# Improved Synthesis and Application of Planar-Chiral Nucleophilic Catalysts in Asymmetric Reactions and Copper-Catalyzed Enantioselective N-H Insertion Reactions

by

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B.S. Chemistry
Loyola University of Chicago, 1991

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

DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

June 2007



Signature of Author: _____

Department of Chemistry
May 22, 2007

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Gregory C. Fu
Thesis Supervisor

Accepted by: _____

Robert W. Field
Chairman, Departmental Committee on Graduate Students

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Thesis Chair

Professor Gregory C. Fu: _____
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Professor Timothy M. Swager: _____
Committee Member

# Improved Synthesis and Application of Planar-Chiral Nucleophilic Catalysts in Asymmetric Reactions and Copper-Catalyzed Enantioselective N-H Insertion Reactions

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## Abstract

The development of an improved synthesis of nucleophilic planar-chiral catalysts is described in Chapter 1. This route is amenable to scale-up and preparative chiral HPLC is unnecessary to resolve the racemic catalysts.

Using planar-chiral catalysts, two synthetic methodology projects have been developed: Chapter 2 describes the first asymmetric synthesis of trans β-lactams, and Chapter 3 describes the asymmetric synthesis of tertiary α-chloroesters. In the chapter describing the asymmetric synthesis of trans β-lactams, we present mechanistic data supporting a novel mechanism, in which the *N*-triflylimine, rather than the ketene, reacts with the catalyst first. In the chapter describing the asymmetric synthesis of tertiary α-chloroesters, we introduced an under-utilized commercially available chlorinating reagent (2,2,6,6-tetrachlorocyclohexanone).

Finally, in chapter 4, the Cu-catalyzed asymmetric synthesis of α-aminoesters via an N-H insertion is described. We have demonstrated that carbamates such as $BocNH_2$ and $CbzNH_2$ are efficient coupling partners in reactions with α-diazoesters to generate highly useful Boc- or Cbz-protected α-aminoesters.

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

## ACKNOWLEDGMENTS

"Ask and it will be given to you; seek and you will find; knock and the door will be opened to you. For everyone who asks receives, he who seeks finds; and to him who knocks, the door will be opened."

Matthew 7:7-8

I want to thank God for all the blessings I've received throughout my life. For the reasons I do not know, he always answers my prayers, and for that I'm truly blessed. I'm also blessed to have a loving family. My mom and dad are my role models. I hope that I can be as good a parent to my children as my parents have been to us. My sister, Jess, has always been there. Without her, I'm not sure how I would have gone through my toughest moments. My parents and Jess always sent me care packages thoughout my five years at MIT. They always seemed to know when I needed to receive something from home. I also want to thank my uncle JJ and auntie Sue for sending me goodie packages. Needless to say, I never had the opportunity to go hungry during graduate school.

I want to thank Greg for accepting me into his research lab. Greg has been an extremely patient advisor who allowed me to spread my wings at my own pace and for that I'm truly grateful. I also appreciate Greg's dedication and respect to science. I hope I can match his integrity throughout my career as a scientist. I also admire Rick Danheiser for his dedication to teaching chemistry. And I thank Rick for giving me a hug on my last cume! I also want to thank my teachers Steve Buchwald, Tim Swager, and Tim Jamison. I did learn quite a bit, but more importantly, I realized that I really do not know much. And for that, I thank them.

I am truly blessed to have close friends in my life: Diane, Joce, Mike, Mark and Diana. Their friendship is truly appreciated. They say you've done well in life if you made one true friend... I definitely have done well in my life. I also have to thank many friends I've left at Abbott: Steve King, Steve Wittenberger, David Barnes, Tony Haight, Margaret Hsu, Seble Wagaw and Subhash Patel. Thank you for continuing to be my friends and colleagues in chemistry. My special thanks to David for having confidence in me when I didn't, and let me talk your ear off about chemistry whenever you came to visit. You really are one of the smartest chemists that I know and admire.

I think one of my biggest accomplishments from graduate school is the people I've met and few people who will be my friends for a lifetime. I'm especially grateful for my friendship

with Sheryl and Angela. I'll never forget all of us sobbing together while watching "The Notebook" and "Love Actually"! And all of us have to thank Christine for introducing us to Giacomo's. I want to also thank Mi Hee, JC and Sunghee for making me laugh and sharing the passion for Korean food whenever possible. Joey, Jon and Timmy let me hang out with them and always made me feel like part of the group during our awkward first year and on. This definitely was a journey to remember. Someday we'll look back on it with fond memories... someday.

I also need to thank numerous people in the Fu lab for making my time in graduate school more enjoyable: Sheryl, Sunghee, Jon, Andres, Steve, Thomas Maier, Thomas Olpp, Neil, Fran, Sean, Michael, Jan, Forrest and Zhe. Additionally, I want to thank Greg, Jacob, Tim and Zhe for proofreading my thesis.

Finally, without Pillsbury, I wouldn't have made it through the last two years in one piece. Thanks for bringing laughter in my life.

Elaine Lee

May 22, 2007

## Preface

Parts of this thesis have been adapted from the following articles written and co-written by the author. The following articles were reproduced in part with permission from the American Chemical Society and Wiley Interscience:

"Catalytic Asymmetric Staudinger Reactions to Form β-Lactams: An Unanticipated Dependence of Diastereoselectivity on the Choice of the Nitrogen Substituent" Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586-11587.

"Catalytic Asymmetric Synthesis of Tertiary Alkyl Chlorides" Lee, E. C.; McCauley, K. M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 977-979.

Dedicated to Mom, Dad and Jess

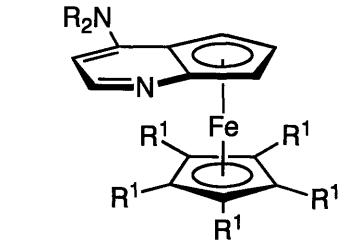
## Table of Contents

# Chapter 1

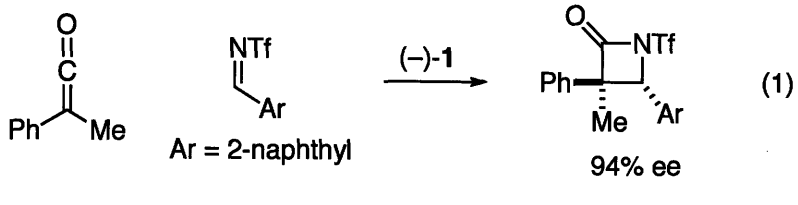
# Improved Synthesis of Nucleophilic Planar-Chiral Catalysts

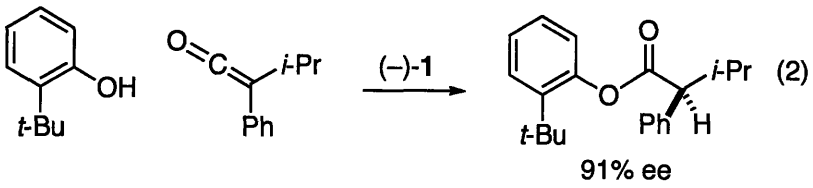
## 1.1 Introduction

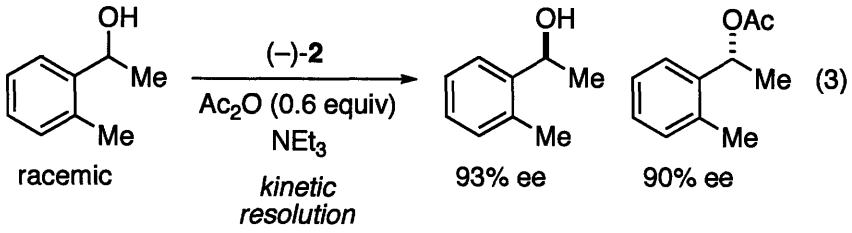
During the past decade, our group have established that planar-chiral derivatives of 4-(dimethylamino)pyridine (DMAP) and 4-(pyrrolidino)pyridine (PPY) serve as effective enantioselective catalysts for a wide variety of transformations (e.g., eq 1–3).[1,2]




$NR_2$ = pyrrolidino $R^1$ = Me (–)-**1**
dimethylamino Ph (–)-**2**



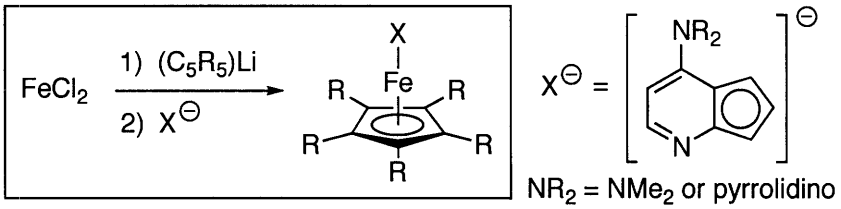




However, one impediment to the use of these methods was the difficulty of the catalyst synthesis. Specifically, the synthesis of catalyst **1** and **2** required 10 steps to obtain the racemic catalyst and HPLC was employed to resolve the enantiomers. Recognizing this limitation, we pursued the development of a more efficient route.

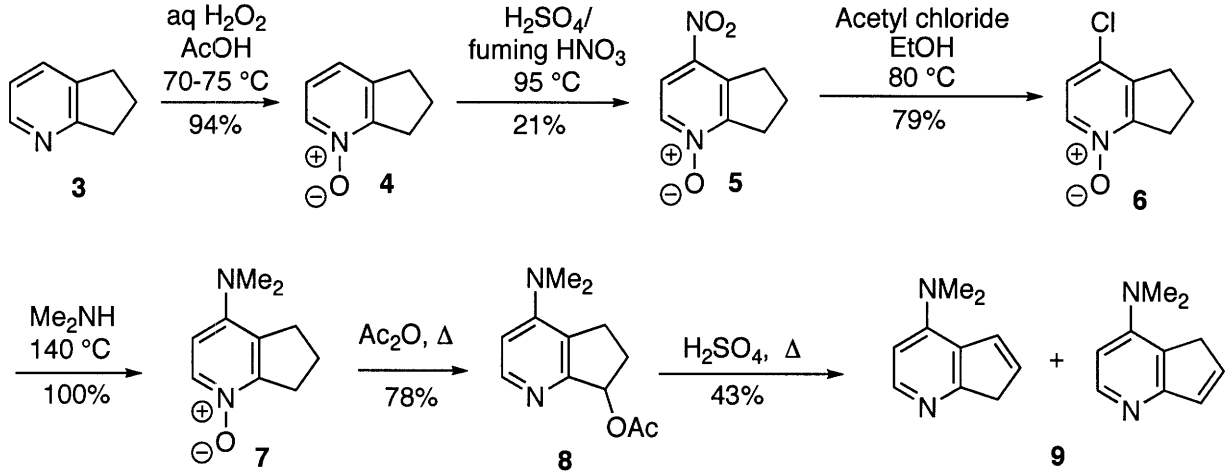
## 1.2 Previous Work

*Scheme 1.* Assembly of Complexes **(–)-1 or 2**



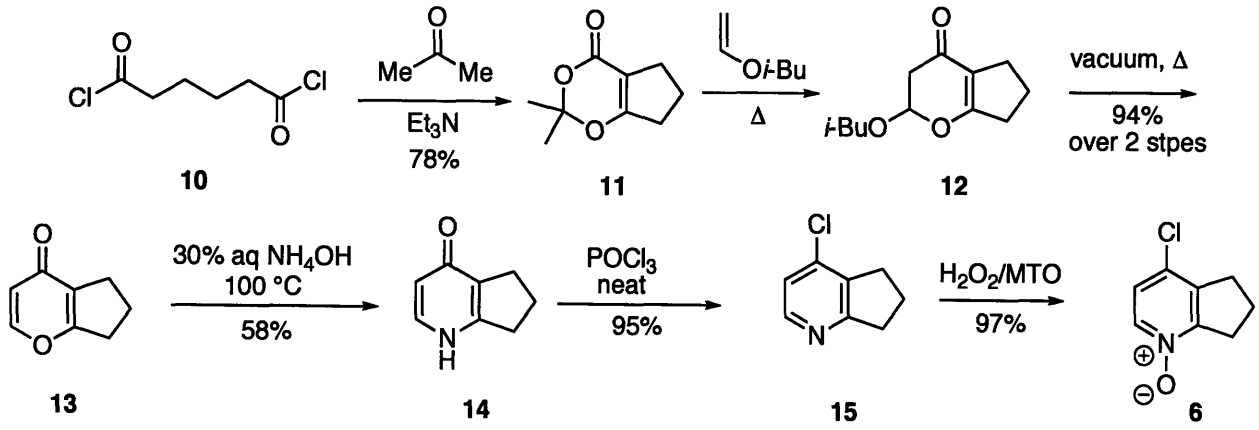

In order to construct complexes **1** and **2**, we adopted the modular approach illustrated in Scheme 1, which involved a one-pot assembly from $FeCl_2$, a cyclopentadienyllithium, and a heterocycle. The initial route to the bicyclic DMAP derivatives (X–H) required six steps from commercially available 2,3-cyclopentenopyridine (**3**) and proceeded in ~5% overall yield (Scheme 2).[3]

*Scheme 2.* Initial Synthesis of 4-Dimethylaminopyridine




The racemic planar-chiral DMAP derivatives **1** and **2** were then synthesized as in Scheme 1, and they were resolved via HPLC on a chiral stationary phase.[3] However, it was later determined that intermediate **5** can decompose violently at >100 °C.[4] As a consequence, our laboratory developed an alternative nine-step synthesis of the bicyclic pyridines that began with adipoyl chloride (Scheme 3).[5]

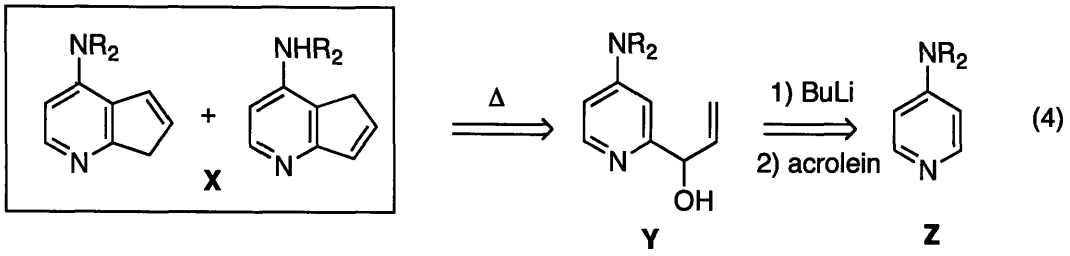
*Scheme 3* An Alternate Route Towards Intermediate **6**




## 1.3 Results and Discussion

### *1.3.1. Efficient Synthesis of Bicyclic DMAP Derivatives*

We began our investigation with various retrosynthetic strategies towards building the bicyclic DMAP derivative (**X**), one of which (acrolein route) is outlined in eq 4.

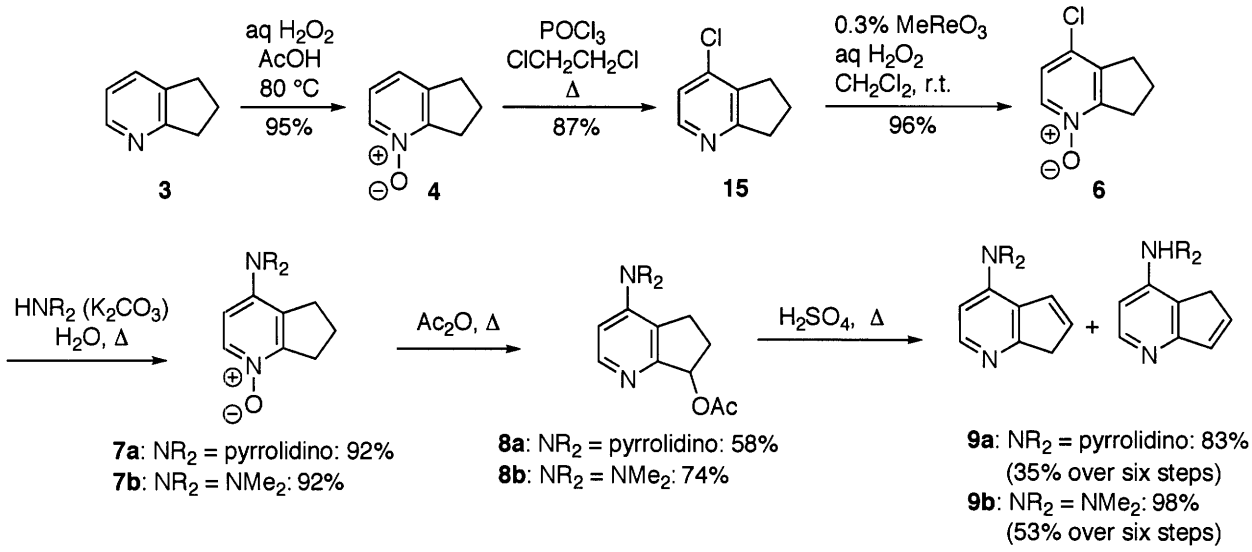



We used the method described by Fort[6] to direct the C2 lithiation of DMAP, and then trapped the organolithium intermediate with acrolein to obtain **Y** in 30% yield. However, all attempts to effect the cyclization (e.g., using TFAA, $H_2SO_4$, $HBF_4$, $BF_3$•$Et_2O$, TsOH, $MgCl_2$, AgOTf, $InCl_3$, $CeCl_3$, or $PPh_3$, at various temperatures) to generate **X** failed. Other retrosynthetic routes[7] investigated include Nazarov and RCM routes, but they were also unsuccessful.

Our new route (Scheme 3) commenced with a two-step procedure that involved the chlorination of the 4-position of the pyridine ring of 2,3-cyclopentenopyridine.[8] This new route

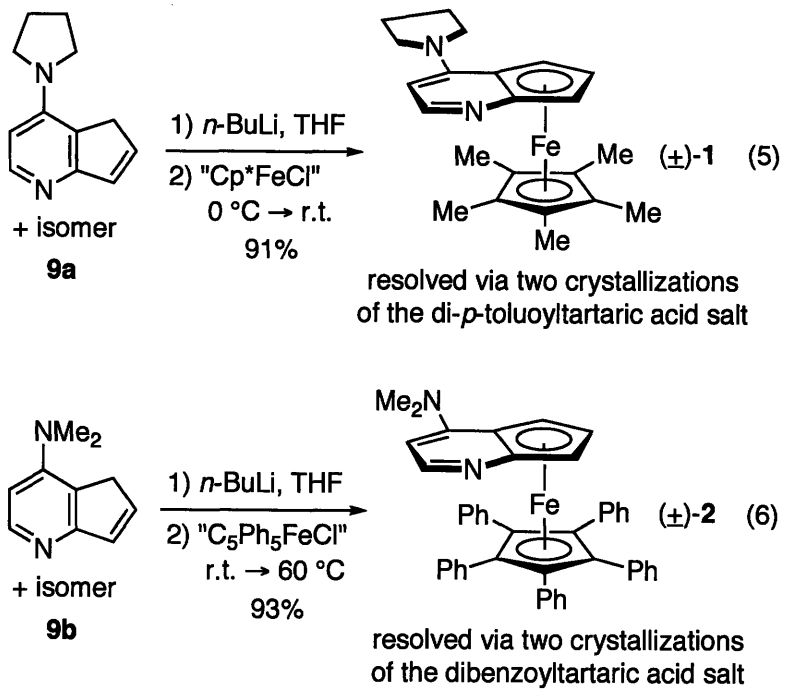
was optimized in collaboration with Dr. Ryan Wurz. Thus, treatment of **3** with $H_2O_2$/AcOH[9] and then $POCl_3$ furnished target compound **15** in good overall yield (83% for two steps). The selective chlorination of **4** in the para position is noteworthy, since reactions of pyridine-*N*-oxides with $POCl_3$ are typically not highly selective for this position.[10]

***Scheme 3.*** Efficient Synthesis of Bicyclic DMAP Derivatives




Next, the pyridine nitrogen of **15** was oxidized in almost quantitative yield ($H_2O_2$ and catalytic $MeReO_3$;[11] 96%), thereby setting the stage for amination of the 4 position and oxidation of the fused five-membered ring. This three-step sequence was conducted on a large scale (>100 g) without chromatographic purification of any intermediate.[12,13]

Pyridine-*N*-oxide **6** is well-suited for the synthesis of a variety of derivatives via substitution of the halide. For our purposes, we needed to effect displacement of the chloride with pyrrolidine and dimethylamine, which was accomplished simply by heating **6** in the presence of aqueous base (92% yield).[14] Treatment of the resulting 4-aminopyridines (**7**) with $Ac_2O$ furnished the desired acetates (**8**), which underwent elimination under acidic conditions to afford the target bicyclic pyridines as mixtures of olefin isomers (**9**).[15] The relative simplicity and low cost of the reagents that are used in this synthetic sequence is noteworthy (Scheme 3). The heterocycles (**9a** and **9b**) can then be complexed to iron in good yield (eq 5 and eq 6).




*1.3.2. Classical Resolution of **1** and **2***

As indicated above, in our early studies, we obtained enantiopure **1** and **2** from the racemic catalysts via preparative HPLC on a chiral stationary phase. The development of classical resolutions of **1** and **2** was achieved with tartaric acid derivatives that furnished the catalysts in >99% ee. These processes were developed by Dr. Ryan Wurz. In the case of **1**, di-*p*-toluoyltartaric acid is the resolving agent of choice (eq 5), whereas, for **2**, dibenzoyltartaric acid has proved to be the most efficient (eq 6).

## 1.4 Conclusions

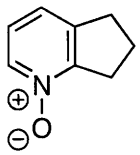
We have developed an improved route to enantiopure planar-chiral DMAP derivatives that addresses several drawbacks associated with earlier approaches. Specifically, a potentially hazardous intermediate is avoided, improved yields are obtained, and preparative chiral HPLC is unnecessary.

## 1.5 Experimental Procedures

*1.5.1. General*

Unless otherwise specified, reactions were performed in the air with no precautions to exclude moisture. Analytical HPLC analyses were carried out on an Agilent Technologies 1100 Series instrument with Daicel Chiralpak® or Regis columns in hexanes/2-propanol or hexanes/$CH_2Cl_2$ mixtures; data are reported as follows: column type, eluent, flow rate, and retention time ($t_r$). Low-resolution mass spectrometric measurements were performed on an Agilent Technologies LC/MSC SL Multimode (ES/APCI) instrument using a Zorbax Eclipse (Agilent) XDB-C18 column (5 μm particle size, 4.6 x 150 mm).

**Materials.** 2,3-Cyclopentenopyridine (6,7-dihydro-5*H*-cyclopenta[*b*]pyridine) (Kinbester Co., Limited (China); >98%[16]) was used as received. Other reagents and solvents were obtained from Strem or Aldrich and used as received.



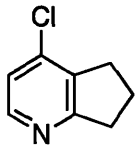
**2,3-Cyclopentenopyridine *N*-oxide (6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 1-oxide; 4).**[9] Glacial acetic acid (500 mL) was added over ~2 min (to control the exotherm) to a 2-liter flask that contained 2,3-cyclopentenopyridine (100 g, 0.84 mol). Then, an aqueous solution of $H_2O_2$ (30%; 90 mL, 0.87 mol) was added, and the flask was fitted with a reflux condenser capped with a septum and a needle (vent). The reaction mixture was heated to 80 °C behind a blast shield (as a precaution; no accidents have occurred). After stirring at 80 °C for 6 h, the solution was treated with additional aqueous $H_2O_2$ (90 mL, 0.87 mol) and stirred for 18 h at 80 °C. Then, the reaction mixture was allowed to cool to room temperature, and the acetic/peracetic acid was removed on a rotary evaporator. The resulting pale-yellow residue was cooled in an ice bath and then carefully treated with aqueous $K_2CO_3$ (100 g in 250 mL of distilled water) until the solution reached pH~10. The mixture was then extracted with $CHCl_3$ (4 x 250 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The product crystallized as a white solid, which was rinsed with methyl *tert*-butyl ether (2 x 200 mL). The washings were concentrated on a rotary evaporator, which led to the precipitation of additional *N*-oxide **4**. This precipitated solid was washed with methyl *tert*-butyl ether (3 x 30 mL) and then combined with the initial batch of product. Compound **4** was dried under vacuum overnight to afford a free-flowing, white crystalline solid (108 g, 95%).

m.p. 121-123 °C;

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, $J$ = 6.2, 0.8 Hz, 1H), 7.13 (d, $J$ = 6.2 Hz, 1H), 7.05-7.11 (m, 1H), 3.17 (t, $J$ = 7.7 Hz, 2H), 3.02 (t, $J$ = 7.7 Hz, 2H), 2.14-2.22 (m, 2H);

$^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.3, 142.4, 137.4, 124.0, 122.7, 31.7, 29.7, 22.2; IR (film) $\nu$ 3391, 2957, 1602, 1441, 1260, 1063, 1011, 800 cm$^{-1}$;

LRMS (ES/APCI) calcd for $C_8H_9NO$ [M+Na$^+$] 158.2, found: 158.1.




**4-Chloro-6,7-dihydro-1,5-pyrindane (4-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine; 15).** Under argon, $POCl_3$ (234 g, 142 mL, 1.52 mol) was added slowly (dropwise over 30 min) to a 0 °C solution of 2,3-cyclopentenopyridine *N*-oxide (**4**; 103 g, 0.76 mol) in anhydrous 1,2-dichloroethane (500 mL) in a 2-L flask that was placed in an ice bath. The reaction mixture, which turned orange-brown, was stirred for 1 h at room temperature (Note: this procedure should be adhered to, in order to avoid a substantial exotherm). The reaction vessel was then fitted with a condenser and slowly heated to reflux for 2 h. Next, the reaction mixture was allowed to cool to room temperature, and the solvent and the excess $POCl_3$ were removed on a rotary evaporator, leading to a viscous brown oil. The flask was placed in an ice bath, and small pieces of ice were cautiously added (~50 g; Note: if too much ice is added initially, then a substantial exotherm will result). The mixture was then treated with a solution of 6 N NaOH (~500 mL) via a dropping funnel (ice was added, in order to keep the reaction at ~5 °C) until pH=7. The mixture was transferred to a separatory funnel and extracted with diethyl ether (6 x 350 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator, affording a dark-orange oil (102 g, 87%). This material was judged to be 94% pure by $^1$H NMR spectroscopy, and it was used in the next step without further purification.

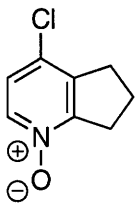
$R_f$ 0.17 (20% EtOAc:hexanes).

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, $J$ = 5.5 Hz, 1H), 7.07 (d, $J$ = 5.4 Hz, 1H), 3.10 (t, $J$ = 7.8 Hz, 2H), 3.01 (t, $J$ = 7.6 Hz, 2H), 2.12-2.20 (m, 2H);

$^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.1, 148.4, 140.5, 135.6, 121.2, 34.9, 29.8, 21.9;

IR (film) $\nu$ 2959, 1583, 1558, 1458, 1390, 903, 817 cm$^{-1}$;

LRMS (ES/APCI) calcd for $C_8H_8ClN$ [M+H$^+$] 154.6, found: 154.1.



**4-Chloro-6,7-dihydro-1,5-pyrindane-*N*-oxide (4-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 1-oxide; 6).** $MeReO_3$ (500 mg, 2.01 mmol, 0.31 mol%) was added to a solution of 4-chloro-6,7-dihydro-1,5-pyrindane (**5**; 100 g, 0.65 mol) in $CH_2Cl_2$ (200 mL) in a 2-L round-bottomed flask. To this stirred solution was added an aqueous solution of $H_2O_2$ (30%; 130 mL, 1.26 mol; in one portion). The flask was then capped with a septum and a needle (vent), and the mixture was allowed to stir at room temperature for 25 h (the reaction mixture turned orange, and then bright yellow as the reaction progressed). Next, the excess $H_2O_2$ was quenched by the addition of small portions of activated $MnO_2$ powder (10-20 mg), which resulted in the rapid evolution of $O_2$. After the effervescence had subsided (~30 min), the dark-green reaction mixture was treated with brine (200 mL) and extracted with $CH_2Cl_2$ (4 x 200 mL). The combined organic extracts were dried over $MgSO_4$ and filtered through a pad of celite. Removal of the solvent on a rotary evaporator resulted in the formation of olive-green crystals, which were dried under vacuum overnight (106 g, 96%). The product was judged to be 92% pure by $^1H$ NMR spectroscopy, and it was used in the next step without further purification.

m.p. 110-113 °C;

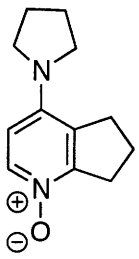
$R_f$ 0.16 (acetone);

$^1H$ NMR (400 MHz, $CDCl_3$) δ 7.99 (d, $J$ = 6.8 Hz, 1H), 7.09 (d, $J$ = 6.8 Hz, 1H), 3.24 (t, $J$ = 7.8 Hz, 2H), 3.07 (d, $J$ = 7.7 Hz, 2H), 2.19-2.27 (m, 2H);

$^{13}C$ NMR (75 MHz, $CDCl_3$) δ 154.4, 140.7, 139.4, 127.0, 125.1, 31.8, 31.2, 21.8;

IR (film) $\nu$ 3406, 3077, 2962, 1662, 1437, 1311, 1264, 1236, 1014, 825, 726 $cm^{-1}$;

LRMS (ES/APCI) calcd for $C_8H_8ClNO$ [M+H$^+$] 170.6, found: 170.0.



**4-Pyrrolidino-6,7-dihydro-1,5-pyrindane-*N*-oxide (7a).** Pyrrolidine (189 g, 221 mL, 2.65 mol) was added slowly (to avoid an exotherm) to a solution of 4-chloro-6,7-dihydro-1,5-pyrindane-*N*-oxide (**6**; 90.0 g, 0.53 mol) and $K_2CO_3$ (89.4 g, 0.54 mol) in distilled water (300 mL) in a 2-L round-bottomed flask. The flask was fitted with a reflux condenser, and the mixture was heated, with stirring, under air at 90-95 °C for 17 h. Then, the reaction mixture was cooled to room temperature, and the solvent was removed on a rotary evaporator, furnishing a black solid. Toluene (100 mL) was added in order to azeotropically remove the remaining water. The product was extracted from the black solid

with 1:1 acetone:$CH_2Cl_2$ (6 x 300 mL). The dark-purple extracts were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated on a rotary evaporator. The resulting purple-black solid was dissolved in warm acetone (120 mL; 40-50 °C), and then methyl *tert*-butyl ether (600 mL) was added. This solution was heated to 70 °C for 10 min, and then it was cooled in an ice bath, leading to the precipitation of *N*-oxide **7a**. The product was collected by filtration (washed with methyl *tert*-butyl ether (300 mL) to remove a purple impurity) and then dried under vacuum overnight, affording a gray, free-flowing solid (100 g, 92%). The product was judged to be >99% pure by $^1$H NMR spectroscopy.

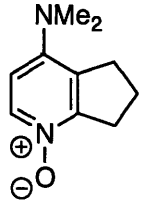
m.p. 80-83 °C;

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, $J$ = 7.1 Hz, 1H), 6.20 (d, $J$ = 7.1 Hz, 1H), 3.47-3.50 (m, 4H), 3.27 (t, $J$ = 7.5 Hz, 2H), 3.15 (t, $J$ = 7.8 Hz, 2H), 2.06-2.14 (m, 2H), 1.97-2.02 (m, 4H);

$^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.7, 145.2, 137.4, 122.8, 107.7, 49.5, 33.1, 29.9, 25.6, 22.3;

IR (film) $\nu$ 3375, 2963, 1624, 1495, 1457, 1230, 982 cm$^{-1}$;

LRMS (ES/APCI) calcd for $C_{12}H_{16}N_2O$ [M+H$^+$] 205.3, found: 205.1.




**4-(Dimethylamino)-6,7-dihydro-1,5-pyrindane-*N*-oxide (7b).** With stirring, 4-chloro-6,7-dihydro-1,5-pyrindane-*N*-oxide (**6**; 40.0 g, 236 mmol) was dissolved in a solution of $Me_2NH$ in water (40 wt%; 100 mL, 790 mmol) in a 500-mL round-bottomed flask. The solution was transferred to a 250-mL stainless steel Parr apparatus (due to the volatility of $Me_2NH$) using additional $Me_2NH$ solution (80 mL, 632 mmol) in order to ensure quantitative transfer. The Parr apparatus was sealed and heated to 75 °C in an oil bath with stirring for 24 h (behind a blast shield, as a precaution). Next, the Parr apparatus was cooled in an ice bath, and the reaction mixture was poured into an Erlenmyer flask. $K_2CO_3$ (39.8 g, 241 mmol) was added, and the mixture was stirred for 30 min. The solution was transferred to a 1-L round-bottomed flask, and the solvent was removed on a rotary evaporator, leading to a black solid. The product was extracted from the solid with 1:1 acetone:$CH_2Cl_2$ (6 x 200 mL). The dark-purple extracts were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated on a rotary evaporator, providing a black crystalline solid that was judged to be 95% pure by $^1$H NMR spectroscopy (38.7 g, 92%).

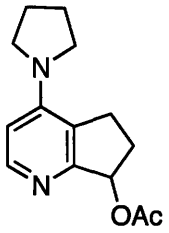
m.p. 150-156 °C;

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, $J$ = 7.2 Hz, 1H), 6.40 (d, $J$ = 7.2 Hz, 1H), 3.16 (t, $J$ = 7.8 Hz, 2H), 3.11 (t, $J$ = 7.4 Hz, 2H), 2.96 (s, 6H), 2.13 (pent. $J$ = 7.5 Hz, 2H);

$^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.7, 147.9, 137.3, 126.4, 109.3, 41.4, 33.1, 29.7, 22.6;

IR (film) $\nu$ 3379, 2957, 1621, 1509, 1434, 1236, 976, 816, 735 cm$^{-1}$;

LRMS (ES/APCI) calcd for $C_{10}H_{14}N_2O$ [M+H$^+$] 179.2, found: 179.2.




**4-Pyrrolidino-7-acetoxy-6,7-dihydro-1,5-pyrindane acetic acid adduct (8a).** In a 1-L flask, a mixture of acetic anhydride (200 g, 185 mL, 1.96 mol) and distilled water (2.1 mL; 117 mmol) was stirred at room temperature for 10 min under nitrogen. The flask was then cooled in an ice bath, and 4-pyrrolidino-6,7-dihydro-1,5-pyrindane-*N*-oxide (**7a**; 50.0 g, 0.24 mol) was added slowly via a glass funnel over 15 min (to prevent an exotherm). The flask was purged with nitrogen, and the mixture was stirred at room temperature for 1 h. The flask was then fitted with a reflux condenser, and the reaction mixture was heated to 80 °C with stirring under nitrogen for 25 h. The solvent was removed on a rotary evaporator from the resulting dark-brown reaction mixture, leading to a brown solid. This solid was dissolved in the minimum amount of $CH_2Cl_2$ (~100 mL), and the solution was passed through a 7-cm pad of silica gel on a 2-L sintered coarse glass frit. The silica gel was rinsed with 30:70 EtOAc:hexane (1 L), 30:60:10 EtOAc:hexane:$Et_3N$ (~1.5 L), and 60:30:10 EtOAc:hexane: $Et_3N$ (5 L), collecting 1-L "fractions". The solvent was removed on a rotary evaporator from the appropriate fractions (as judged by TLC). The resulting beige solid was suspended in methyl *tert*-butyl ether (150 mL) and filtered through a Buechner funnel. The solid was rinsed with additional portions of methyl *tert*-butyl ether (2 x 50 mL; the product is somewhat soluble in this solvent, so large volumes should not be used), resulting in a free-flowing, cream-colored solid. The desired product was dried under vacuum overnight (98-99% pure according to $^1$H NMR spectroscopy; acetic acid adduct; 43.5 g, 58%).

m.p. 119-120 °C;

$R_f$ 0.51 (9:1 EtOAc:$Et_3N$);

$^1$H NMR (400 MHz, $CDCl_3$) δ 11.38 (br s, 1H), 8.17 (d, $J$ = 6.0 Hz, 1H), 6.28 (d, $J$ = 6.0 Hz, 1H), 6.05 (dd, $J$ = 7.5, 5.1 Hz, 1H), 3.54-3.58 (m, 4H), 3.33-3.42 (m, 1H), 3.11-3.18 (m, 1H), 2.50-2.59 (m, 1H), 2.13 (s, 3H), 2.07 (s, 3H), 1.95-2.02 (m, 5H);

$^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.6, 171.1, 158.7, 152.0, 147.3, 120.4, 107.2, 49.3, 30.5, 29.4, 25.6, 22.0, 21.3;

IR (film) *v* 2976, 2871, 1736, 1606, 1515, 1372, 1243, 834 $cm^{-1}$;

LRMS (ES/APCI) calcd for $C_{14}H_{18}N_2O_2$ [M+H$^+$] 247.3, found: 247.1.


