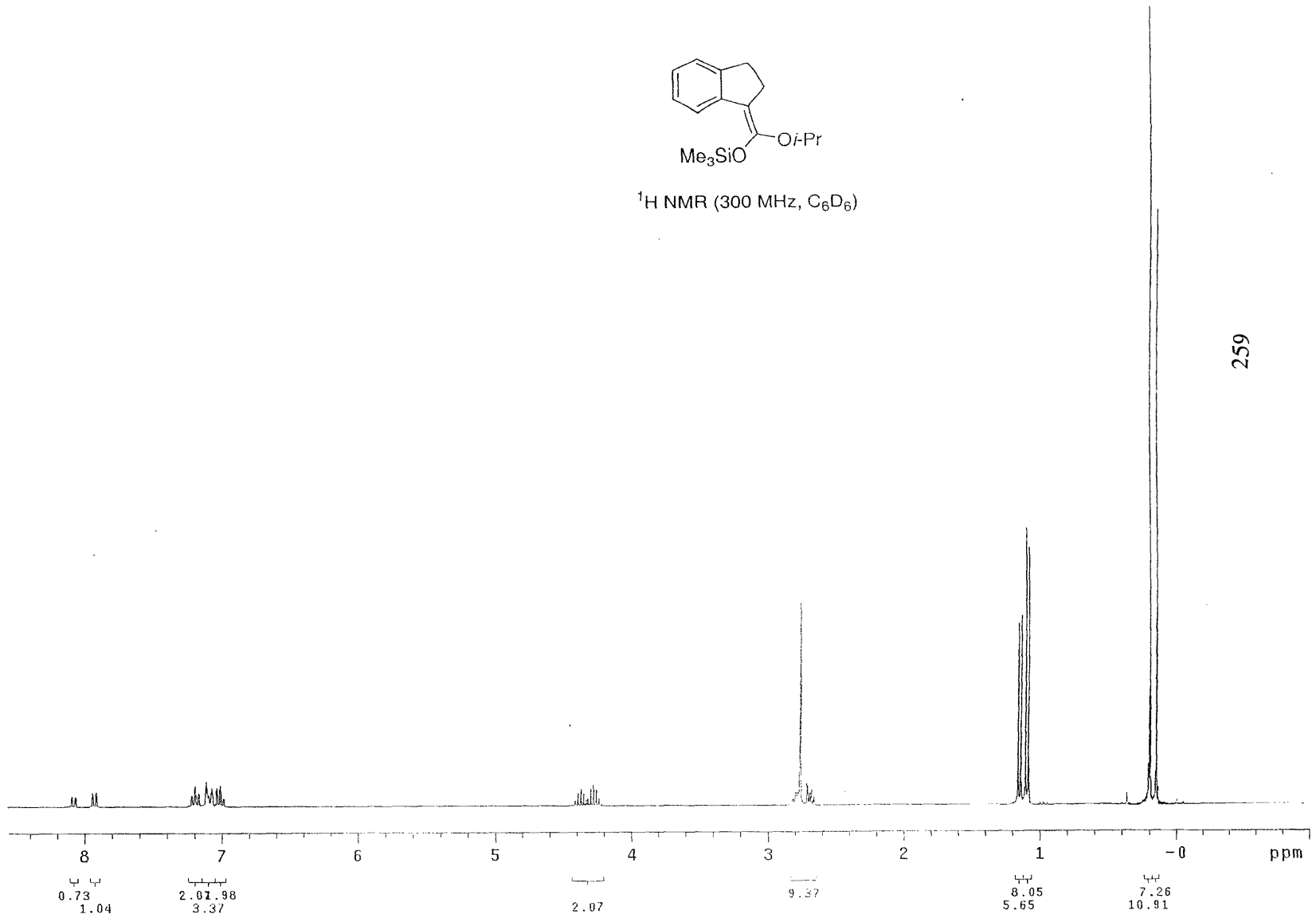


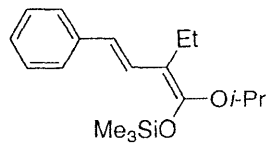

S
Et
OSiMe2t-Bu
i-PrO
1H NMR (500 MHz, C6D6)
257
8
7
6
5
4
3
2
1
-0
ppm
5.12
10.01
1.00
2.89
0.12



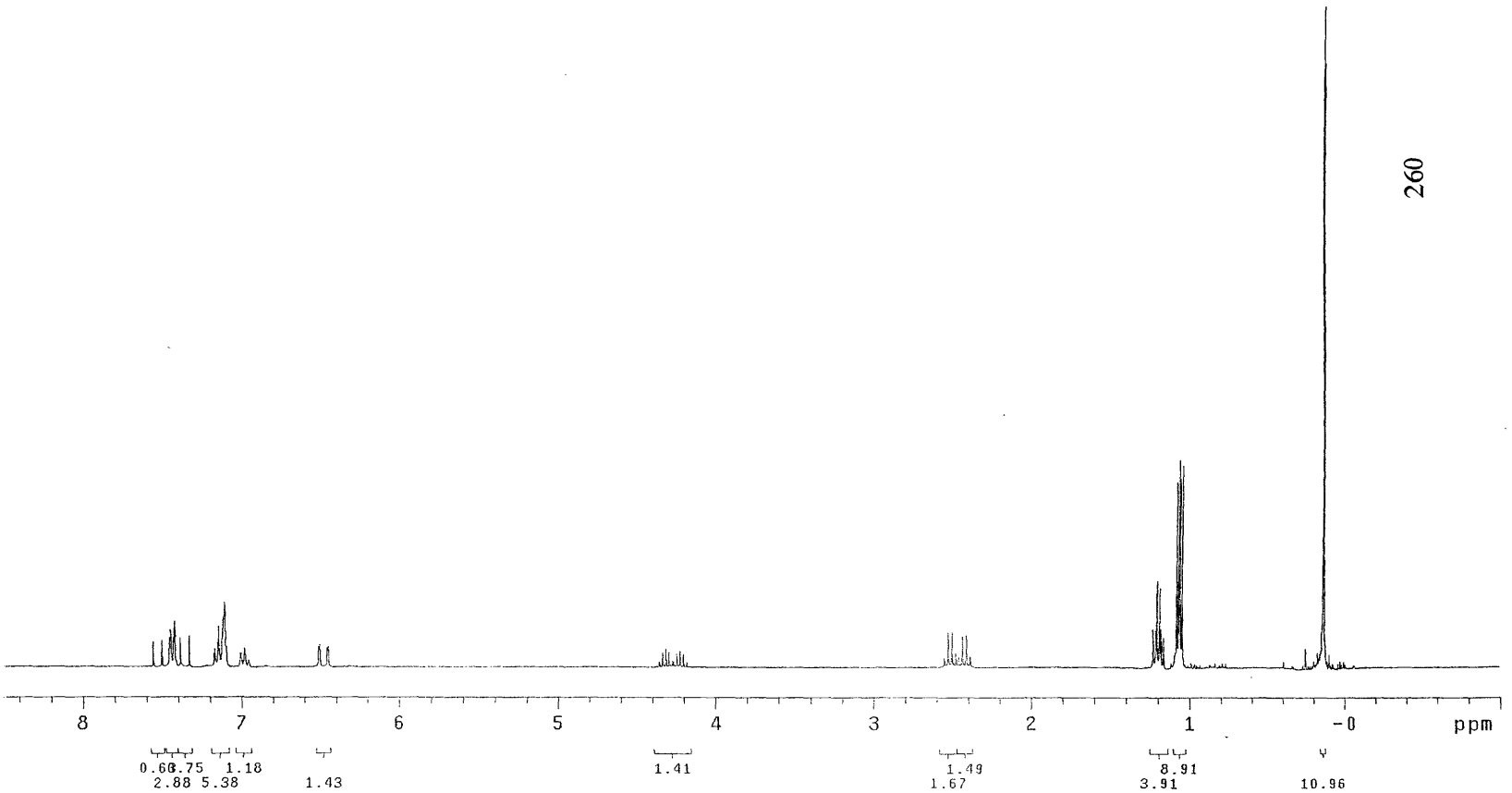
^{1}H NMR (300 MHz, C_6D_6)

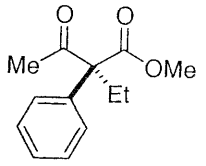



Me3SiO
Oi-Pr
1H NMR (300 MHz, C6D6)
8
7
6
5
4
3
2
1
-0
ppm
0.73
1.04
2.01
1.98
3.37
2.07
9.37
8.05
5.65
7.26
10.91

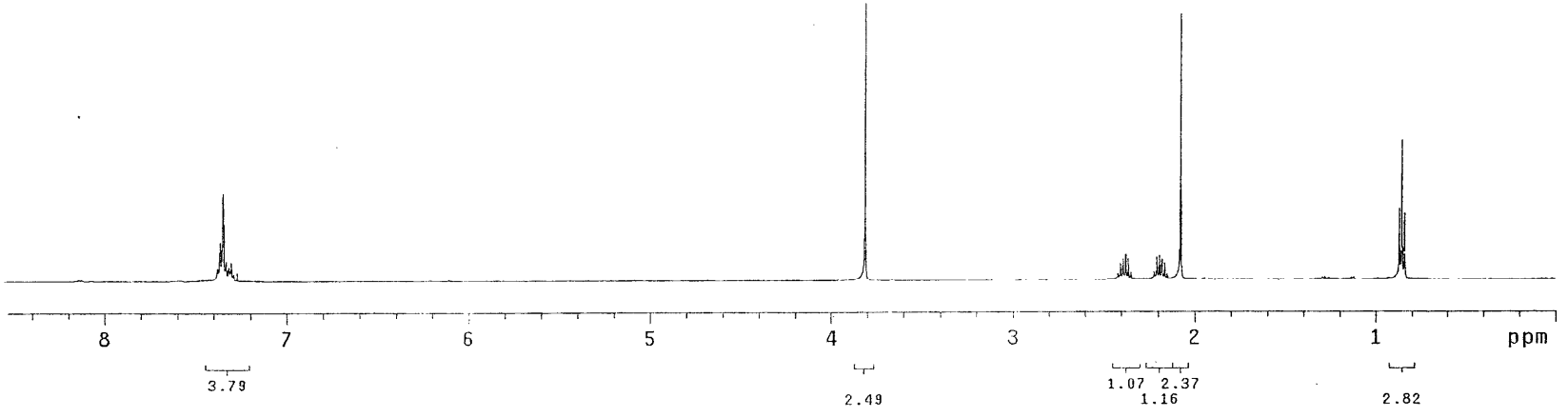


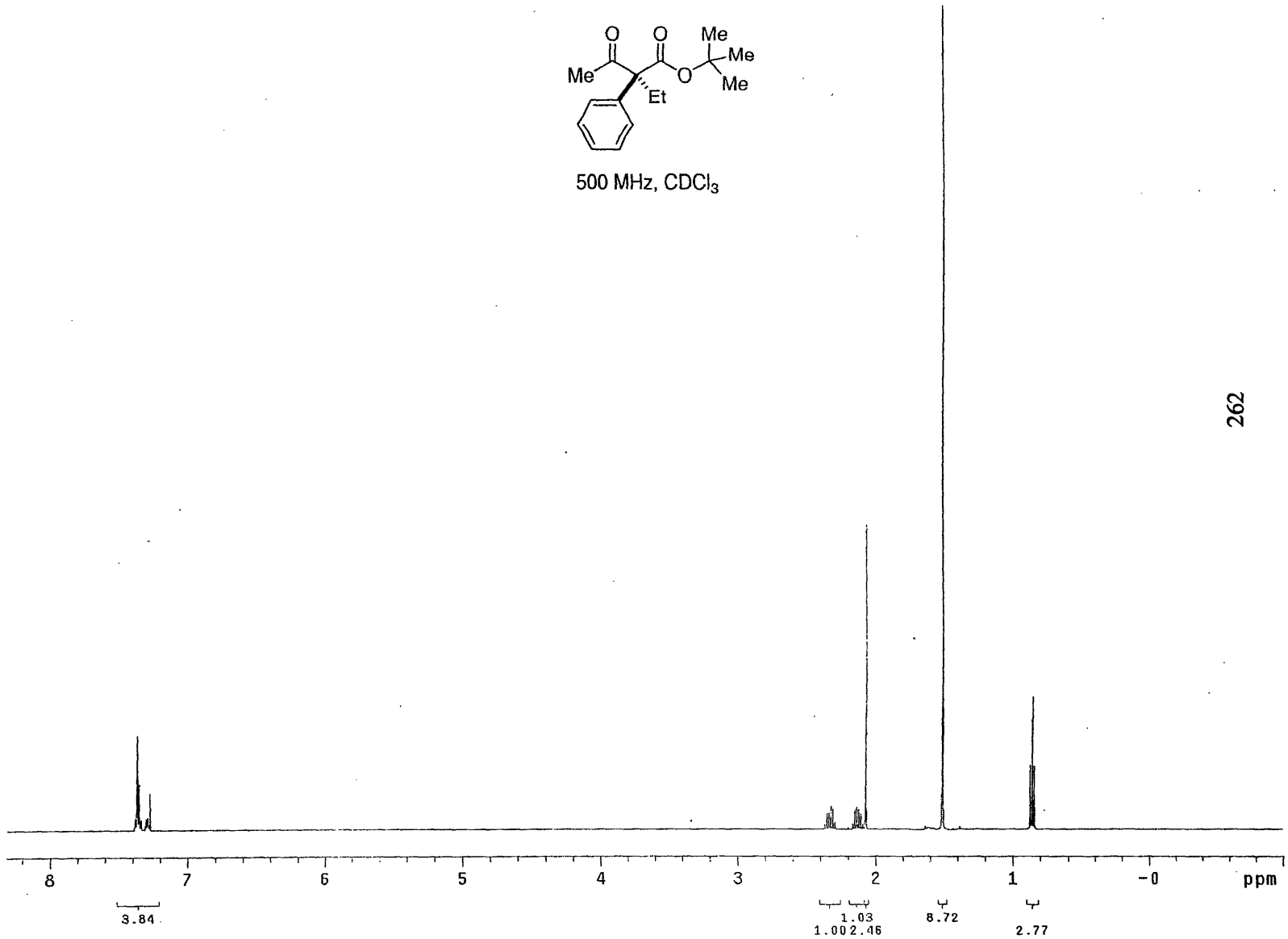
^{1}H NMR (300 MHz, C_6D_6)

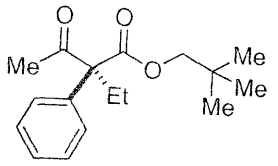




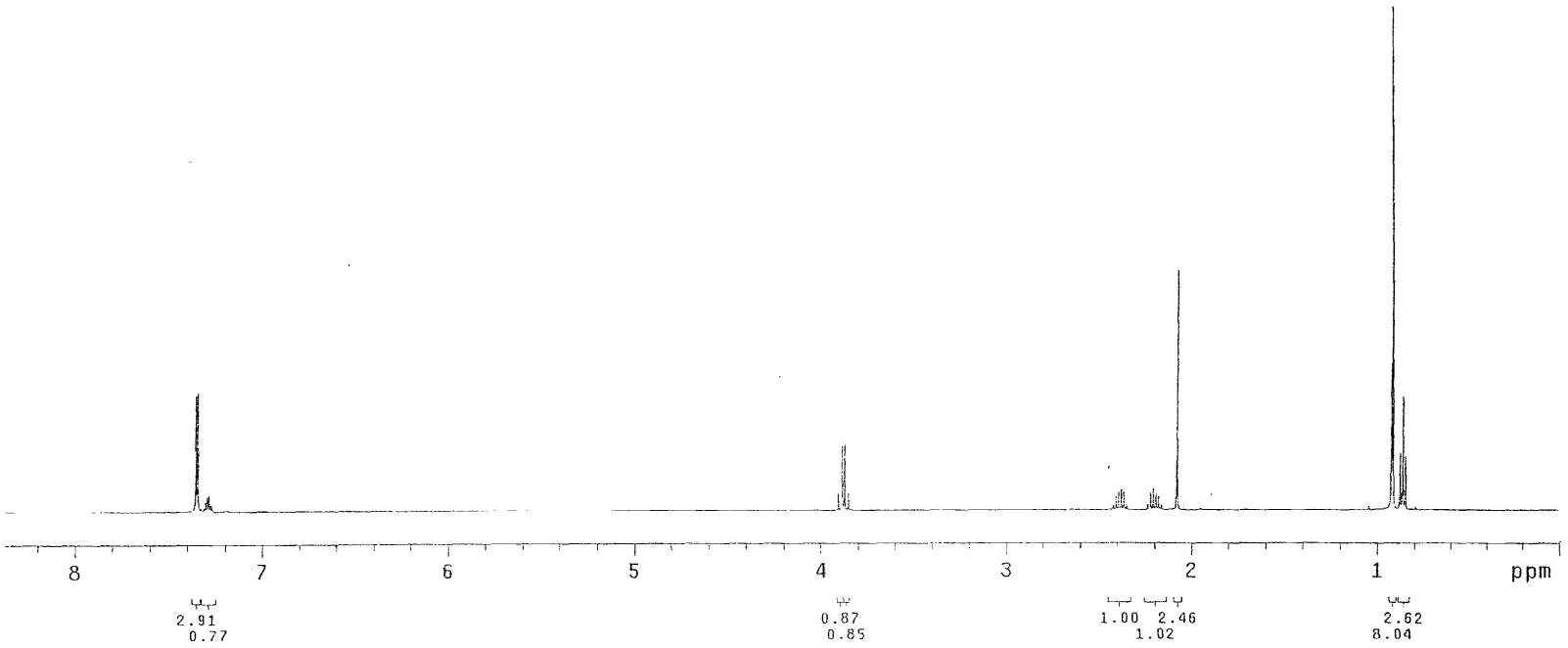
500 MHz, $CDCl_3$

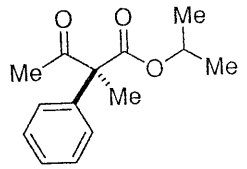



O
O
Me
Me
Me
O
Et
500 MHz, CDCl3
8
7
6
5
4
3
2
1
-0
ppm
3.84
1.03
1.00
2.46
8.72
2.77