**4-(Dimethylamino)-7-acetoxy-6,7-dihydro-1,5-pyrindane acetic acid adduct (8b).** Acetic anhydride (149 g, 138 mL, 1.46 mol) was added to a 1-L flask (in a 0 °C ice bath) that contained 4-(dimethylamino)-6,7-dihydro-1,5-pyrindane-*N*-oxide (**7b**; 26.0 g, 0.146 mol). Distilled water (1.25 mL, 69.4 mmol)[7] was added, and the solution was stirred at 0 °C for 30 min. The flask was then fitted with a reflux condenser and heated to 75-80 °C for 24 h under nitrogen. Next, the dark-brown reaction mixture was concentrated on a rotary evaporator, leading to a brown solid, which was dissolved in the minimum amount of $CH_2Cl_2$ (~50 mL) and passed through a pad of silica gel, eluting with 2:3 EtOAc:hexane (500 mL) and then 45:45:10 EtOAc:hexane:$Et_3N$ (800 mL). The desired product was dried under vacuum overnight (tan solid; 98-99% pure according to $^1$H NMR spectroscopy; acetic acid adduct; 30.4 g, 74%).

m.p. 62-67 °C;

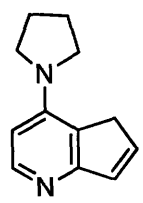
$R_f$ 0.53 (9:1 EtOAc:$Et_3N$);

$^1$H NMR (400 MHz, $CDCl_3$) δ 11.03 (br s, 1H), 8.22 (d, *J* = 5.9 Hz, 1H), 6.43 (d, *J* = 5.9 Hz, 1H), 6.05 (dd, *J* = 7.4, 5.2 Hz, 1H), 3.16-3.22 (m, 1H), 3.05 (s, 6H), 3.00-3.05 (m, 1H), 2.52-2.58 (m, 1H), 2.14 (s, 3H), 2.07 (s, 3H), 1.97-2.03 (m, 1H);

$^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.9, 170.9, 159.8, 155.0, 148.1, 122.3, 108.0, 41.2, 30.7, 29.7, 21.8, 21.2;

IR (film) *v* 3383, 2945, 1733, 1587, 1509, 1439, 1371, 1243, 1024, 962, 816 $cm^{-1}$;

LRMS (ES/APCI) calcd for $C_{12}H_{16}N_2O_2$ [M+H$^+$] 221.3, found: 221.1.




**4-Pyrrolidinopyrindine (4-(pyrrolidin-1-yl)-7*H*-cyclopenta[*b*]pyridine; 9a).** 4-Pyrrolidino-7-acetoxy-6,7-dihydro-1,5-pyrindane acetic acid adduct (**8a**; 20.0 g, 81.2 mmol) was slowly added in small portions (to avoid an exotherm) to a flask that contained concentrated $H_2SO_4$ (35 mL; in a 0 °C ice bath). The flask was capped under air with a septum and a needle (vent), and then it was heated to 60-65 °C in an oil

bath for 80 min. Next, the reaction mixture was cooled in an ice bath, and ice was added. A solution of NaOH (6 N; ~240 mL) was added slowly over 30-40 min until pH~11 (white precipitate formed). The reaction mixture was extracted with EtOAc (3 x 300 mL) and $CH_2Cl_2$ (3 x 250 mL), and the organic extracts were dried over $Na_2SO_4$ ($Et_3N$ (15 mL) was added, since the product is stabilized by the presence of a weak base), filtered, and concentrated on a rotary evaporator. The resulting brown residue was purified by column chromatography, eluting with 45:45:10 EtOAc:hexane:$Et_3N$ (200 mL) and then 90:10 EtOAc:$Et_3N$ (600 mL). The product, a yellow-green crystalline solid, was judged to be >98% pure by $^1H$ NMR spectroscopy (~60:40 mixture of olefin isomers; 10.1 g, 83%). Note: This compound is somewhat sensitive, and it is best to use it immediately. Alternatively, it can be stored in a freezer under an inert atmosphere for several weeks without noticeable degradation.

m.p. 84-86 °C (mix of isomers);

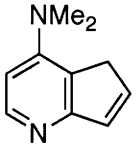
$R_f$ 0.27 (45:45:10 EtOAc:hexanes:$Et_3N$);

$^1H$ NMR (400 MHz, $CDCl_3$) δ Major isomer: 8.17 (d, $J$ = 5.9 Hz, 1H), 6.98 (dt, $J$ = 5.7, 1.8 Hz, 1H), 6.80 (dt, $J$ = 5.7, 2.0 Hz, 1H), 6.26 (d, $J$ = 5.9 Hz, 1H), 3.74-3.78 (m, 2H), 3.60-3.66 (m, 4H), 2.00-2.11 (m, 4H); Minor isomer: 8.10 (d, $J$ = 5.9 Hz, 1H), 7.22 (dt, $J$ = 6.1, 2.0 Hz, 1H), 6.37 (dt, $J$ = 6.2, 2.1 Hz, 1H), 6.34 (d, $J$ = 5.9 Hz, 1H), 3.60-3.66 (m, 4H), 3.46-3.48 (m, 2H), 2.00-2.11 (m, 4H);

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ Major isomer: 164.6, 149.4, 148.5, 136.9, 134.1, 118.7, 104.7, 48.6, 38.9, 25.5; Minor isomer: 166.9, 147.0, 146.0, 130.6, 128.1, 121.7, 105.7, 49.5, 40.8, 25.7;

IR (film) $\nu$ 3367, 2969, 2868, 1693, 1591, 1570, 1484, 1395, 1357, 1059, 900, 800, 708 $cm^{-1}$;

LRMS (ES/APCI) calcd for $C_{12}H_{14}N_2$ [M+H$^+$] 187.3, found: 187.1.




**4-(Dimethylamino)pyrindine (*N,N*-dimethyl-7*H*-cyclopenta[*b*]pyridin-4-amine; 9b).** 4-(Dimethylamino)-7-acetoxy-6,7-dihydro-1,5-pyrindane acetic acid adduct (**8b**; 2.70 g, 9.63 mmol) was added in one portion to concentrated $H_2SO_4$ (6.0 mL) in an ice bath. The mixture was stirred for 10 min at 0 °C, and then it was heated to 60-65 °C in an oil bath for 75 min. Next, the reaction mixture was cooled in an ice bath, and ice was added. The reaction was then slowly quenched over 15 min by the dropwise addition of NaOH (6 N solution; ~45 mL) until pH~11 (white precipitate formed). The reaction mixture was extracted with EtOAc (6 x 100 mL), and the organic extracts were dried over $Na_2SO_4$ ($Et_3N$ (5 mL) was

added, since the product is stabilized by the presence of a weak base), filtered, and concentrated on a rotary evaporator. The resulting yellow residue was purified by column chromatography, eluting with 45:45:10 EtOAc:hexane:$Et_3N$ (300 mL), which yielded a yellow-green crystalline solid (judged to be >99% pure by $^1H$ NMR spectroscopy; ~70:30 mixture of olefin isomers; 1.52 g, 98%). Note: This compound is somewhat sensitive, and it is best to use it immediately. Alternatively, it can be stored in a freezer under an inert atmosphere for several weeks without noticeable degradation.

m.p. 59-63 °C (mix of isomers);

$R_f$ 0.39 (9:1 EtOAc:$Et_3N$);

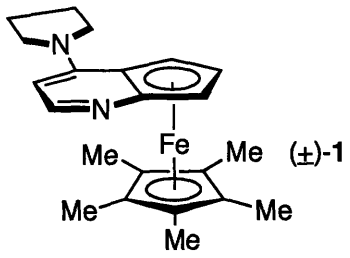
$^1H$ NMR (400 MHz, $CDCl_3$) δ Major isomer: 8.18 (d, $J$ = 5.9 Hz, 1H), 6.93-6.96 (m 1H), 6.76-6.78 (m, 1H), 6.35 (d, $J$ = 5.9 Hz, 1H), 3.63 (s, 2H), 3.14 (s, 6H); Minor isomer: 8.10 (d, $J$ = 5.9 Hz, 1H), 7.14 (dt, $J$ = 8.1, 1.9 Hz, 1H), 6.46 (d, $J$ = 5.9 Hz, 1H), 6.42 (dt, $J$ = 6.1, 2.1 Hz, 1H), 3.43 (s, 2H), 3.11 (s, 6H);

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ Major isomer: 165.2, 152.6, 148.8, 137.0, 134.2, 120.1, 105.5, 41.4, 39.6; Minor isomer: 167.1, 150.8, 146.3, 130.4, 129.4, 123.9, 106.8, 42.2, 40.9;

IR (film) $\nu$ 2885, 1691, 1589, 1570, 1386, 1373, 1189, 1029, 801 $cm^{-1}$;

LRMS (ES/APCI) calcd for $C_{10}H_{12}N_2$ [M+H$^+$] 161.2, found: 161.1.

### *1.5.2. Synthesis and Resolution of 1 and 2*



(±)-1

**4-Pyrrolidinopyrindinyl-pentamethylcyclopentadienyl iron (1).** A solution of *n*-BuLi (1.6 M in hexanes; 24.1 mL, 38.6 mmol) was added dropwise over 2 min to a solution of pentamethylcyclopentadiene (5.26 g, 38.6 mmol) in anhydrous THF (200 mL) in a 0 °C ice bath under nitrogen. The resulting white suspension was stirred for 1 h at 0 °C.

Separately, anhydrous THF (80 mL) was added to powdered $FeCl_2$ (4.90 g, 38.6 mmol) in a 2-L round-bottomed flask. The mixture was sonicated for 1 h, resulting in a fine suspension. Next, the mixture was cooled to 0 °C, and the solution that contained the Cp*Li was added by cannula over 10 min to the suspension of $FeCl_2$, leading to a homogeneous green solution, which was stirred at 0 °C for 2.5 h.

In a 250-mL round-bottomed flask, a 0 °C solution of 4-pyrrolidinopyrindine (6.54 g, 35.1 mmol) in anhydrous THF (80 mL) was treated with *n*-BuLi (1.6 M solution in hexanes; 22.4 mL, 35.8 mmol; dropwise addition), and the resulting dark yellow-brown solution was stirred at 0 °C for an additional 1.5 h. This solution was then added by cannula over 15 min to the 0 °C solution of Cp*FeCl, resulting in a dark-purple solution. This mixture was stirred for 18 h, during which time it was allowed to slowly warm to room temperature. Next, the reaction mixture was poured onto a column of silica gel, eluting first with 65:30:5 hexane:EtOAc:$Et_3N$ (600 mL) and then with 90:10 EtOAc:$Et_3N$ (1.5 L). The purple fractions were collected, and the solvents were removed on a rotary evaporator, thereby providing racemic **1** in >99% purity as judged by $^1$H NMR spectroscopy (12.0 g, 91%).

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, $J$ = 5.1 Hz, 1H), 5.59 (d, $J$ = 5.2 Hz, 1H), 4.54 (dd, $J$ = 2.7, 1.1 Hz, 1H), 4.35 (dd, $J$ = 2.8, 1.1 Hz, 1H), 3.74 (t, $J$ = 2.8 Hz, 1H), 3.57 (br s, 4H), 2.07-2.10 (m, 4H), 1.65 (s, 15H);

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.3, 156.3, 152.1, 111.3, 93.8, 78.4, 74.4, 73.2, 67.1, 64.0, 49.3, 25.7 (br), 9.9;

IR (KBr) $\nu$ 2966, 2902, 2865, 1538, 1487, 1380, 1338, 1021, 907, 730 cm$^{-1}$;

LRMS (ES/APCI) calcd for $C_{22}H_{28}FeN_2$ [M+H$^+$] 377.3, found: 377.2;

Elem. anal. calcd for $C_{22}H_{28}FeN_2$: C, 70.22; H, 7.50; N, 7.44, found: C, 70.02; H, 7.54; N, 7.44;

**Classical resolution of 4-pyrrolidinopyrindinyl-pentamethylcyclopentadienyl iron (1).** First crystallization: Under nitrogen, a solution of di-*p*-toluoyl-D-tartaric acid (531 mg, 1.37 mmol) in nitrogen-purged EtOAc (40 mL) was added dropwise over 5 min to a stirred solution of pure, racemic 4-pyrrolidinopyrindinyl-pentamethylcyclopentadienyl iron (**1**; 2.07 g, 5.48 mmol) in anhydrous $CH_2Cl_2$ (20 mL) in a 250-mL flask. The resulting dark-purple suspension was stirred at room temperature for 14 h under nitrogen, and then it was allowed to stand for 1-3 h. Next, the suspension was filtered, and the solid was rinsed with hexanes (10 mL). The filtrate was concentrated and then purified by passage through a column of silica gel (the column should be loaded using 100% EtOAc), washing first with EtOAc to remove traces of degradation products (yellow-brown bands) and then with 90:10 EtOAc:$Et_3N$ (~150 mL) to elute catalyst **1** as a blood-red solution. The appropriate fractions were collected and concentrated on a rotary evaporator. HPLC analysis revealed an enantiomeric excess of 57% (950 mg, 46%; fast-eluting enantiomer

on chiral HPLC, (+)-(*R*) configuration). Daicel OD column, flow: 1.0 mL/min, eluent: 50:50:0.4 2-propanol:hexane:$Et_2NH$. $t_r$ (+)-(*R*): 4.67 min; (–)-(*S*): 11.22 min.

The purple solid from the filter cake was dissolved in $CH_2Cl_2$ (25 mL), and the solution was treated with a small amount of $Et_3N$ (0.5 mL) and passed through a column of silica gel, eluting with 90:10 EtOAc:$Et_3N$ (~150 mL). The bright-red fractions were collected. HPLC analysis revealed an enantiomeric excess of 91% (810 mg, 39%; slow-eluting enantiomer on chiral HPLC, (–)-(*S*) configuration).

Note: Column chromatography of catalyst **1** can be performed in the air. However, solutions of catalyst **1** that are exposed to air for extended periods of time (i.e., hours) will decompose slightly, leading to the formation of a polar compound that leaves a brown band on the top of silica gel columns.

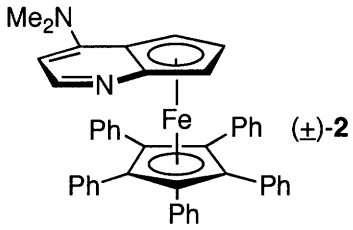
Recrystallization of the solid from the first crystallization: Calculation of the required amount of resolving agent: mmol of resolving agent = (mmol of catalyst **1**) x 0.5 x (fraction of the major enantiomer (e.g., 0.955 for 91% ee)).

A solution of di-*p*-toluoyl-D-tartaric acid (397 mg, 1.03 mmol) in nitrogen-purged EtOAc (14 mL) was added dropwise over 5 min to a stirred solution of enantioenriched **1** (the solid from the first crystallization; 810 mg, 2.15 mmol, 91% ee) in anhydrous $CH_2Cl_2$ (8 mL) in a 250-mL flask under nitrogen. The resulting dark-purple suspension was stirred at room temperature for 14 h under nitrogen, and then it was allowed to stand for 1-3 h. The suspension was filtered, and the purple solid was "worked up" as described for the first crystallization: 719 mg, 35% (based on the starting amount of racemic **1**). HPLC analysis revealed >99% enantiomeric excess of the slow-eluting enantiomer on chiral HPLC, (–)-(*S*)- configuration.

Recrystallization of the filtrate from the first crystallization: A solution of di-*p*-toluoyl-L-tartaric acid (383 mg, 0.990 mmol) in nitrogen-purged EtOAc (17 mL) was added dropwise over 5 min to a stirred solution of enantioenriched **1** (the filtrate from the first crystallization; 950 mg, 2.53 mmol, 57% ee) in anhydrous $CH_2Cl_2$ (9 mL) in a 250-mL flask under nitrogen. Within a few minutes, a dark-purple suspension had formed. This mixture was stirred at room temperature for 14 h under nitrogen, and then it was allowed to stand for 1-3 h. The suspension was filtered, and the purple solid was "worked up" as described for the first crystallization: 665 mg, 32% (based on the starting amount of racemic **1**). HPLC analysis revealed >99% enantiomeric excess of the fast-eluting enantiomer on chiral HPLC, (+)-(*R*) configuration.

(–)-(*S*)-**1**: $[\alpha]^{20}_{D} = -2{,}280°$ ($c = 0.00046$, $CHCl_3$).

m.p. 155-160 °C (decomp.; >99% ee);



(±)-**2**

**4-(Dimethylamino)pyrindinyl-pentaphenylcyclopentadienyl iron (2).** A solution of *n*-BuLi (1.6 M in hexanes; 5.45 mL, 8.73 mmol) was added dropwise over 2 min to a mixture of pentaphenylcyclopentadiene (3.90 g, 8.72 mmol) suspended in anhydrous THF (86 mL) under nitrogen. The solution, which was initially homogenous and yellow, was allowed to stir for 2 h, at which time it was red-orange. Separately, anhydrous THF (40 mL) was added to powdered $FeCl_2$ (1.07 g, 8.44 mmol) in a 500 mL round-bottomed flask. The mixture was sonicated for 30 min, yielding a fine suspension. The solution that contained the pentaphenylcyclopentadienyl anion was then added by cannula over 2 min to the suspension of $FeCl_2$, resulting in a beige solution. The reaction mixture was stirred at room temperature for 2 h.

A solution of *n*-BuLi (1.6 M solution in hexanes; 4.54 mL, 7.27 mmol) was added dropwise over 2 min to a solution of 4-(dimethylamino)pyrindine (1.17 g, 7.27 mmol) in anhydrous THF (35 mL) at 0 °C in a 250-mL round-bottomed flask. The resulting dark yellow-brown solution was stirred at 0 °C for 1.5 h. Then, this solution was added by cannula over 2 min to the solution of $C_5Ph_5FeCl$ (at room temperature), resulting in a brown solution. The reaction mixture was heated to 60 °C for 3.5 h. Next, the reaction mixture was poured onto a column of silica gel, which was eluted with 45:45:10 EtOAc:hexane:$Et_3N$ (200 mL). The resulting solution was concentrated to a dark-purple solid on a rotary evaporator, and this crude material was purified by column chromatography, first eluting with $CH_2Cl_2$ (400 mL) to remove the excess $C_5Ph_5H$ and then with 90:10 $CH_2Cl_2$:$Et_3N$ (400 mL), which provided the catalyst as a tight purple band. The purple fractions were collected and concentrated on a rotary evaporator to afford the title compound in >99% purity as judged by $^1H$ NMR spectroscopy (purple powder; 4.51 g, 93%).

m.p. 238-241 °C;

$^1H$ NMR (400 MHz, $CDCl_3$) δ 8.17 (d, $J$ = 5.2 Hz, 1H), 7.13-7.16 (m, 5H), 7.05-7.12 (m, 10H), 6.94-6.96 (m, 10H), 5.87 (d, $J$ = 5.2 Hz, 1H), 5.11 (br s, 1H), 4.92-4.94 (m, 1H), 4.28-4.30 (m, 1H), 2.94 (br s, 6H);

$^{13}C$ NMR (75 MHz, $CDCl_3$) δ 158.6, 153.9, 135.3, 132.6, 127.1, 126.2, 113.4, 99.5, 86.0, 77.9, 77.7, 69.6, 66.1, 41.7;

IR (film) *v* 3055, 2952, 1537, 1502, 1351, 1075, 1027, 741, 700 $cm^{-1}$;

LRMS (ES/APCI) calcd for $C_{45}H_{36}FeN_2$ [M+H$^+$] 661.6, found: 661.2;

Elem. anal. calcd for $C_{45}H_{36}FeN_2$ (660.64): C, 81.81; H, 5.49; N, 4.24, found: C, 81.62; H, 5.49; N, 4.41;

**Classical resolution of 4-(dimethylamino)pyrindinyl-pentaphenylcyclopentadienyl iron (2).** First crystallization: In the air, a suspension of racemic 4-(dimethylamino)pyrindinyl-pentaphenylcyclopentadienyl iron (**2**; 2.62 g, 3.97 mmol) and $CH_2Cl_2$ (45 mL) in a 250-mL flask was sonicated for ~10 min until all of catalyst **2** had dissolved. Next, the solution was diluted with THF (18 mL), and then a solution of anhydrous dibenzoyl-L-tartaric acid (711 mg, 1.98 mmol)[17] in THF (18 mL)[18] was added dropwise by pipette over 1 min to the stirred solution of catalyst **2**. The resulting dark-purple solution was sonicated for ~6 min. The flask was then fitted with a septum, and the flask was vigorously stirred and purged with nitrogen until a purple suspension formed. This suspension was stirred for 20 h, and then it was allowed to stand for 1.5 h without stirring. Next, the mixture was filtered, and the purple solid that was collected was rinsed with hexanes (10 mL). The material in the filtrate was purified by passing it through a column of silica gel, rinsing first with EtOAc to remove traces of degradation products (yellow or brown) and then with 90:10 EtOAc:$Et_3N$ (~100 mL) to elute the catalyst as a dark-purple band. The highly colored fractions were collected and concentrated on a rotary evaporator. HPLC analysis revealed an enantiomeric excess of 44% (1.71 g, 65%; fast-eluting enantiomer on chiral HPLC, (+)-(*R*) configuration). Regis Whelk O-2 column, flow: 0.9 mL/min, eluent: 60:40:0.4 $CH_2Cl_2$:hexanes:$Et_2NH$. $t_r$ (+)-(*R*): 6.4 min; (–)-(*S*): 9.6 min.

The purple solid from the filter cake was dissolved in $CH_2Cl_2$ (10 mL) and $Et_3N$ (1 mL). This solution was passed through a column of silica gel, eluting with 90:10 EtOAc:$Et_3N$ (~100 mL). The dark-purple fractions were collected and concentrated on a rotary evaporator. HPLC analysis revealed an enantiomeric excess of 97% (910 mg, 35%; slow-eluting enantiomer on chiral HPLC, (–)-(*S*) configuration).

Notes: 1) Column chromatography of catalyst **2** can be performed in the air with essentially no concern for decomposition. 2) The equivalents of the resolving agent that are used for the resolution of catalyst **2** is double that used in the resolution of catalyst **1.**

Recrystallization of the solid from the first crystallization: Calculation of the required amount of resolving agent: mmol of resolving agent = (mmol of catalyst **2**) x (fraction of the major enantiomer (e.g., 0.965 for 93% ee)).

A mixture of enantioenriched **2** (the solid from the first crystallization; 910 mg, 1.38 mmol; 97% ee) and $CH_2Cl_2$ (21 mL) in a 250-mL flask under air was sonicated until all of catalyst **2** had dissolved (~10 min). Next, the solution was diluted with THF (9 mL), and then a solution of anhydrous dibenzoyl-L-tartaric acid (486 mg, 1.36 mmol) in THF (10 mL; this solution was filtered before use) was added dropwise via pipette over 1 min to the stirred solution of **2**. The resulting dark-purple mixture was sonicated for ~5 min, leading to the formation of a large amount of a purple precipitate. The mixture was stirred for ~20 min, during which time it became less viscous. The flask was purged with nitrogen for 2-3 min, and then it was stoppered with a septum and allowed to stir for 20 h. Next, the mixture was allowed to stand without stirring for 3 h, and then it was filtered. The purple solid was "worked up" as described for the first crystallization. HPLC analysis revealed an enantiomeric excess >99% (830 mg, 32% (based on the starting amount of racemic **2**); slow-eluting enantiomer on chiral HPLC, (–)-(*S*) configuration).

Recrystallization of the filtrate from the first crystallization: A mixture of enantioenriched **2** (the filtrate from the first crystallization; 1.71 g, 2.59 mmol; 44% ee) and $CH_2Cl_2$ (39 mL) in a 250-mL flask was sonicated until all of the catalyst had dissolved (~10 min). Next, the solution was diluted with THF (17 mL), and a solution of dibenzoyl-D-tartaric acid monohydrate (701 mg, 1.86 mmol) in THF (17 mL; this solution was filtered before use) was added dropwise via pipette over 1 min to the stirred solution of **2**. The resulting dark-purple mixture was sonicated for ~6 min. Next, while stirring the mixture, the flask was purged with nitrogen for 2-3 min. Stirring was continued overnight (20 h), leading to a slurry. The mixture was allowed to stand without stirring for 1 h, and then it was filtered through a sintered glass frit. The purple solid was rinsed with hexanes (10 mL) and then suspended in $CH_2Cl_2$ (10 mL). $Et_3N$ (~1 mL) was added until the solution was homogeneous. The solution was passed through a column of silica gel, eluting with 95:5 EtOAc:$Et_3N$ (~100 mL). The dark-purple fractions were collected and concentrated on a rotary evaporator. HPLC analysis revealed an enantiomeric excess of >99% (1.01 g, 39% (based on the starting amount of racemic **2**); fast-eluting enantiomer on chiral HPLC, (+)-(*R*) configuration).

(+)-(*R*)-**2**: $[\alpha]^{20}_{D} = +940°$ ($c = 0.00024$, $CHCl_3$).

m.p. 280-281 °C (decomp.; >99% ee);

## 1.6 References and Notes


1. For reviews, see: a) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542–547; b) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412–420.
2. For recent work, see: a) Lee, E. C.; McCauley, K. M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 977–979; b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264–14265; c) Bappert, E.; Mueller, P.; Fu, G. C. *Chem. Commun.* **2006**, 2604–2606; d) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586–11587; e) Schaefer, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4606–4608; f) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176–6177; g) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604–5607; h) Mermerian, A. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 949–952.
3. (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230–7231; b) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.
4. We thank Dr. Thomas Roper of GlaxoSmithKline for pointing out this possibility and Mr. Roy Flanagan of GlaxoSmithKline for conducting calorimetry studies.
5. Ruble, J. C. Ph.D. Thesis, Massachusetts Institute of Technology, 1999.
6. (a) Cuperly, D.; Gros, P.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 238-241. (b) Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375-3383.
7. The Nazarov route was investigated by Jon Wilson and RCM route was investigated by Dr. Ryan Wurz.
8. In part because it is a subunit of pharmaceuticals such as Cefpirome/Cefrom, 2,3-cyclopentenopyridine is produced on a large scale.
9. Robison, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 6254–6257.
10. For example, the reaction of pyridine-*N*-oxide with $POCl_3$ proceeds with 70:30 selectivity favoring the formation of 2-chloropyridine (Yamanaka, H.; Araki, T.; Sakamoto, T. *Chem. Pharm. Bull.* **1988**, *36*, 2244–2247). We observe almost none (<5%) of the 2-chloropyridine.
11. Coperet, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740–1741. In the presence of $H_2O_2$/AcOH, the oxidation was relatively slow.
12. We have been able to synthesize compound **6** from 2,3-cyclopentenopyridine in two, rather than three, steps. However, these shorter routes are less practical than the sequence illustrated in Scheme 2.
13. All of the large-scale reactions were performed by Dr. Ryan Wurz.
14. Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534–551.
15. For a precedent with the parent compound (i.e., without a 4-dialkylamino group), see Reference 7.
16. Purchase price (September 2006): $900/kg (including airborne delivery).
17. Either anhydrous dibenzoyl-L-tartaric acid or its monohydrate can be employed.
18. Because the solution was somewhat cloudy, it was filtered before it was used.

# Chapter 2

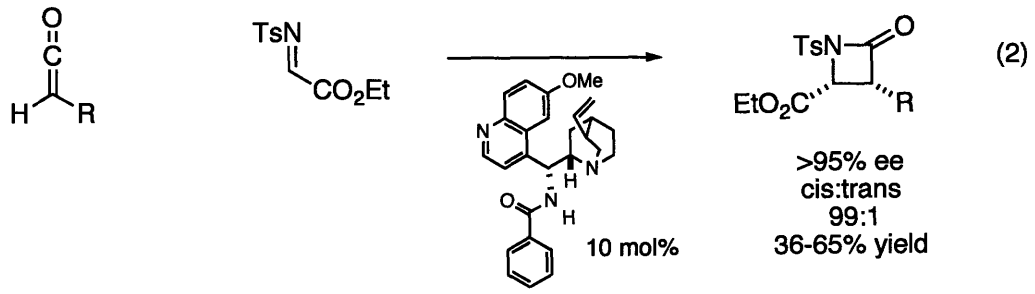
## Asymmetric Synthesis of Trans β-Lactams Catalyzed by a Planar-Chiral Nucleophilic Catalyst

## 2.1 Introduction

The development of methods for the synthesis of β-lactam-containing compounds has been well-established in the literature[1] mainly due to the importance of Penicillin and cephalosphorin[2] based antibiotics. However, the need for more potent antibiotics exists as a consequence of the growing resistance of microbial organisms toward common antibiotics. In addition to their importance as targets for medicinal chemistry, enantiopure β-lactams are versatile chiral building blocks in organic synthesis. For instance, β-lactams are found in semisynthesis of compounds displaying anti-cancer activity, such as paclitaxel (Taxol)[3] and docetaxel (Taxotere),[4] where an enantiopure β-lactam is used to install the β-amino acid-derived side chain. As a result, much effort has been expended towards the development of uniquely functionalized β-lactams.[5] Among the numerous methods of constructing β-lactams, the well-known Staudinger reaction,[6] i.e., the coupling of a ketene and an imine, is one of the most attractive methods as it offers an efficient and convergent route to β-lactams (eq 1).

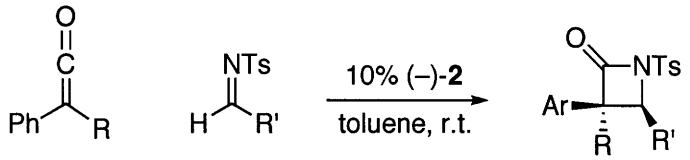

(1)

Although asymmetric β-lactams have received considerable attention, many of the methods for their synthesis are based on the utilization of chiral auxiliaries, and there are currently a limited number of reports on *catalytic asymmetric* processes that produce β-lactams. Specifically, there are examples of asymmetric Staudinger reactions of monosubstitued ketenes and imines to afford predominately cis β-lactams.[7] In such cases, the trans diastereomer can be accessed through a base induced epimerization.




(2)

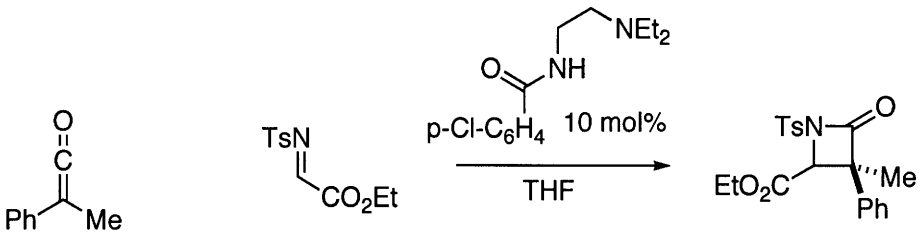
In contrast, Staudinger reactions of disubstituted ketenes are much less common,[8] despite the fact that β-lactams that bear two α substituents are an important class of target molecules.[9] Recently, contributions from both the Lectka (eq 2)[7b,10] and our laboratory (eq 3)[11] have broadened the scope in this area through the use of nucleophilic catalysts, which have been found to be highly efficient for the production of enantiomerically enriched cis β-lactams.




(3)

cis:trans
up to 15:1
89-98% ee
88-98% yield

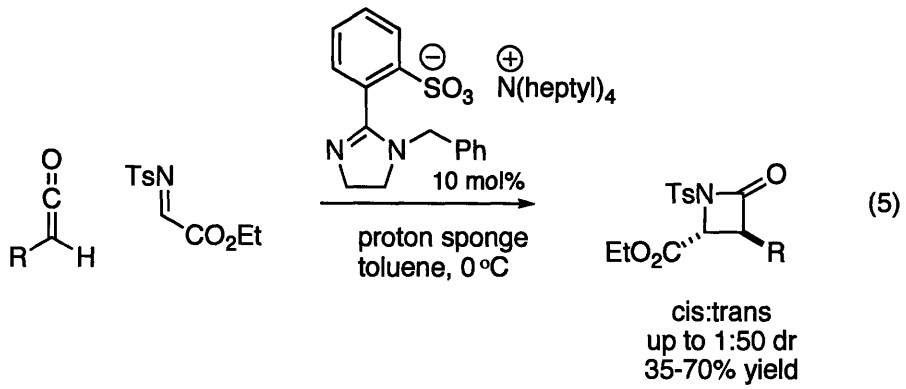
Of course, for such α,α'-disubstituted β-lactams, the trans diastereomer cannot be generated from the cis isomer through base-induced epimerization. Interestingly, Lectka reported *one* example of a catalyst system in which the trans isomer is the predominant product (eq 4).[10b]




(4)

cis:trans
3:97
one example

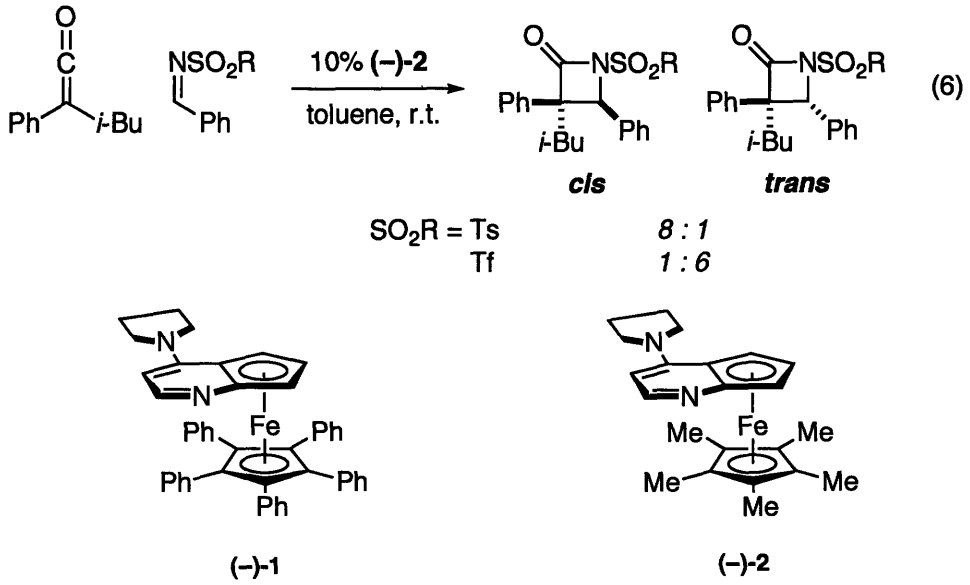
More recently, along with our published report,[13] Lectka reported a *diastereoselective* synthesis of trans β-lactams with monosubstituted ketenes (eq 5).[14]




(5)

## 2.2 Previous Work

Previous work in our laboratories demonstrated that planar-chiral nucleophile (–)-**2** catalyzes the asymmetric Staudinger reaction to generate cis β-lactams in excellent ee (81-98%) with good substrate scope (13 examples, eq 3).[11] Since it was believed that the electron-withdrawing protecting group on the nitrogen of the imine plays a crucial role in the success of the catalytic version of the Staudinger reaction, various protecting groups were screened in order to determine their effect on the coupling reaction. Unlike in the case of *p*-toluenesulfonyl (Ts) protected imines, which affords cis β-lactams,[11] it was discovered that trifluoromethanesulfonyl (triflyl, Tf) protected imines resulted primarily in the formation of trans β-lactams (eq 6)![12]




(6)

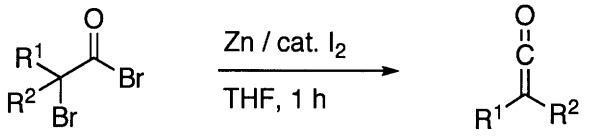
*Figure 1*. Planar-chiral nucleophilic catalysts used for the synthesis of β-lactams.

## 2.3 Results and Discussion

### *2.3.1. Synthesis of Ketenes*

To demonstrate the generality of trans-selective β-lactam transformations, we began by evaluating a more diverse set of ketenes to expand the substrate scope. Unlike many aryl ketenes, mono- and dialkyl ketenes are known to be unstable,[15] and, in nearly all cases, they were generated in situ for the subsequent reaction. Among the several well-established procedures for generating ketenes,[16] it was determined that the zinc-mediated di-dehalogenation of α-bromo acid bromides[17] would be most compatible with our reaction (this method avoids the use of an amine base that can also catalyze the reaction of a ketene with an imine). The zinc-mediated di-dehalogenation typically requires prolonged stirring, and it is often assisted by microwave irradiation or sonication to accelerate the reaction. Exposing unstable mono- and/or dialkyl ketenes to such conditions is problematic since Lewis acid catalyzed dimerization/polymerization is also accelerated; thus resulting in poor and irreproducible yields of the desired ketenes. In order to synthesize ketenes more reliably, an iodine-accelerated zinc-mediated di-dehalogenation method was developed that does not require any external assistance such as sonication (Table 1). Iodine is postulated to not only aid in activation of the zinc metal, but may also be involved in a halogen exchange, generating a more reactive acyl iodide during the reaction.