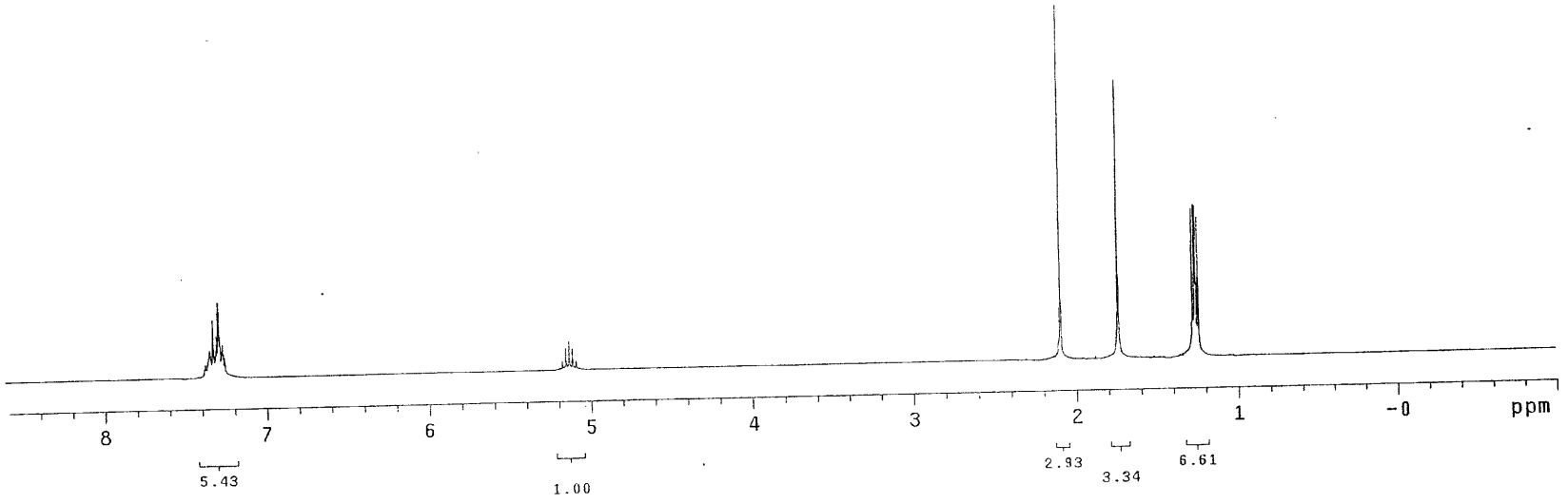


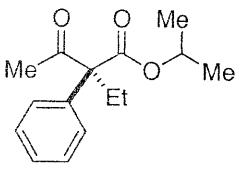
500 MHz, $CDCl_3$



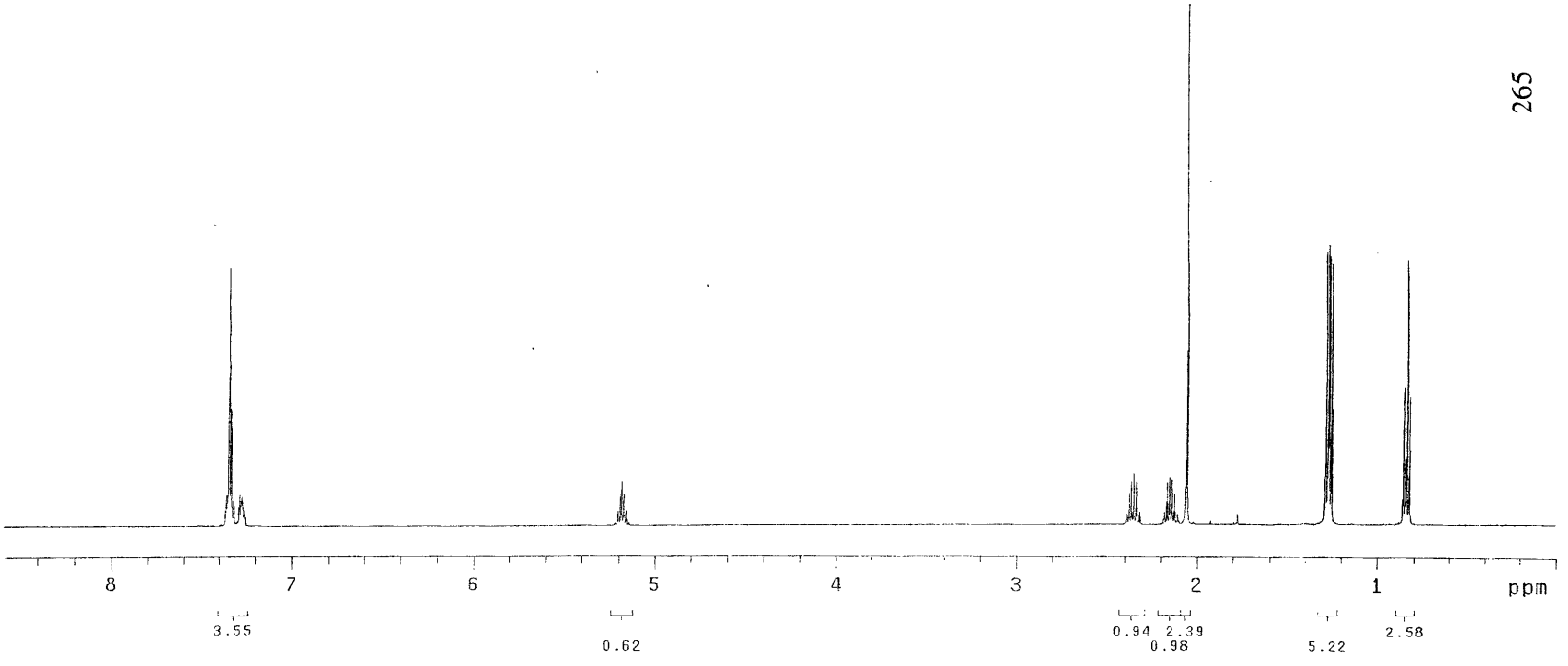


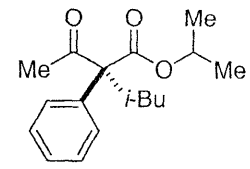
300 MHz, $CDCl_3$



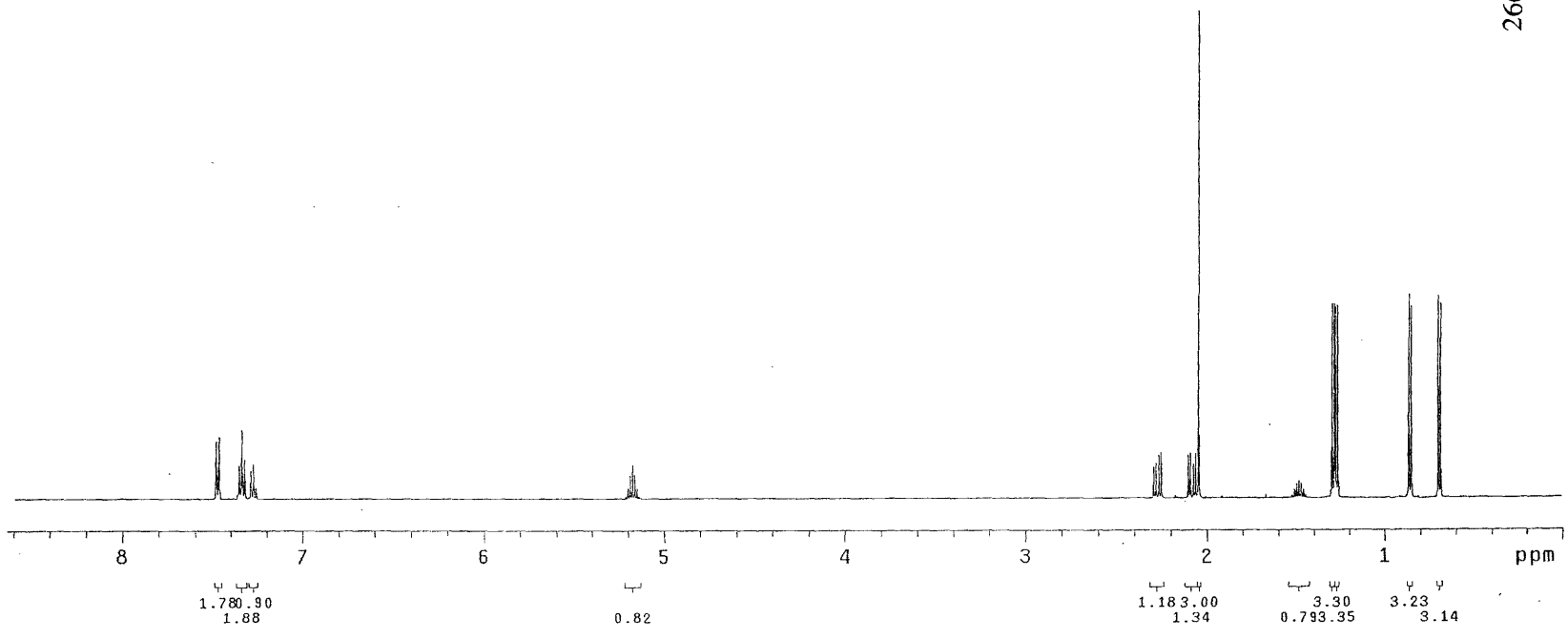


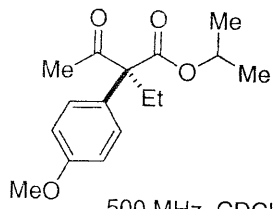
500 MHz, $CDCl_3$



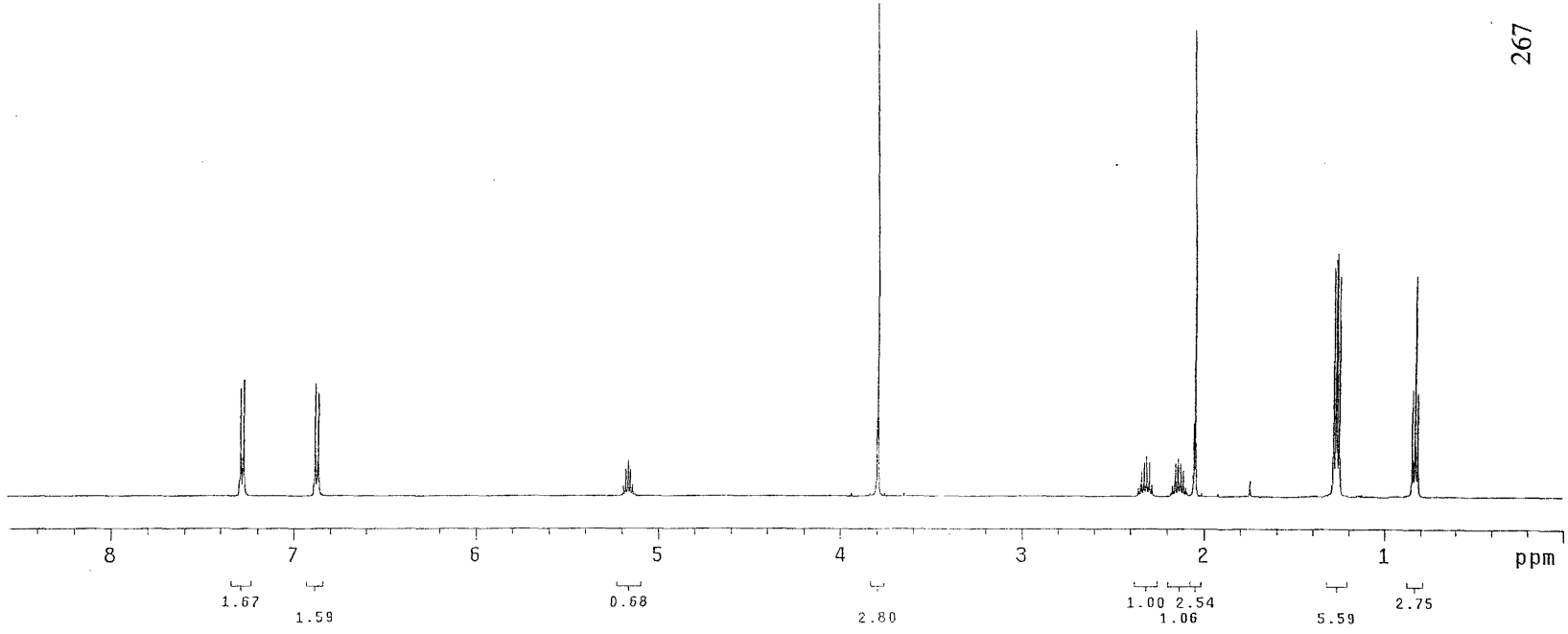


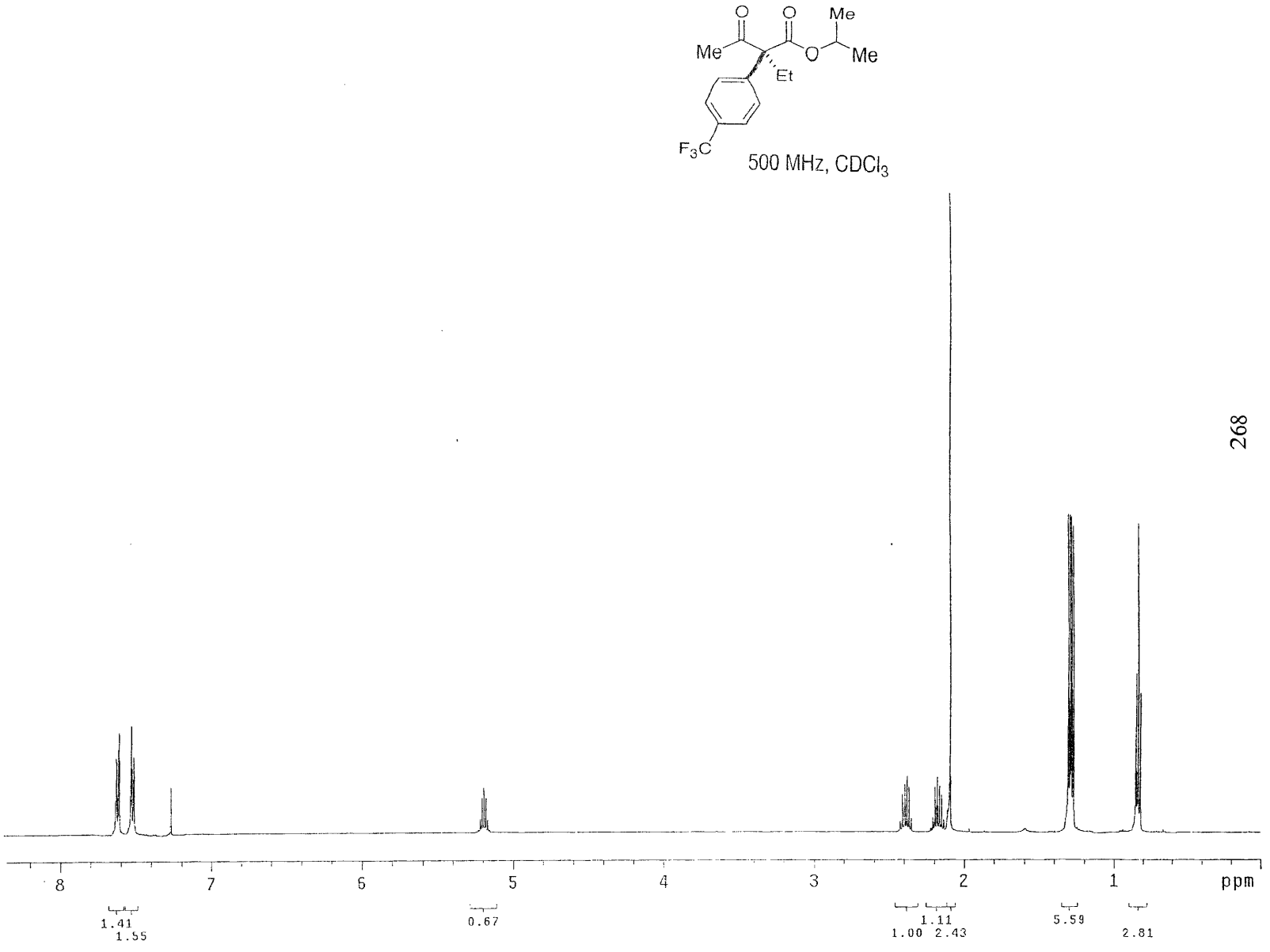
500 MHz, $CDCl_3$

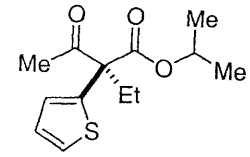




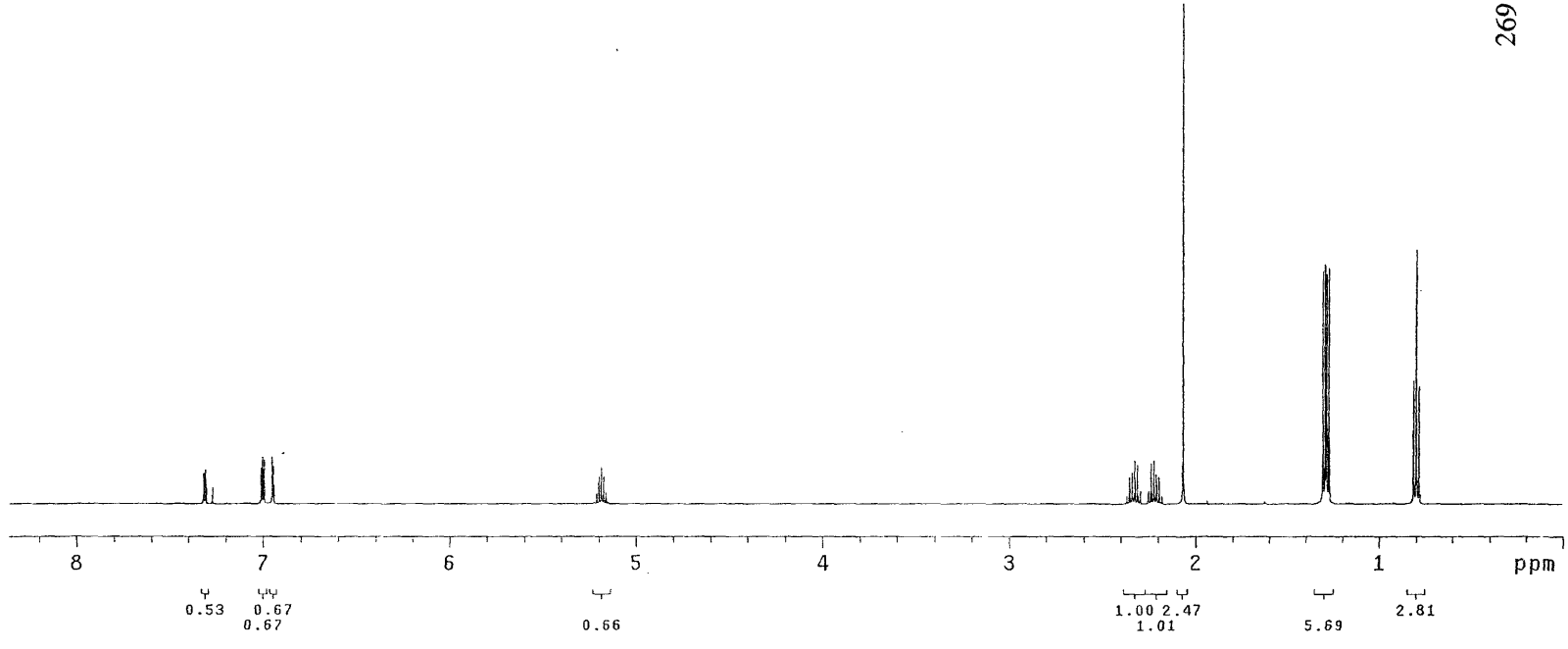
500 MHz, $CDCl_3$

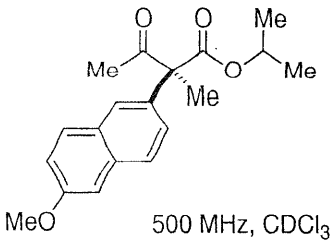



O
O
Me
Me
O
Me
Et
F3C
500 MHz, CDCl3
8
7
6
5
4
3
2
1
ppm
1.41
1.55
0.67
1.00
1.11
2.43
5.59
2.81