***Table 1***. Optimized Conditions for the Generation of Mono- and Dialkyl Ketenes




| entry | $R^1$ | $R^2$ | temp | yield (%)[a] |
|---|---|---|---|---|
| 1 | Et | H | –40 °C | 67 |
| 2[b] | Cy | H | –40 °C | 30 |
| 3 | *i*-Pr | H | 0 °C | 50 |
| 4 | *t*-Bu | H | 0 °C | 62 |
| 5 | *i*-Pr | Me | 0 °C | 76 |
| 6 | *t*-Bu | Me | r.t. | 84 |
| 7[c] | $CH_2$Cyp | Me | r.t. | 41 |

[a] Isolated yield after quenching with propylamine. [b] Reaction time: 30 min reaction. [c] Toluene was used as a co-solvent.

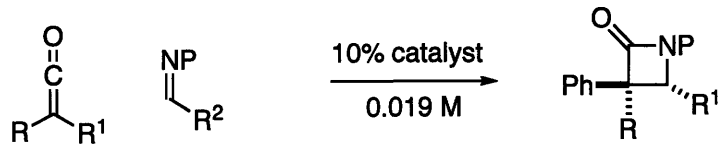
Ketene formation via the iodine-promoted zinc-mediated di-dehalogenation reaction can be performed at temperatures varying from –40 °C to room temperature. A range of monoalkyl ketenes, including unstable ethyl and cyclohexyl ketenes (entries 1 and 2), can be generated in moderate yields. However, these substrates were not employed in the cycloaddition reaction with imines due to the rapid background reaction (i.e., reaction occurred without catalyst; hence, low enantioselectivites were observed). Mono-substituted isopropyl and *tert*-butyl ketenes (entries 3 and 4), as well as isopropyl-, *tert*-butyl-, and cyclopentyl methyl- substituted methyl ketenes (entries 5, 6, and 7) were also generated in moderate yields.

Aryl alkyl ketenes were generated from the corresponding acid chloride, which was dehydrohalogenated with an amine base. The resulting aryl alkyl ketene is stable to purification via distillation and able to be stored at low temperature (–30 °C) for an extended period of time.

### *2.3.2. Asymmetric Trans-Selective Staudinger Reactions of Unsymmetrical Mono- and Dialkyl Ketenes Catalyzed by (–)-2*

The initial result obtained with a triflyl-protected imine to generate a trans β-lactam (eq 6) prompted us to explore various protecting groups in order to determine if better diastereoselectivity could be achieved (Table 2). Hence, we explored the electronic and steric effect of the protecting groups (mesyl vs. tosyl vs. triflyl). Additionally, a variety of ketenes (monoalkyl, dialkyl and arylalkyl ketenes) were subjected to the reaction conditions to determine the role of the structure of the ketene on the diastereoselectivity of the reaction. For the reactions of monoalkyl and dialkyl ketenes, generation of the trans β-lactam was favored when the imine was protected with a more electron-deficient protecting group (i.e., triflate) whereas tosylate- or mesylate- protected imines generated little to no selectivity (entry 1 vs. 2 and entries 3-5). Interestingly, DMAP-catalyzed reactions afforded poor stereoselectivity (entries 11-12). These results support the hypothesis that the trans-selectivity stems from the more electron-deficient nature of triflyl-protected imines (versus mesylate- or tosylate-protected imines).

***Table 2.*** Probing Trans-Selectivity with Respect to the Imine Protecting Group

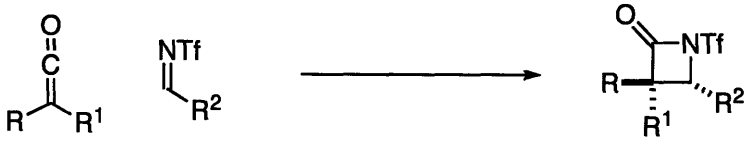



| entry | catalyst | R | $R^1$ | $R^2$ | temp | P | dr (trans:cis) |
|---|---|---|---|---|---|---|---|
| 1[a] | (–)-**1** | *t*-Bu | H | Ph | –78 °C to r.t. | Ts | 50:50 |
| 2[a] | (–)-**1** | *t*-Bu | H | Ph | –78 °C to r.t. | Tf | 91: 9 |
| 3[b] | (–)-**2** | *i*-Pr | Me | Ph | –78 °C to r.t. | Ts | 50:50 |
| 4[b] | (–)-**2** | *i*-Pr | Me | Ph | –78 °C to r.t. | Tf | 89:11 |
| 5[b] | (–)-**2** | *i*-Pr | Me | Ph | –78 °C to r.t. | Ms | 33:67 |
| 6[a] | DMAP | Ph | *i*-Bu | Ph | r.t. | Ts | 67:33 |
| 7[a] | DMAP | Ph | *i*-Bu | Ph | r.t. | Tf | 67:33 |

[a] In dichloromethane. [b] In toluene.

Next, a comprehensive screening study for determining optimal conditions for the synthesis of trans β-lactams was conducted with respect to catalyst, solvent, and temperature. The results of this study are summarized in Table 3. During the course of our optimization studies, we have found that the highly sensitive nature of this reaction necessitated modification of reaction conditions based on ketene to obtain acceptable enantioselectivity. As exemplified in Table 3, catalyst (–)-**2** performed better overall compared to (–)-**1** (entry 5 vs. 8) in generating good enantioselectivity. However, a decrease in catalyst loading from 10% to 5% yielded poorer enantioselectivity (entry 3 vs. 4 and 5 vs. 6). The solvent employed in the reaction was crucial in obtaining good stereoselection. Since the ketenes are generated in situ in THF, a suitable co-solvent was investigated and was found to be either DCM or toluene, depending on the substrate (entries 1 vs. 5). Additionally, the effect of concentration was examined (0.09 M vs. 0.019 M) and it was determined that more dilute conditions afforded better ee for all substrates examined.

*Table 3*. Reaction Optimization with Respect to Catalyst and Solvent

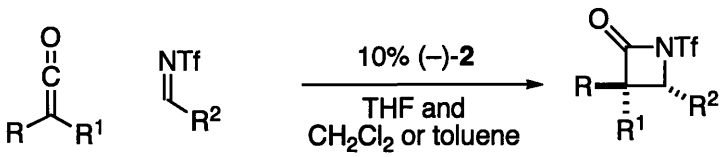



| entry | R | $R^1$ | $R^2$ | catalyst (mol%) | solvent | temp | trans:cis[a] | ee (%)[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | *t*-Bu | H | Ph | (–)-**2** (10) | THF/DCM | –78 °C | 95:5 | 78 |
| 2 | *t*-Bu | H | Ph | (–)-**2** (10) | THF/toluene | –78 °C | 75:15 | 28 |
| 3 | *t*-Bu | H | Ph | (–)-**1** (10) | THF/DCM | –78 °C | 91:9 | 85 |
| 4 | *t*-Bu | H | Ph | (–)-**1** (5) | THF/DCM | –78 °C | 86:14 | 71 |
| 5 | *i*-Pr | Me | Ph | (–)-**2** (10) | THF/toluene | –78 °C | 89:11 | 90 |
| 6 | *i*-Pr | Me | Ph | (–)-**2** (5) | THF/toluene | –78 °C | 86:14 | 82 |
| 7 | *i*-Pr | Me | Ph | (–)-**2** (10) | THF/DCM | –78 °C | 80:20 | 62 |
| 8 | *i*-Pr | Me | Ph | (–)-**1** (10) | THF/toluene | –78 °C | 92:8 | 47 |

[a] Diastereomeric ratios determined by 1H NMR of crude product mixtures. [b] Enantiomeric excess determined by chiral GLC or HPLC.

On the basis of these observations, we applied the optimized conditions to a variety of substrate combinations (Table 4). Thus, a mono-substituted alkyl ketene (entry 1) and unsymmetrical dialkyl ketenes (entries 2 and 3) reacted to form trans β-lactams in good stereoselection (up to 93:7 dr and 53-81% ee) and yield (52-95%). It should be noted that a tetrasubstituted stereogenic center is constructed in the reactions involving disubstituted unsymmetrical ketenes (entries 2-8). For a mono-substituted isopropyl ketene, no diastereoselectivity was observed for reaction with (–)-**2** whereas with (–)-**1**, relatively poor yield and stereoselectivity was observed (81:19 dr, 45% ee; 22% yield). Imines with electron-deficient aryl groups worked well to provide moderate stereoselection (up to 83:17 dr and 67-95% ee) and yields (77-87%, entries 4-5). Additionally, an electron-rich imine (entry 6) and a sterically demanding imine (entry 7) were both well tolerated in the reaction. In most of the reactions, catalyst recovery (70-85%) was easily achieved by column chromatography.

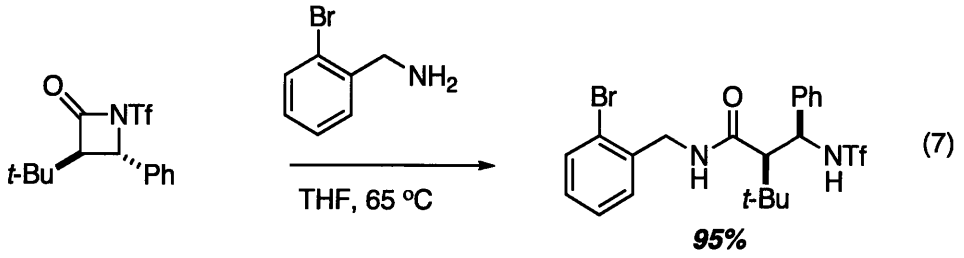
***Table 4.*** Scope with Respect to the Mono- and Dialkylketenes and Imines

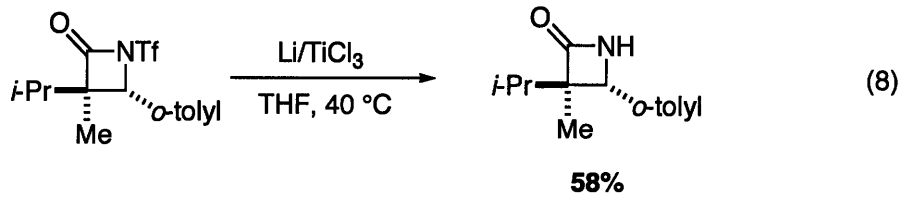



| entry | R | $R^1$ | $R^2$ | Trans:cis[a] | ee (%)[a] | yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | *t*-Bu | H | Ph | 93:7 | 78 | 52 |
| 2 | *i*-Pr | Me | Ph | 86:14 | 81 | 95 |
| 3 | $CH_2$Cyp | Me | Ph | 69:31 | 53 | 81 |
| 4 | *i*-Pr | Me | 4-F-$C_6H_4$ | 83:17 | 95 | 77 |
| 5 | *i*-Pr | Me | 4-$(CF_3)C_6H_4$ | 79:21 | 67 | 87 |
| 6 | *i*-Pr | Me | 4-(OMe)$C_6H_4$ | 90:10 | 68 | 92 |
| 7 | *i*-Pr | Me | o-tolyl | 68:32 | 78 | 96 |
| 8 | *i*-Pr | Me | 2-napthyl | 84:16 | 75 | 87 |

[a] Average of two runs. See Supporting Experimental for details.

β-Lactams are interesting targets not only because of their bioactivity, but also because they are useful precursors to other important families of compounds, such as β-amino acids. In order to demonstrate the utility of the β-lactams generated by our catalytic system, we further transformed several β-lactams into useful intermediates. A ring-opening reaction was conducted on an α-monosubstitued β-lactam with an amine to afford a β-amino amide (eq 7). Additionally, the *N*-triflyl protecting group was cleaved (eq 8) to obtain the desired product in 58% yield.[18] Both of these transformations proceeded without an erosion in stereochemical purity.

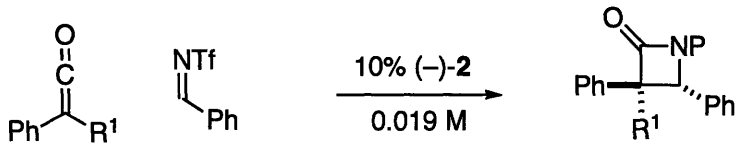


*2.3.3. Asymmetric Trans-Selective Staudinger Reactions of Unsymmetrical Aryl Alkyl Ketenes Catalyzed by (–)-2*

We have also explored the electronic effect of the N-protecting group with respect to aryl alkyl ketenes. As was observed with reactions with mono- and dialkyl ketenes, reactions with aryl alkyl ketenes generated acceptable diastereoselectivity favoring the desired trans β-lactams when the imine was protected with a triflyl group (Table 5).

***Table 5.*** Probing Trans-Selectivity with Respect to the Imine Protecting Group

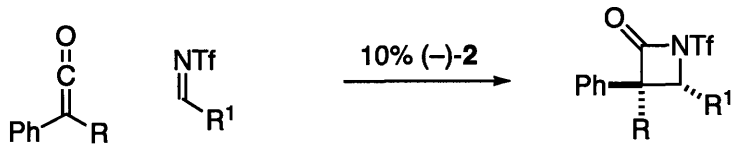



| entry | $R^1$ | temp | P | dr (trans:cis) |
|---|---|---|---|---|
| 1[b] | Me | 0 °C to r.t. | Tf | 97:3 |
| 2[a] | Me | 0 °C to r.t. | Ms | 80:20 |
| 3[a] | Et | 0 °C to r.t. | Ms | 17:83 |
| 4[a] | *i*-Bu | r.t. | Tf | 96:4 |
| 5[a] | *i*-Bu | r.t. | Ms | 50:50 |

[a] In dichloromethane. [b] In toluene.

A second comprehensive screening study was conducted for the reactions of unsymmetrical aryl alkyl ketenes with *N*-triflyl imines (Table 6). The stereoselectivity was found to be sensitive to the choice of reaction temperature (0 °C to room temperature) and the choice of solvent (DCM and/or toluene).

***Table 6.*** Reaction Optimization with Respect to Solvent and Temperature

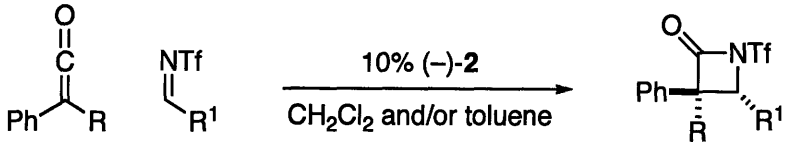



| entry | R | $R^1$ | solvent | temp | trans:cis[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Me | Ph | toluene | 0 °C | 92:8 | 58 |
| 2 | Me | Ph | DCM | 0 °C | 98:2 | 83 |
| 3 | *i*-Bu | Ph | DCM | 0 °C | 94:6 | 36 |
| 4 | *i*-Bu | Ph | DCM | r.t. | 98:2 | 74 |
| 5 | Me | 4-(OMe)$C_6H_4$ | toluene | 0 °C | 86:14 | 70 |
| 6 | Me | 4-(OMe)$C_6H_4$ | DCM | 0 °C | 67:33 | 61 |
| 7 | Me | 4-(OMe)$C_6H_4$ | toluene/DCM | 0 °C | 88:12 | 58 |
| 8 | Me | 4-F-$C_6H_4$ | toluene | 0 °C | 98:2 | 79 |
| 9 | Me | 4-F-$C_6H_4$ | DCM | 0 °C | 98:2 | 78 |
| 10 | Me | 4-F-$C_6H_4$ | toluene/DCM | 0 °C | 96:4 | 89 |

[a] Diastereomeric ratios determined by $^1$H NMR analysis of crude product mixtures.
[b] Enantiomeric excess determined by chiral GLC or HPLC.

We were pleased to find that a range of aryl alkylketenes and imines react to produce an array of β-lactams not only with good trans diastereoselectivity, but also with useful enantioselectivity (Table 7). It is interesting to note that a sterically hindered imine was tolerated extremely well (entry 7), forming the β-lactam in 99% ee. Imines with varying degrees of electron density also led to useful stereoselectivities (up to 97:3 dr and 69-85% ee; entry 4-6). In addition, we examined the coupling of a symmetrical disubstituted ketene (entry 10); gratifyingly, the desired β-lactam was generated in excellent ee.

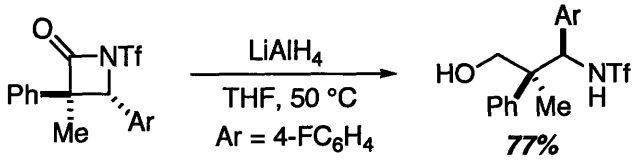
***Table 7.*** Scope: Aryl Alkylketenes and Imines



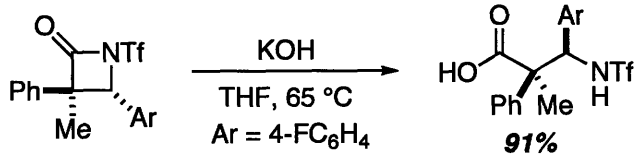

| entry | R | $R^1$ | trans:cis | ee (%)[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | Et | Ph | 86:14 | 63 | 60 |
| 2 | Me | Ph | 98:2 | 81 | 83 |
| 3 | *i*-Bu | Ph | 97:3 | 63 | 72 |
| 4 | Me | 4-$FC_6H_4$ | 96:4 | 85 | 84 |
| 5 | Me | 4-$(CF_3)C_6H_4$ | 97:3 | 69 | 80 |
| 6 | Me | 4-$(OMe)C_6H_4$ | 81:19 | 82 | 76 |
| 7 | Me | *o*-tolyl | 81:19 | 99 | 89 |
| 8 | Me | 2-Br-$C_6H_4$ | 80:20 | 84 | 79 |
| 9 | Me | 2-naphthyl | 98:2 | 94 | 76 |
| 10 | Ph | Ph | – | 98 | 62 |

[a] All data are the average of two experiments. [b] Enantiomeric excess of the trans diastereomer. [c] Yield of the mixture of diastereomers.

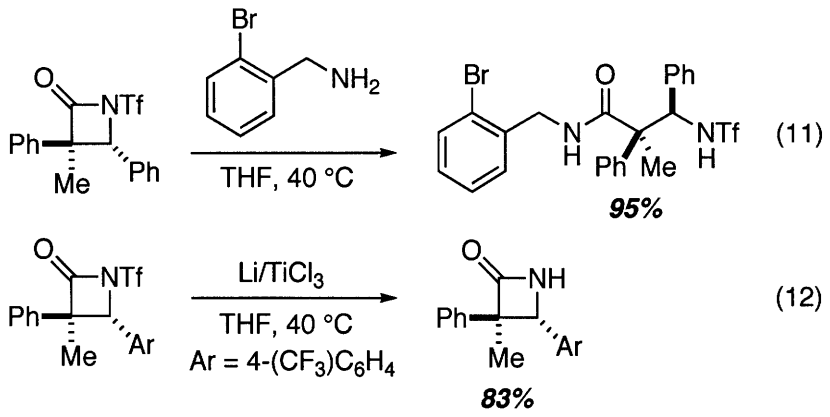
Various α,α'-disubstitued β-lactams were derivatized in good yields without an erosion in stereochemical purity (eq 9-12) to obtain useful families of compounds. For example, an α,α'-disubstitued β-lactam was reduced to generate a protected γ-amino alcohol (eq 9) or subjected to hydrolysis to generate a β-amino acid (eq 10). Additionally, a ring-opening reaction was conducted with an amine to afford a β-amino amide (eq 11) and the *N*-triflyl protecting group was cleaved (eq 12) to obtain the unprotected β-lactam.[18] All of these transformations proceeded without an erosion in stereochemical purity. To the best of our knowledge, only one report has described the synthesis of an *N*-triflyl β-lactam,[19] and no investigations of their reactivity have been reported.




(9)




(10)




*2.3.4. Mechanistic Discussion*

There are at least two possible mechanisms for the catalytic asymmetric Staudinger reaction. In the first mechanism, the nucleophilic catalyst first reacts with a ketene to generate a reactive zwitterionic enolate (**A**), which can then add to the electrophilic imine to form **B**. Subsequently, ring closure can occur to afford the desired β-lactam (Figure 2).[8,9]

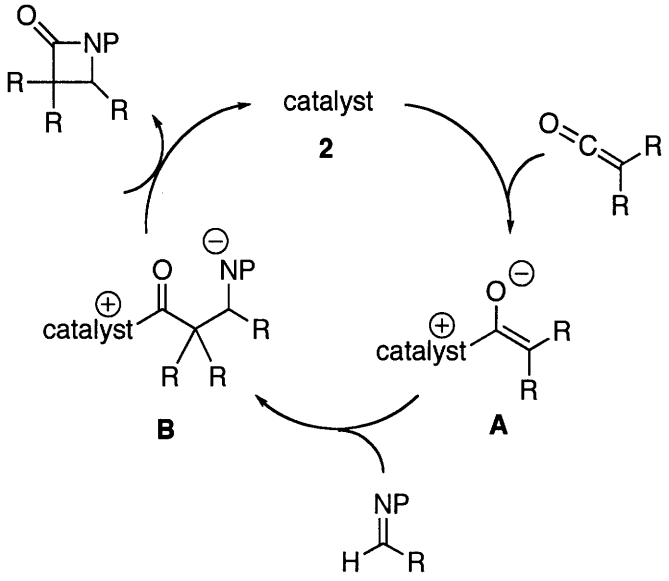



***Figure 2.*** A mechanism for nucleophile-catalyzed Staudinger reactions: A "ketene-first" pathway.

In the second mechanism, the nucleophilic catalyst first adds to the imine to generate zwitterionic intermediate **C**, which can then add to a ketene to generate a subsequent zwitterionic intermediate **D**. Finally, cyclization of **D** generates the desired β-lactam (Figure 3).

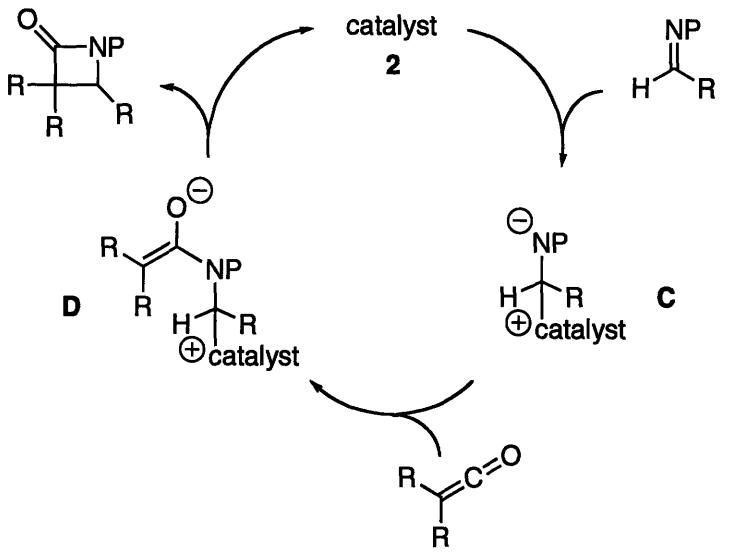
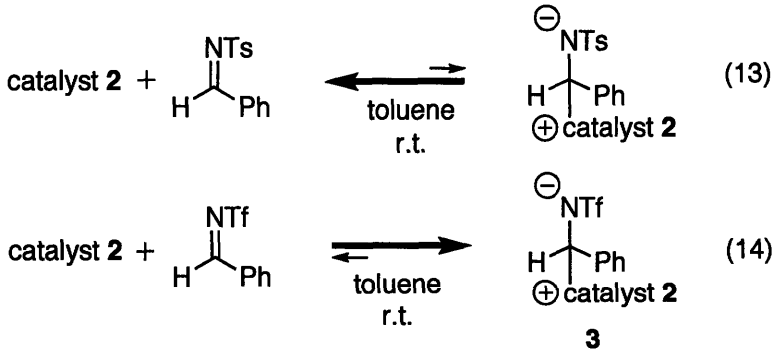



*Figure 3.* A mechanism for nucleophile-catalyzed Staudinger reactions: An "imine-first" pathway

Taking into account the remarkable dependence of the cis/trans diastereoselectivity on the choice of the *N*-sulfonyl group (eq 6), we began our investigation by examining the reactivity of the catalyst (**2**) with a ketene in the absence of an imine, as well as with an imine in the absence of a ketene. The $^{1}$H NMR spectrum of the reaction between catalyst (**2**) and phenyl methyl ketene was inconclusive (i.e., no identifiable peaks were observed). Interestingly, while there was no evidence by $^{1}$H NMR of a reaction between the catalyst and *N*-tosyl phenylimine (eq 9), the catalyst reacted quantitatively with *N*-triflyl phenylimine to furnish **3** (eq 10).




Hence, the differing electrophilicity of the two imines leads to divergent behavior in the presence of **2**. Moreover, we were able to obtain an X-ray crystal structure the product of a stoichiometric reaction between **2** and *N*-triflyl phenylimine, complex **3** (Figure 4).

Interestingly, the absolute configuration of **3** is the opposite of what would be predicted for the β-lactam on the basis of Figure 3. We hypothesized that the diastereomer of **3** that was crystallized was the more stable (or crystalline) adduct of (**3**), and less stable adduct of **3** was the actual complex that was participating in the reaction that generated the trans β-lactam (i.e., Curtin-Hammett conditions).[20] Moreover, it was determined that when **3** was allowed to react with a stoichiometric amount of phenyl methyl ketene, trans-3-methyl-3,4-diphenyl-*N*-triflyl β-lactam was isolated as the predominant diasteromer (86:14 dr), thus establishing that **3** was a chemically and kinetically competent potential intermediate in the reaction cycle.

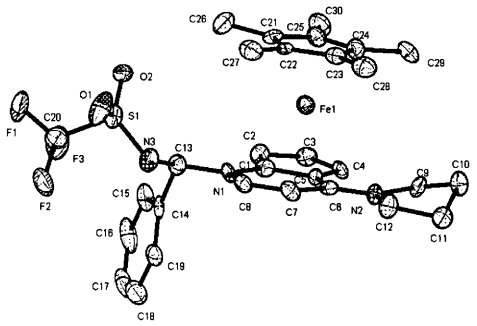
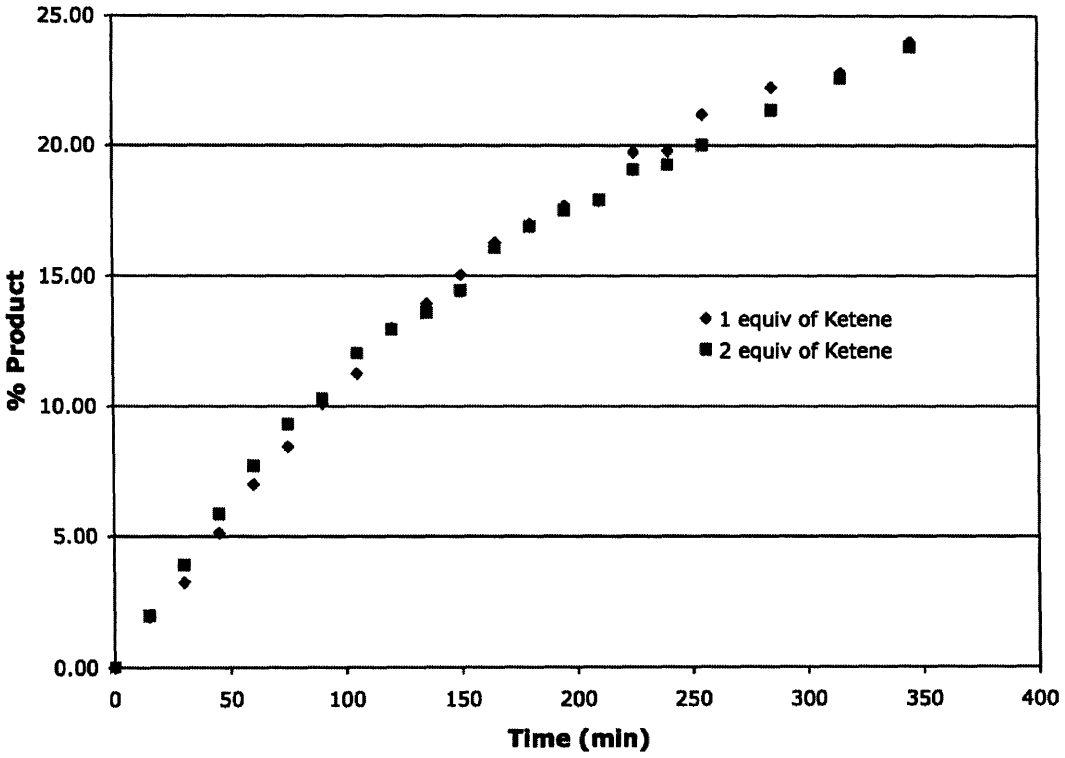



***Figure 4***. X-ray crystal structure of catalyst **2**-*N*-triflyl phenylimine adduct, **3**. Thermal elipsoids are at 30% probability.

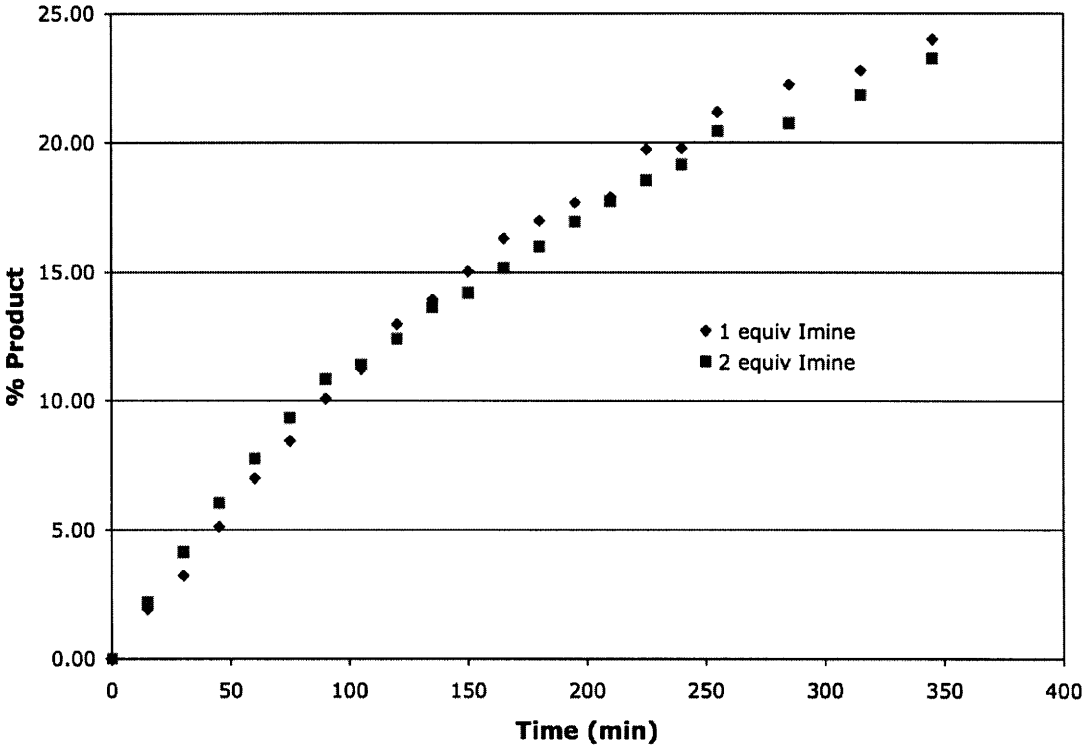
Additionally, kinetic experiments provided further insight into the reaction mechanism. The rate law for the coupling reaction of *N*-triflyl phenylimine with phenyl methyl ketene at –20 °C in $CD_2Cl_2$ was zero order with respect to ketene (Chart 1) *and* imine (Chart 2), with the overall reaction being first order with respect to catalyst only. This data correlated well with the proposed "imine-first" pathway outline in Figure 3, and suggested that the rate-determining step of the reaction would be the ring-closure from the 3-component adduct **D** in Figure 3.

*Chart 1.* Percent product vs. time plot for the reaction of *N*-triflyl phenylimine with phenyl methylketene at –20 °C with respect to 1 and 2 equivalents of ketene[a]



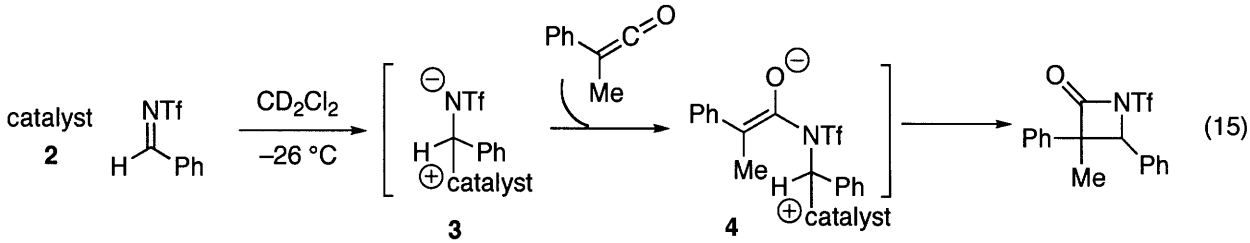

[a]All data are the average of two experiments.

*Chart 2.* Percent product vs. time plot for the reaction of *N*-triflyl phenylimine with phenyl methylketene at –20 °C with respect to 1 and 2 equivalents of imine[a]




[a]All data are the average of two experiments.

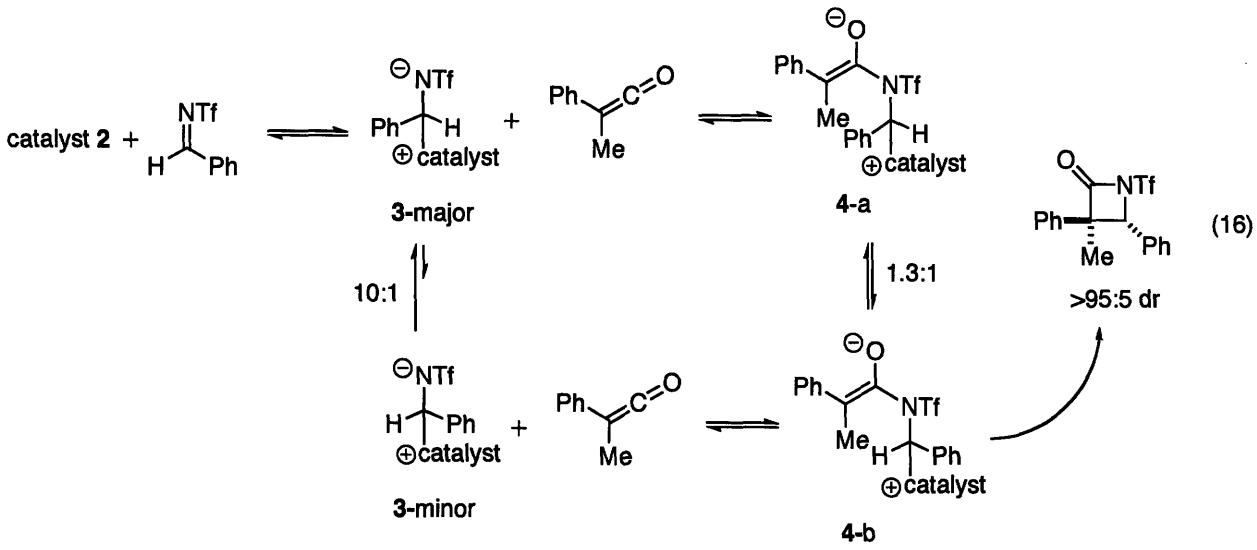
Furthermore, **4** was observed independently via $^1$H NMR at –26 °C (eq 15). This evidence strongly suggested that **4** was actually the resting state of the catalytic cycle rather than (**3**) as we initially presumed.




(15)

Subsequently, we were also able to detect relevant signals in the $^1$H NMR spectrum corresponding to (**4**) and not (**3**) during the catalytic reaction between *N*-triflyl phenylimine and phenyl methyl ketene, confirming **4** as the resting state of the catalytic cycle (Figure 5). Additional $^1$H NMR studies on **4** provided some noteworthy results: the initial diastereomeric ratio of **3** at –78 °C is approximately 10:1; however, after addition of phenyl methyl ketene, the

dr of **4** is approximately 1.3:1. After warming the sample to 22 °C, the desired β-lactam is formed in >95:5 dr (eq 16).



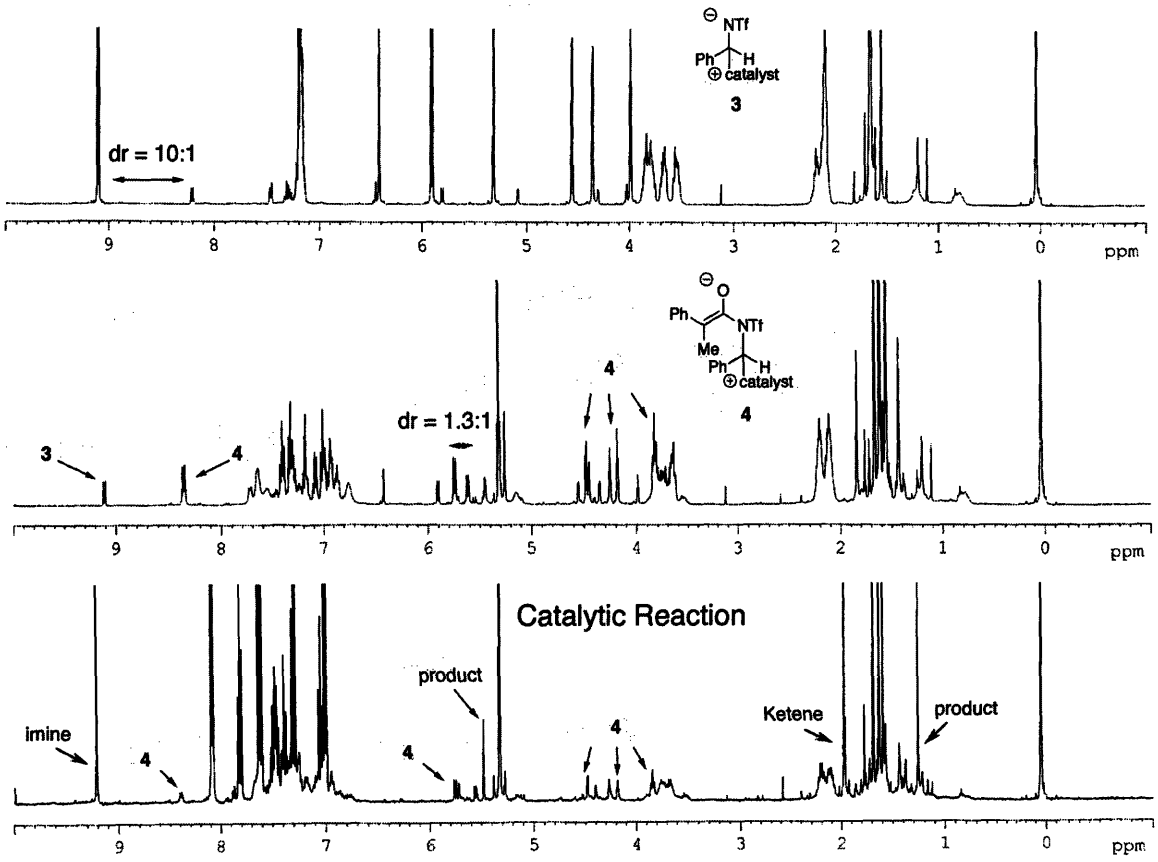
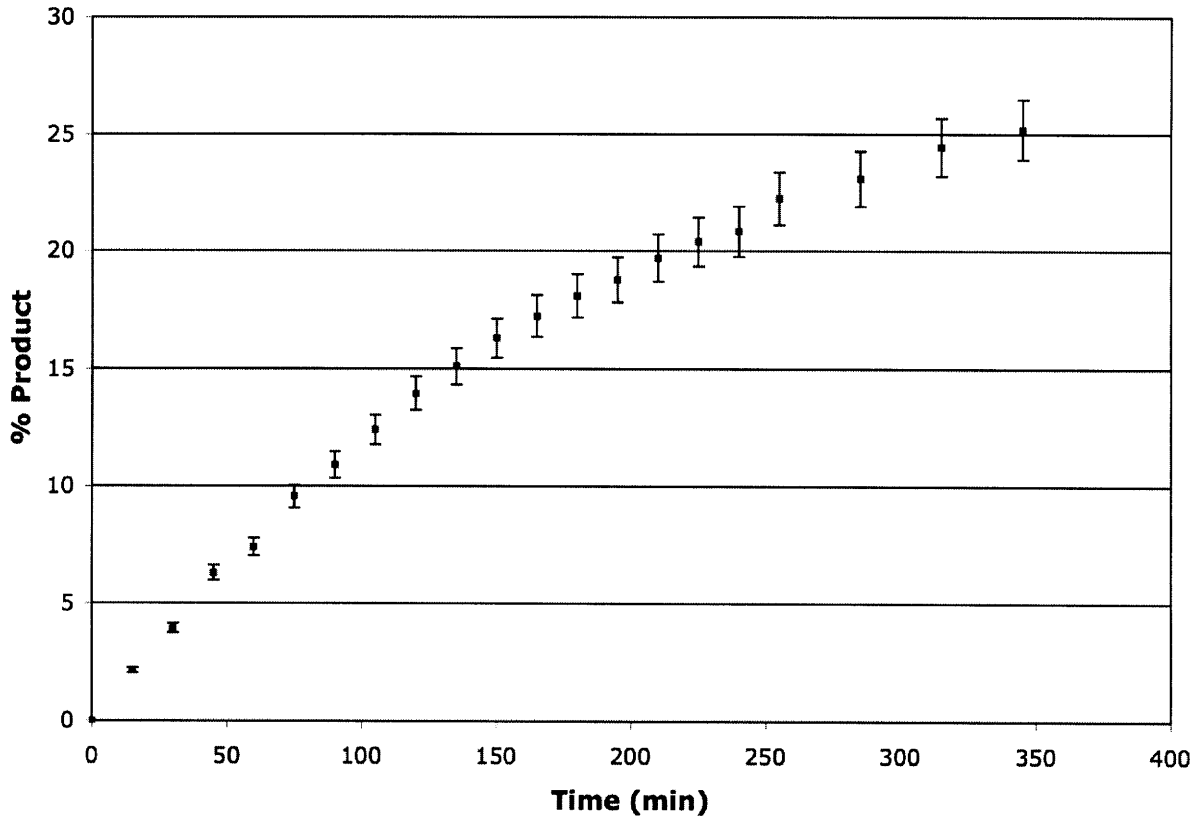




*Figure 5.* $^1$H NMR spectra of independently generated adduct **3** and adduct **4**, and that of the reaction described in equation 15.

In addition to our rate-law study, the $^1$H NMR results from a catalytic reaction (Figure 5) are consistent with our hypothesis that each step in the catalytic cycle exists in rapid equilibrium until the formation of **4**, again confirming that **4** is the resting state of the catalytic cycle. The hypothesis that the initial steps in the catalytic cycle are reversible offers an explanation as to why the absolute configuration of (**3**) is not what one would have expected or the basis of the stereochemistry of the major β-lactam product.

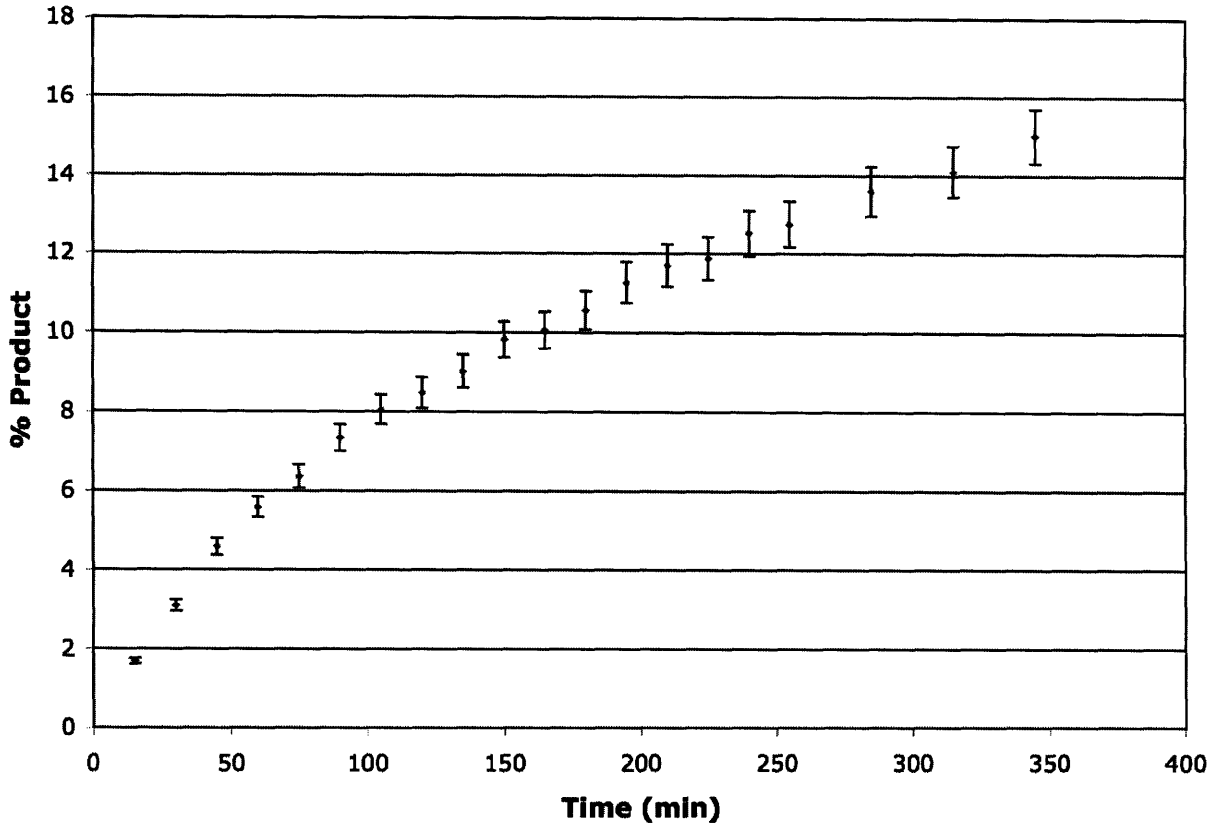
Finally, the α-secondary kinetic isotope effect was determined via $^1$H NMR based on reactions of protio-*N*-triflyl phenylimine with phenyl methyl ketene (Chart 3) and α-deutero *N*-triflyl phenylimine with phenyl methyl ketene (Chart 4) in $CD_2Cl_2$ at -20 °C.

***Chart 3.*** α-Secondary Kinetic Isotope Effect Study: Reaction of α-Protio-*N*-Triflyl Phenylimine[a]




[a]All data are the average of two experiments. Reactions were conducted in $CD_2Cl_2$ at –20 °C. The average error was calculated to be 5% (based upon the mean error for each data point) for each data point.

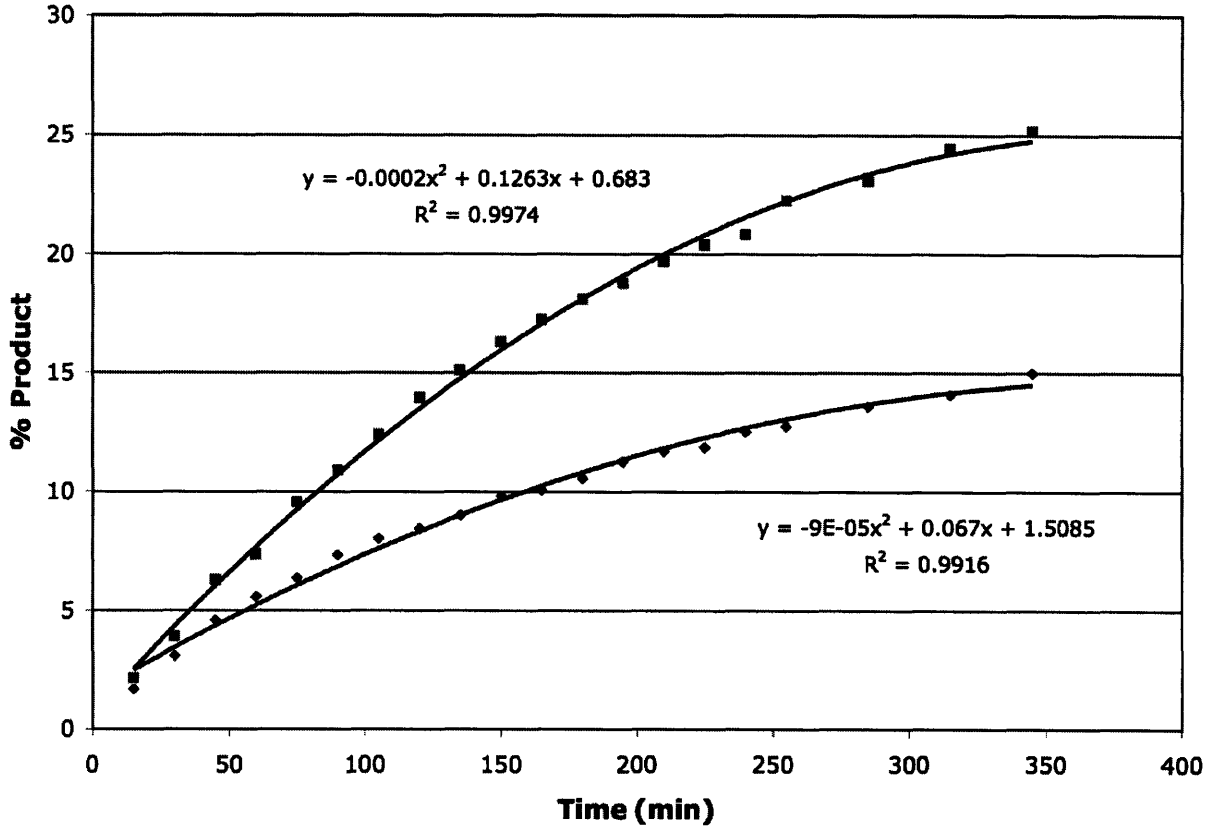
*Chart 4.* α-Secondary Kinetic Isotope Effect Study: Reaction of α-Deuterated *N*-Triflyl Phenylimine[a]




[a]All data are the average of two experiments. Reactions were conducted in $CD_2Cl_2$ at –20 °C. The average error was calculated to be 5% (based upon the mean error for each data point) for each data point.

A regression analysis was conducted for the data depicted in Charts 4 and 5. From the quadratic equations that fit the data with $R^2 > 0.99$, we were able to determine that there is a substantial normal α-secondary kinetic isotope effect for reactions of undeuterated versus α-deuterated imines ($k_H/k_D$=1.89) (Chart 5). The $k_H/k_D$ value was calculated based on the term x since the value for $x^2$ was negligible.

*Chart 5.* α-Secondary Kinetic Isotope Effect Study: Comparison of α-Deuterated and α-Non-Deuterated *N*-Triflyl Phenylimine[a]




Although not definitive, the substantial normal α-secondary kinetic isotope effect we observed was consistent with the hypothesis that in the transition state of the rate-determining step, there was a hybridization change from $sp^3$ to $sp^2$:[20] such hybridization change is not expected for the "ketene-first" pathway. On the other hand, a normal α-secondary kinetic isotope effect is expected for the "imine-first" pathway if the cyclization step is the turnover-limiting. Therefore, we believe this evidence strongly supports the "imine-first" pathway over the "ketene-first" pathway.

### *2.3.5. Determination of Absolute Configuration*

The absolute configuration of the aryl alkyl substituted β-lactams was established by x-ray crystallography of a representative compound generated from phenyl methyl ketene and 2-bromophenyl *N*-triflyl imine (Table 6, entry 8), which was crystallized from benzene/pentane

(1:3) at –30 °C. The bis-alkyl substituted β-lactam generated from isopropyl methyl ketene and 4-fluorophenyl *N*-triflyl imine (Table 4, entry 4) was crystallized from 2-propanol/pentane (1:3) at ambient temperature, and its absolute configuration was also determined by x-ray crystallography. Adduct **A** was crystallized from acetonitrile at –30 °C, and the absolute configuration of this compound was determined by x-ray crystallography.

## 2.4 Conclusions

In summary, we have demonstrated that trans β-lactams can be generated via catalysis with a planar-chiral derivative of PPY. A wide array of *N*-triflylimines with various mono- and di-substituted alkyl and aryl ketenes react with good enantioselectivity and yield. We have also presented mechanistic data supporting a novel mechanism, in which the *N*-triflylimine, rather than the ketene, reacts with the catalyst, via the "imine-first" pathway outlined in Figure 3.

## 2.5 Experimental Procedures

### *2.5.1. General*

All air- and moisture-sensitive manipulations were carried out with standard Schlenk technique under nitrogen or in a glove box under nitrogen.

Toluene, $CH_2Cl_2$, and THF were purified by passing through a neutral alumina column under argon prior to use. 2,3-Dimethylbutyric acid (Karl Industries), 3,3-dimethylbutyric acid (Aldrich), 2-phenylpropionic acid (TCI), 2-bromobenzylamine (Aldrich), thionyl chloride (Alfa Aesar), dimethyl ethylamine (Aldrich), *N*-propylamine (Aldrich), 1-bromo-2-methylpropane (Aldrich), methyliodide (Aldrich), $LiAlH_4$ (1.0 M in THF, Aldrich), lithium wire (Alfa Aesar), $TiCl_3$ (Aldrich) were used as received. Zinc metal (Stream) was activated with hydrochloric acid. *N*-Buthyllithium (2.89 M in THF, Alfa Aesar) was titrated prior to use.

4-Fluorobenzaldehyde, 4-(trifluoromethyl)-benzaldehyde, *o*-tolualdehyde, 2-bromobenzaldehyde, *p*-anisaldehyde, and benzaldehyde were distilled prior to use.

2-Bromo-3,3-dimethylbutyryl bromide, 2-bromo-3-methylbutyryl bromide and 2-bromo-2,3-dimethylbutyryl bromide were synthesized according to a literature procedure for a related compound.[21] Planar-chiral catalysts were prepared and resolved as previously reported.[22]

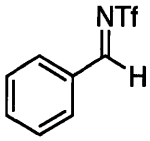
$^1$H NMR spectra were recorded on either Varian Mercury 300 or INOVA500 spectrometer at ambient temperature. $^{13}$C NMR spectra were obtained with complete proton decoupling on a Varian INOVA501 spectrometer (126 MHz) at ambient temperature. $^{19}$F NMR spectra were obtained on a Varian Mercury 300 spectrometer (282 MHz) at ambient temperature and the chemical shifts are referenced to external trifluoroacetic anhydride at –78 ppm.

$^1$H NMR spectra for the mechanism investigation was recorded on Bruker 400 spectrometer (400 MHz) at temperatures ranging from –80 to –20 °C. The initial target temperature was calibrated with methanol and equilibrated over 1.5 h.

Infrared spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. Optical rotations were measured on a Perkin Elmer Model 241 polarimeter. Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. Yields are not optimized.

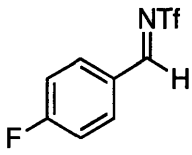
### *2.5.2. Synthesis of Imines and Ketenes*

1,1,1-Trifluoro-*N*-sulfinyl-methanesulfonamide ($CF_3SO_2NSO$) was synthesized according to the literature procedure[23] where 4 N HCl in dioxane (0.5 equiv) was incorporated as an additive after 3 days of reflux in thionyl chloride.



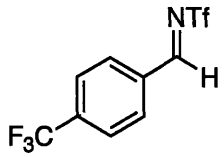

The general procedure was followed: benzaldehyde (900 mg, 4.61 mmol) and $CF_3SO_2NSO$ (489 mg, 4.61 mmol) in 1,2-dichloroethane (5.0 mL). The reaction mixture was concentrated to dryness, and the product was purified via distillation (300 mtorr, distillation temp at 72–75 °C). Product: 785 mg (77%) as colorless oil, which solidified upon standing.

$^1$H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.08 (dd, J = 7.0, J = 1.0 Hz, 2H), 7.80 (m, 1H), 7.62 (t, J = 7.5 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 180.1, 137.6 (x2), 132.9, 131.7, 129.9 (x2), 119.3 (q, $^1J_{CF}$ = 321.3). $^{19}$F NMR (282 MHz, $C_6D_6$) δ –77.9. HRMS (EI, m/e) calcd for $C_8H_6F_3NO_2S$ (M+) 237.0071, found 237.0055. FTIR ($CH_2Cl_2$) 3058, 1595, 1564, 1364, 1223, 739 $cm^{-1}$.



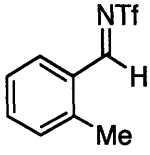

4-Fluorobenzaldehyde (211 mg, 1.70 mmol, freshly distilled) and $CF_3SO_2NSO$ (332 mg, 2.56 mmol) were dissolved in anhydrous 1,2-dichloroethane (2.7 mL). The resulting solution was heated to reflux under a nitrogen atmosphere for 16 h. The solvent was then removed under vacuum, leaving a slightly tan solid. The crude solid was dissolved in $CH_2Cl_2$/pentane (1:1) and filtered through a pad of Celite. The filtrate was concentrated and redissolved in pentane under reflux conditions. Clean product was crystallized upon slow cooling, which was then isolated as a white, crystalline solid. Yield: 285 mg (75%).

$^1$H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.13 (m, 2H), 7.31 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 178.4, 168.6 (d, $^1J_{CF}$ = 263.5 Hz), 135.7 (d, $^3J_{CF}$ = 10.4 Hz) (x2), 128.2, 119.3 (q, $^1J_{CF}$ = 321.9 Hz), 117.6(d, $^2J_{CF}$ = 22.4 Hz)(x2). $^{19}$F NMR (282 MHz, $C_6D_6$) δ –77.9, –98.3. HRMS (EI, m/e) calcd for $C_8H_5F_4NO_2S$ (M+) 254.9977, found 254.9981. FTIR ($CH_2Cl_2$) 3056, 1569, 1223, 740 cm$^{-1}$. M.p. 61–63 °C.



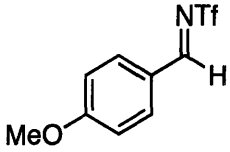

The general procedure was followed: 4-(trifluoromethyl)-benzaldehyde (890 mg, 5.12 mmol, freshly distilled) and $CF_3SO_2NSO$ (1.00 g, 5.12 mmol) in 1,2-dichloroethane (10 mL). Product: 967 mg (62%) as a white, crystalline solid.

$^1$H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.21 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 178.6, 138.1 (q, $^2J_{CF}$ = 32.8 Hz), 134.4, 132.9 (x2), 126.8 (q, $^3J_{CF}$ = 3.5 Hz) (x2), 123.2 (q, $^1J_{CF}$ = 272.9 Hz), 119.3 (q, $^1J_{CF}$ = 321.8 Hz), $^{19}$F NMR (282 MHz, $CDCl_3$) δ –64.2, –77.0. HRMS (EI, m/e) calcd for $C_9H_5F_6NO_2S$ (M+) 304.9945, found 304.9938. FTIR ($CH_2Cl_2$) 3056, 1604, 1266, 1226, 740 cm$^{-1}$. M.p. 45–46 °C.



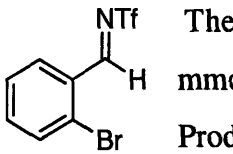

The general procedure was followed: *o*-tolualdehyde (308 mg, 2.56 mmol, freshly distilled) and $CF_3SO_2NSO$ (500 mg, 2.56 mmol) in 1,2-dichloroethane (5.0 mL). Product: 302 mg (47%) as a tan, crystalline solid.

$^1$H NMR (500 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.13 (dd, J = 7.0, J = 1.5 Hz, 1H), 7.65 (dt, J = 6.0 J = 1.5 Hz, 1H), 7.39 (m, 2H), 2.70 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 178.6, 144.7, 137.3, 132.7, 132.4, 129.9, 127.4, 119.4 (q, $^1J_{CF}$ = 321.3 Hz), 20.2. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –77.5. HRMS (EI, m/e) calcd for $C_9H_9F_3NO_2S$ (M+) 251.0228, found 251.0212. FTIR ($CH_2Cl_2$) 3055, 1558, 1265, 738 cm$^{-1}$. M.p. 63–65 °C.



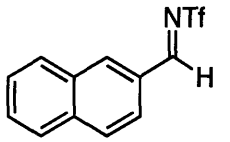

The general procedure was followed: *p*-anisaldehyde (717 mg, 5.27 mmol) and $CF_3SO_2NSO$ (1.03 g, 5.27 mmol) in 1,2-dichloroethane (10 mL). Product: 1.00 g (71%) as a white crystalline solid.

$^1H$ NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.04 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 6.5 Hz, 2H), 3.96 (s, 3H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 178.6, 167.8, 135.9 (x2), 124.7, 144.7, 119.4 (q, $^1J_{CF}$ = 321.2 Hz), 56.2. $^{19}F$ NMR (282 MHz, $CDCl_3$) δ –77.6. HRMS (EI, m/e) calcd for $C_9H_8F_3NO_3S$ (M+), found 267.0167. FTIR ($CH_2Cl_2$) 3057, 1551, 1220, 824, 740 $cm^{-1}$. M.p. 78–79 °C.




The general procedure was followed: 2-Bromobenzaldehyde (462 mg, 2.45 mmol) and $CF_3SO_2NSO$ (478 mg, 2.45 mmol) in 1,2-dichloroethane (5.0 mL). Product: 334 mg (44%) of slightly tan, crystalline solid.

$^1H$ NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.61 (dt, J = 6.0, J = 1.5 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H). $^{13}C$ NMR (126MHz, $CDCl_3$) δ 179.1, 138.3, 134.6, 131.7, 131.0, 130.6, 128.7, 119.3 (q, $^1J_{CF}$ = 321.3 Hz). $^{19}F$ NMR (282 MHz, $C_6D_6$) δ –77.5. HRMS (EI, m/e) calcd for $C_9H_9F_3NO_2S$ (M+) 314.9176, found 314.9169. FTIR ($CH_2Cl_2$) 3055, 1582, 1266, 739 $cm^{-1}$. M.p. 44–46 °C.




The general procedure was followed: 2-Naphthaldehyde (155 mg, 0.992 mmol) and $CF_3SO_2NSO$ (194 mg, 0.992 mmol) in 1,2-dichloroethane (2.0 mL). Product: 220 mg (77%) as a pale-yellow, crystalline solid.

$^1H$ NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.52 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.76 (t, J = 7.0 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 180.0, 139.5, 137.8, 132.7, 131.2, 130.3, 130.0, 129.4, 128.5, 128.0, 124.1, 119.4 (q, $^1J_{CF}$ = 321.3). $^{19}F$ NMR (282 MHz, $C_6D_6$) δ –77.8. HRMS (EI, m/e) calcd for $C_{12}H_8F_3NO_2S$ (M+) 287.0228, found 287.0214. FTIR ($CH_2Cl_2$) 3055, 1563, 1266, 739 $cm^{-1}$. M.p. 124–126 °C.

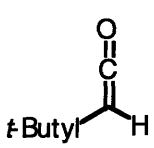



**Table 1, entry 4.** A solution of 2-bromo-3,3-dimethylbutyryl bromide (0.0775 mmol, 1.0 equiv) in THF (0.3 mL) was added to a sonicated slurry of zinc powder

(0.252 mmol, 3.2 equiv) in THF (0.1 mL). Then, a catalytic amount of iodine dissolved in THF (0.1 mL) was added into the reaction mixture, and the slurry was stirred at 0 °C for 1 h. Vacuum transfer yielded the desired ketene as a clear, colorless solution, which was immediately used in the Staudinger reaction.

The yield of ketene was quantified by quenching the vacuum-transferred solution with propylamine (2.0 equiv) at –78 °C and warming to room temperature. The resulting mixture was concentrated to give a white residue (62% yield).

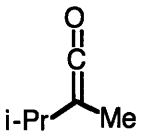



**Table 1, entry 5**. Isopropyl methyl ketene was generated in 76% yield, using the same procedure as for *t*-butyl ketene.

Phenyl methyl ketene, phenyl ethyl ketene, phenyl isobutyl ketene, and diphenyl ketene were synthesized according to literature procedure[24] with dimethyl ethylamine as a base. In the case of phenyl methyl ketene, diethyl ether was used as a solvent instead of THF.

### *2.5.3. Catalytic Enantioselective Synthesis of Trans β-Lactams*

Method A:

In a nitrogen-filled glovebox, a solution of acid bromide (1.0 equiv) in THF was added to a Schlenk tube containing a sonicated slurry of zinc powder (3.2 equiv) in THF. Then, iodine crystals dissolved in THF (0.1 mL) were added into the reaction mixture, and the slurry was stirred at 0 °C for 1 h. The resulting ketene was vacuum-transferred into a Schlenk tube containing a stirred solution of **(–)-2** (0.1 equiv) and *N*-triflyl imine (1.1 equiv) in toluene at –78 °C. The reaction mixture was then gradually warmed to room temperature overnight, and the desired product was purified and isolated by flash silica-gel column chromatography. The diastereomeric ratio was determined by NMR analysis of crude material obtained from diethyl ether extraction and subsequent silica-gel plug filtration of the reaction mixture before purification.

Method B:

In a nitrogen-filled glovebox, dissolved *N*-triflyl imine (1.0 equiv) and **(–)-2** (0.1 equiv) in either toluene or dichloromethane and was cooled to 0 °C in an ice bath under a nitrogen atmosphere. To this, ketene (1.0 equiv) dissolved in toluene solution was added over approximately 1 min, and the syringe was rinsed with toluene. The resulting solution was allowed to warm to room temperature while stirring overnight. The desired product was purified and isolated by flash silica-gel column chromatography.

Method C:

In a nitrogen filled glovebox, a solution of *N*-triflyl imine (1.0 equiv) and **(–)-2** (0.1 equiv) in a mixture of toluene/dicholoromethane and was cooled to 0 °C in an ice bath under a nitrogen atmosphere. To this, ketene (1.0 equiv) dissolved in toluene solution was added over approximately 1 min, and the syringe was rinsed with dichloromethane. The resulting solution was allowed to warm to room temperature while stirring overnight. The desired product was purified and isolated by flash silica-gel column chromatography.

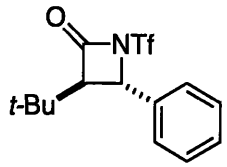



**Table 4, entry 1.** General method A was followed. A solution of 2-bromo-3,3-dimethylbutyryl bromide (120 mg, 0.47 mmol) in THF (1.9 mL) was added to a sonicated slurry of zinc powder (97.3 mg, 1.49 mmol) in THF (0.6 mL). Then, iodine crystals (1.80 mg, 7.10 μmol), dissolved in THF (0.6 mL), were added into the reaction mixture and the slurry was stirred at 0 °C for 1 h. The resulting ketene was vacuum-transferred into a Schlenk tube containing a stirred solution of **(–)-2** (10.8 mg, 28.8 μmol) and 1,1,1-trifluoro-*N*-(phenylmethylene)-methanesulfonamide (75.1 mg, 0.32 mmol) in $CH_2Cl_2$ (12 mL) at –78 °C. The reaction mixture was then gradually warmed to room temperature overnight, and the desired product was purified and isolated by flash silica-gel column chromatography (2.5% EtOAc/hexanes). Yield: 51.9 mg (54%) of a slightly yellowish oil. GC analysis: 78% ee [CP-Chirasil-Dex CB column; 140 °C (5 min), 1.0 °C/min to 170 °C; 14.37 psi He; retention times: 14.0 min (major), 13.7 min (minor)].

Second run (same scale): Yield: 48.3 mg (50%), 77% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.01 (m, 3H), 6.92 (m, 2H), 4.73 (d, J = 3.5 Hz, 1H), 2.76 (d, J = 4.0 Hz, 1H), 0.68 (s, 9H). $^{13}$C NMR (126 MHz, CDCl3) δ 165.5, 136.0, 129.8, 129.4 (x2), 126.8 (x2), 119.3 (q, $^1J_{CF}$ = 322.5), 72.2, 61.9, 33.1, 27.1 (x3). $^{19}$F NMR (282 MHz, $C_6D_6$) δ

–77.6. FTIR (NaCl) 1823, 1410, 1211, 1145, 739 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{14}H_{16}F_3NO_3S$ (M+Na) 358.0803, found 358.0703. $[\alpha]^{20}_D$ –73.3 (*c* 0.002, $CH_2Cl_2$, 77% ee).

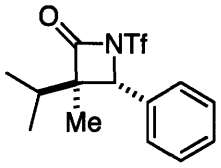



**Table 4, entry 2.** General method A was followed. A solution of 2-bromo-2,3-dimethylbutyryl bromide (80.0 mg, 0.31 mmol) in THF (1.2 mL) was added to a sonicated slurry of zinc powder (97.3 mg, 1.49 mmol) in THF (0.4 mL). Then, iodine crystals (0.40 mg, 1.58 μmol), dissolved in THF (0.4 mL), were added into the reaction mixture, and the slurry was stirred at 0 °C for 1 h. The resulting ketene was vacuum-transferred into a Schlenk tube containing a stirred solution of **(–)-2** (8.80 mg, 23.5 μmol) and 1,1,1-trifluoro-*N*-(phenylmethylene)-methanesulfonamide (61.3 mg, 0.26 mmol) in toluene (10.4 mL) at –78 °C. The product was purified by flash silica-gel column chromatography (10% EtOAc/hexanes). Yield: 72.9 mg (92%) of colorless oil, which solidified upon standing. HPLC analysis: 80% ee [Daicel CHIRALCEL OJ-H column; 0.5 mL/min; solvent system: 0.3% isopropanol/hexanes; retention times: 33.6 min (major), 20.5 min (minor)].

Second run (same scale): Yield: 77.3 mg (98%), 81% ee.

$^1H$ NMR (500 MHz, $C_6D_6$) δ 6.99 (m, 3H), 6.90 (m, 2H), 4.82 (s, 1H), 1.68 (septet, J = 7.0 Hz, 1H), 0.68 (d, J = 7.0 Hz, 3H), 0.64 (d, J = 7.0 Hz, 3H), 0.42 (s, 3H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 169.7, 133.4, 129.2, 129.0(x2), 127.0 (x2), 119. 5 (q, $^1J_{CF}$ = 323.0), 71.6, 67.6, 33.9, 17.9, 17.6, 12.7. $^{19}F$ NMR (282 MHz, $C_6D_6$) δ –76.8. FTIR (NaCl) 1820, 1411, 1212, 740 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{14}H_{16}F_3NO_3S$ (M+Na) 358.0803, found 358.0693. $[\alpha]^{20}_D$ – 141.1 (*c* 0.003, $CH_2Cl_2$, 80% ee).

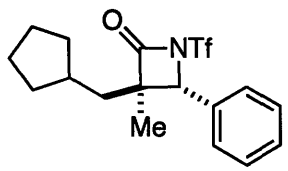



**Table 4, entry 3.** General method A was followed. A solution of 2-bromo-3-cyclopentyl-2-methylproyryl bromide (150 mg, 0.50 mmol) in toluene (1.5 mL) was added to a sonicated slurry of zinc powder (105 mg, 1.61 mmol) in THF (0.8 mL). Then, iodine crystals (0.80 mg, 3.15 μmol), dissolved in THF (0.8 mL), were added into the reaction mixture, and the slurry was stirred at room temperature for 1 h. The resulting ketene was vacuum-transferred into a Schlenk tube containing a stirred solution of **(–)-2** (7.80 mg, 20.6 μmol) and 1,1,1-trifluoro-*N*-(phenylmethylene)-methanesulfonamide (53.8 mg, 0.23 mmol) in toluene (7.7 mL) at –78 °C. The product was purified by flash silica-gel column chromatography (10% EtOAc/hexanes). Yield as a mixture

of two diastereomers: 65.9 mg (85%) of a colorless oil. The major diastereomer was separated (2.5% EtOAc/hexanes) as colorless oil. Yield: 27.0 mg (34%). GC analysis: 54% ee [CP-Chirasil-Dex CB column; 140 °C (1 min), 0.5 °C/min to 180 °C; 8.33 psi He; retention times: 62.6 min (major), 63.2 min (minor)].