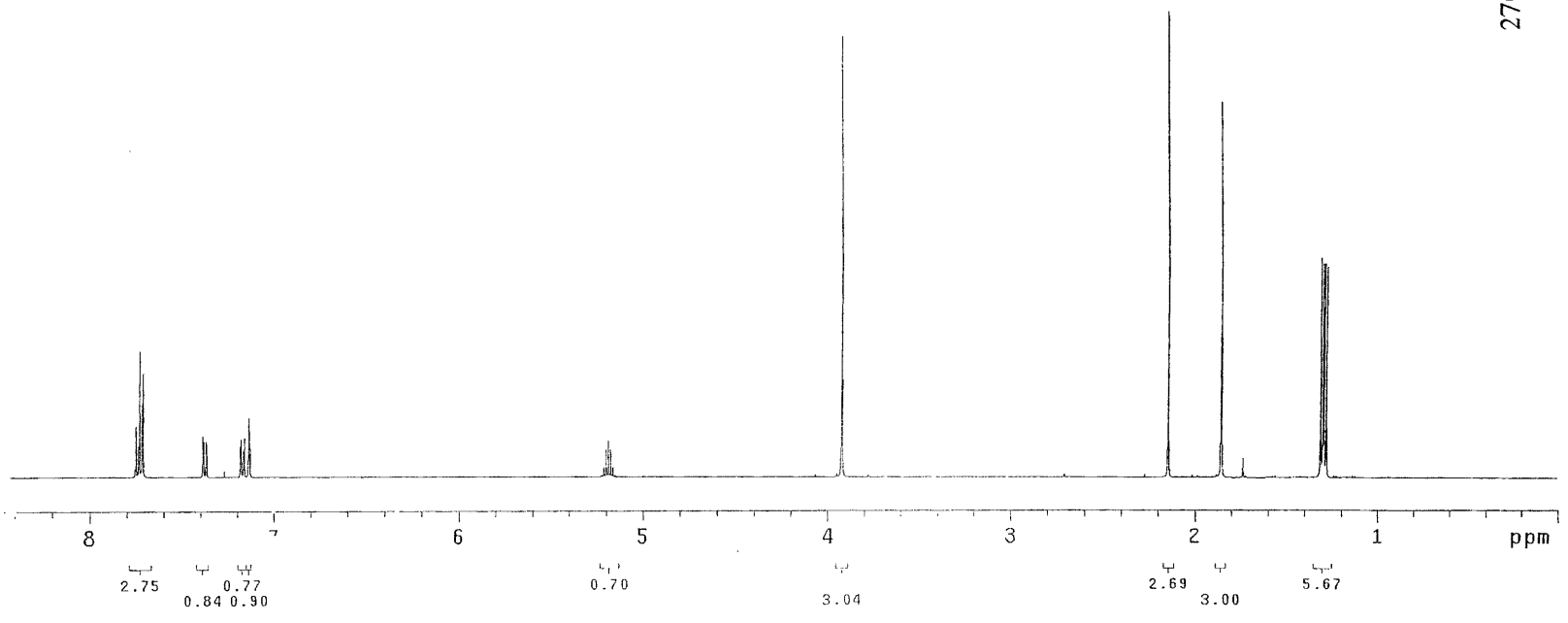


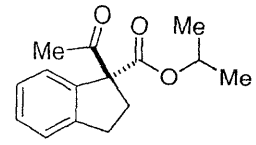
500 MHz, $CDCl_3$



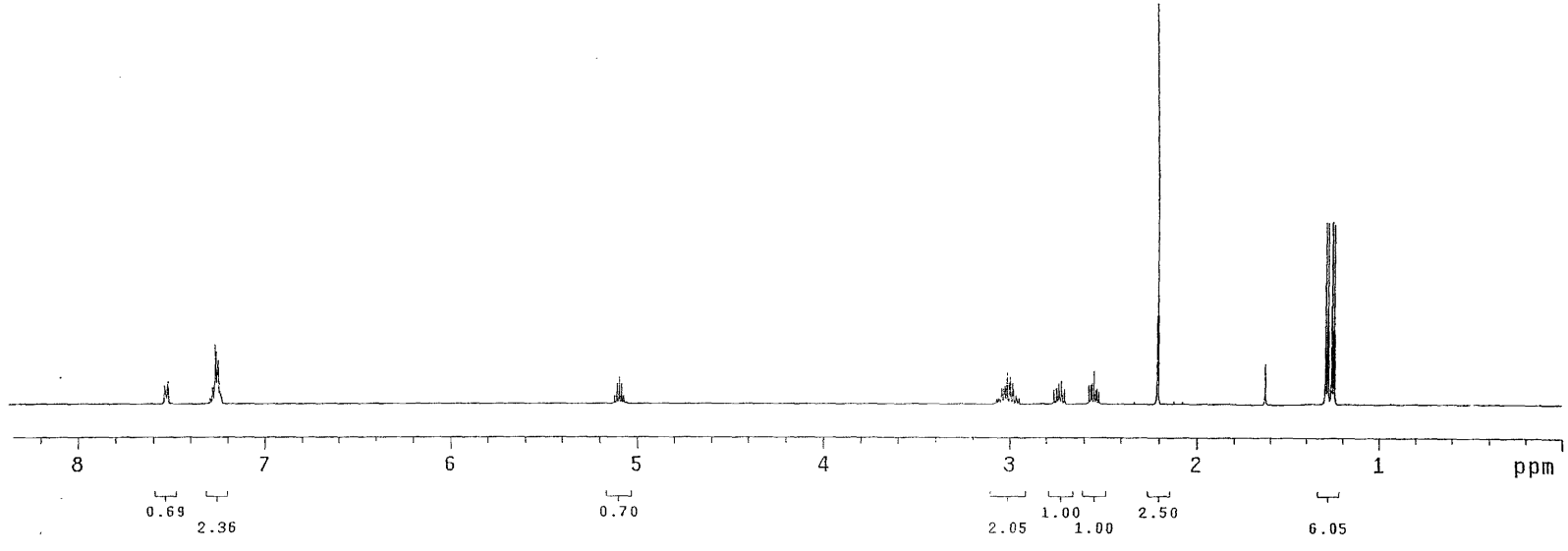


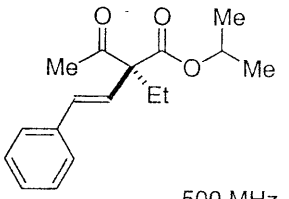
500 MHz, $CDCl_3$



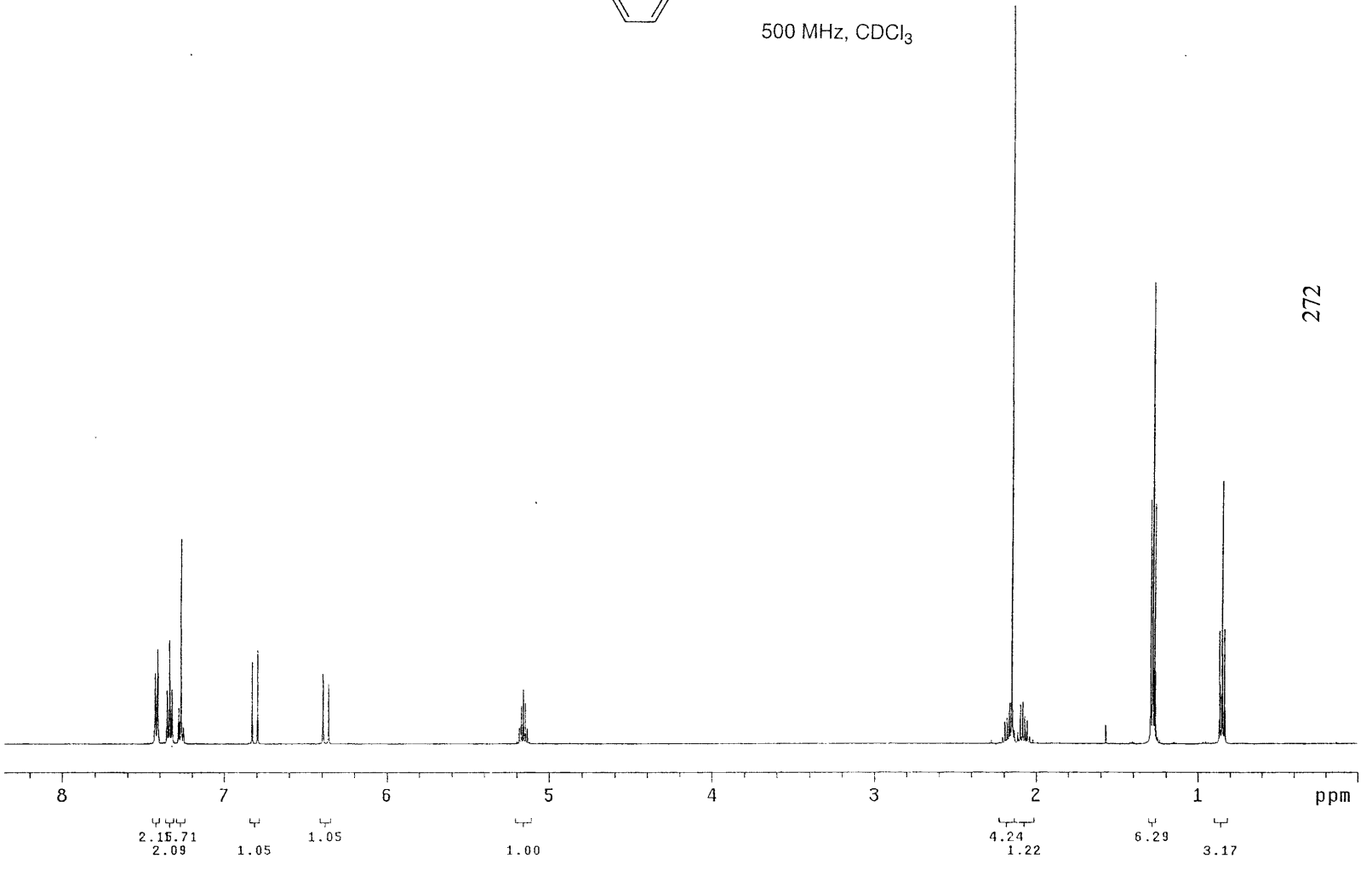


500 MHz, $CDCl_3$

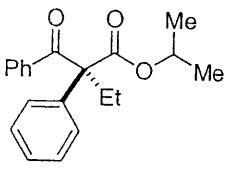




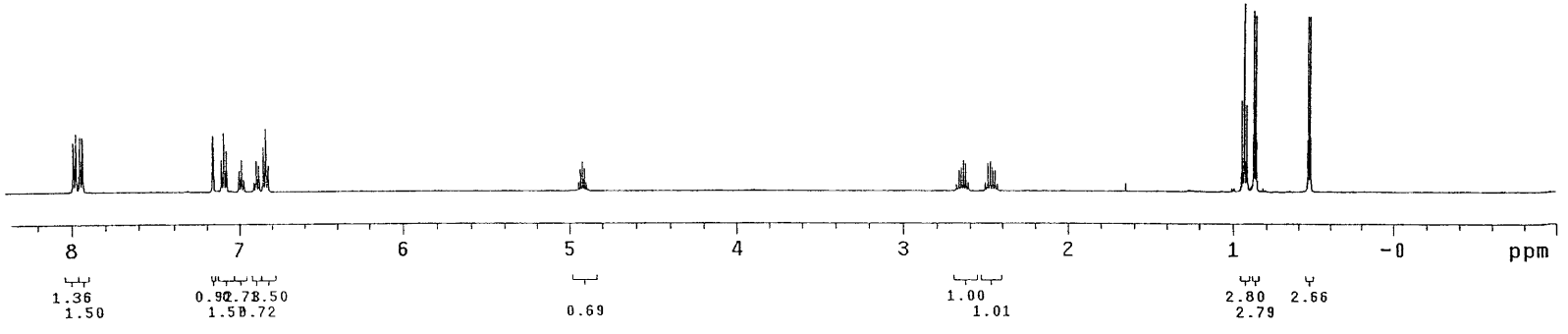
500 MHz, $CDCl_3$

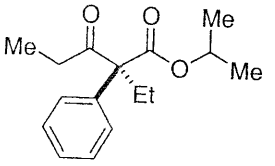


272

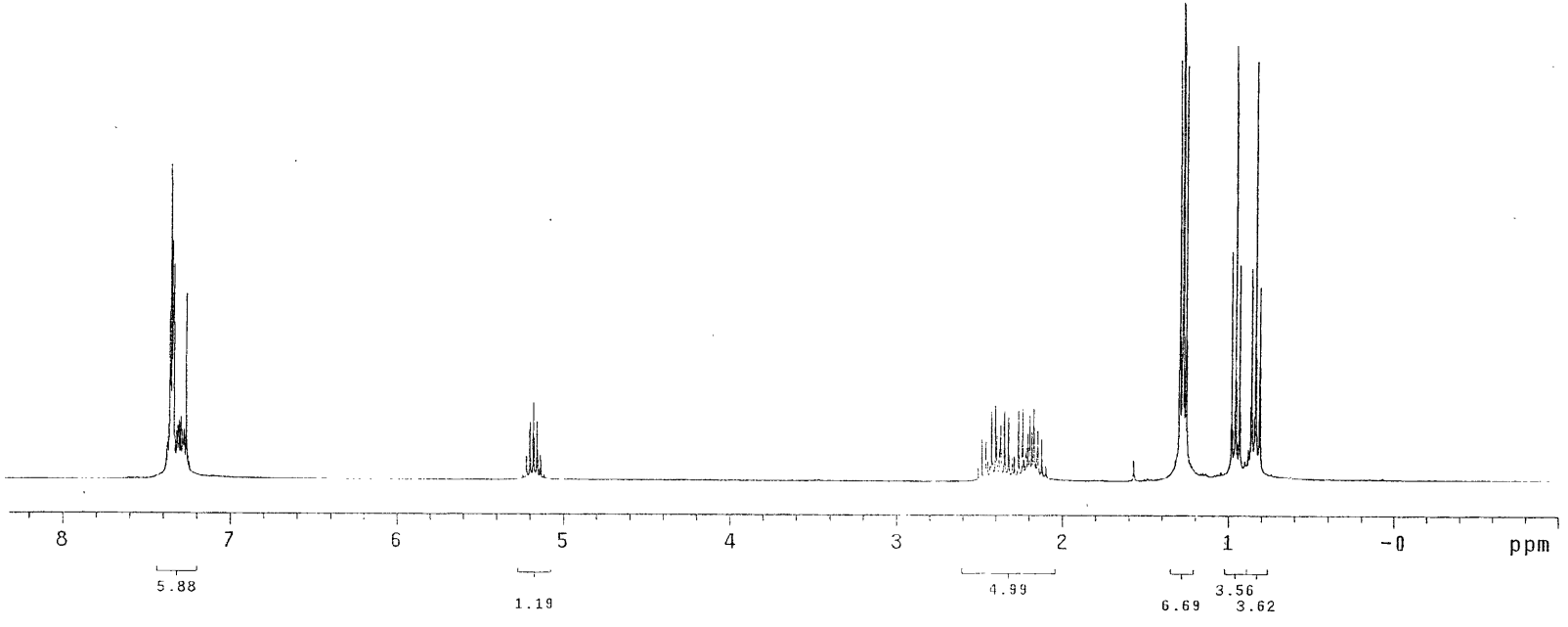

O
O
Me
Ph
O
Me
Et