Second run (200 mg scale): Yield: 80.9 mg (79%) of colorless oil. The major diastereomer yield: 39.1 mg (38%), 51% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.01 (m, 3H), 6.95 (m, 2H), 4.88 (s, 1H), 1.59 (m, 4H), 1.47 (m, 3H), 1.33 (m, 2H), 0.85 (m, 2H), 0.52 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 170.1, 133.4, 129.4, 129.0 (x2), 127.0 (x2), 119.6 (q, $^1J_{CF}$ = 323.0), 69.6, 62.8, 42.8, 36.5, 34.4, 34.3, 25.3, 25.1, 16.2. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.4. FTIR (NaCl) 2955, 1824, 1411, 1207 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{20}F_3NO_3S$ (M+Na) 398.1116, found 398.1016. $[\alpha]^{20}_D$ –59.4 (*c* 0.002, $CH_2Cl_2$, 54% ee).

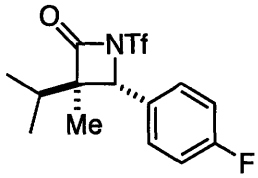



**Table 4, entry 4.** General method A was followed. A solution of 2-bromo-2,3-dimethylbutyryl bromide (84.5 mg, 0.33 mmol) in THF (1.3 mL) was added to a sonicated slurry of zinc powder (68.6 mg, 1.05 mmol) in THF (0.4 mL). Then, iodine crystals (0.40 mg, 1.58 μmol), dissolved in THF (0.4 mL), was added into the reaction mixture and the slurry was stirred at 0 °C for 1 h. The resulting ketene was vacuum-transferred into a Schlenk tube containing a stirred solution of **(–)-2** (9.40 mg, 24.9 μmol) and 1,1,1-trifluoro-*N*-(4-fluorophenylmethylene)-methanesulfonamide (70.0 mg, 0.27 mmol) in toluene (11 mL) at –78 °C. The product was purified by flash silica-gel column chromatography (2.5% EtOAc/hexanes). Yield as a mixture of two diastereomers: 68.0 mg (77%) of a colorless oil. The major diastereomer was separated (2% EtOAc/hexanes) as colorless oil. Yield: 44.0 mg (50%). HPLC analysis: 93% ee [Daicel CHIRALCEL OJ-H column; 0.6 mL/min; solvent system: 0.3% isopropanol/hexanes; retention times: 33.6 min (major), 20.5 min (minor)].

Second run (same scale): Yield as a mixture of two diastereomers: 68.3 mg (77%), 97% ee. Yield of the major diastereomer: 33.6 mg (38%).

$^1$H NMR (300 MHz, $C_6D_6$) δ 6.65 (m, 4H), 4.71 (s, 1H), 1.68 (septet, J = 6.6 Hz, 1H), 0.66 (d, J = 6.6 Hz, 3H), 0.61 (d, J=7.0, 3H), 0.36 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.5, 163.1(d, $^1J_{CF}$ = 248.7), 129.3 (d, $^4J_{CF}$ = 2.9), 128.8(d, $^3J_{CF}$ = 8.6) (x2), 119.5 (q, $^1J_{CF}$ = 323.0),

116.2(d, $^2J_{CF}$ = 21.9) (x2), 67.0, 66.4, 33.9, 17.9, 17.6, 12.7. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.7, –113.0. FTIR (NaCl) 1822, 1411, 1214, 741 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{14}H_{15}F_4NO_3S$ (M+Na) 376.0709, found 376.0595. $[\alpha]^{20}_D$ –152.7 (*c* 0.003, $CH_2Cl_2$, 93% ee).

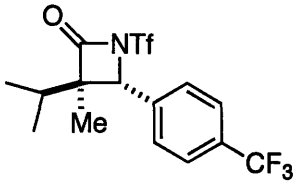



**Table 4, entry 5.** General method A was followed. A solution of 2-bromo-2,3-dimethylbutyryl bromide (65.8 mg, 0.26 mmol) in THF (1.0 mL) was added to a sonicated slurry of zinc powder (53.4 mg, 0.82 mmol) in THF (0.3 mL). Then, iodine crystals (0.30 mg, 1.18 μmol), dissolved in THF (0.3 mL), were added into the reaction mixture, and the slurry was stirred at 0 °C for 1 h. The resulting ketene was vacuum-transferred into a Schlenk tube containing a stirred solution of **(–)-2** (7.30 mg, 19.4 μmol) and 1,1,1-trifluoro-*N*-(4-trifluoromethylphenylmethylene)-methanesulfonamide (65.0 mg, 0.21 mmol) in toluene (8.6 mL) at –78 °C. The product was purified by flash silica-gel column chromatography (2% EtOAc/hexanes). Yield as a mixture of two diastereomers: 68.6 mg (88%) of a colorless oil. The major diastereomer was separated (2% EtOAc/hexanes) as colorless oil. Yield: 42.6 mg (54%). GC analysis: 66% ee [CP-Chirasil-Dex CB column; 120 °C (2 min), 2.0 °C/min to 180 °C; 13.49 psi He; retention times: 19.4 min (major), 19.2 min (minor)].

Second run (same scale): Yield as a mixture of two diastereomers: 67.3 mg (86%), 67% ee. Yield of the major diastereomer: 29.5 mg (38%).

$^1$H NMR (300 MHz, $C_6D_6$) δ 7.23 (d, J = 8.1 Hz, 2H), 6.75 (d, J = 8.1 Hz, 2H) 4.72 (s, 1H), 1.65 (septet, J = 6.6 Hz, 1H), 0.65 (d, J = 6.9 Hz, 3H), 0.61 (d, J = 6.9 Hz, 3H), 0.28 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.1, 137.6, 131.5 (q, $^2J_{CF}$ = 32.8), 127.4 (x2), 126.1 (q, $^3J_{CF}$ = 3.4)(x2), 123.9 (q, $^1J_{CF}$ = 272.3), 119.5 (q, $^1J_{CF}$ = 323.0), 66.8, 66.7, 33.9, 18.0, 17.6, 12.9. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –63.1, –76.6. FTIR (NaCl) 1824, 1413, 1266, 740 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{15}H_{15}F_6NO_3S$ (M+Na) 426.0677, found 426.0580. $[\alpha]^{20}_D$ –112.2 (*c* 0.003, $CH_2Cl_2$, 66% ee).

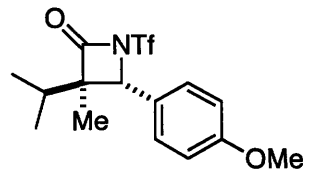



**Table 4, entry 6.** General method A was followed. A solution of 2-bromo-2,3-dimethylbutyryl bromide (84.9 mg, 0.33 mmol) in THF (1.3 mL) was added to a sonicated slurry of zinc powder (68.8 mg, 1.05 mmol) in THF (0.3 mL). Then, iodine crystals (0.40 mg, 1.58 μmol),

dissolved in THF (0.4 mL), were added into the reaction mixture and the slurry was stirred at 0 °C for 1 h. The resulting ketene was vacuum-transferred into a Schlenk tube containing a stirred solution of (–)-**2** (9.40 mg, 25.0 μmol) and 1,1,1-trifluoro-*N*-(4-methoxyphenylmethylene)-methanesulfonamide (73.5 mg, 0.28 mmol) in toluene (11 mL) at –78 °C. The product was purified by flash silica-gel column chromatography (2.4% EtOAc/hexanes). Yield as a mixture of two diastereomers: 84.4 mg (92%) of a colorless oil. HPLC analysis: 68% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 1.0% isopropanol/hexanes; retention times: 6.10 min (major), 5.61 min (minor)].

Second run (same scale): Yield as a mixture of two diastereomers: 83.0 mg (91%), 67% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 6.84 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 8.1 Hz, 2H) 4.83 (s, 1H), 3.32 (s, 3H), 1.70 (septet, J = 6.5 Hz, 1H), 0.71 (d, J=7.0 Hz, 3H), 0.65 (d, J = 6.5 Hz, 3H), 0.50 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 170.0, 160.3, 128.36 (x2), 125.2, 119.5 (q, $^1J_{CF}$ = 323.0), 114.4 (x2), 67.5, 66.2, 55.5, 33.9, 17.9, 17.6, 12.7. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.8. FTIR (NaCl) 2970, 1819, 1410, 1266, 741 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{15}H_{18}F_3NO_4S$ (M+Na) 388.0909, found 388.0801. $[\alpha]^{20}_D$ –117.9 (*c* 0.003, $CH_2Cl_2$, 68% ee).

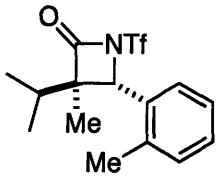



**Table 4, entry 7.** General method A was followed. A solution of 2-bromo-2,3-dimethylbutyryl bromide (80.0 mg, 0.31 mmol) in THF (1.2 mL) was added to a sonicated slurry of zinc powder (64.9 mg, 0.99 mmol) in THF (0.4 mL). Then, iodine crystals (0.40 mg, 1.58 μmol), dissolved in THF (0.4 mL), were added into the reaction mixture, and the slurry was stirred at 0 °C for 1 h. The resulting ketene was vacuum-transferred into a Schlenk tube containing a stirred solution of (–)-**2** (8.80 mg, 23.5 μmol) and 1,1,1-trifluoro-*N*-(2-methylphenylmethylene)-methanesulfonamide (65.0 mg, 0.26 mmol) in toluene (10.4 mL) at –78 °C. The product was purified by flash silica column chromatography (10% EtOAc/hexanes). Yield as a mixture of two diastereomers: 76.8 mg (94%) of a colorless oil.

Second run (same scale): Yield as a mixture of two diastereomers: 80.0 mg (97%).

$^1$H NMR (500 MHz, $C_6D_6$) δ 6.96 (m, 3H) 6.84 (m, 1H), 5.26 (s, 1H), 1.86 (s, 3H), 1.69 (septet, J = 6.5 Hz, 1H), 0.81 (d, J = 6.5 Hz, 3H), 0.76 (d, J = 11.2, 3H), 0.52 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.5, 135.7, 131.3, 130.9, 129.1, 127.0, 126.4, 119.4 (q, $^1J_{CF}$ = 322.5),

67.6, 63.8, 34.4, 19.9, 18.5, 18.0, 13.7. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –77.1. FTIR (NaCl) 1820, 1411, 1210, 1140, 1073 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{15}H_{18}F_3NO_3S$ (M+Na) 372.0959, found 426.0580. $[\alpha]^{20}_D$ –45.1 (*c* 0.003, $CH_2Cl_2$, 78% ee).

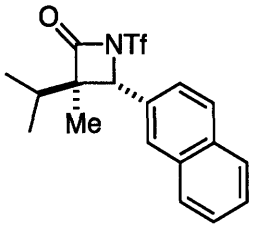
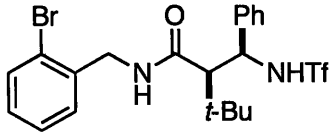



**Table 4, entry 8.** General method A was followed. A solution of 2-bromo-2,3-dimethylbutyryl bromide (64.5 mg, 0.25 mmol) in THF (1.0 mL) was added to a sonicated slurry of zinc powder (52.3 mg, 0.80 mmol) in THF (0.3 mL). Then, iodine crystals (0.30 mg, 1.18 μmol), dissolved in THF (0.3 mL), were added into the reaction mixture, and the slurry was stirred at 0 °C for 1 h. The resulting ketene was vacuum-transferred into a Schlenk tube containing a stirred solution of **(–)-2** (7.20 mg, 19.0 μmol) and 1,1,1-trifluoro-*N*-(2-napthylmethylene)-methanesulfonamide (60.0 mg, 0.21 mmol) in toluene (8.4 mL) at –78 °C. The product was purified by flash silica column chromatography (10% EtOAc/hexanes). Yield as a mixture of two diastereomers: 74.1mg (89%) of a colorless oil. The major diastereomer was separated (2% EtOAc/hexanes) as colorless oil. Yield: 38.9 mg (49%). HPLC analysis: 77% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 1.0% isopropanol/hexanes; retention times: 6.89 min (major), 6.41 min (minor)].

Second run (same scale): Yield as a mixture of two diastereomers: 67.8 mg (85%), 73% ee. Yield of the major diastereomer: 53.7 mg (67%).

$^1$H NMR (300 MHz, $C_6D_6$) δ 7.54 (m, 2H), 7.49 (d, J=8.5 Hz, 1H), 7.46 (s, 1H), 7.24 (m, 2H), 7.07 (dd, J = 7.0, J = 1.5 Hz, 1H), 5.03 (s, 1H), 1.65 (septet, J = 7.0 Hz, 1H), 0.73 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 7.0 Hz, 3H), 0.46 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.8, 133.6, 133.1, 130.9, 128.9, 128.2, 128.0, 127.1 (d, J = 2.6) (x2), 126.8, 123.9, 119.6 (q, $^1J_{CF}$ = 323.0), 67.9, 66.6, 34.1, 18.0, 17.6, 12.7. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.3. FTIR (NaCl) 1820, 1411, 1266, 740 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{18}H_{18}F_3NO_3S$ (M+Na) 408.0959, found 408.0857. $[\alpha]^{20}_D$ –123.9 (*c* 0.003, $CH_2Cl_2$, 94% ee).

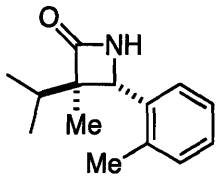



**Eq. 3.** A THF (1.3 mL) solution of the β-lactam from Table 4, entry 1 (39.0 mg, 0.12 mmol) was added to 2-bromobenzyl amine (23.7 mg, 0.13 mmol). The reaction mixture was stirred at 65 °C for 4 h and stirred overnight at ambient temperature. The resulting reaction mixture was

concentrated down to dryness and purified by flash chromatography (5–10% EtOAc/hexanes) and yielded 57.0 mg (94%) of white solid.

HPLC analysis: 77% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 5.0% isopropanol/hexanes; retention times: 11.2 min (major), 23.1 min (minor)].

$^1$H NMR (500 MHz, $C_6D_6$) δ 9.07 (d, J = 6.5 Hz, 1H), 7.22 (dd, J = 7.0, 1.0 Hz, 1H), 7.02 (m, 3H), 6.95 (m, 2H), 6.82 (m, 1H), 6.74 (dd, J = 6.0, J = 2.0 Hz, 1H), 6.66 (td, J = 6.0, J = 1.5 Hz, 1H), 5.09 (d, J = 5.5 Hz, 1H), 4.64 (m, 1H), 4.16 (dd, J = 8.5, J = 6.5 Hz, 1H), 3.96 (dd, J = 9.5, J = 5.5 Hz, 1H), 1.43 (d, J = 2.5 Hz, 1H), 1.01 (s, 9H). $^{13}$C NMR (126 MHz, CDCl3) δ 172.9, 140.9, 136.2, 132.9, 130.8, 129.6, 128.9 (x2), 127.9, 127.86, 125.7 (x2), 123.9, 119.2 (q, $^1J_{CF}$ = 320.8), 62.1, 57.3, 44.0, 34.3, 29.0 (x3). $^{19}$F NMR (282 MHz, $CDCl_3$) δ –78.3. FTIR (NaCl) 3413, 1650, 1416, 1371, 1215, 1198 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{21}H_{24}BrF_3N_2O_3S$ (M+Na) 543.0643 found 545.0503. $[\alpha]^{20}_D$ –19.9 (*c* 0.001, $CH_2Cl_2$, 77% ee). M.p. 89–93 °C.




**Eq. 4.** The β-lactam (50.0 mg, 0.20 mmol) from Table 4, entry 7 was deprotected [$TiCl_3$ (4.0 equiv) and Li metal (14.0 equiv) in THF (2.5 mL) at 40 °C for 4 h] to determine the enantiomeric excess. The reaction is quenched with 5% $K_2CO_3$ (1.0 mL) in an ice bath. The mixture is diluted with EtOAc/$H_2O$ (1:1) and filtered through a pad of Celite. The organic layer is washed with saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated to obtain crude material. Product was further purified via flash silica-gel chromatography (10–20% EtOAc/hexanes). Yield: 25.7 mg (59%) of a white, waxy residue. GC analysis: 78% ee [Chiraldex G-TA; 140 °C (5 min), 0.5 °C/min to 180 °C; 5.0 psi He; retention times: 21.0 min (major), 18.9 min (minor)].

Second run with β-lactam (30.0 mg, 0.120 mmol): 14.5 mg (56%), 77% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.25 (m, 1H), 7.05 (m, 2H) 6.94 (m, 1H), 6.29 (broad s, 1H), 4.29 (s, 1H), 1.90 (s, 3H), 1.80 (septet, J = 6.5 Hz, 1H), 1.06 (d, J = 11.0 Hz, 3H), 1.05 (d, J = 10.5 Hz, 3H), 0.73 (s, 3H). $^{13}$C NMR (126 MHz, $C_6D_6$) δ 173.8, 137.8, 135.5, 130.8, 127.8, 127.0, 126.7, 65.2, 56.7, 33.6, 19.9, 19.2, 18.7, 14.6. FTIR (NaCl) 3401, 1758. 1266. 896, 740 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{14}H_{19}NO$ (M+H) 218.1467, found 218.1548. $[\alpha]^{20}_D$ –23.0 (*c* 0.002, $CH_2Cl_2$, 77% ee).

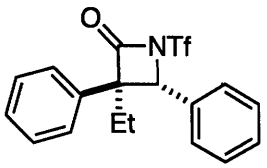



**Table 6, entry 1.** General method B was followed. 1,1,1-Trifluoro-*N*-(phenylmethylene)-methanesulfonamide (56.4 mg, 0.24 mmol) and **(–)-2** (8.90 mg, 23.8 μmol) were dissolved in toluene (11 mL) and cooled to –78 °C under a nitrogen atmosphere. To this, a phenyl ethyl ketene (34.8 mg, 0.24 mmol), dissolved in toluene (1.2 mL), was added over approximately 1 minute, and the syringe was rinsed with toluene (0.3 mL). The resulting solution was allowed to warm to room temperature while stirring overnight. The product was purified by flash silica column chromatography (5–10% EtOAc/hexanes). Yield as a mixture of two diastereomers: 54.3 mg (60%) of colorless oil. The major diastereomer was separated (2.5% EtOAc/hexanes) as colorless oil. Yield: 36.6 mg (40%). HPLC analysis: 68% ee [Daicel CHIRALCEL AD-H column; 0.5 mL/min; solvent system: 1.0% isopropanol/hexanes; retention times: 10.7 min (major), 9.92 min (minor)].

Second run (same scale): Yield as a mixture of two diastereomers: 54.0 mg (59%). Yield of the major diastereomer: 33.0 mg (36%), 65% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.22 (m, 2H), 6.99-7.09 (m, 8H), 5.23 (s, 1H), 1.51 (qq, J = 7.0, J = 7.5 Hz, 1H), 0.99 (qq, J = 7.0, J = 8.0 Hz, 1H), 0.45 (t, J = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.7, 137.1, 132.7, 129.7, 129.5 (x2), 129.1 (x2), 128.5, 127.3 (x2), 126.1 (x2), 119.5 (q, $^1J_{CF}$ = 323.0), 71.2, 69.7, 27.4, 8.69. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.1. FTIR (NaCl) 1818, 1413, 1266, 1212, 740 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{18}H_{16}F_3NO_3S$ (M+Na) 406.0803, found 406.0682. $[\alpha]^{20}_D$ –104.0 (*c* 0.003, $CH_2Cl_2$, 68% ee).

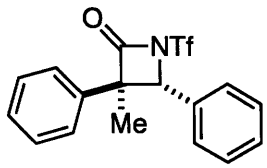



**Table 6, entry 2.** General method B was followed. 1,1,1-Trifluoro-*N*-(phenylmethylene)-methanesulfonamide (47.4 mg, 0.20 mmol) and **(–)-2** (7.50 mg, 20.0 μmol) were dissolved in $CH_2Cl_2$ (10.2 mL) and was cooled to 0 °C under a nitrogen atmosphere. To this, phenyl methyl ketene (26.4 mg, 0.20 mmol), dissolved in $CH_2Cl_2$ (1.0 mL), was added over approximately 2 min, and the syringe was rinsed with $CH_2Cl_2$ (0.3 mL). The product was purified by flash silica column chromatography (5–20% EtOAc/hexanes). Yield: 60.9 mg (82%) of a milky oil. GC analysis: 79% ee [CP-Chirasil-Dex CB column; 170 °C (10 min), 0.5 °C/min to 180 °C; 9.17 psi He; retention times: 27.0 min (major), 27.4 min (minor)].

Second run (same scale): Yield: 62.3 mg (84%), 83% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.21–7.19 (m, 2H), 7.01–7.05 (m, 6H), 6.94 (m, 2H) 5.24 (s, 1H), 0.83 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.3, 139.2, 132.8, 129.7 (x2), 129.2 (x2), 128.6 (x2), 127.0 (x2), 125.4 (x2), 119.5 (q, $^1J_{CF}$ = 323.5), 71.3, 65.9, 20.4. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.2. FTIR (NaCl) 1821, 1413, 1213, 1146 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{14}F_3NO_3S$ (M+Na) 392.0803, found 392.0525. $[\alpha]^{20}_D$ –99.7 (*c* 0.003, $CH_2Cl_2$, 79% ee).

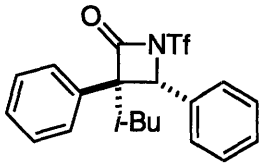



**Table 6, entry 3.** General method B was followed. 1,1,1-Trifluoro-*N*-(phenylmethylene)-methanesulfonamide (68.1 mg, 0.29 mmol) and **(–)-2** (10.8 mg, 28.7 μmol) were dissolved in $CH_2Cl_2$ (12.1 mL) and stirred at room temperature under a nitrogen atmosphere. To this, isobutyl phenyl ketene (50.0 mg, 0.29 mmol), dissolved in $CH_2Cl_2$ (1.9 mL), was added over approximately 1 min, and the syringe was rinsed with $CH_2Cl_2$ (1.1 mL). The product was purified by flash silica column chromatography (2.5-10% EtOAc/hexanes). Yield: 87.8 mg (74%) of a colorless oil.

Second run (same scale): Yield: 83.0 mg (70%).

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.28 (m, 2H), 7.08-6.99 (m, 8H), 5.23 (s, 1H), 1.48 (dd, J = 7.5, J = 6.5 Hz, 1H), 1.28 (m, 1H), 1.17 (dd, J = 4.5, J = 10.0 Hz, 1H), 0.66 (d, J = 6.5 Hz, 3H), 0.22 (d, J = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, $C_6D_6$) δ 167.6, 138.5, 133.4, 129.9 (x2), 129.8, 129.3 (x2), 128.7, 128.68, 127.9 (x2), 126.5 (x2), 72.1, 69.9, 42.7, 25.0, 24.2, 23.3. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –75.9. FTIR (NaCl) 1816, 1413, 1266, 739 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{20}H_{20}F_3NO_3S$ (M+Na) 434.1116, found 434.1016. $[\alpha]^{20}_D$ –65.3 (*c* 0.002, $CH_2Cl_2$).

The β-lactam (46.5 mg, 0.11 mmol) was reduced to the alcohol [1.0 M $LiAlH_4$ (3.0 equiv) in THF] to determine the enantiomeric excess. Yield: 38.0 mg (81%) white, waxy residue. HPLC analysis: 63% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 1.0% isopropanol/hexanes; retention times: 27.6 min (major), 25.4 min (minor)]. Second run: 63% ee.

Alcohol: $^1$H NMR (500 MHz, $C_6D_6$) δ 7.31 (d, J = 7.5 Hz, 2H), 7.25 (m, 4H), 7.16-7.08 (m, 4H), 4.99 (s, 1H), 3.61 (d, J = 11.0 Hz, 1H), 3.23 (d, J = 11.0 Hz, 1H), 1.42 (dd, J = 9.5, J = 4.5 Hz, 1H), 1.26 (broad s, 1H), 1.00 (m, 1H), 0.84 (dd, J = 8.0, J = 6.0 Hz, 1H), 0.42 (broad s, 1H), 0.38 (d, J = 6.5 Hz, 3H), 0.36 (d, J = 8.0 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 140.3, 138.0, 128.8 (x4), 128.4(x2), 128.3, 127.9 (x2), 127.3, 119.1 (q, $^1J_{CF}$ = 320.8), 67.9, 65.0, 50.2, 46.4, 25.0, 24.9, 24.5. $^{19}$F NMR (282 MHz, $CDCl_3$) δ –78.6. FTIR (NaCl) 3605, 1423, 1266,

1199, 1229, 740 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{20}H_{24}F_3NO_3S$ (M+Na) 438.1429, found 438.1334. $[\alpha]^{20}_D$ –1.0 (*c* 0.003, $CH_2Cl_2$, 63% ee).

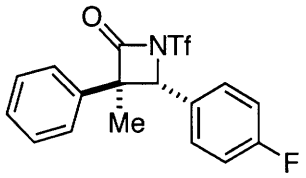



**Table 6, entry 4.** General method C was followed. 1,1,1-Trifluoro-*N*-[(4-fluorophenyl)methylene]-methanesulfonamide (50.0 mg, 0.20 mmol) and **(–)-2** (7.40 mg, 19.6 μmol) were dissolved in a mixture of $CH_2Cl_2$ (4.6 mL) and toluene (4.3 mL) and cooled to 0 °C under a nitrogen atmosphere. To this, phenyl methyl ketene (25.9 mg, 0.20 mmol), dissolved in toluene (1.0 mL), was added over approximately 1 min, and the syringe was rinsed with $CH_2Cl_2$ (0.7 mL). The product was purified by flash silica column chromatography (10% EtOAc/hexanes). Yield: 63.2 mg (83%) of colorless oil. HPLC analysis: 87% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 1.0% isopropanol/hexanes; retention times: 7.68 min (major), 6.72 min (minor)].

Second run (same scale): Yield: 64.0 mg (84%), 83% ee.

$^1H$ NMR (500 MHz, $C_6D_6$) δ 7.15 (m, 2H), 7.06 (m, 3H), 6.69 (m, 4H), 5.13 (s, 1H), 0.78 (s, 3H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 168.1, 163.4(d, $^1J_{CF}$ = 250.0 Hz), 139.0 (x2), 129.8 (x2), 128.9(d, $^3J_{CF}$ = 8.7 Hz) (x2), 128.7, 125.3 (x2), 119.5 (q, $^1J$ = 323.7 Hz), 116.4(d, $^2J_{CF}$ = 21.9 Hz) (x2), 70.7, 65.9, 20.4. $^{19}F$ NMR (282 MHz, $C_6D_6$) δ –76.2, –112.3. FTIR (NaCl) 1822, 1414, 1213 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{13}F_4NO_3S$ (M+Na) 410.0552, found 410.0460. $[\alpha]^{20}_D$ –105.5 (*c* 0.003, $CH_2Cl_2$, 87% ee).

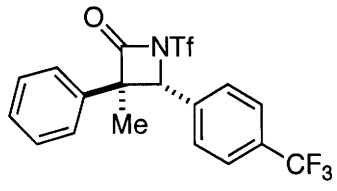



**Table 6, entry 5.** General method C was followed. 1,1,1-Trifluoro-*N*-[(4-trifluoromethylphenyl)methylene]-methanesulfonamide (60.0 mg, 0.20 mmol) and **(–)-2** (7.40 mg, 19.7 μmol) were dissolved in a mixture of $CH_2Cl_2$ (4.6 mL) and toluene (4.2 mL) and cooled to 0 °C under a nitrogen atmosphere. To this, phenyl methyl ketene (26.0 mg, 0.20 mmol), dissolved in toluene (1.0 mL), was added over approximately 1 min, and the syringe was rinsed with $CH_2Cl_2$ (0.6 mL). The product was purified by flash silica column chromatography (2.5% EtOAc/hexanes). Yield: 70.8 mg (82%) of colorless oil. HPLC analysis: 68% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 1.0% isopropanol/hexanes; retention times: 6.63 min (major), 6.06 min (minor)]. The enantiomeric excess can be further improved by

crystallization of the racemate from pentane where mother liquor is enriched with desired product. Yield: 54.9 mg (64%), 89% ee.

Second run (same scale): Yield: 66.0 mg (77%), 70% ee. Further purification yields 56.2 mg (65%), 84% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.27 (d, J = 8.5 Hz, 2H), 7.13 (m, 2H), 7.06 (m, 3H), 6.78 (d, J = 8.0 Hz, 2H), 5.12 (s, 1H), 0.70 (s, 3H). $^{13}$C NMR (126 MHz, CDCl3) δ 167.7, 138.6, 136.9, 131.9(q, $^2J_{CF}$ = 32.8 Hz), 129.9 (x2), 128.9, 127.5 (x2), 126.3(q, $^3J_{CF}$ = 4.0 Hz) (x2), 125.3 (x2), 123.9 (q, $^1J_{CF}$ = 272.3 Hz), 119.5 (q, $^1J_{CF}$ = 323.7 Hz), 70.5, 66.2, 20.3. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –63.1, –76.1. FTIR (NaCl) 1825, 1420, 1266, 740 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{18}H_{13}F_6NO_3S$ (M+Na) 460.0520, found 460.0423. $[\alpha]^{20}_D$ –87.3 (*c* 0.003, $CH_2Cl_2$, 89% ee).

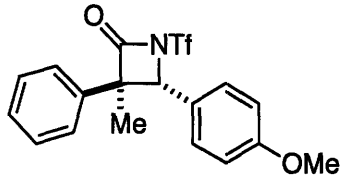



**Table 6, entry 6.** General method B was followed. 1,1,1-Trifluoro-*N*-(4-methoxy-phenylmethylene)-methanesulfonamide (50.0 mg, 0.19 mmol) and **(–)-2** (7.00 mg, 18.7 μmol) were dissolved in toluene (8.5 mL) and was cooled to 0 °C under a nitrogen atmosphere. To this, phenyl methyl ketene (24.7 mg, 0.19 mmol), dissolved in toluene (0.9 mL), was added over approximately 1 min, and the syringe was rinsed with toluene (0.4 mL). The resulting solution was allowed to warm to room temperature while stirring overnight. The product was purified by flash silica column chromatography (2.5% EtOAc/hexanes). Yield as a mixture of two diastereomers: 56.0 mg (75%) of a pale yellow oil. HPLC analysis: 81% ee [Daicel CHIRALCEL AS-H column; 0.5 mL/min; solvent system: 1.0% isopropanol/hexanes; retention times: 16.8 min (major), 18.0 min (minor)].

Second run (same scale): Yield as a mixture of two diastereomers: 57.6 mg (77%), 83% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.23 (m, 2H), 7.06 (m, 2H), 7.02 (m, 1H), 6.88 (m, 2H), 6.64 (m, 2H), 5.24 (s, 1H), 3.24 (s, 3H), 0.92 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.5, 160.6, 139.4, 129.7 (x2), 128.5, 128.5 (x2), 125.3 (x2), 124.5, 119.5 (q, $^1J_{CF}$ = 323.7), 114. 6 (x2), 71.3, 65.8, 55.5, 20.5. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –75.9. FTIR (NaCl) 3057, 1819, 1412, 1265, 740 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{18}H_{16}F_3NO_3S$ (M+Na) 406.0803, found 406.0681. $[\alpha]^{20}_D$ –23 (*c* 0.003, $CH_2Cl_2$, 81% ee).

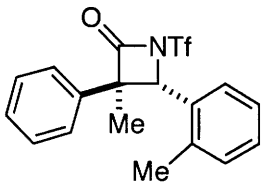



**Table 6, entry 7.** General method B was followed. 1,1,1-Trifluoro-*N*-(2-methyl-phenylmethylene)-methanesulfonamide (55.8 mg, 0.22 mmol) and **(–)-2** (8.40 mg, 22.2 μmol) were dissolved in toluene (10 mL) and cooled to 0 °C under a nitrogen atmosphere. To this, phenyl methyl ketene (29.3 mg, 0.22 mmol), dissolved in toluene (1.1 mL), was added over approximately 2 min, and the syringe was rinsed with toluene (0.6 mL). The resulting solution was allowed to warm to room temperature while stirring overnight. The product was purified by flash silica column chromatography (5% EtOAc/hexanes). Yield as a mixture of two diastereomers: 75.7 mg (89%) of a colorless oil. The major diastereomer was separated (2.5-5% EtOAc/hexanes) as colorless oil. Yield: 52.1 mg (61%). HPLC analysis: >99% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 1.0% isopropanol/hexanes; retention times: 13.7 min (major), 15.8 min (minor)].

Second run (same scale): Yield as a mixture of two diastereomers: 75.6 mg (89%). Yield of the major diastereomer: 50.2 mg (59%), >99% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.32 (m, 1H), 7.19 (m, 2H), 6.94-7.05 (m, 5H), 6.79 (m, 1H), 5.58 (s, 1H), 1.64 (s, 3H), 0.88 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.0, 138.4, 135.9, 131.2 (x2), 129.7 (x2), 129.3, 128.9, 126.5, 126.4, 125.5 (x2), 119.6 (q, $^1J_{CF}$ = 323.7), 69.5, 65.5, 19.9, 17.5. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.3. FTIR (NaCl) 1820, 1414, 1266, 740 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{18}H_{16}F_3NO_3S$ (M+Na) 406.0803, found 406.0681. $[\alpha]^{20}_D$ –135.0 (*c* 0.003, $CH_2Cl_2$, >99% ee).

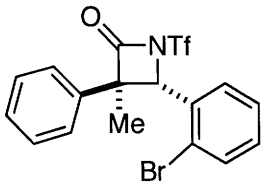



**Table 6, entry 8.** General method C was followed. 1,1,1-Trifluoro-*N*-[(2-bromophenyl)methylene]-methanesulfonamide (50.0 mg, 0.16 mmol) and **(–)-2** (5.90 mg, 15.8 μmol) were dissolved in a mixture of $CH_2Cl_2$ (3.7 mL) and toluene (3.4 mL) and cooled to 0 °C under a nitrogen atmosphere. To this, phenyl methyl ketene (20.9 mg, 0.16 mmol), dissolved in toluene (0.8 mL), was added over approximately 2 min, and the syringe was rinsed with $CH_2Cl_2$ (0.5 mL). The product was purified by flash silica column chromatography (2.5% EtOAc/hexanes). Yield as a mixture of two diastereomers: 53.6 mg (76%) of colorless oil. The major diastereomer was separated (2.5–5% EtOAc/hexanes) as colorless oil. Yield: 22.8 mg (32%). GC analysis: 85% ee [CP-Chirasil-

Dex CB column; 175 °C (5 min), 0.25 °C/min to 195 °C; 9.31 psi He; retention times: 39.8 min (major), 40.3 min (minor)].

Second run (same scale): Yield as a mixture of two diastereomers: 58.1 mg (82%), 83% ee. Yield of the major diastereomer: 20.6 mg (29%).

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.45 (m, 2H), 7.23 (dd, J = 6.0, J = 1.5 Hz, 1H), 7.11 (m, 3H), 7.03 (m, 1H), 6.81 (m, 1H), 6.58 (td, J = 6.5, J = 1.5 Hz, 1H) (m, 4H), 5.95 (s, 1H), 0.90 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.5, 137.9, 133.8, 133.1, 130.9, 129.3 (x2), 128.9, 128.4, 128.0, 126.1 (x2), 123.1, 119.6 (q, $^1J_{CF}$ = 323.0), 70.4, 66.5, 18.1. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.2. FTIR (NaCl) 1823, 1415, 1266, 740 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{13}BrF_3NO_3S$ (M+Na) 469.9752, found 469.9650. $[\alpha]^{20}_D$ –138.2 (*c* 0.003, $CH_2Cl_2$, 85% ee).

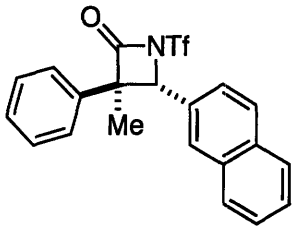



**Table 6, entry 9.** General method B was followed. 1,1,1-Trifluoro-*N*-(2-napthylmethylene)-methanesulfonamide (50.0 mg, 0.17 mmol) and **(–)-2** (6.50 mg, 17.4 μmol) were dissolved in $CH_2Cl_2$ (8.0 mL) and cooled to 0 °C under a nitrogen atmosphere. To this, phenyl methyl ketene (23.0 mg, 0.17 mmol) dissolved in $CH_2Cl_2$ (0.9 mL) was added over approximately 2 min, and the syringe was rinsed with $CH_2Cl_2$ (0.3 mL). The resulting solution was allowed to warm to room temperature while stirring overnight. The product was purified by flash silica column chromatography (10% EtOAc/hexanes). Yield: 56.0 mg (77%) of colorless oil. HPLC analysis: 93% ee [Daicel CHIRALCEL OD-H column; 0.5 mL/min; solvent system: 1.0% isopropanol/hexanes; retention times: 15.0 min (major), 21.0 min (minor)].