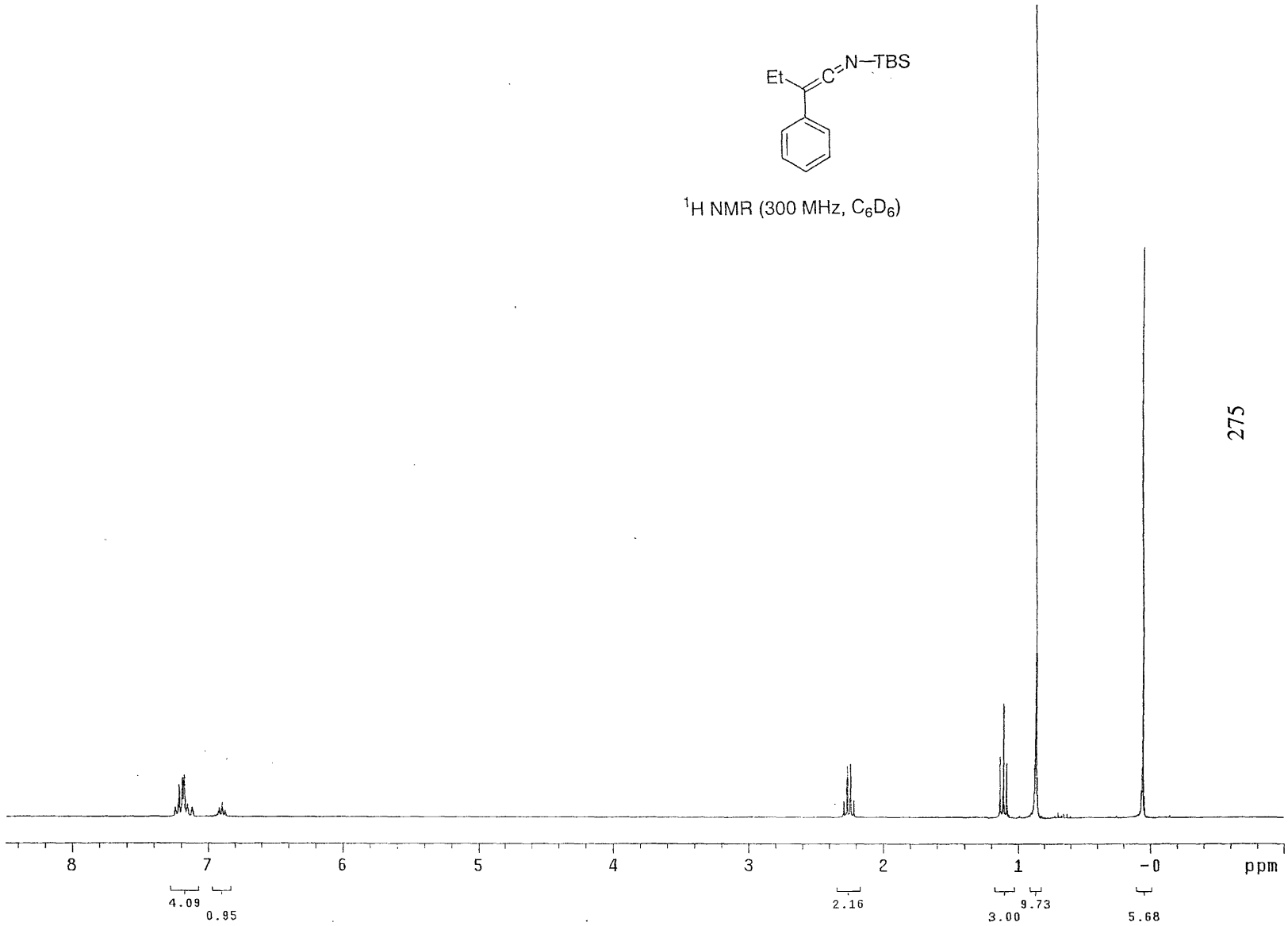
500 MHz, C_6D_6

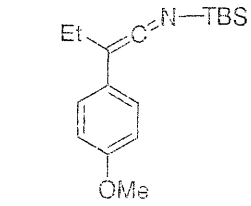

8
7
6
5
4
3
2
1
-0
ppm
1.36
1.50
0.90
1.50
2.73
0.72
8.50
0.69
1.00
1.01
2.80
2.79
2.66



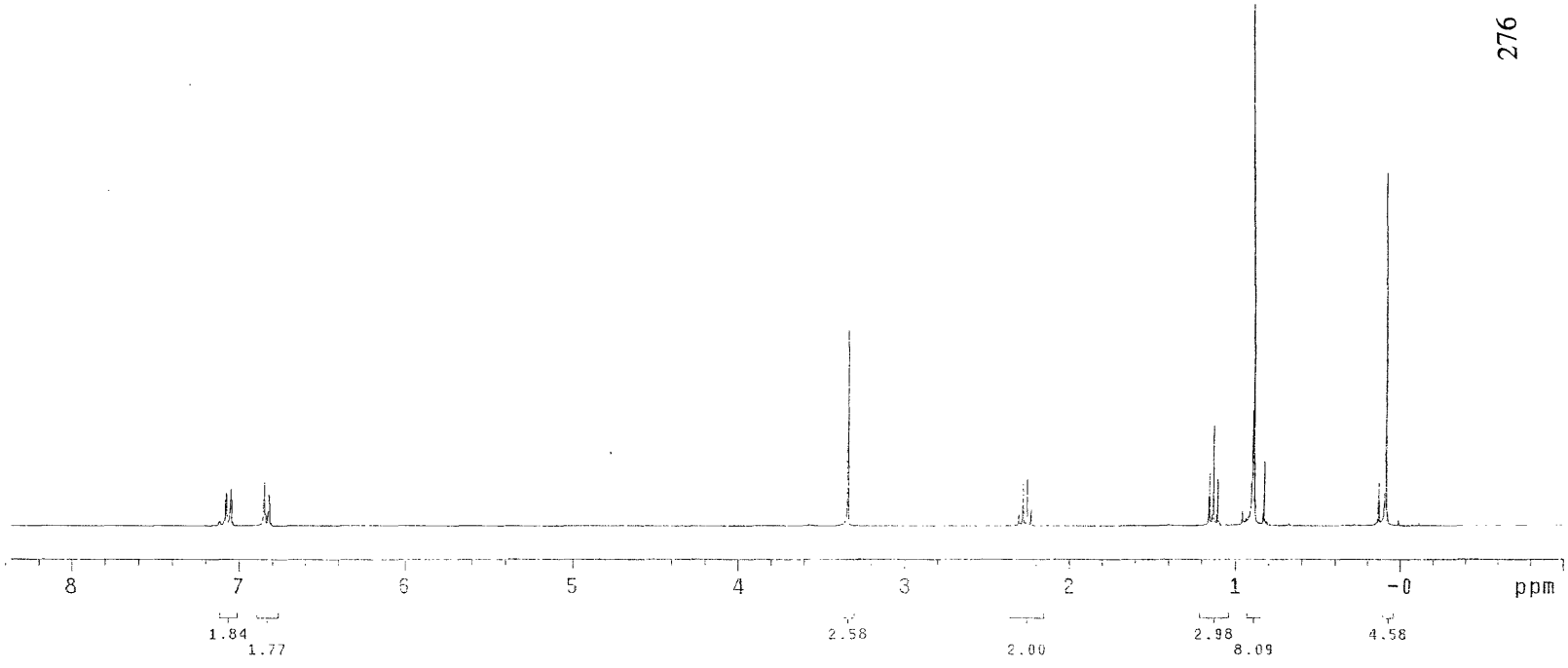
300 MHz, $CDCl_3$

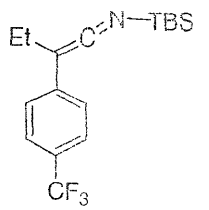



Et
C
N—TBS
^{1}H NMR (300 MHz, C_6D_6)
8
7
6
5
4
3
2
1
-0
ppm
4.09
0.95
2.16
3.00
9.73
5.68

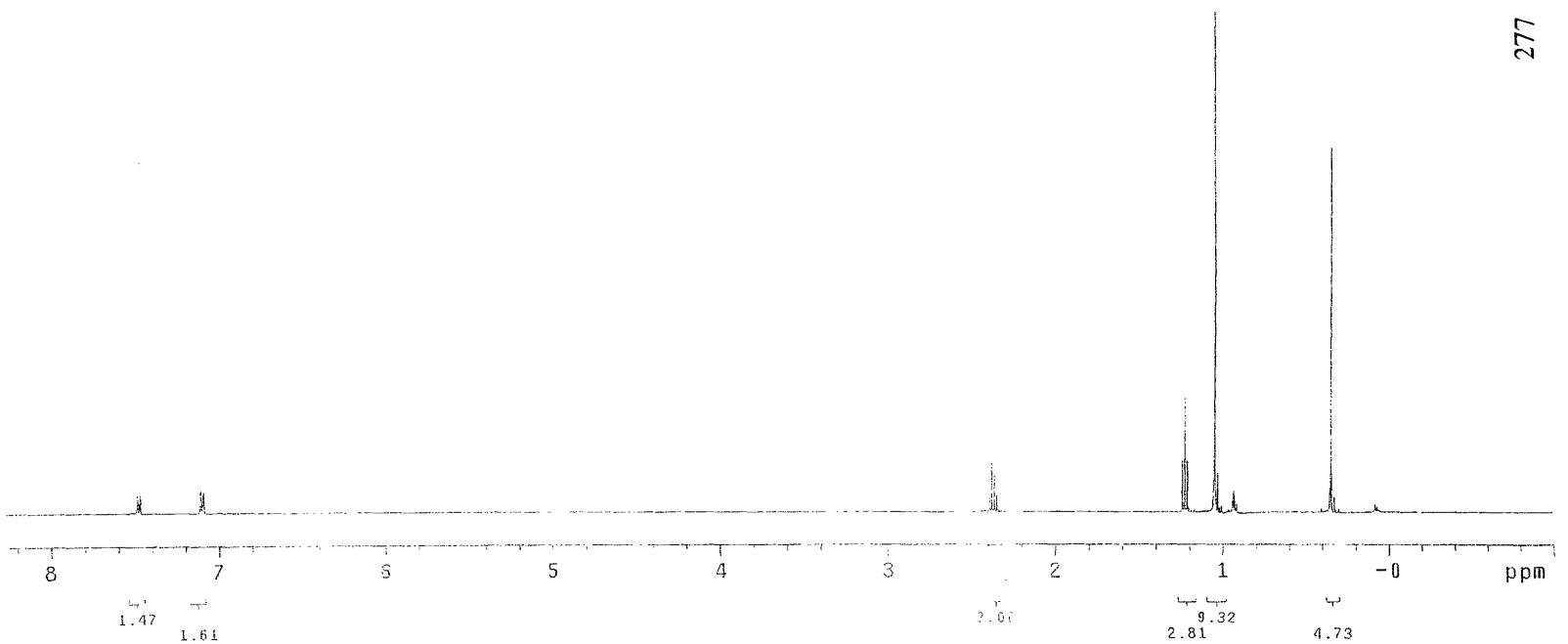


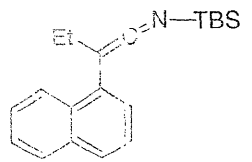
^{1}H NMR (300 MHz, C_6D_6)



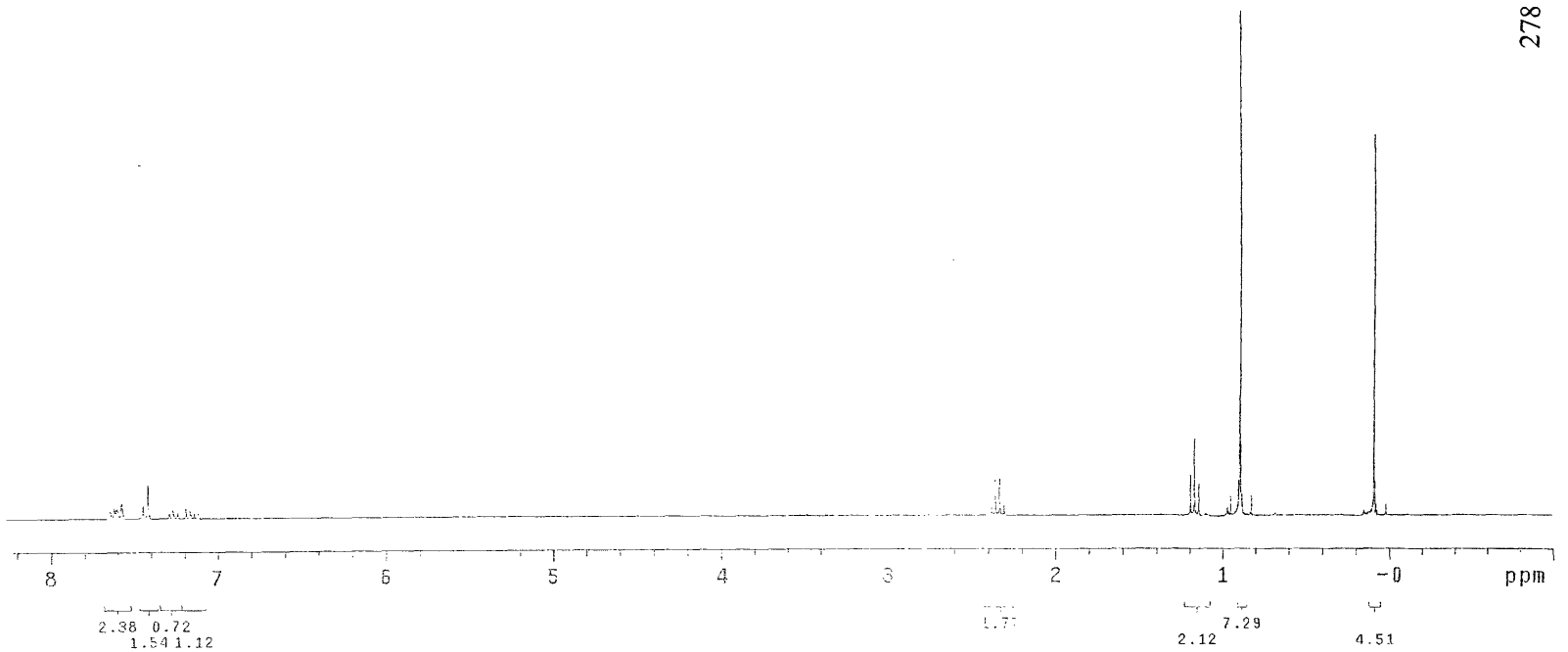


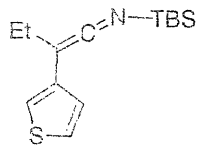
^{1}H NMR (500 MHz, CD_2Cl_2)



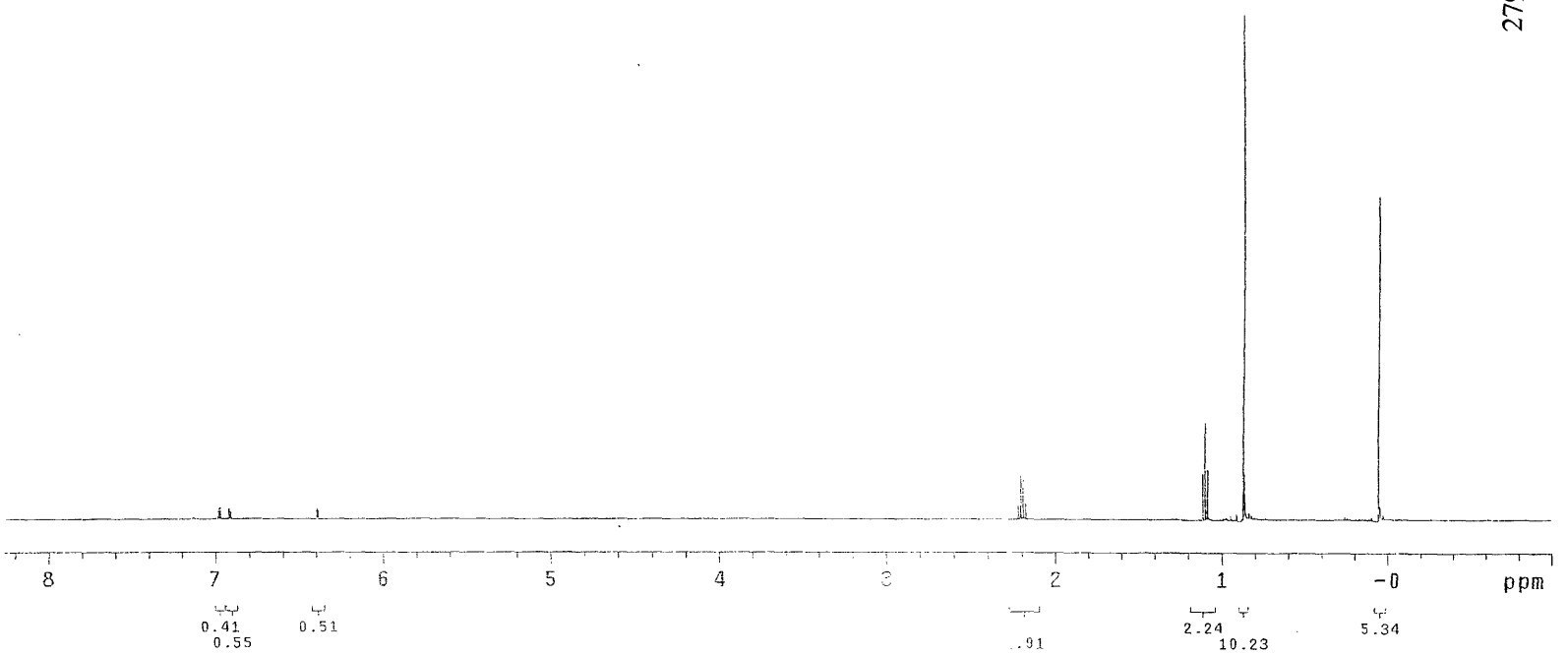


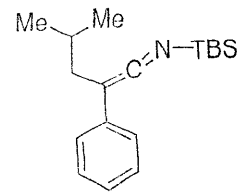
^{1}H NMR (300 MHz, C_6D_6)



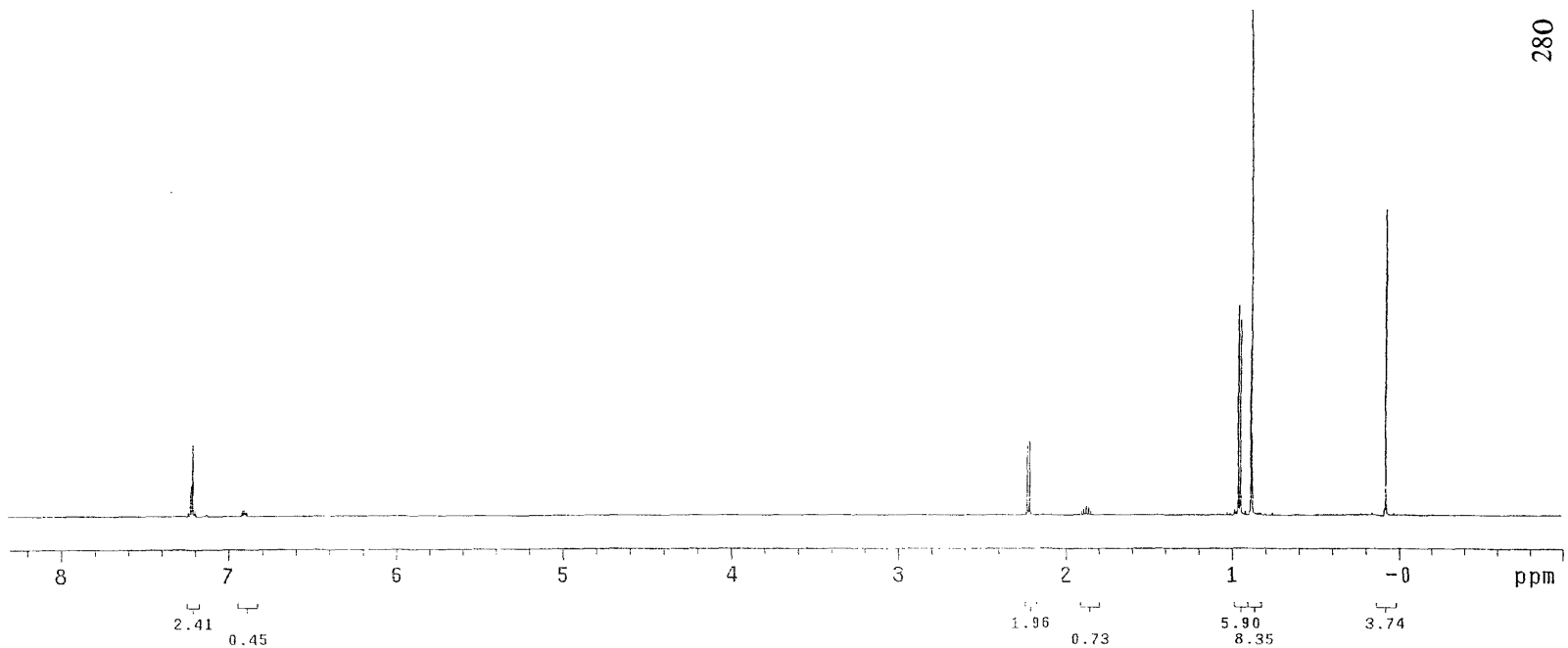


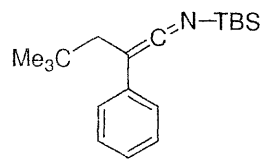
^{1}H NMR (500 MHz, C_6D_6)



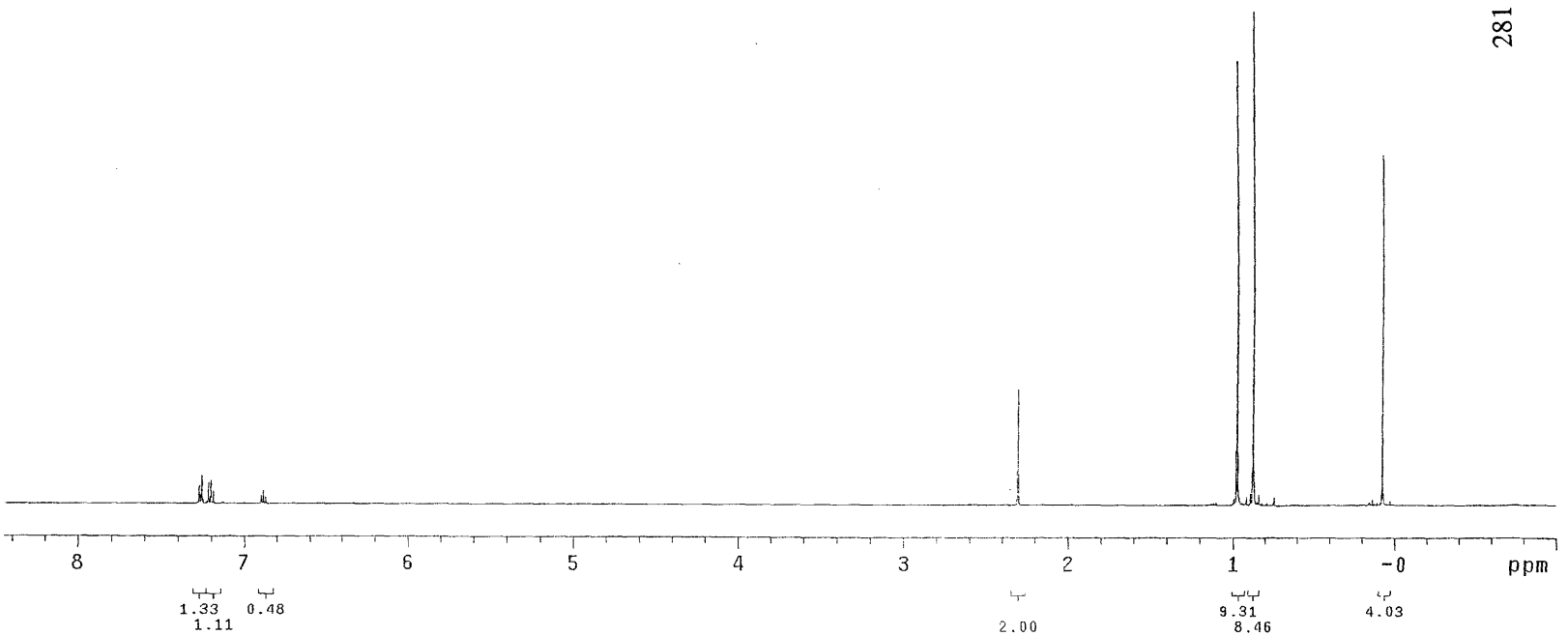


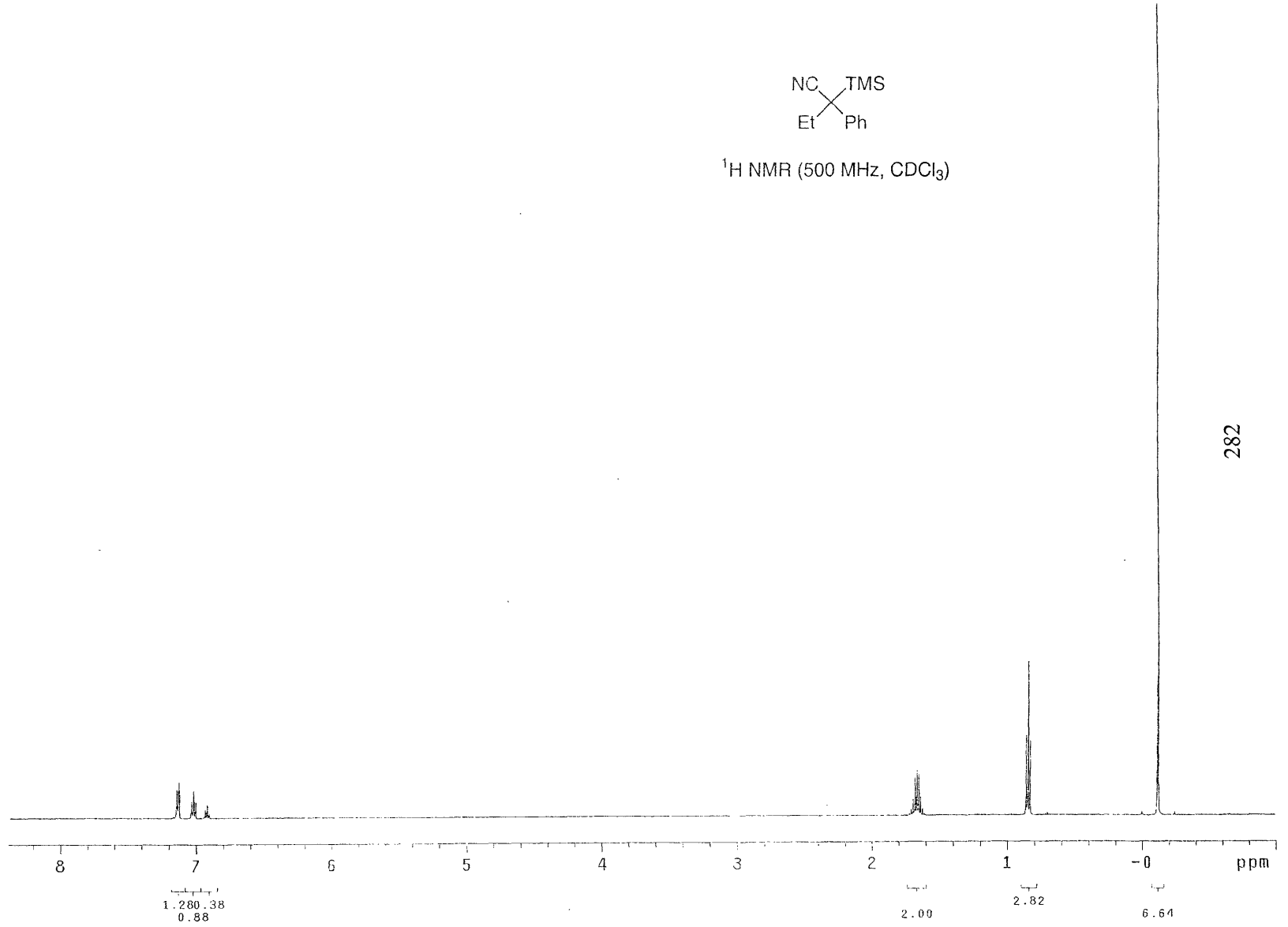
^{1}H NMR (500 MHz, C_6D_6)