Second run (same scale): Yield: 54.3 mg (74%), 94% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.59–7.49 (m, 4H), 7.27–7.24 (m, 3H), 7.13-7.04 (m, 5H), 5.44 (s, 1H), 0.88 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.3, 139.3, 133.8, 133.2, 130.2, 129.8 (x2), 129.2, 128.7, 128.3, 128.1, 127.3, 127.28, 126.9, 125.4 (x2), 123.8, 119.6 (q, $^1J_{CF}$ = 323.0), 71.5, 66.1, 20.4. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.2. FTIR (NaCl) 1821, 1413, 1215, 739 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{21}H_{16}F_3NO_3S$ (M+Na) 442.0803, found 442.0692. $[\alpha]^{20}_D$ –68.8 (*c* 0.003, $CH_2Cl_2$, 93% ee).

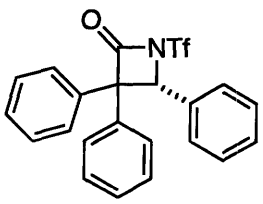
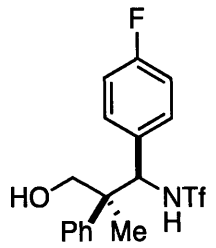



**Table 6, entry 10.** General method B was followed. 1,1,1-Trifluoro-*N*-(phenylmethylene)-methanesulfonamide (56.7 mg, 0.24 mmol) and **(–)-2**

(9.00 mg, 23.9 μmol) were dissolved in $CH_2Cl_2$ (11 mL) and cooled to 0 °C under a nitrogen atmosphere. To this, diphenyl ketene (46.4 mg, 0.24 mmol) dissolved in $CH_2Cl_2$ (1.2 mL) was added over approximately 3 min, and the syringe was rinsed with $CH_2Cl_2$ (0.4 mL). The product was purified by flash silica column chromatography (10% EtOAc/hexanes). Yield: 60 mg (60%) of milky oil. HPLC analysis: >99% ee [Daicel CHIRALCEL OD column; 1.0 mL/min; solvent system: 5.0% isopropanol/hexanes; retention times: 4.90 min (major), 5.74 min (minor)].

Second run (same scale): Yield: 65.0 mg (63%), 97% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.46 (m, 2H), 7.02 (m, 2H), 6.96 (m, 1H) 6.88–6.80 (m, 7H), 6.68 (m, 3H), 5.95 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.4, 138.4, 135.4, 132.9, 129.5 (x3), 128.7, 128.6 (x2), 128.58(x2), 128.01 (x2), 127.97, 127.8 (x2), 126.9 (x2), 119. 3 (q, $^1J_{CF}$ =323.0), 74.9, 70.7. $^{19}$F NMR (282 MHz, $C_6D_6$) δ –76.4. FTIR (NaCl) 1814, 1414, 1266, 739 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{22}H_{16}F_3NO_3S$ (M+Na) 454.0803, found 454.0692. $[\alpha]^{20}_D$ –25.9 (*c* 0.003, $CH_2Cl_2$, >99% ee).



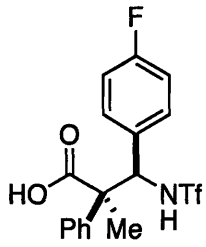

**Eq 5.** A solution of LiAlH4 (1.0 M in THF; 0.16 mL; 3.0 equiv) was added to a solution of the β-lactam (20.0 mg, 51.5 mmol; 87% ee) in THF (0.7 mL). The resulting mixture was heated to 50 °C for 3 h. Then, it was then cooled to 0 °C, and the reaction was quenched by the addition of 1 N NaOH (200 mL). The resulting slurry was dried over $MgSO_4$ and filtered. The filtrate was concentrated, and the residue was purified by column chromatography (40% $Et_2O$/hexanes), which furnished the alcohol as a colorless film (15.9 mg, 79%).

The ee of the product was determined by trifluoroacetylating (trifluoroacetic anhydride) the alcohol. GC analysis: 88% ee [CP-Chirasil-Dex CB column; 175 ∞C (5 min), 0.25 °C/min to 195 ∞C; 9.31 psi He; retention times: 23.0 min (major), 22.7 min (minor)].

Second run (same scale): Yield: 15.0 mg (74%), 88% ee.

$^1$H NMR (500 MHz, CDCl3) δ 7.49 (m, 2H), 7.43 (m, 2H), 7.34 (m, 1H), 7.26 (m, 2H), 7.05 (m, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.01 (d, J = 8.0 Hz, 1H), 4.15 (dd, J = 8.0, J = 3.0 Hz, 1H), 3.79 (dd, J = 8.0, J = 2.5 Hz, 1H), 2.01 (s, 1H), 1.26 (s, 1H), 1.16 (s, 3H). $^{13}$C NMR (126 MHz, CDCl3) δ 162.6 (d, $^1J_{CF}$ = 247 Hz), 141.8, 130.0 (d, $^3J_{CF}$ = 8.1 Hz), 129.1, 128.5, 127.7, 127.1, 119.3 (q, $^1J_{CF}$ = 321 Hz), 115.4 (d, $^2J_{CF}$ = 21.9 Hz), 67.2, 66.3, 46.7, 23.7. FTIR (NaCl)

3608, 3055, 1266, 742 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{17}F_4NNaO_3S$ (M+Na) 414.0757, found 414.0757. $[a]^{20}_D$–1.45 (c 0.75, $CH_2Cl_2$, 88% ee).

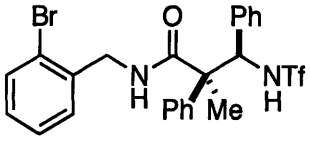



**Eq 6.** A 1 N solution of KOH (374 mL, 0.38 mmol) was added to a solution of the β-lactam (72.4 mg, 0.19 mmol; 79% ee) in ethanol (1.5 mL). The resulting mixture was heated to reflux for 2 h and then stirred at room temperature overnight. It was then cooled to 0 °C, and the reaction was quenched by the addition of a solution of 1 N HCl (400 mL). The product was extracted with MTBE, and the organic layer was washed with saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated, furnishing a waxy, white solid (68.4 mg, 90%).

The ee of the product was determined by reducing the acid to the alcohol (excess 1.0 M $LiAlH_4$ in THF at room temperature), and then trifluoroacetylating the alcohol (trifluoroacetic anhydride). GC analysis: 80% ee [CP-Chirasil-Dex CB column; 175 °C (5 min), 0.25 °C/min to 195 °C; 9.31 psi He; retention times: 23.0 min (major), 22.7 min (minor)].

Second run (β-lactam: 30.0 mg, 78% ee): Yield: 28.8 mg (92%), 79% ee.

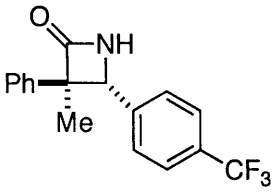
$^1$H NMR (500 MHz, $C_6D_6$) δ 7.60 (m, 4H), 7.38 (m, 2H), 7.28 (m, 1H), 7.10 (m, 2H), 4.97 (broad s, 1H), 3.27 (s, 1H), 1.25 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.0, 162.3 (d, $^1J_{CF}$ = 248 Hz), 142.0, 133.3, 129.6, 128.6, 127.6, 127.0, 119.2 (q, $^1J_{CF}$ = 322 Hz), 114.9 (d, $^2J_{CF}$ = 22.4 Hz), 65.6, 56.4, 21.3. $^{19}$F NMR (282 MHz, $CD_3OD$) δ –80.2, –117.2. FTIR (NaCl) 3574, 1607, 1397, 1369, 1266, 1228, 1203, 740 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{15}F_4NNaO_4S$ (M+Na) 428.0658, found 428.0550. $[a]^{20}_D$ +42 (c 0.25, $CH_2Cl_2$, 79% ee).




**Eq 7.** A solution of the β-lactam (21.0 mg, 56.9 mmol; 79% ee) in THF (0.7 mL) was added to 2-bromobenzylamine (11.6 mg, 62.5 mmol). The reaction mixture was stirred at 40 °C for 4 h and then at room temperature overnight. The resulting mixture was concentrated and purified by flash chromatography (5–10% EtOAc/hexanes), which furnished 31.0 mg (98%) of a white solid. HPLC analysis: 79% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 10.0% isopropanol/hexanes; retention times: 6.68 min (major), 10.7 min (minor)].

Second run (same scale; β-lactam: 83% ee): Yield: 28.8 mg (91%), 83% ee.

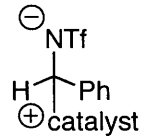
$^1$H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 8.5 Hz, 1H), 7.54 (dd, J = 7.5, J = 1.0 Hz, 1H), 7.41–7.20 (m, 11H), 6.35 (m, 1H), 4.75 (d, J = 8.5 Hz, 1H), 4.63 (dd, J = 8.5, J = 6.0 Hz, 1H), 4.49 (dd, J = 9.0, J = 6.0 Hz, 1H), 1.41 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 175.0, 141.4, 137.7, 136.3, 133.1, 131.1, 129.8, 129.1, 128.6, 128.55, 128.48, 128.0, 127.9, 126.6, 124.0, 119.1 (q, $^1J_{CF}$ = 321 Hz), 67.4, 54.1, 44.5, 25.0. FTIR (NaCl) 3456, 3054, 1649, 1421, 1265, 739 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{24}H_{22}BrF_3N_2NaO_3S$ (M+Na) 577.0379, found 577.0346. [a]$^{20}_D$ –7.1 (c 0.19, $CH_2Cl_2$, 79% ee). M.p. 166–167 °C.




**Eq 8.** Lithium metal (4.40 mg, 0.640 mmol) was combined with $TiCl_3$ (14.1 mg, 91.4 mmol) in THF (1.2 mL) in a Schlenk tube, and the resulting mixture was heated to reflux for 30 min. The solution was allowed to cool, and then a solution of the β-lactam (20.0 mg, 45.7 mmol; 89% ee) in THF (0.6 mL) was added slowly. The resulting mixture was heated at 40 °C for 3 h and then at room temperature for 12 h. The mixture was then cooled in an ice bath and quenched with 5% $K_2CO_3$ (1.0 mL). A 1:1 mixture of $Et_2O/H_2O$ (1.0 mL) was added, and then the reaction mixture was filtered through a pad of Celite. The organic layer was separated, washed with saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated. The product was purified by flash chromatography (20–50% $Et_2O$/hexanes). Yield: 11.9 mg (85%) of cloudy oil.
HPLC analysis: 90% ee [Daicel CHIRALCEL AD-H column; 1.0 mL/min; solvent system: 10% isopropanol/hexanes; retention times: 10.5 min (major), 8.85 min (minor)].

Second run (same scale; β-lactam: 89% ee): Yield: 11.3 mg (81%), 90% ee.

$^1$H NMR (500 MHz, $C_6D_6$) δ 7.48 (m, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.20 (m, 2H), 7.10 (m, 1H), 6.73 (d, J = 8.5 Hz, 2H), 5.08 (broad s, 1H), 4.23 (s, 1H), 0.91 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.4, 141.6, 141.3, 130.7 (q, $^2J_{CF}$ = 32.8 Hz), 129.2, 127.7, 127.0, 126.02, 125.98 (q, $^3J_{CF}$ = 4.0 Hz), 123.3 (q, $^1J_{CF}$ = 328 Hz), 64.7, 63.4, 20.0. FTIR (NaCl) 3251, 2927, 1762. 1326. 740 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{14}F_3NNaO$ (M+Na) 328.0920, found 328.0911. [a]$^{20}_D$ –9.2 (c 0.21, $CD_2Cl_2$, 90% ee).




**3**

**Eq 14.** *N*-Benzylidene-1,1,1-trifluoromethanesulfonamide (3.20 mg, 13.3 mmol) and (–)-**2** (5.00 mg, 13.3 mmol) were dissolved in $CD_2Cl_2$ (0.5 mL).

$^1$H NMR (400 MHz, $CD_2Cl_2$, –27 °C) δ 9.11 (d, J = 7.4 Hz, 1H), 7.18 (m, 5H), 6.42 (s, 1H), 5.91 (d, J = 7.4 Hz, 1H), 4.55 (d, J = 2.3 Hz, 1H), 4.35 (d, J = 2.2 Hz, 1H), 3.99 (dd, J = 5.8, J = 2.9 Hz, 1H), 3.82 (m, 2H), 3.68 (m, 1H), 3.54 (m, 1H), 2.19 (m, 1H), 2.12 (m, 3H), 1.67 (s, 15H). $^{13}$C NMR (126 MHz, $CD_2Cl_2$, r.t.) δ 128.9, 128.3, 126.7, 119.6 (q, $^1J_{CF}$ = 327 Hz), 93.7, 81.4, 79.4, 77.2, 66.3, 64.6, 51.4, 26.7, 25.0, 10.1, 1.3. $^{19}$F NMR (282 MHz, $CD_2Cl_2$) δ –79.4.

**Chart 1 and 2. Kinetics Experiment**

*Standard Condition:* Reaction with 1 equivalent of ketene and 1 equivalent of imine

*N*-Benzylidene-1,1,1-trifluoromethanesulfonamide (4.74 mg, 20.0 mmol) and (–)-**2** (750 μg, 2.00 μmol) in $CD_2Cl_2$ (1.0 mL) were combined at –20 °C. After 15 min at –20 °C, phenyl methyl ketene (2.64 mg, 20.0 mmol) in $CD_2Cl_2$ (0.1 mL) was added while maintaining the temperature at –20 °C. The reaction was monitored over 6 h at –20 °C, taking data points every 15 min.

Reaction with 2 equivalent of ketene and 1 equivalent of imine

Standard conditions were used except with phenyl methyl ketene (5.29 mg, 40.0 mmol), which was added as a solution in $CD_2Cl_2$ (0.1 mL).

Reaction with 1 equivalent of ketene and 2 equivalent of imine

*N*-Benzylidene-1,1,1-trifluoromethanesulfonamide (9.48 mg, 40.0 mmol) was used.

**Chart 4. α-Secondary Kinetic Isotope Effects**

α-Deuterated *N*-benzylidene-1,1,1-trifluoromethanesulfonamide (4.74 mg, 20.0 mmol) and (–)-**2** (750 μg, 2.00 μmol) in $CD_2Cl_2$ (1.0 mL) were combined at –20 °C. After 15 min at –20 °C, phenyl methyl ketene (2.64 mg, 20.0 mmol) was added as a solution in $CD_2Cl_2$ (0.1 mL) while maintaining –20 °C. Reaction was monitored over 6 h at –20 °C, taking data points every 15 min.

## 2.6 References and Notes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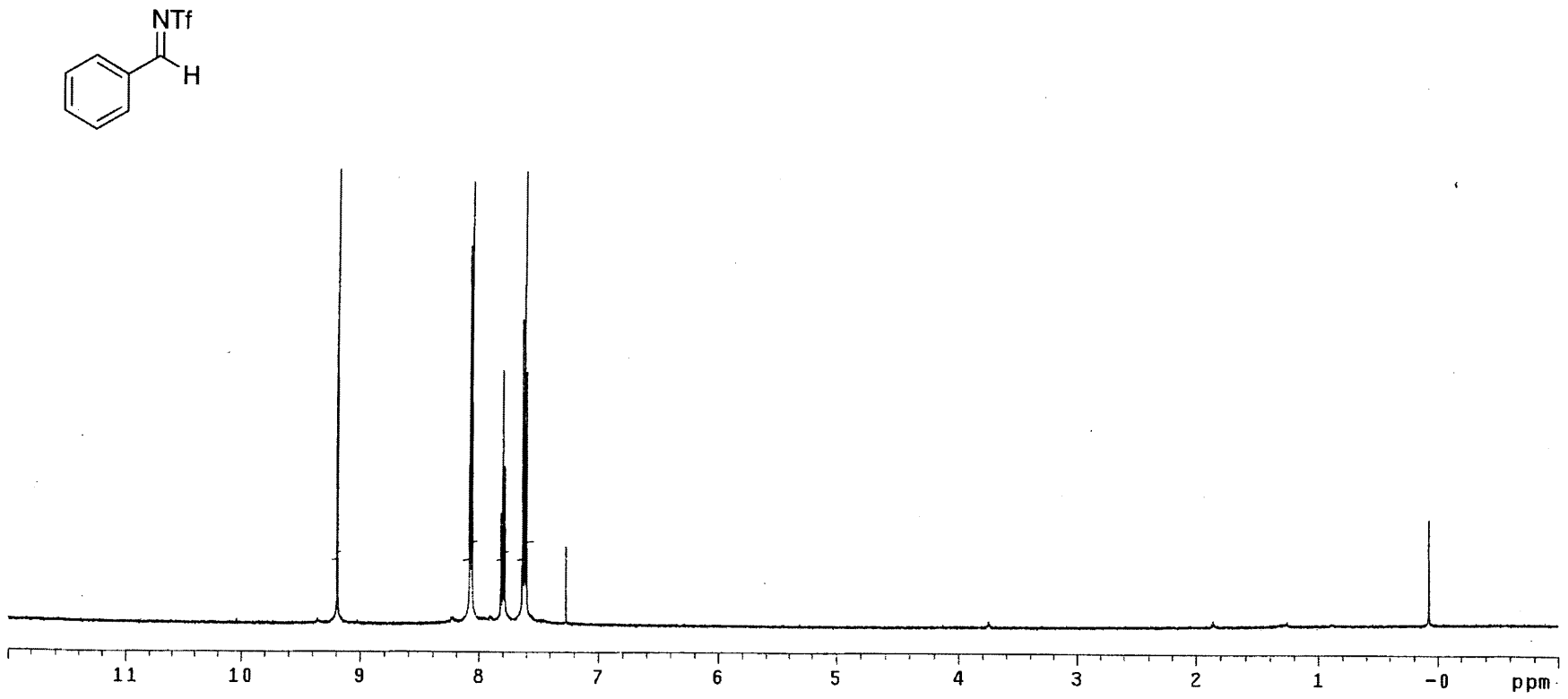
## 2.7 $^{1}$H NMR for Selected Compounds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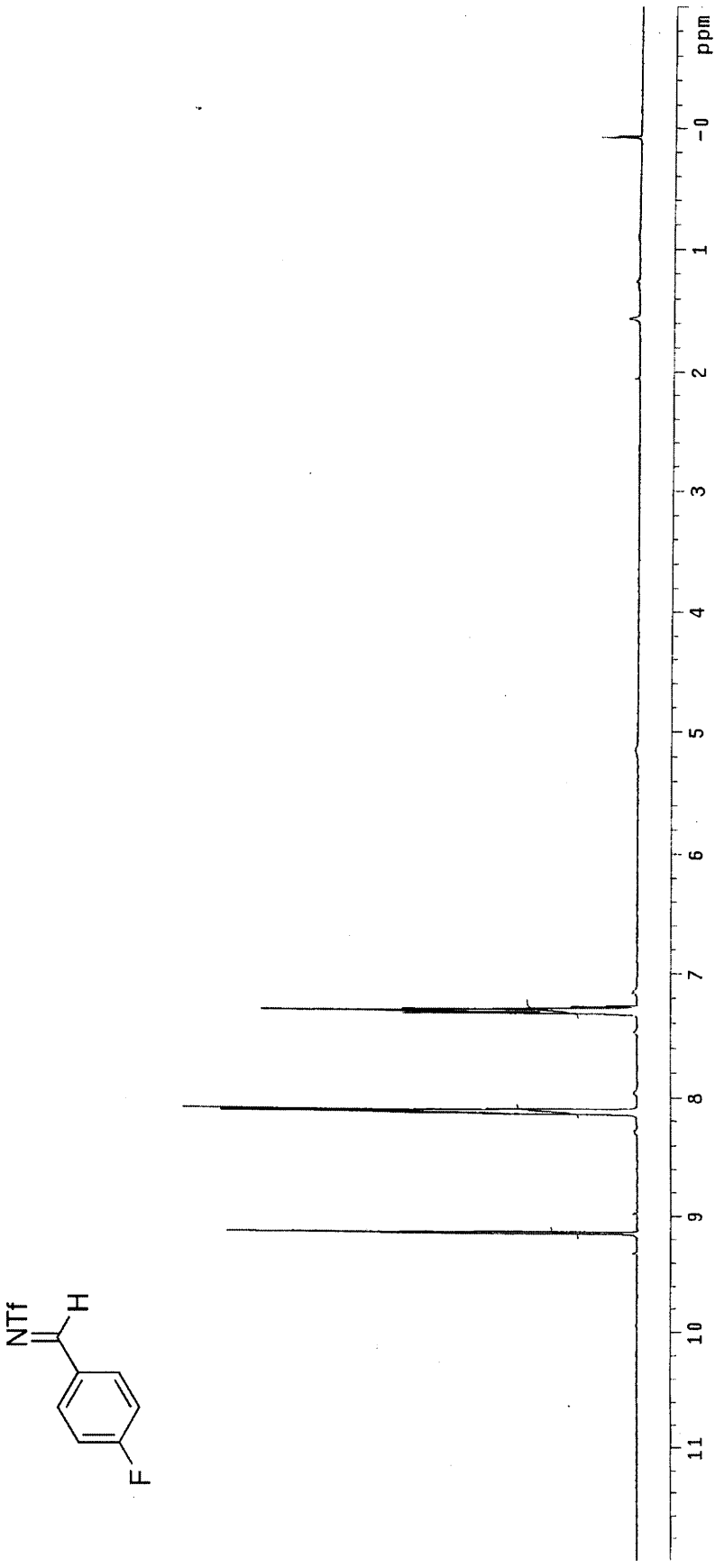
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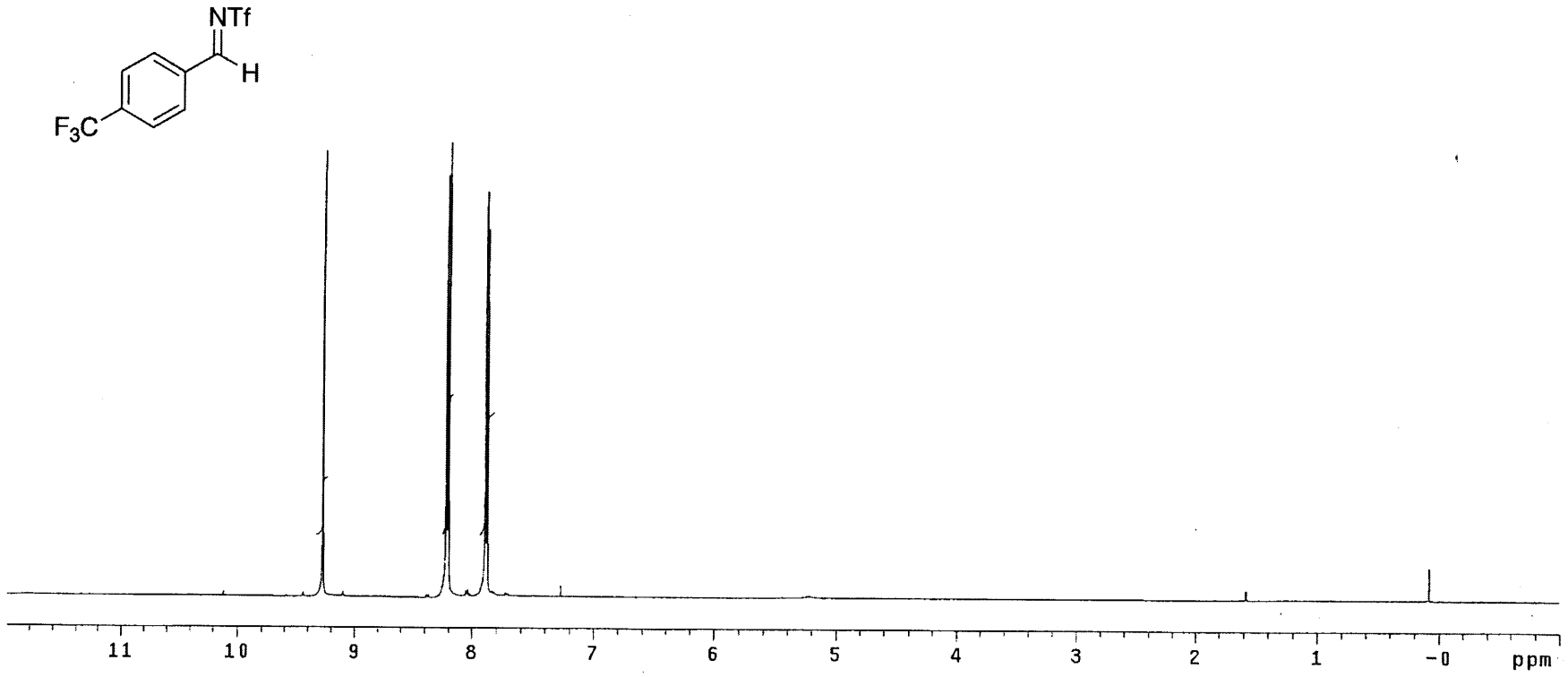
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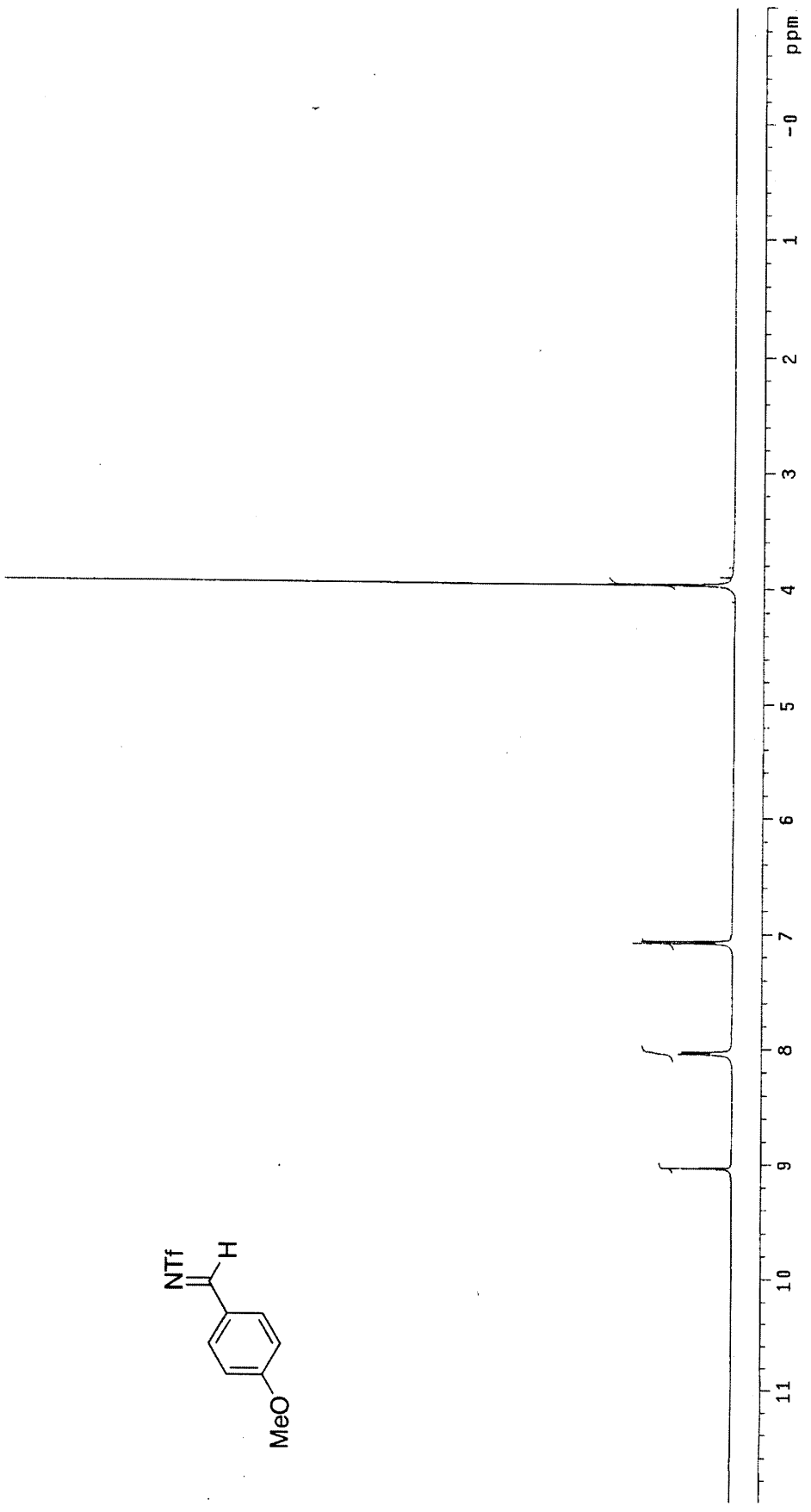
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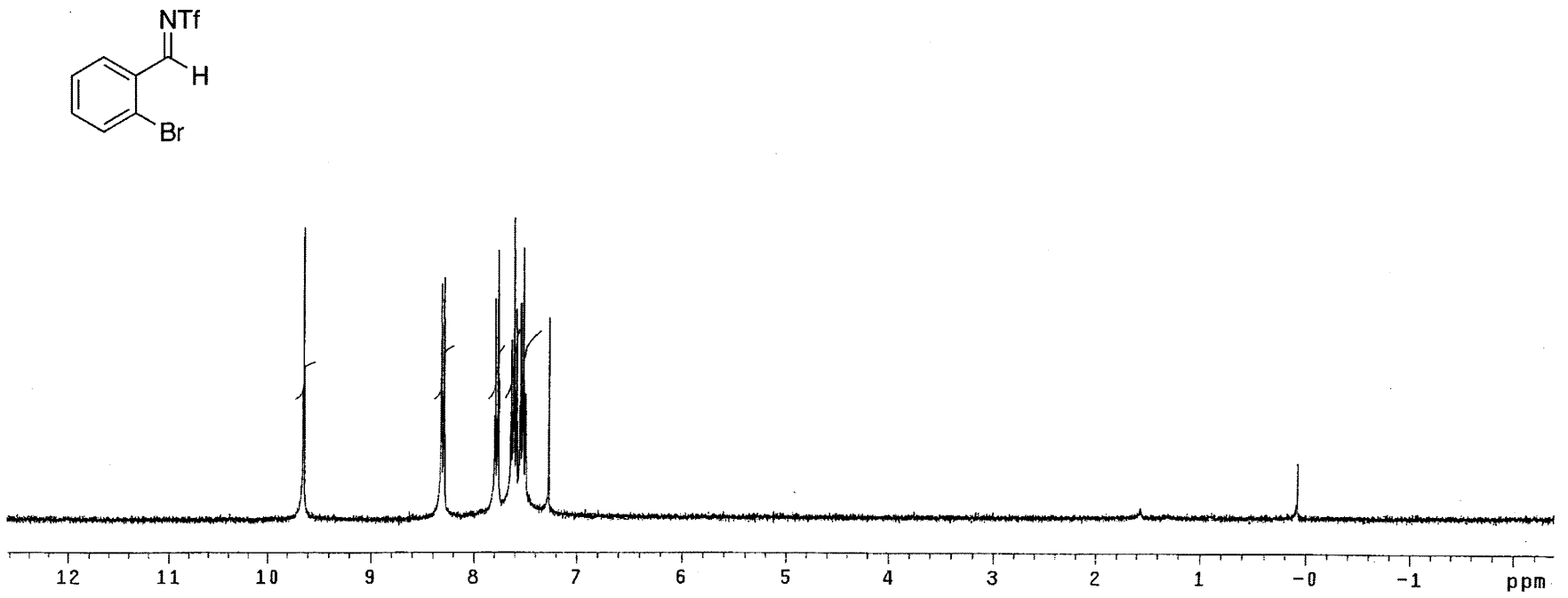
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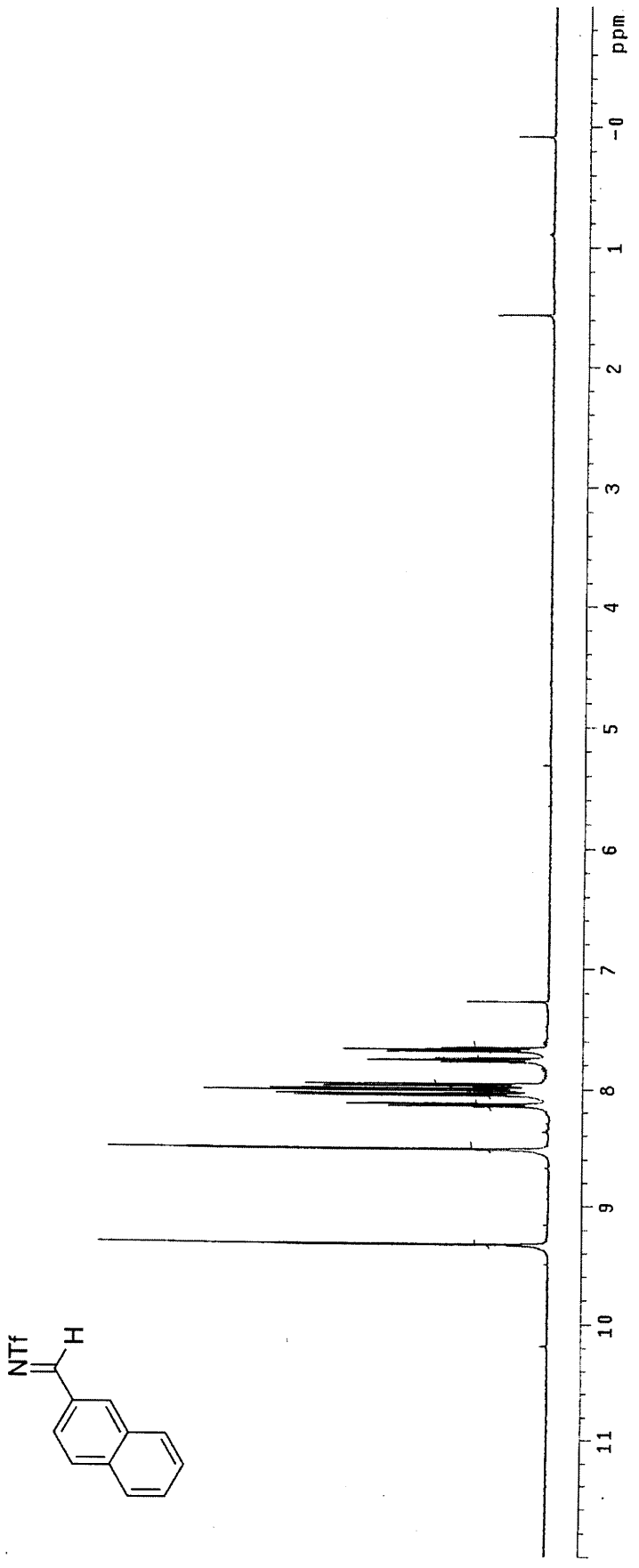
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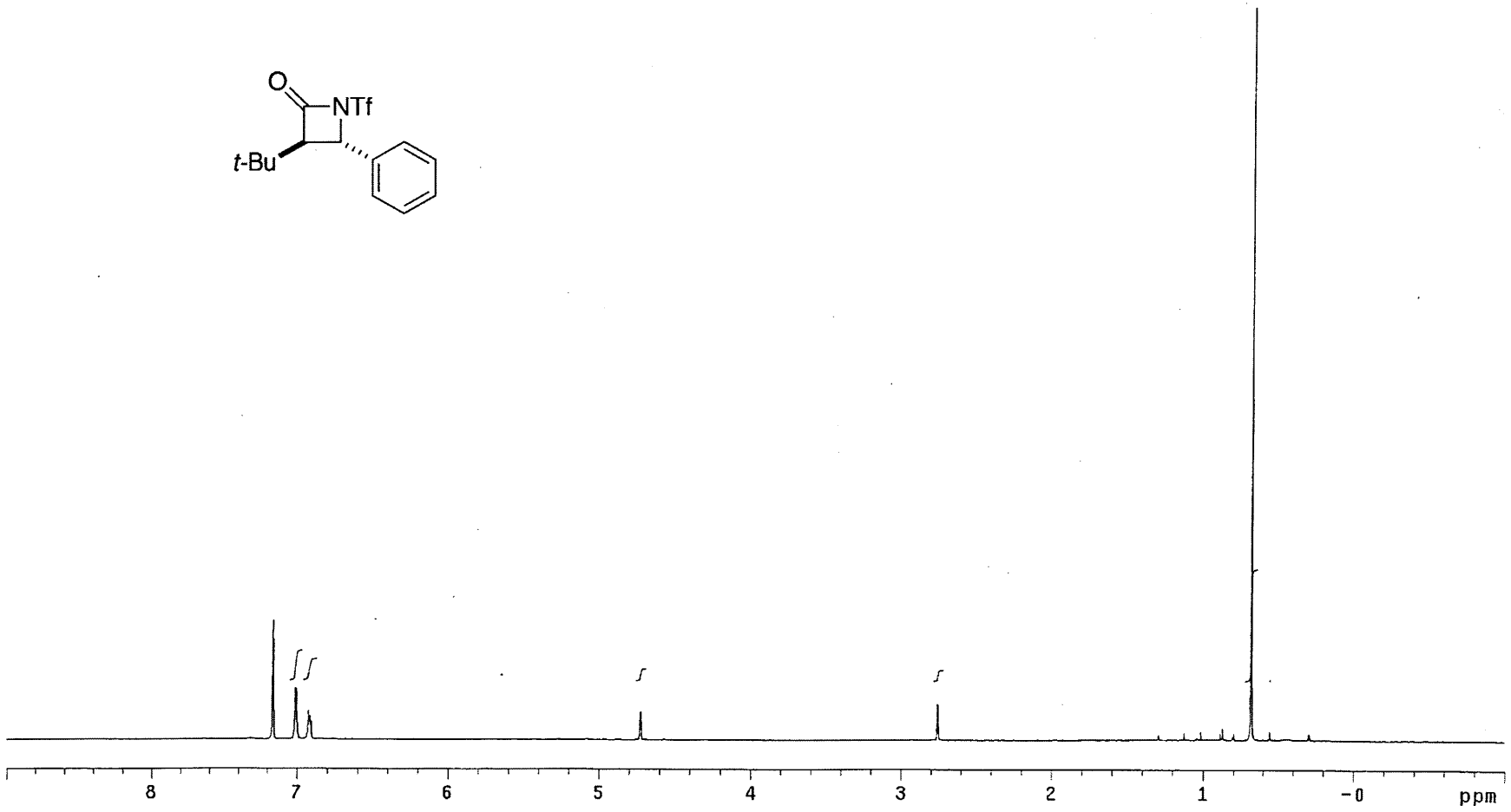
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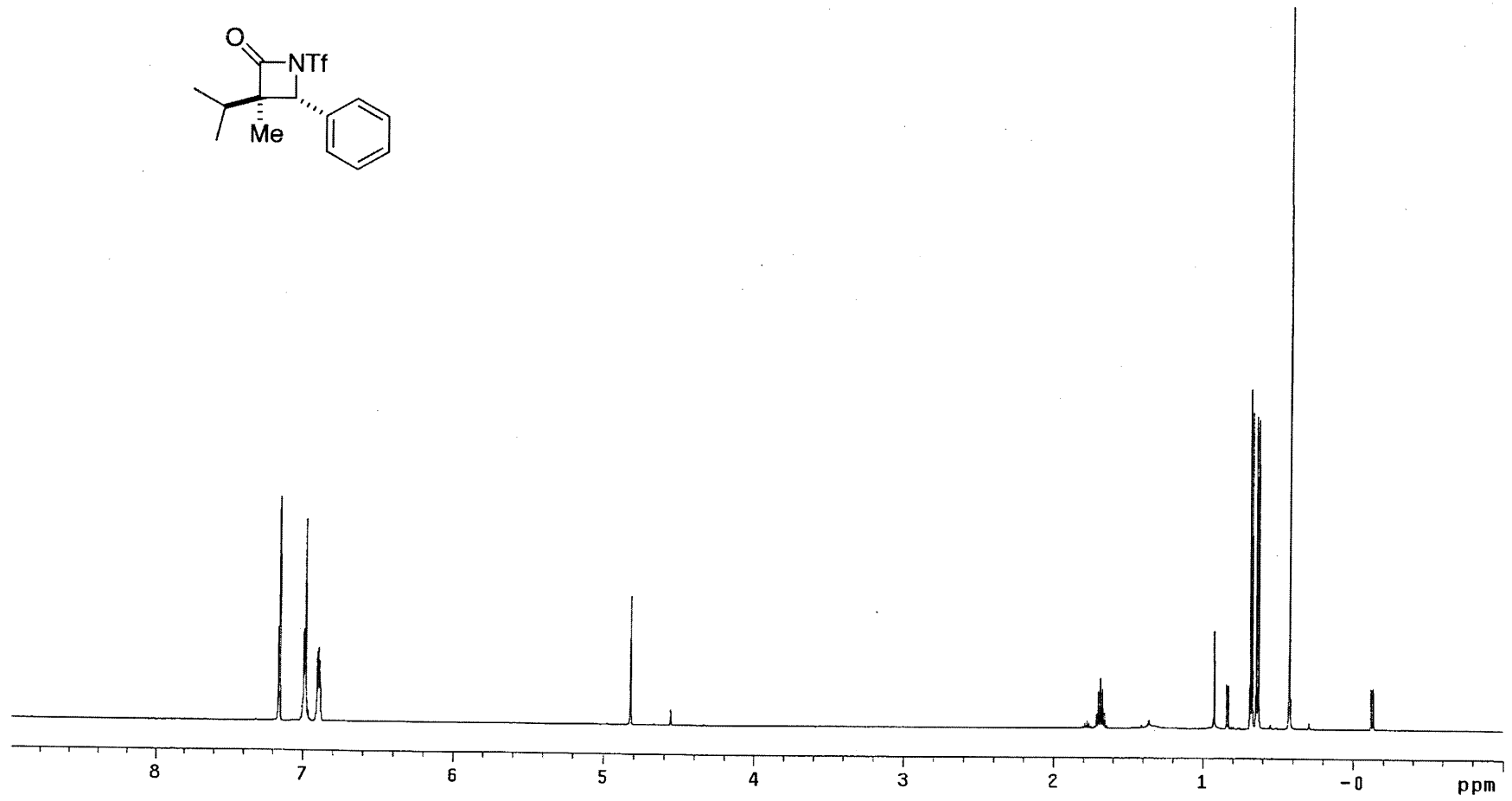
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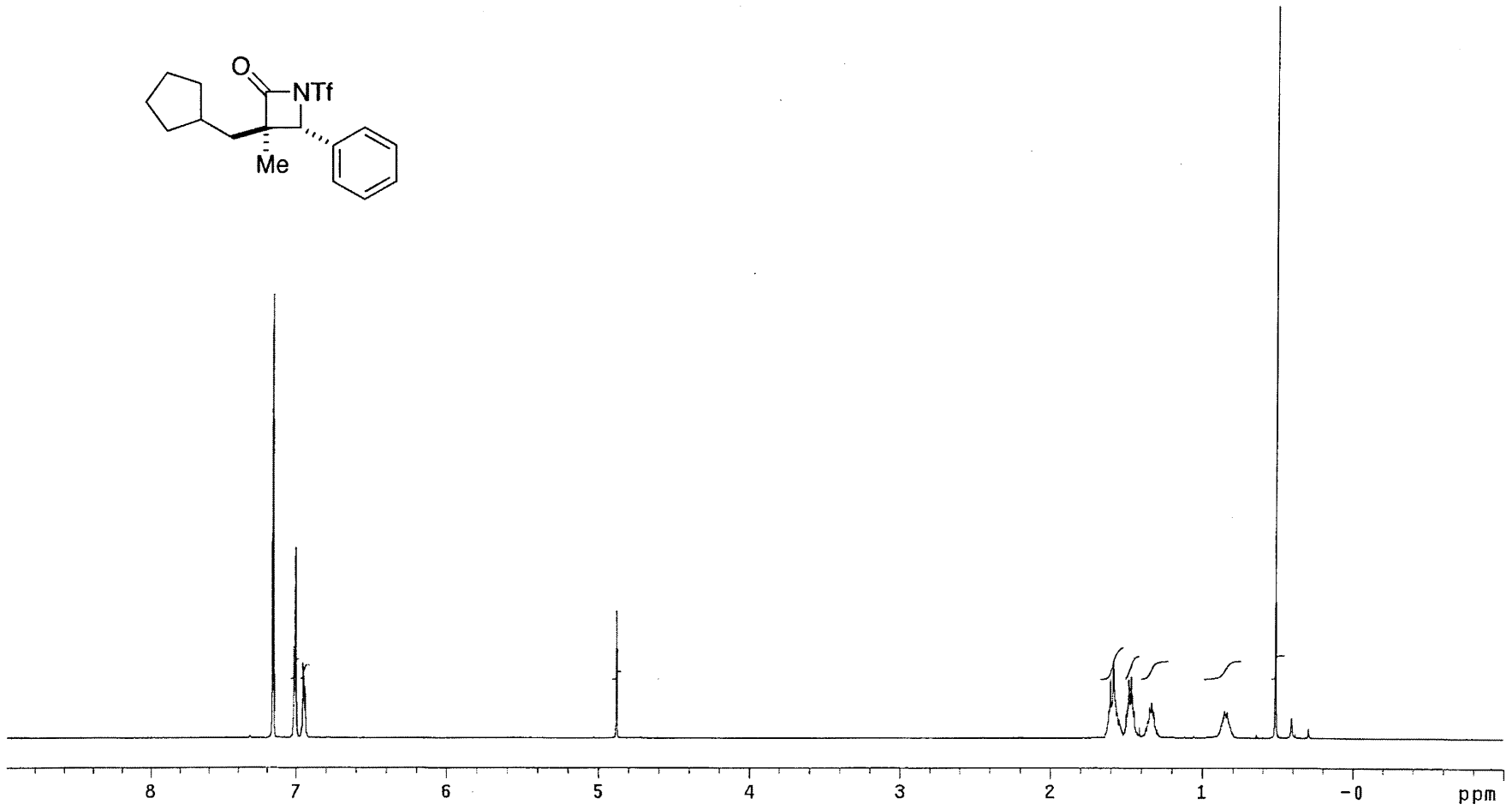
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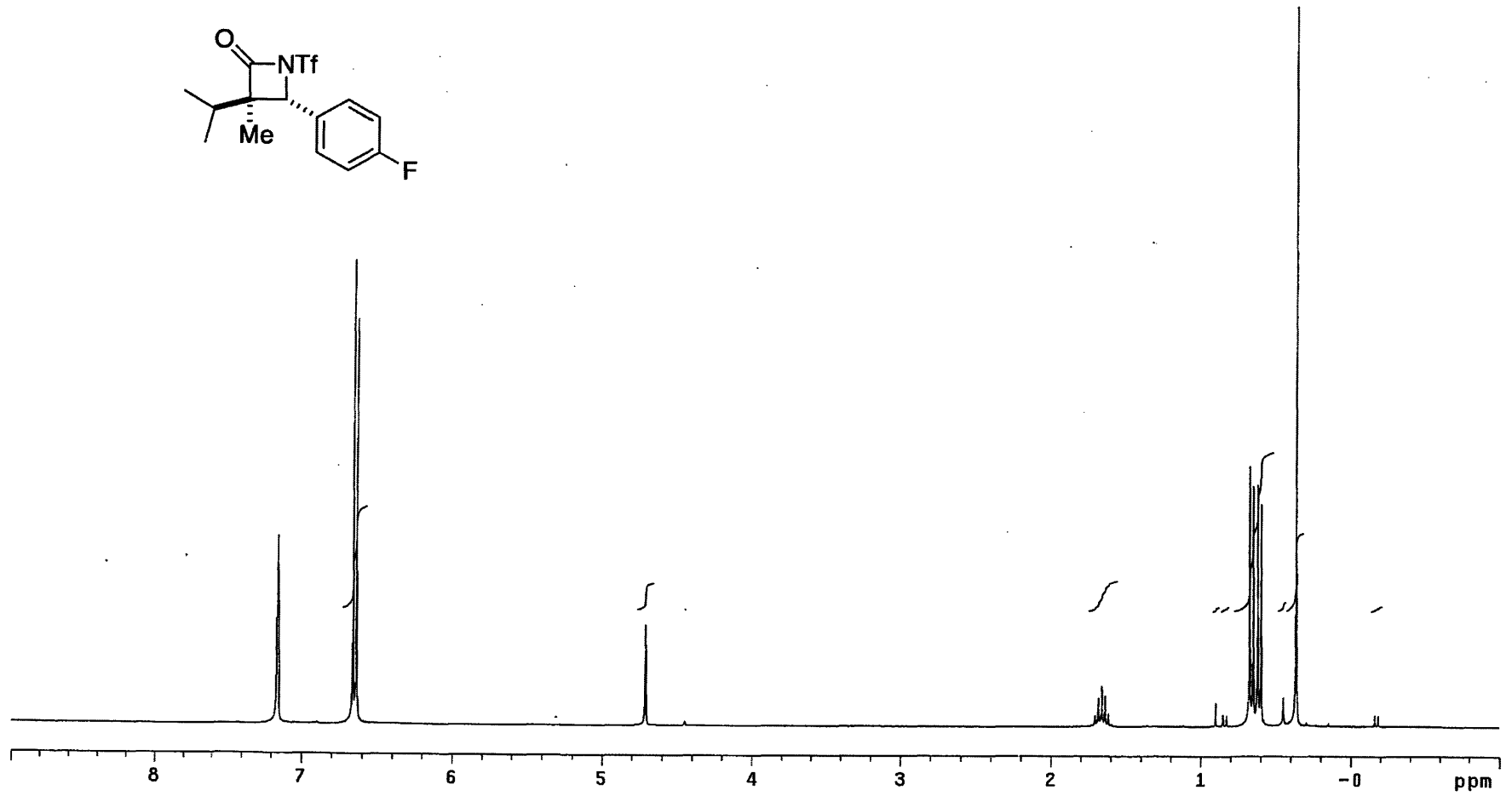
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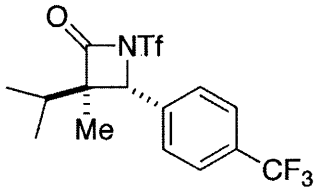
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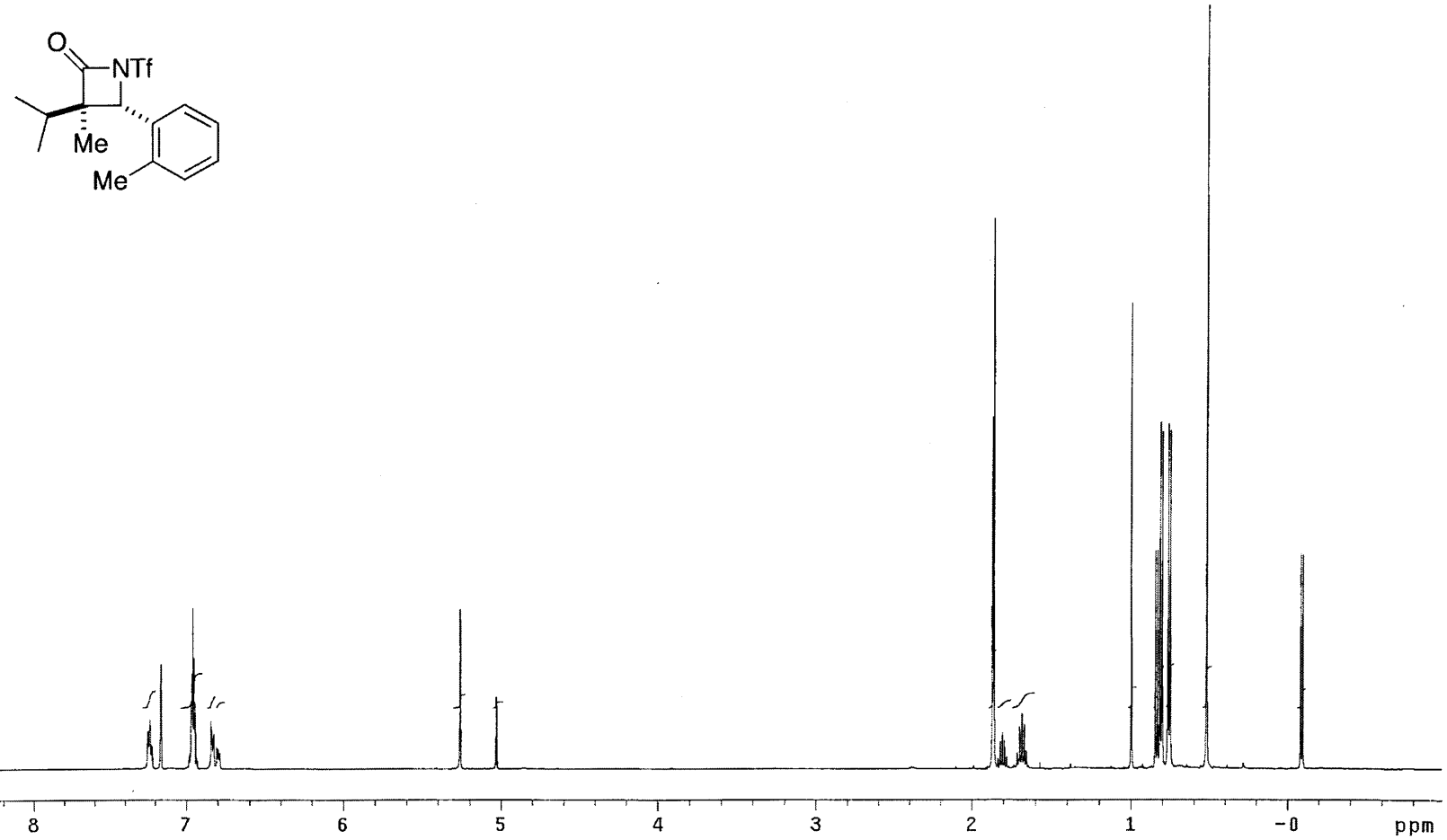
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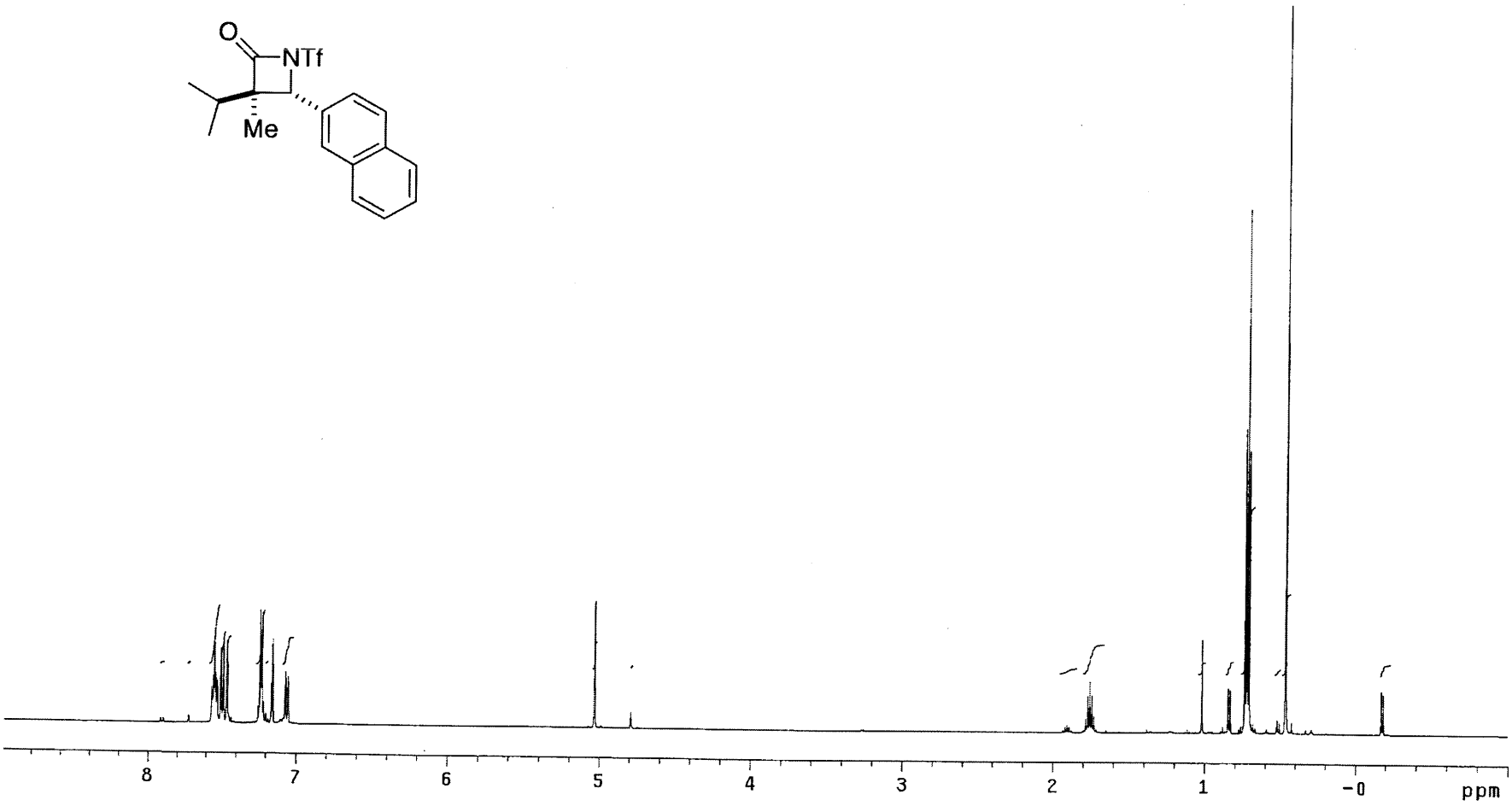