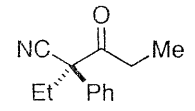




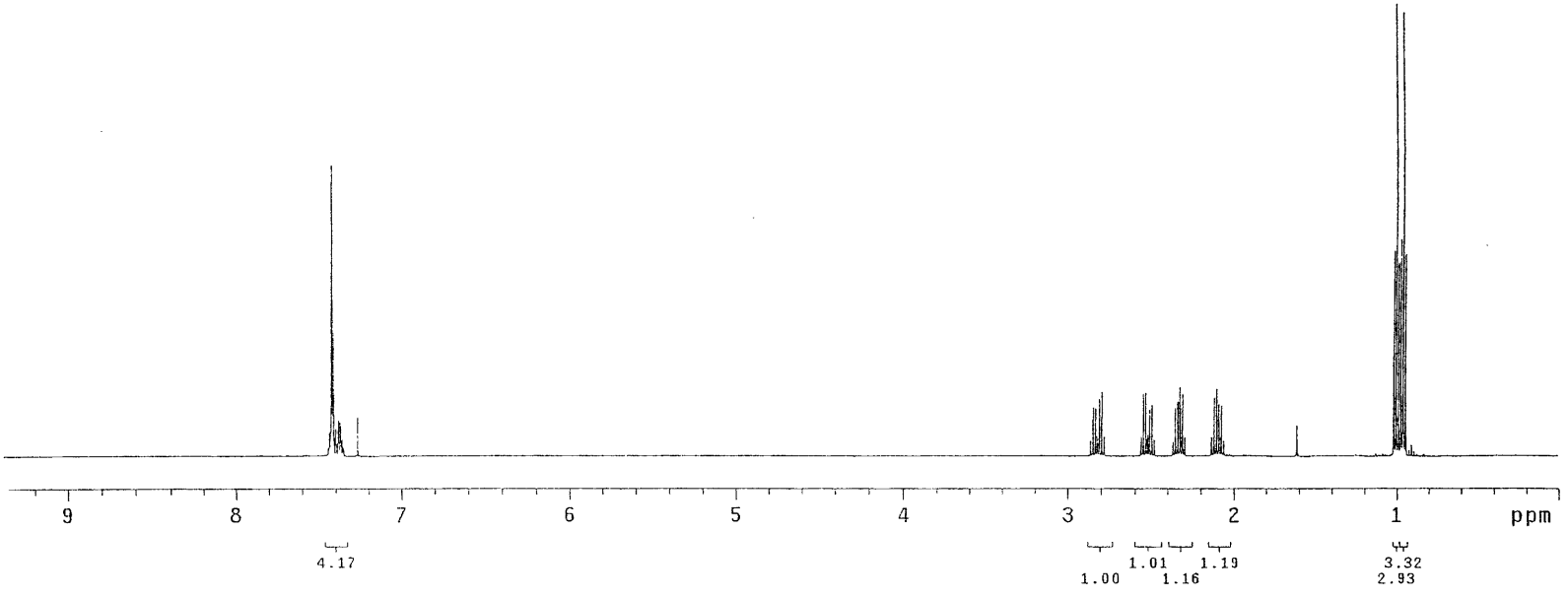
^{1}H NMR (500 MHz, C_6D_6)

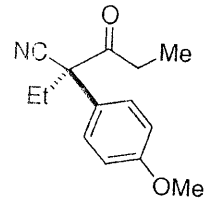



NC
TMS
Et
Ph
^{1}H NMR (500 MHz, $CDCl_3$)
282
8
7
6
5
4
3
2
1
-0
ppm
1.28
0.38
0.88
2.00
2.82
6.64

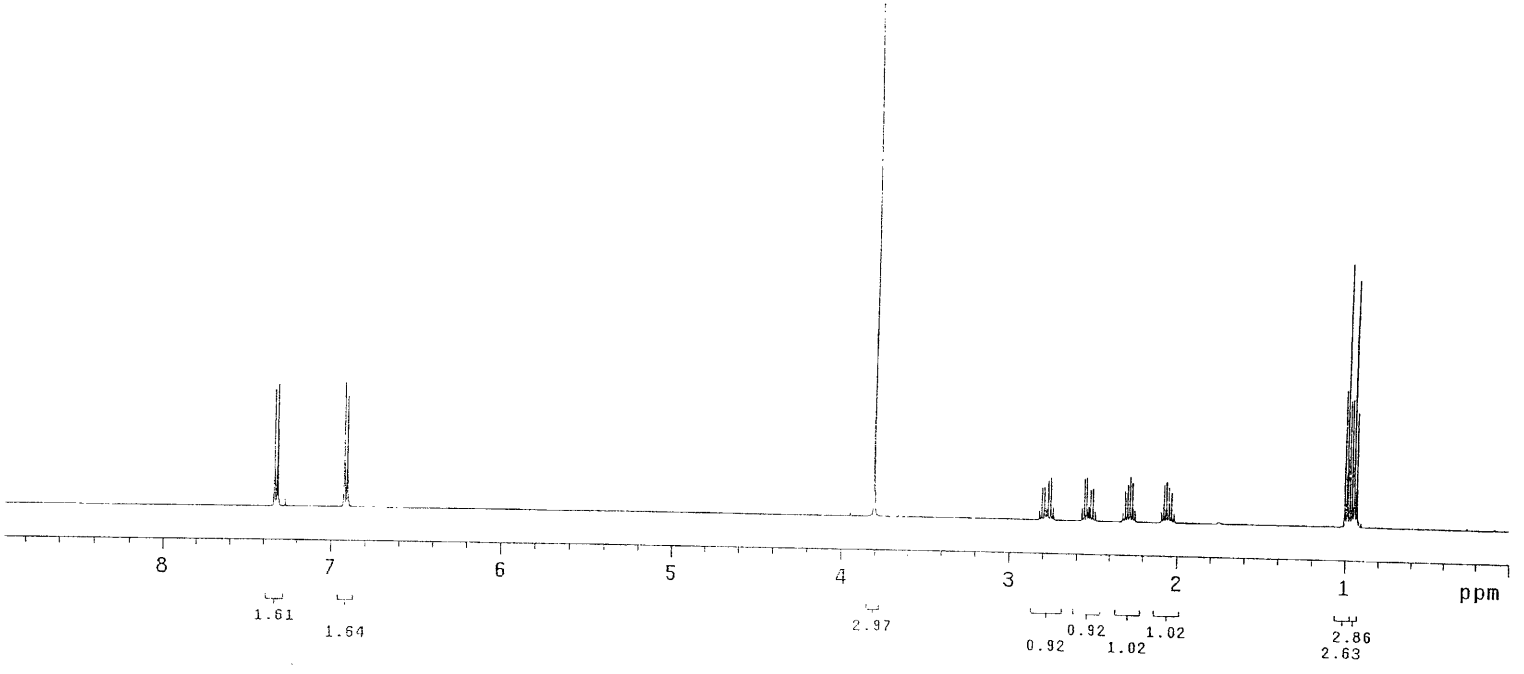


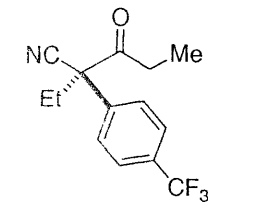
^{1}H NMR (500 MHz, $CDCl_3$)



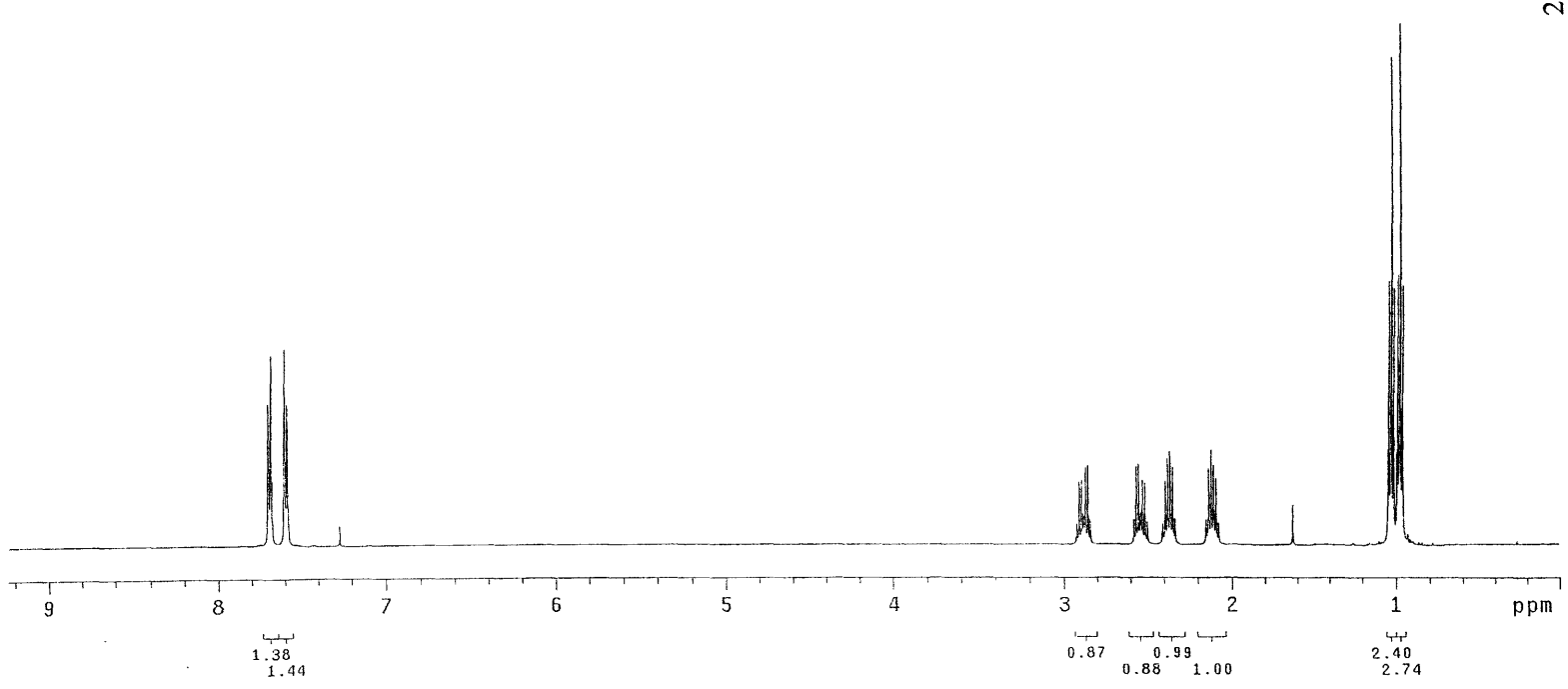


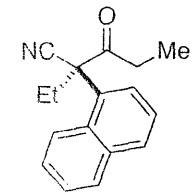
^{1}H NMR (500 MHz, $CDCl_3$)



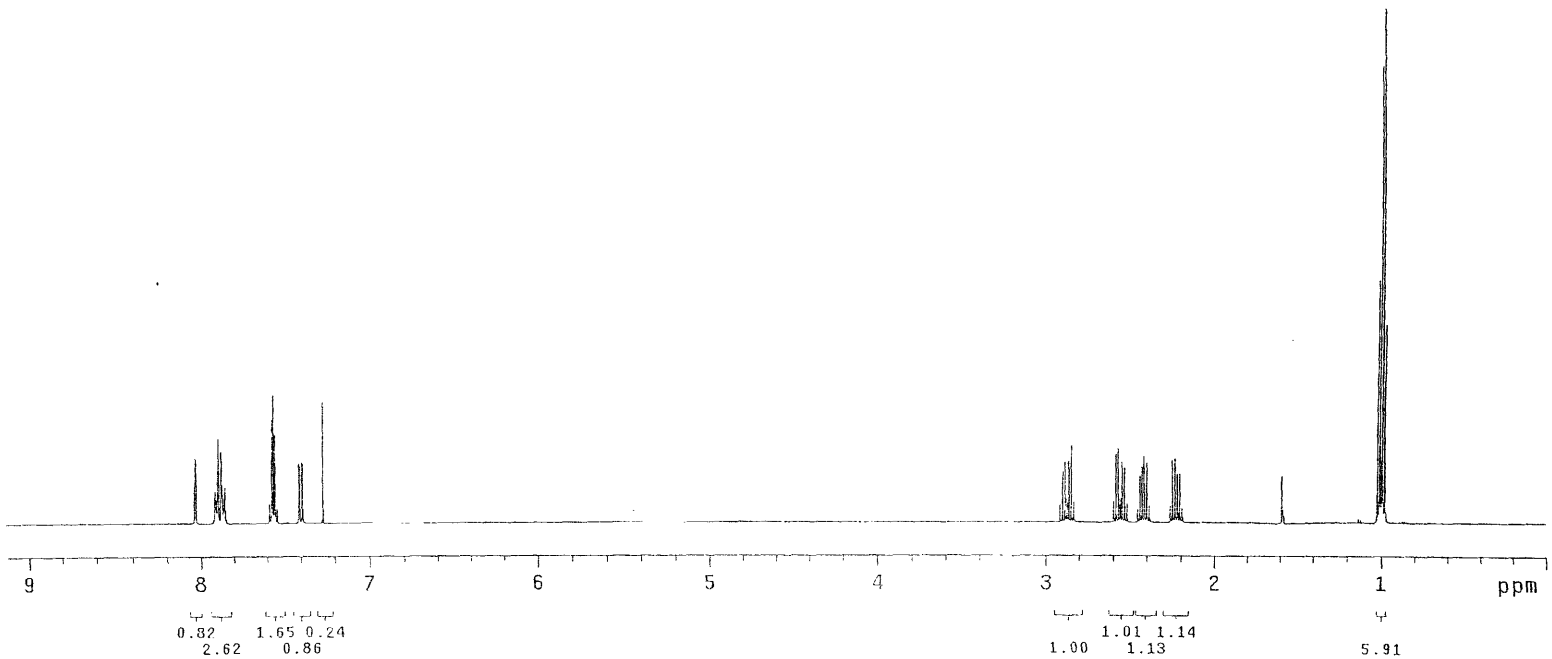


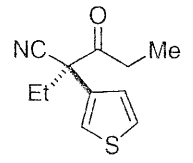
^{1}H NMR (500 MHz, $CDCl_3$)



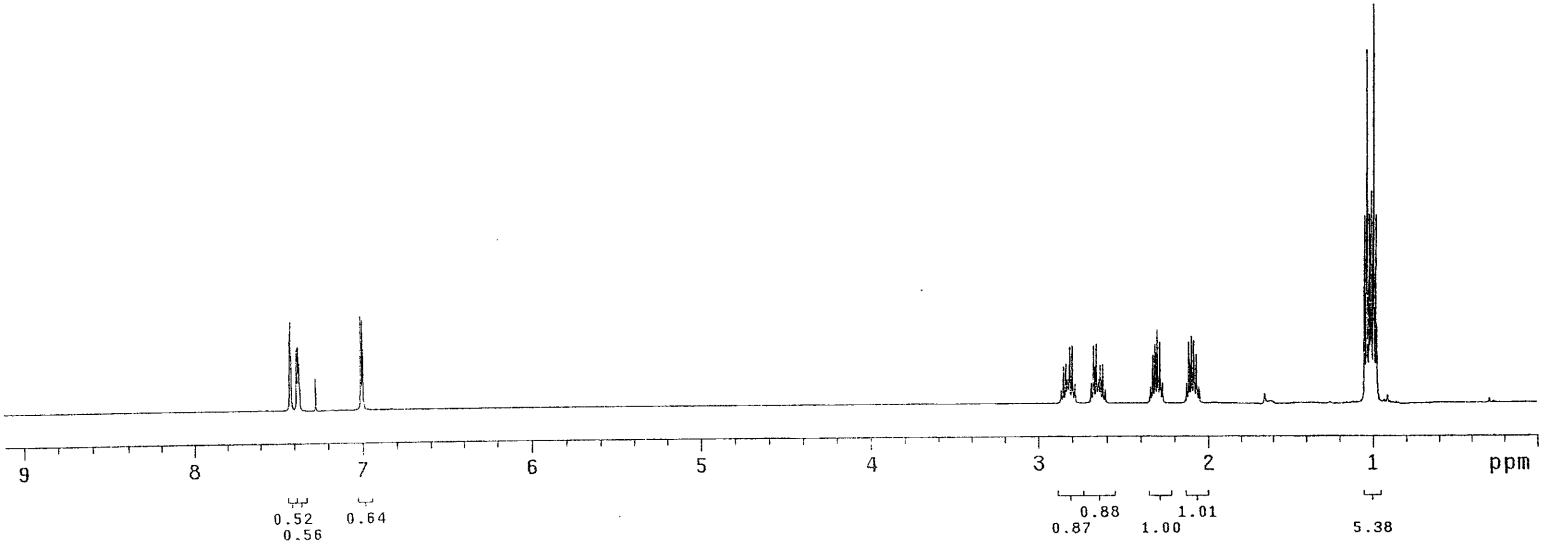


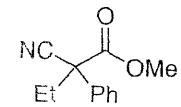
^{1}H NMR (500 MHz, $CDCl_3$)



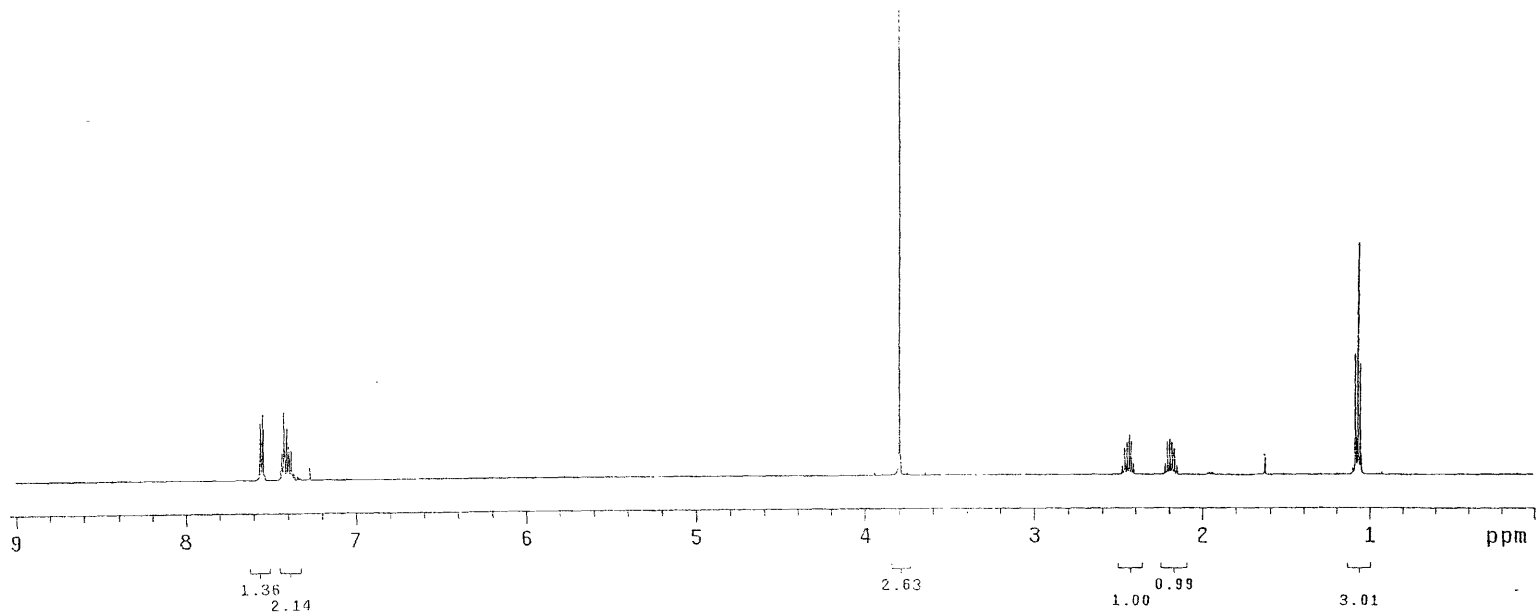


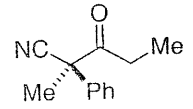
^{1}H NMR (500 MHz, $CDCl_3$)



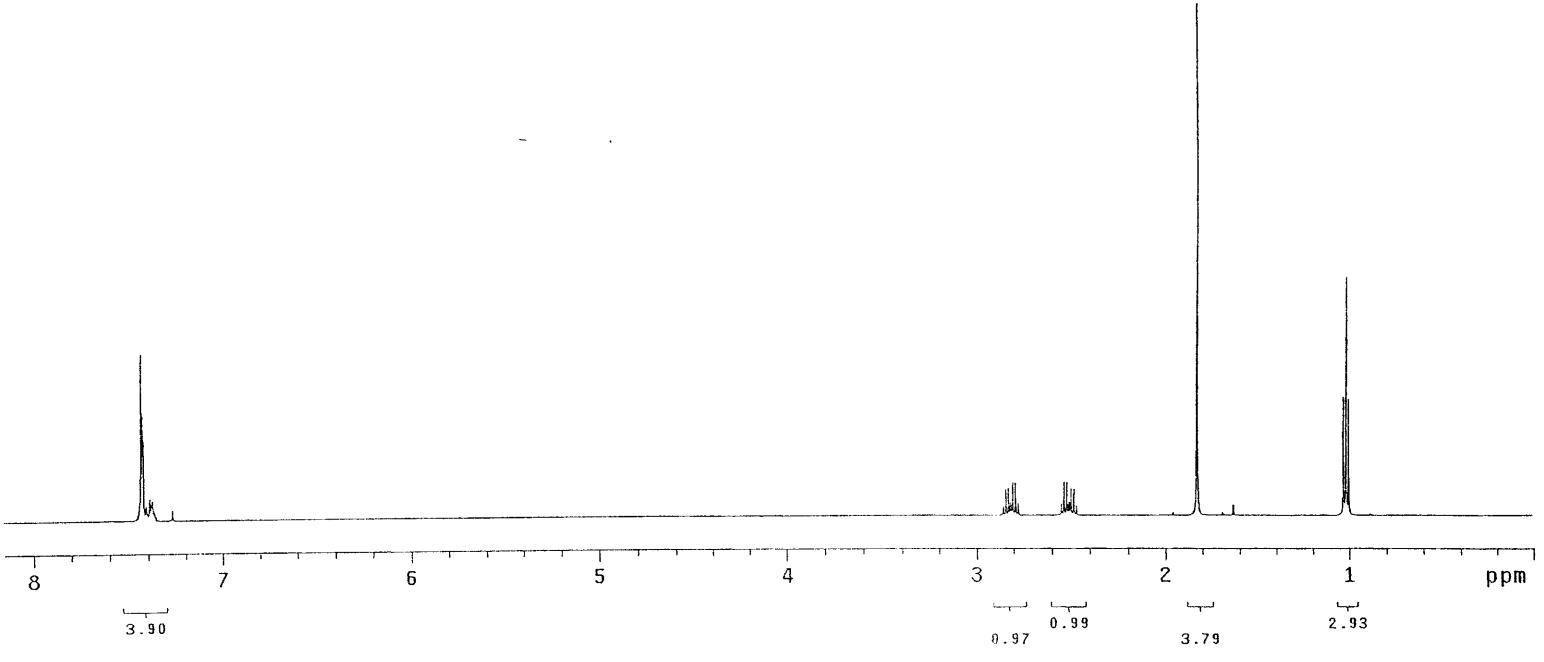


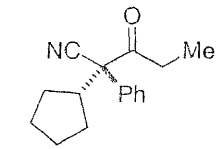
^{1}H NMR (500 MHz, $CDCl_3$)



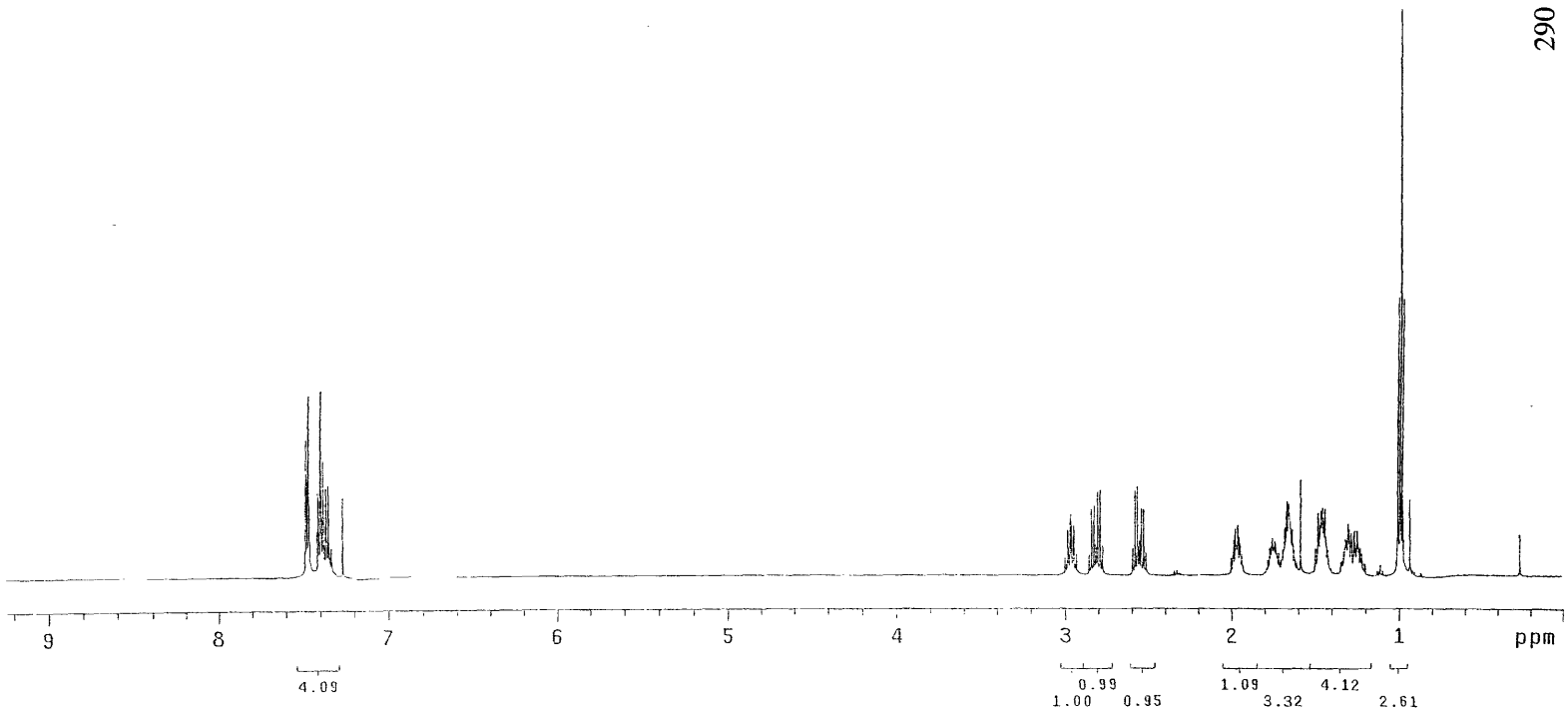


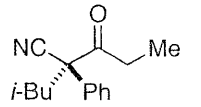
^{1}H NMR (500 MHz, $CDCl_3$)



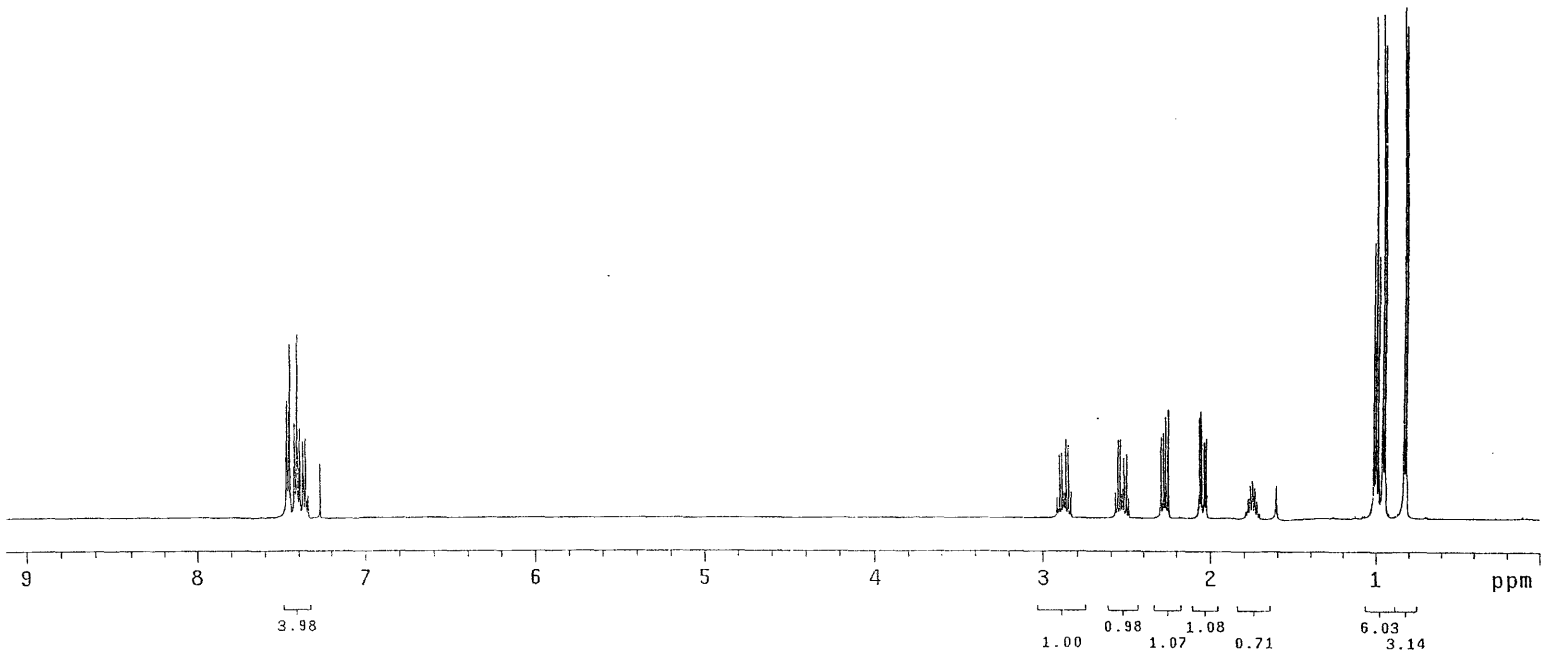


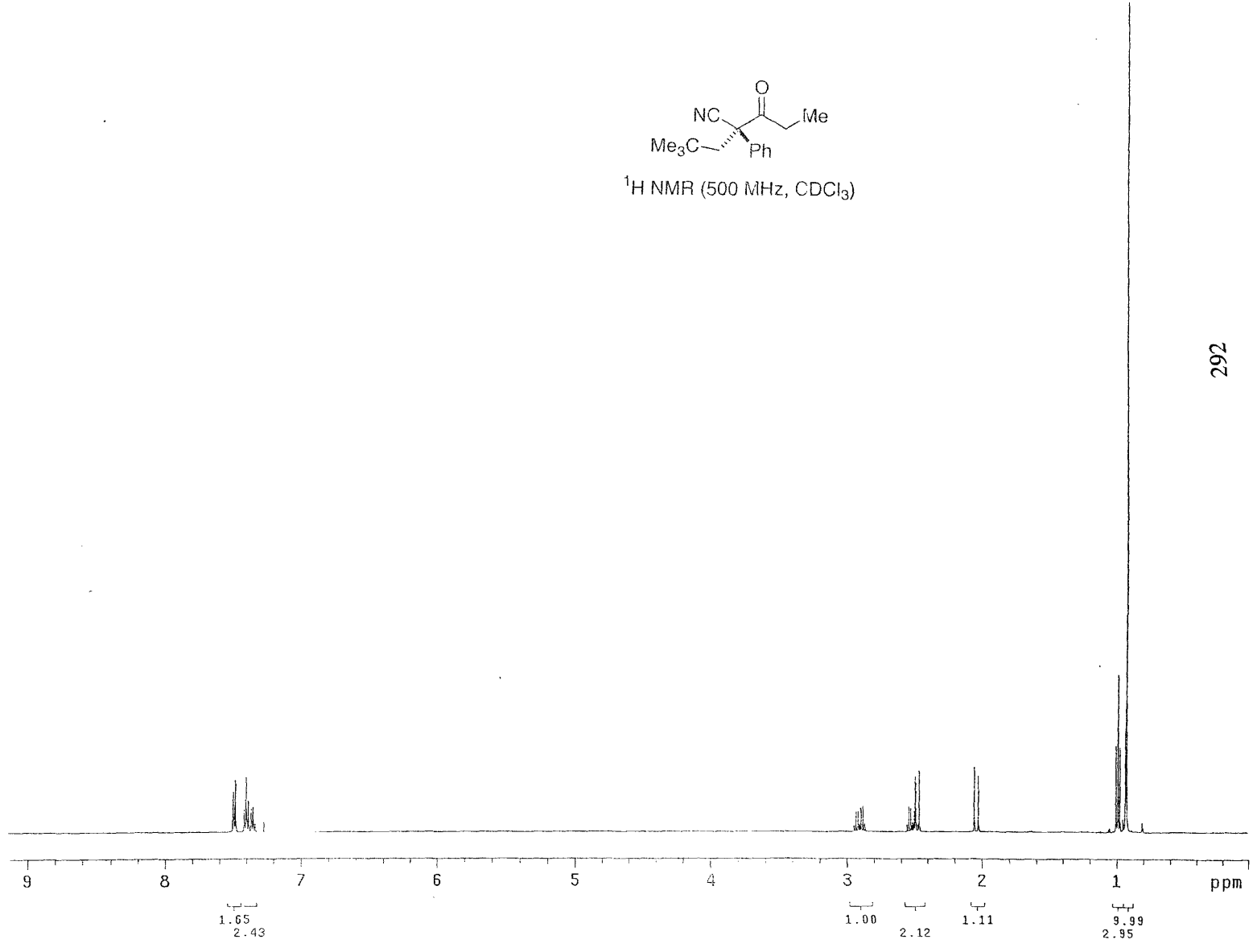
^{1}H NMR (500 MHz, $CDCl_3$)





^{1}H NMR (500 MHz, $CDCl_3$)




O
NC
Me
Me3C
Ph
1H NMR (500 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
ppm
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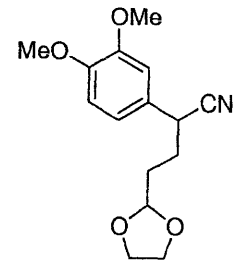
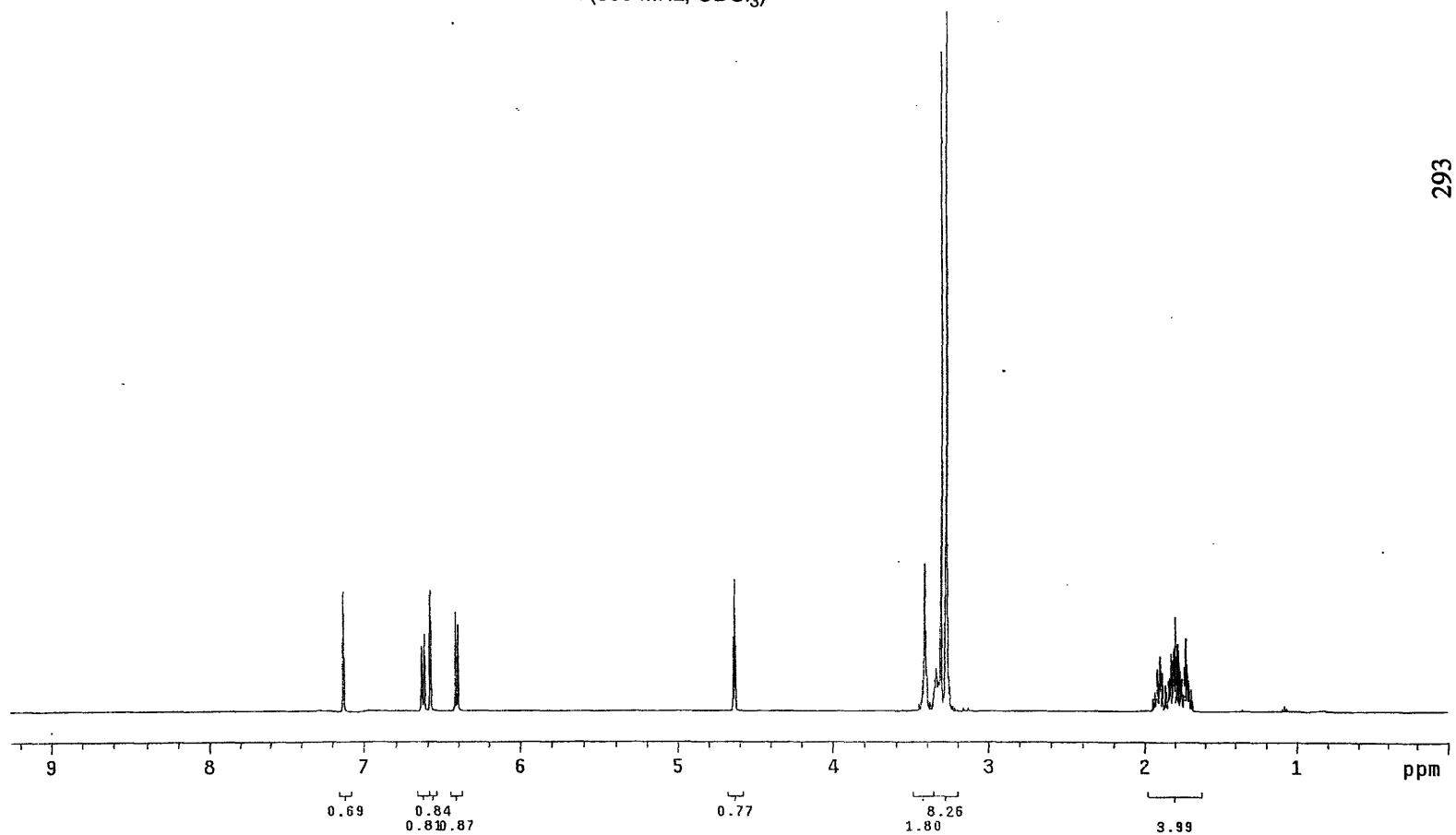
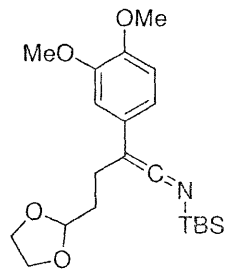
2.43
1.00
2.12
1.11
9.99
2.95

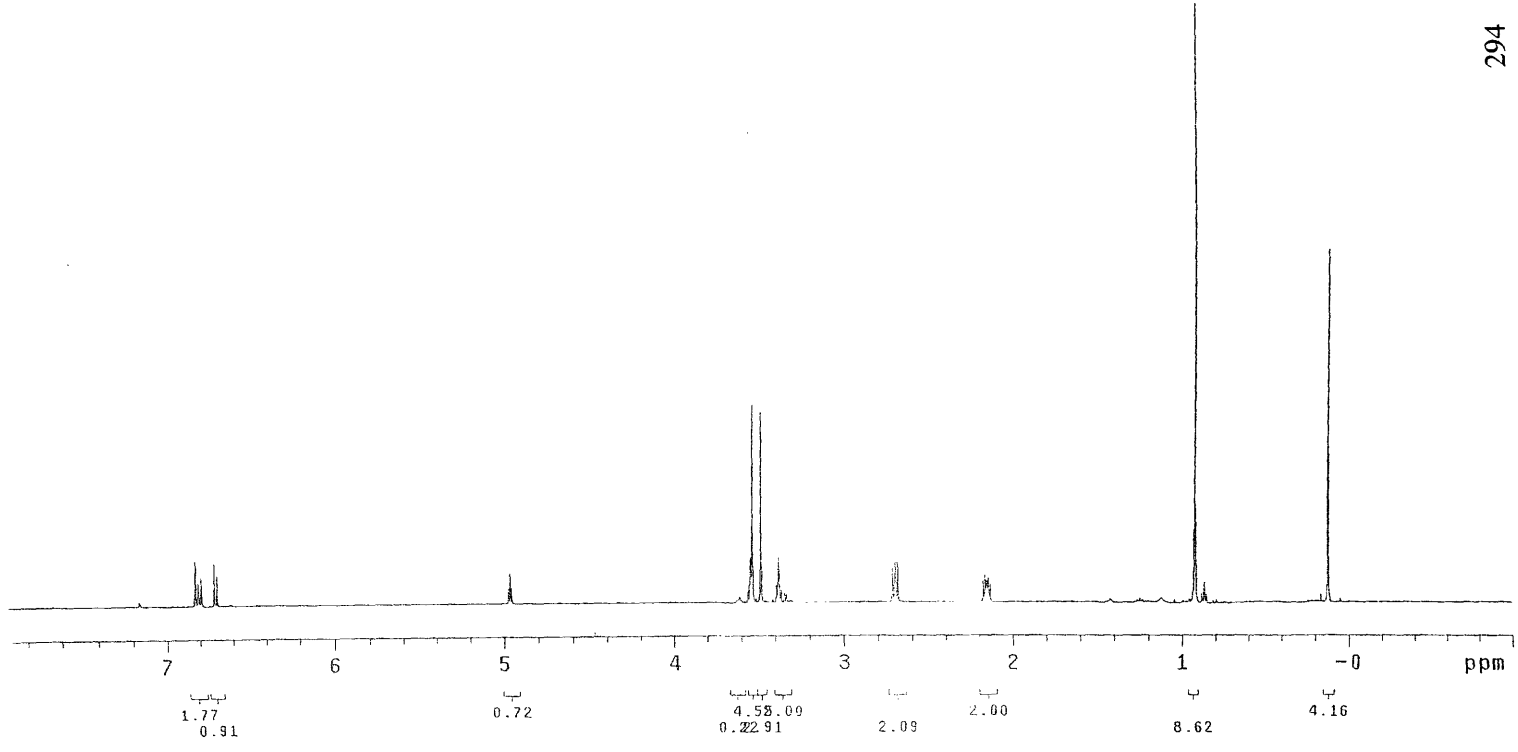


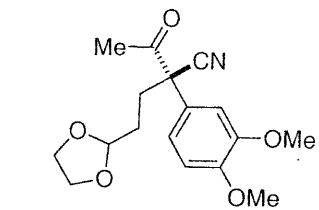
^{1}H NMR (500 MHz, $CDCl_3$)



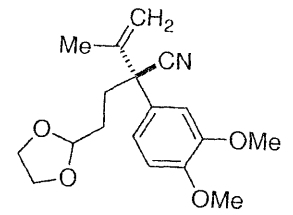


^{1}H NMR (500 MHz, C_6D_6)

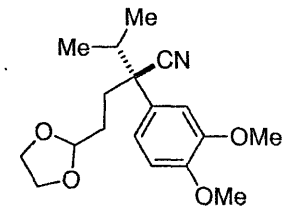




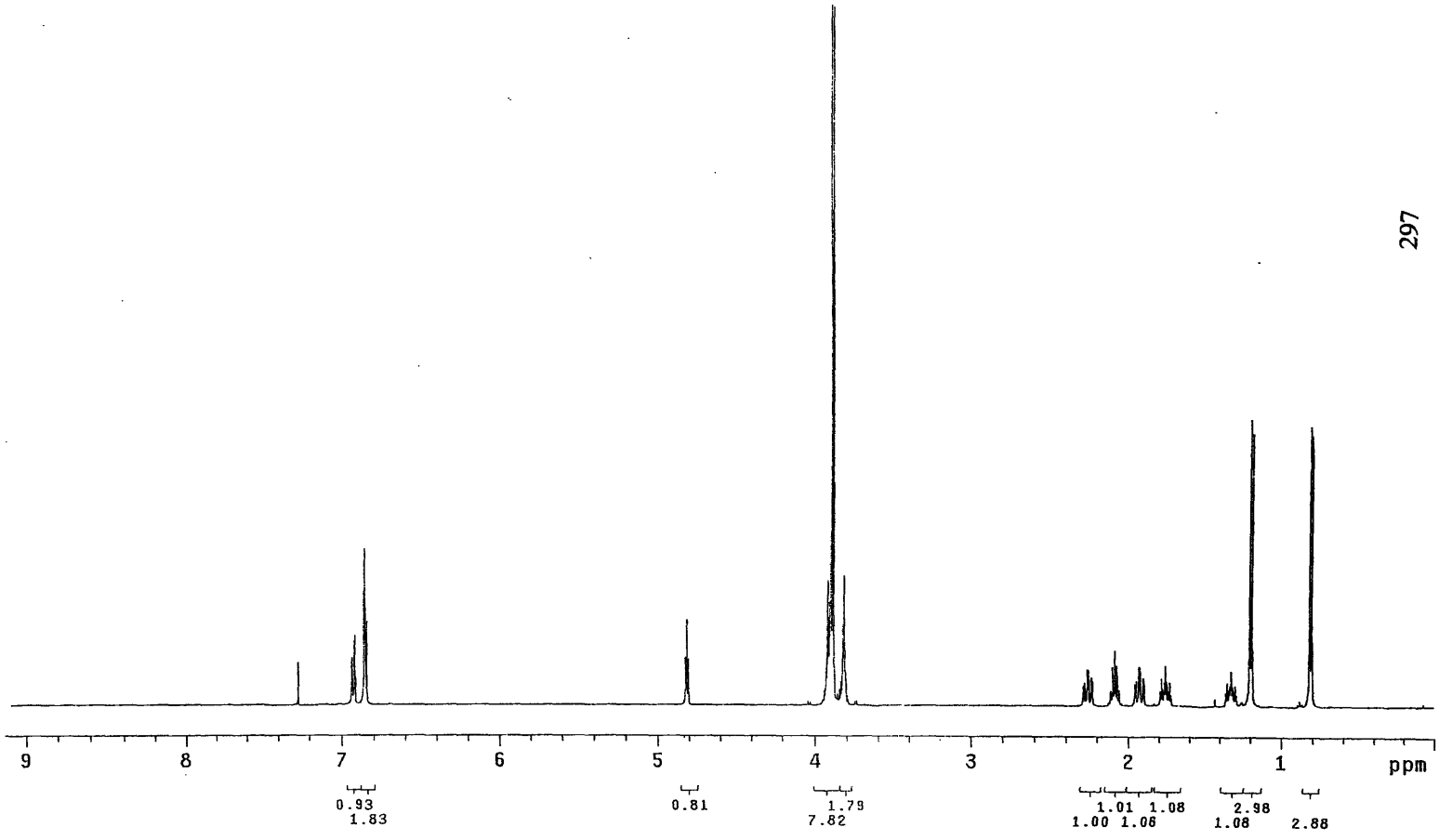
^{1}H NMR (500 MHz, $CDCl_3$)

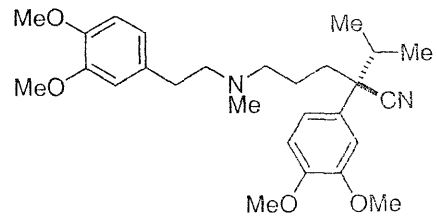


^{1}H NMR (500 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)





^{1}H NMR (500 MHz, $CDCl_3$)