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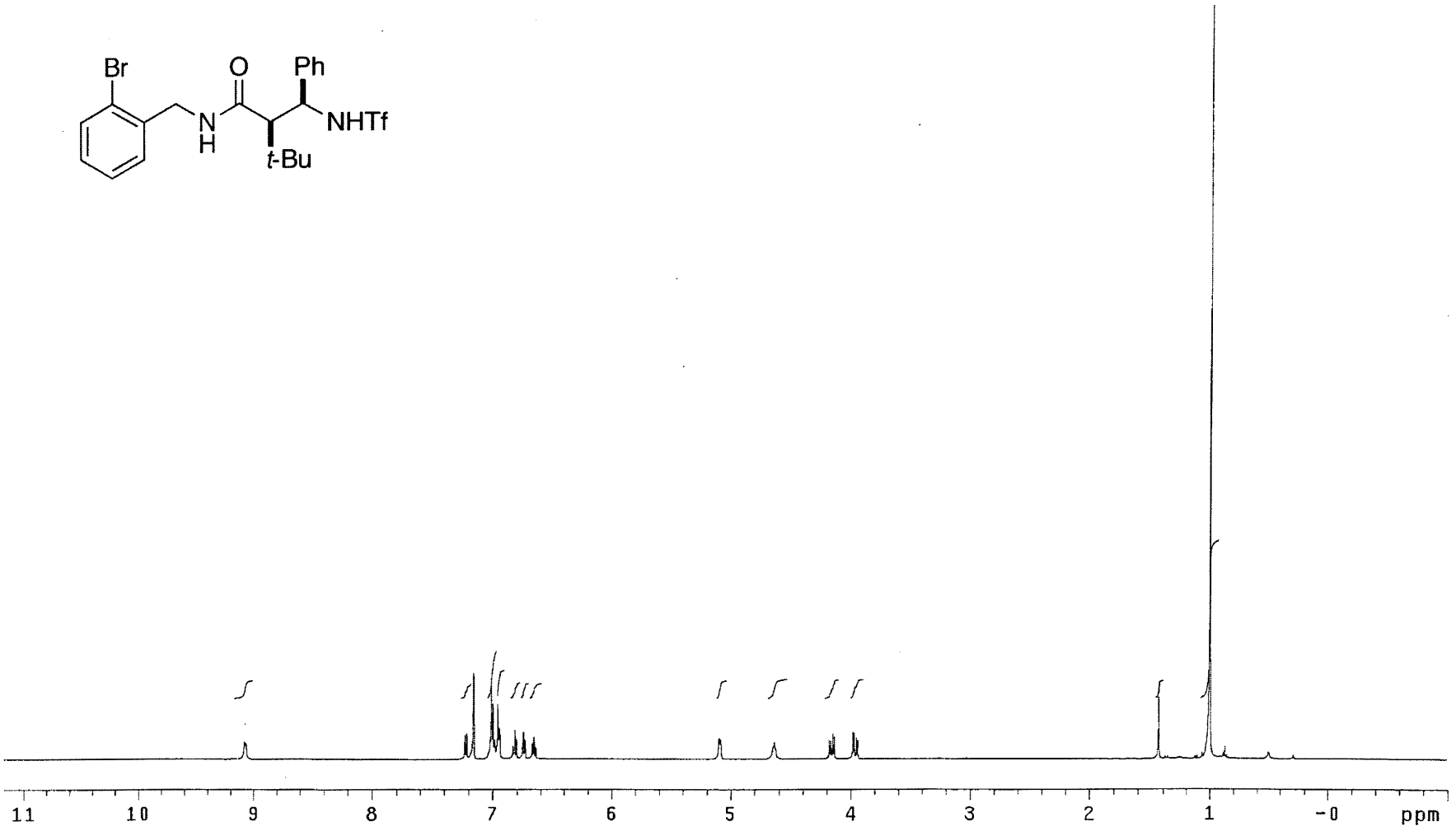
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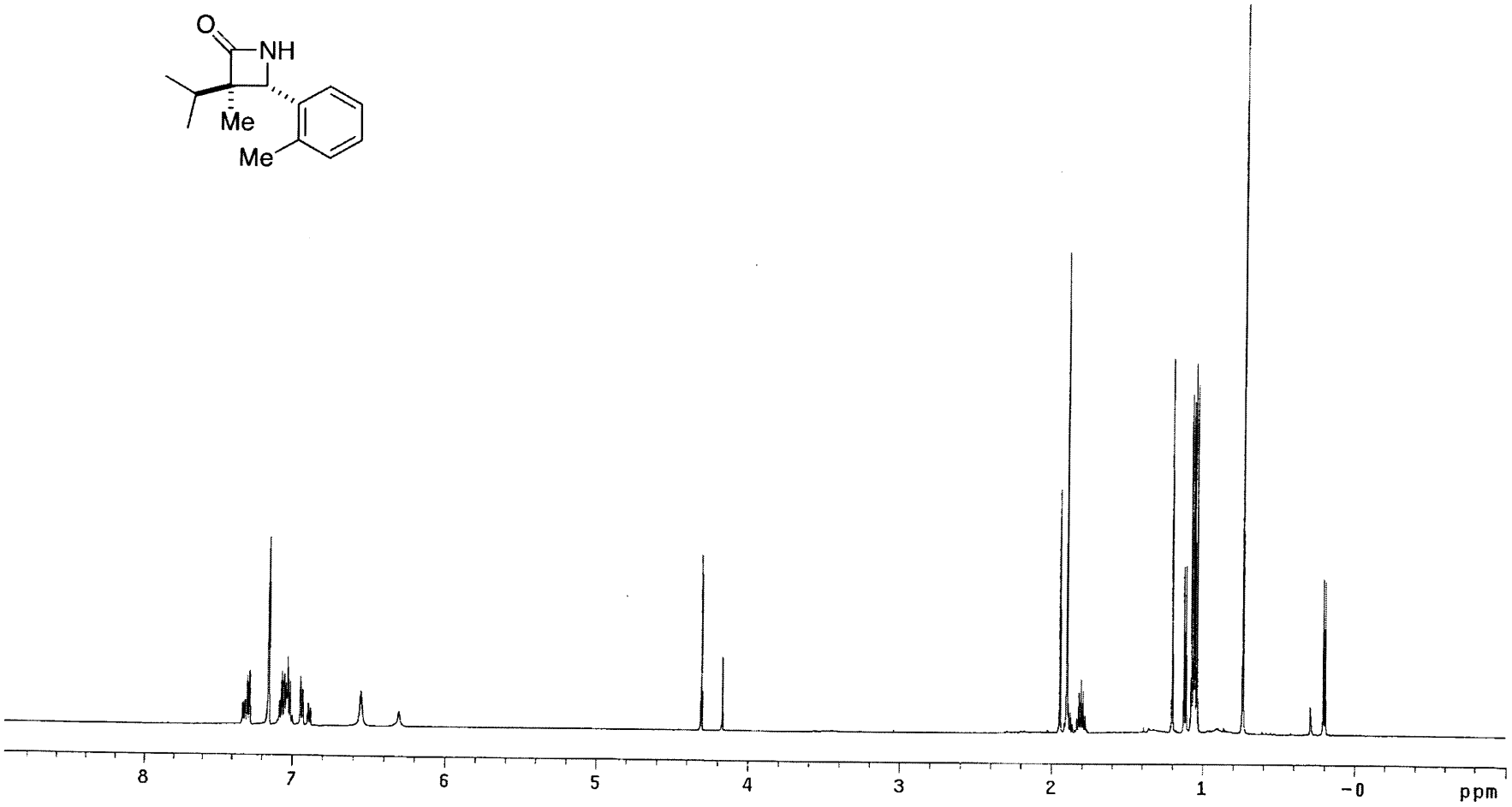
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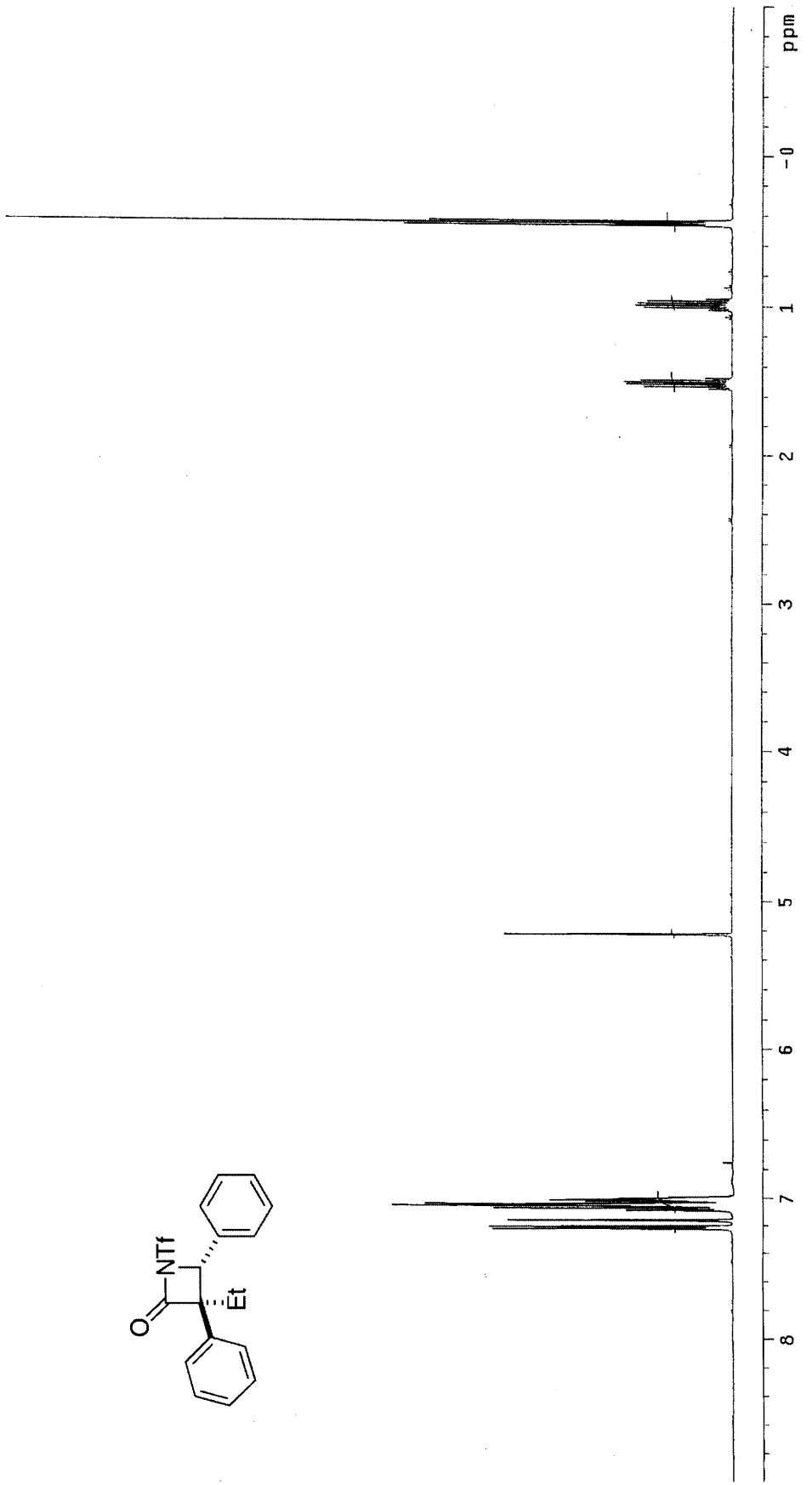
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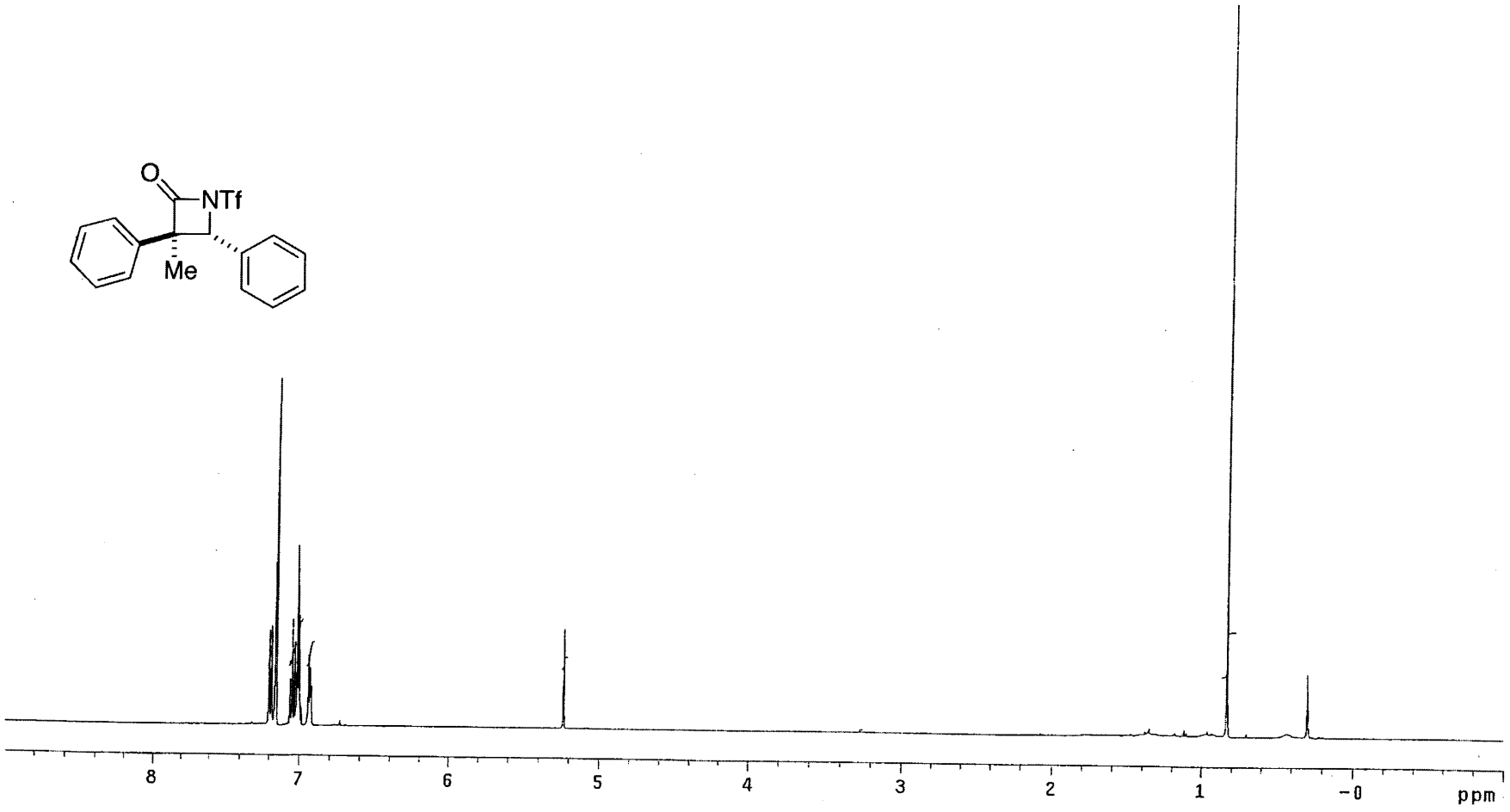
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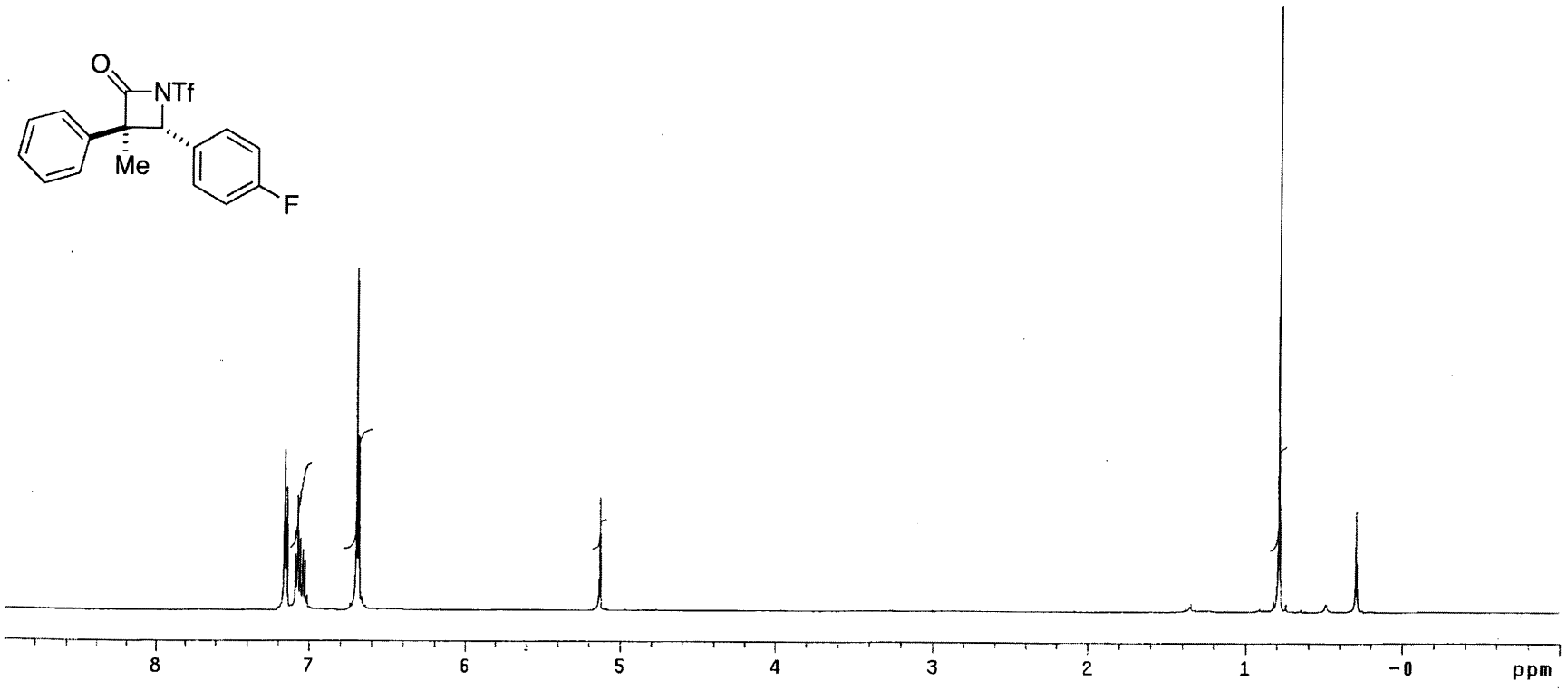
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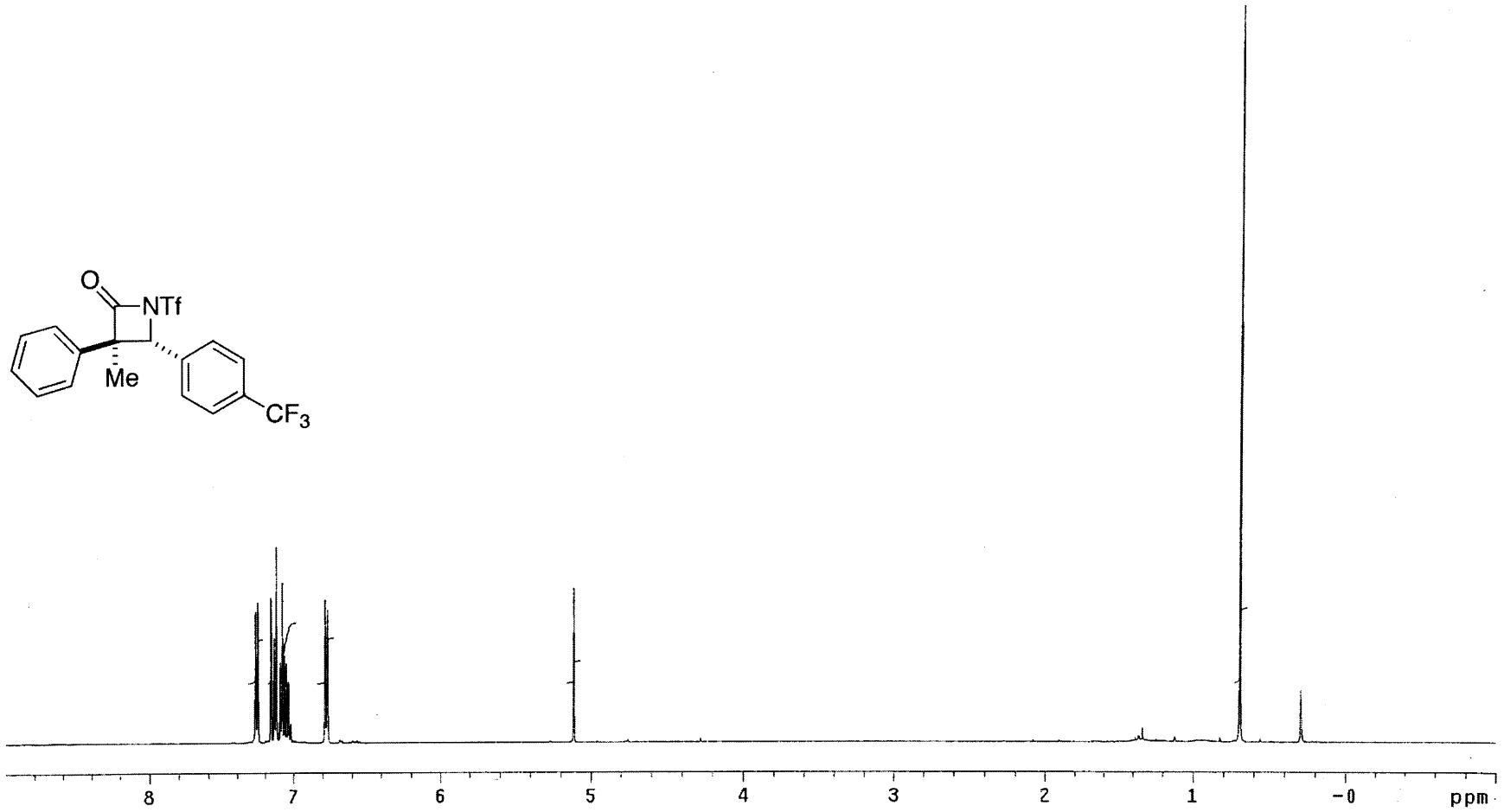
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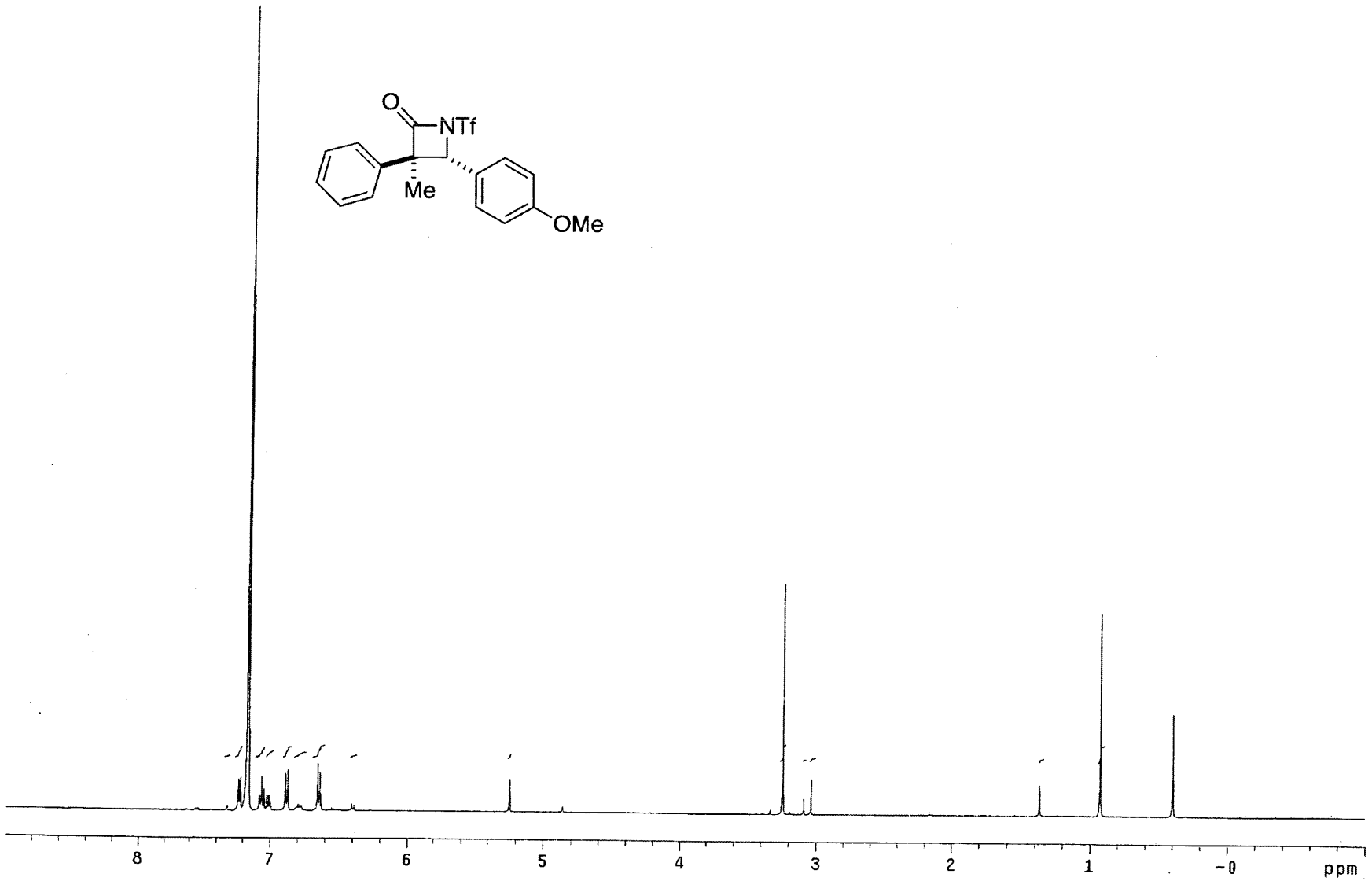
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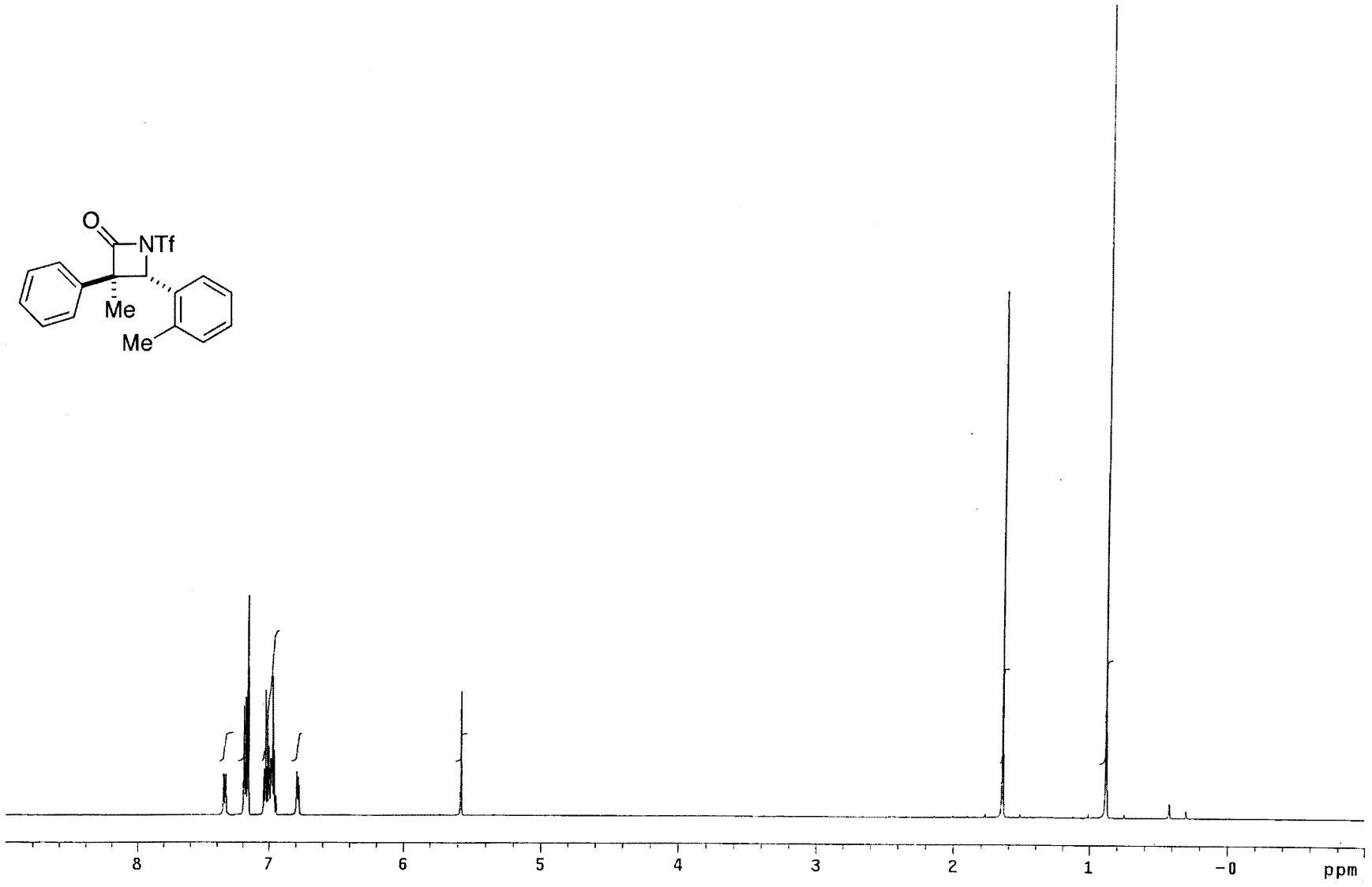
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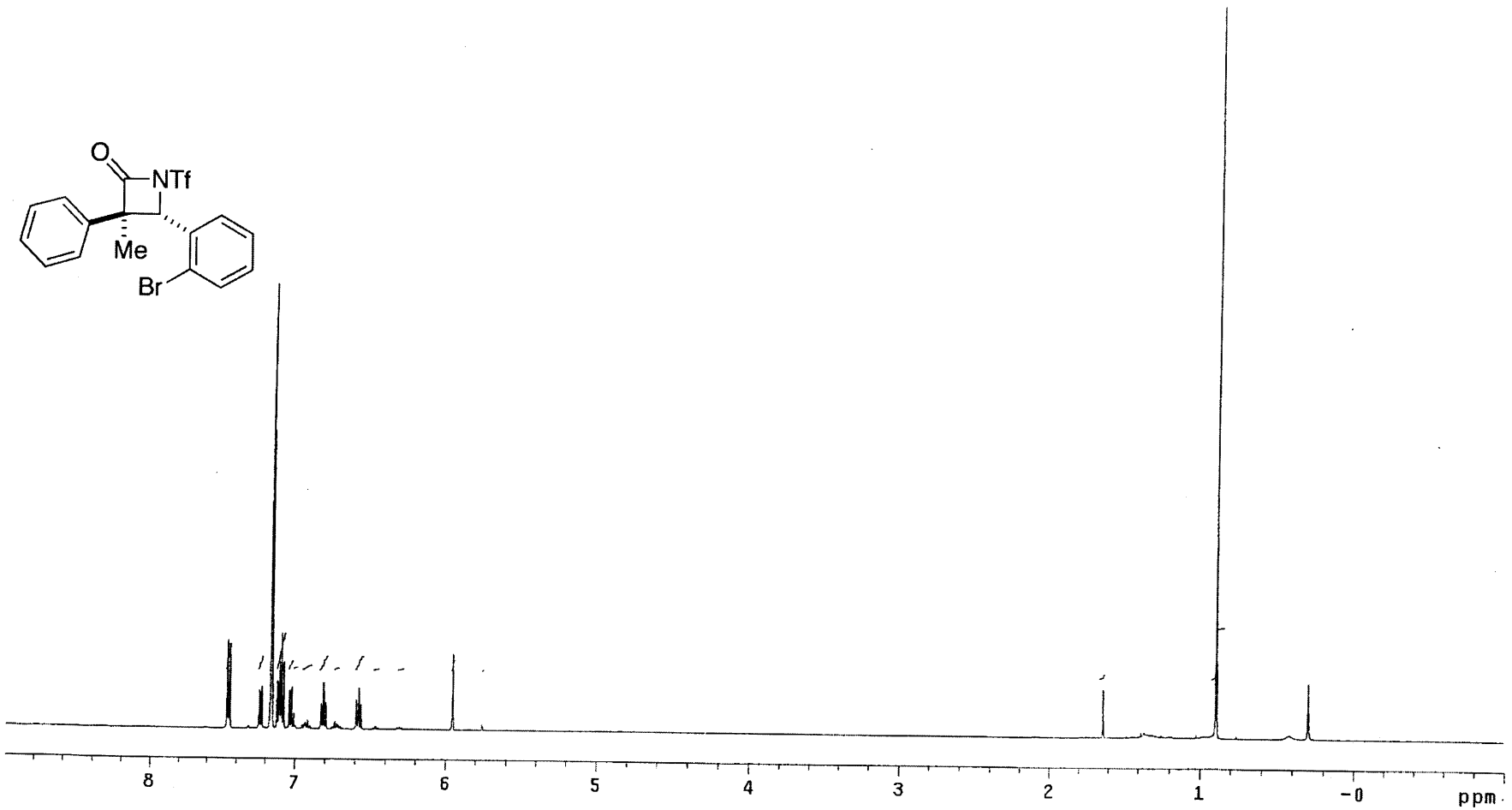
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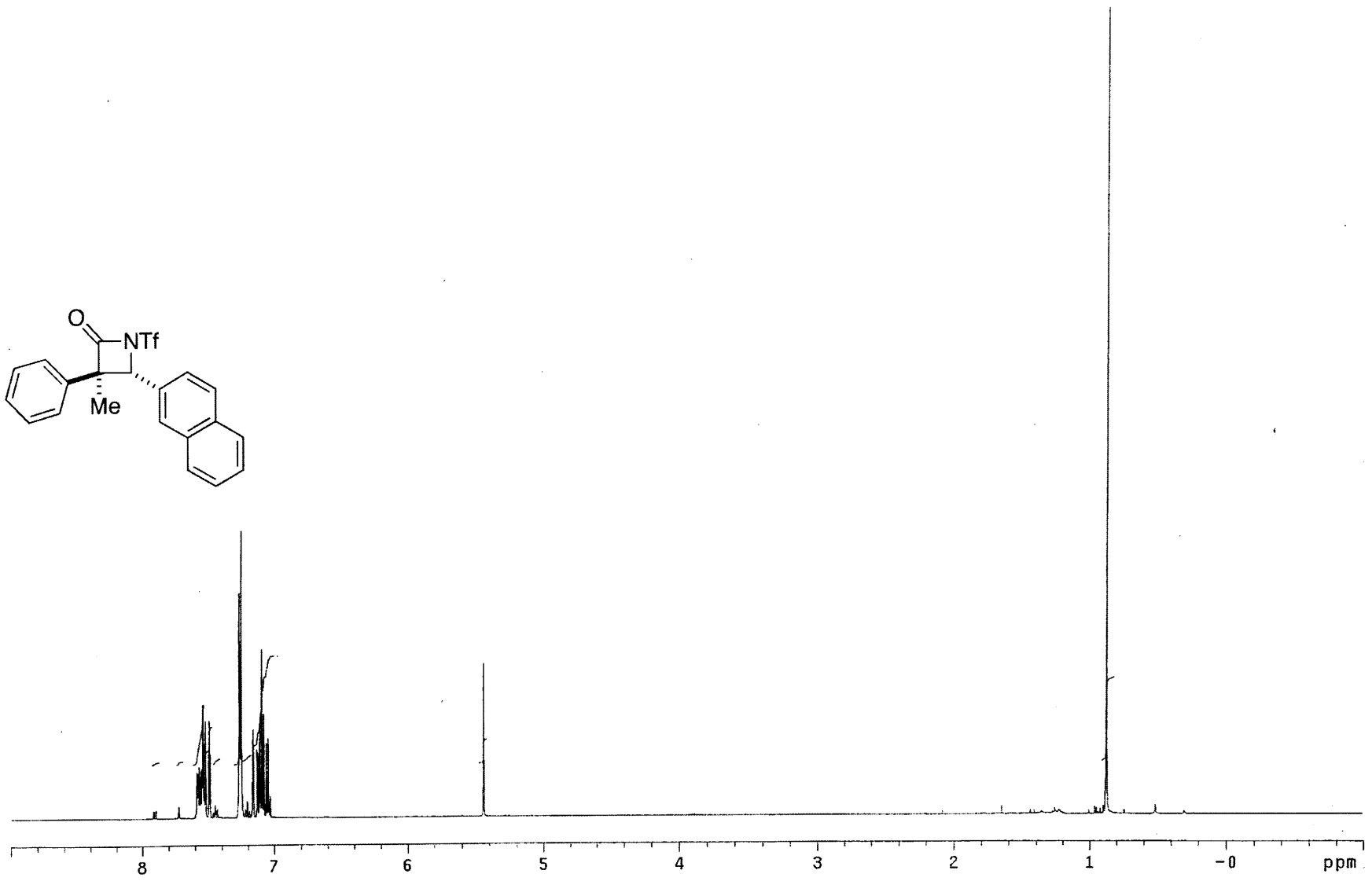
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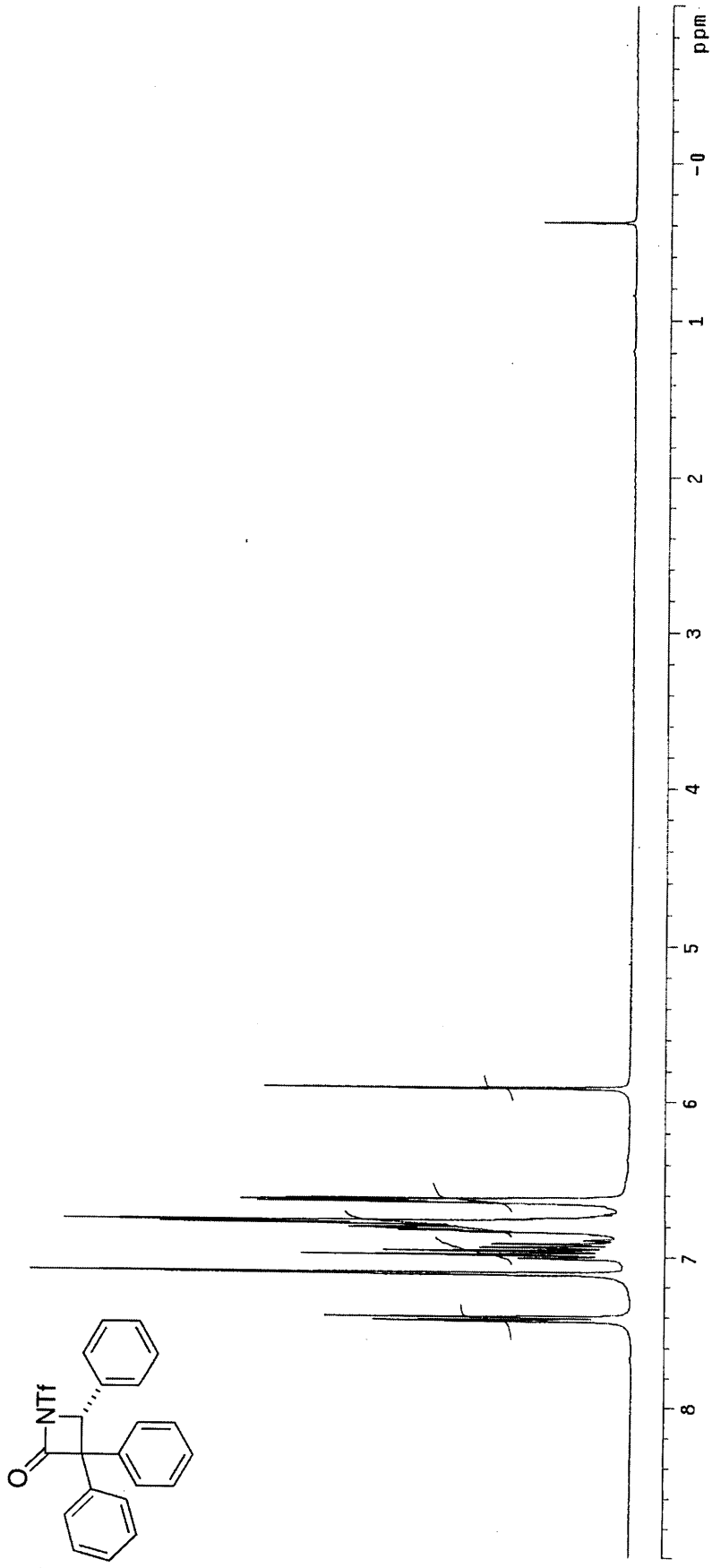
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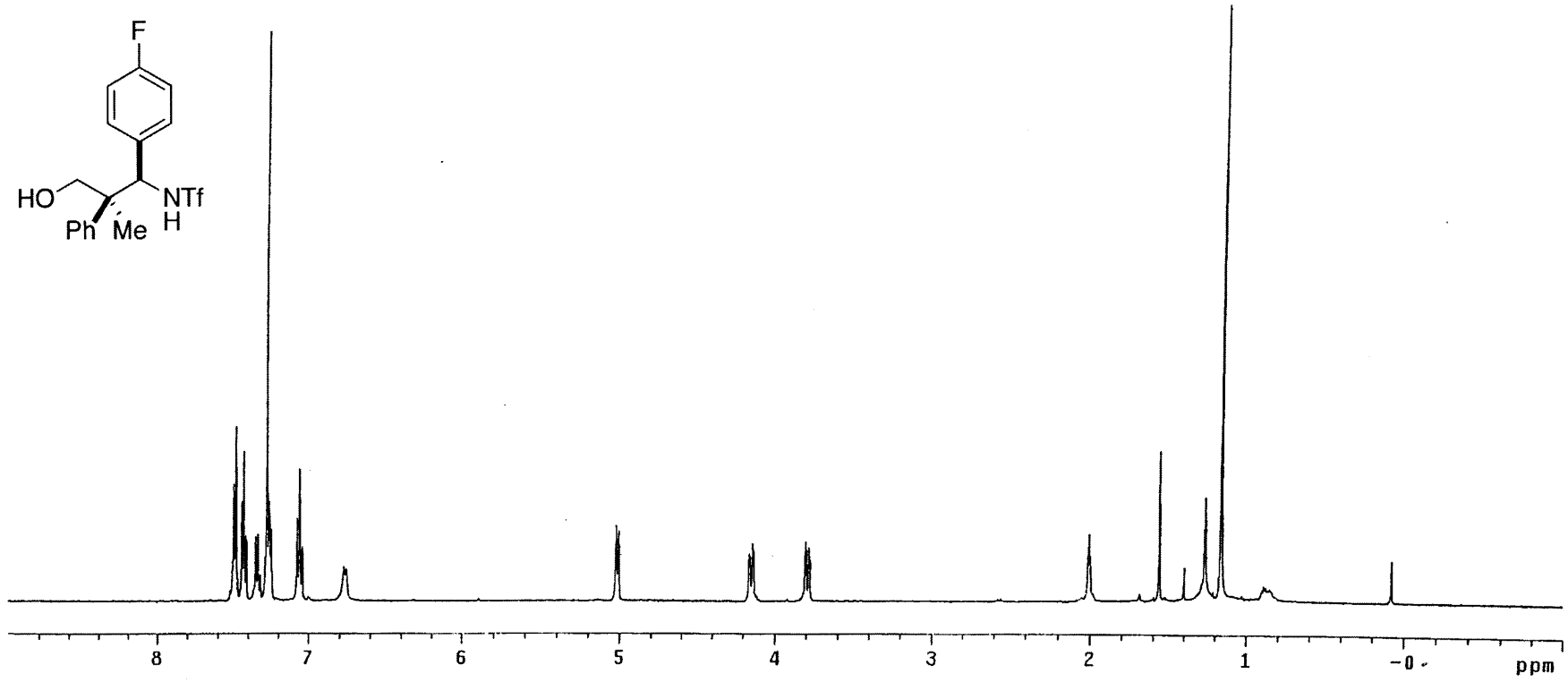
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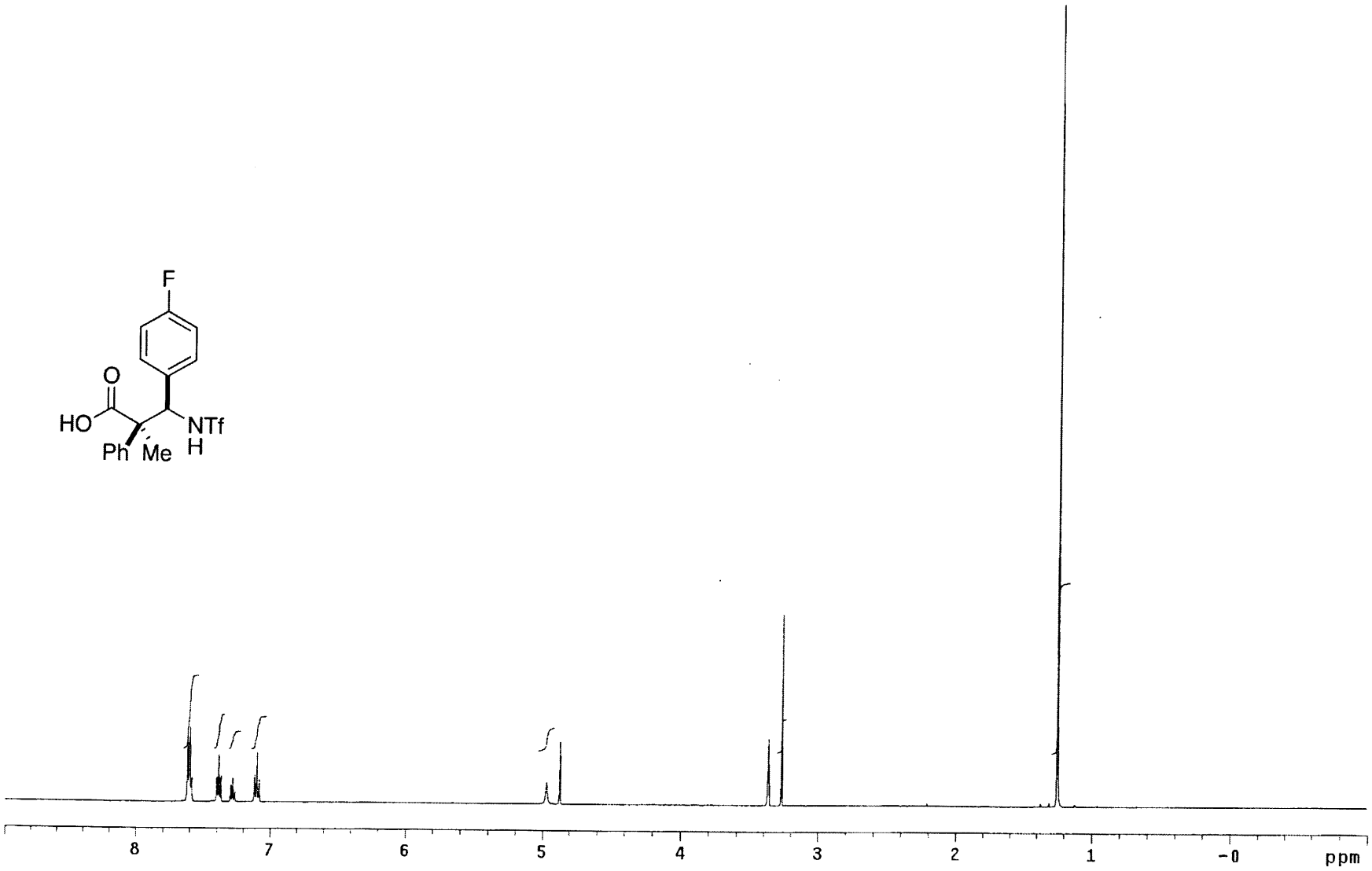
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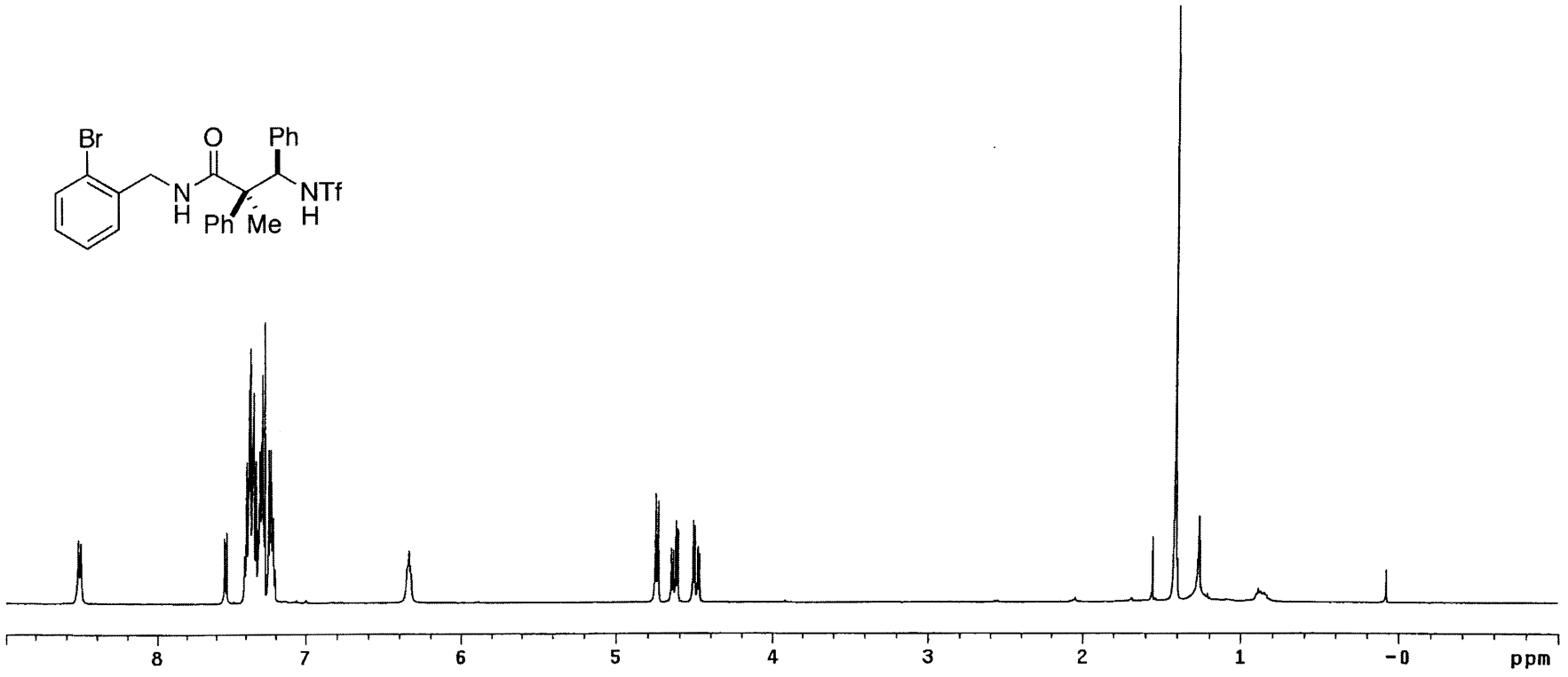
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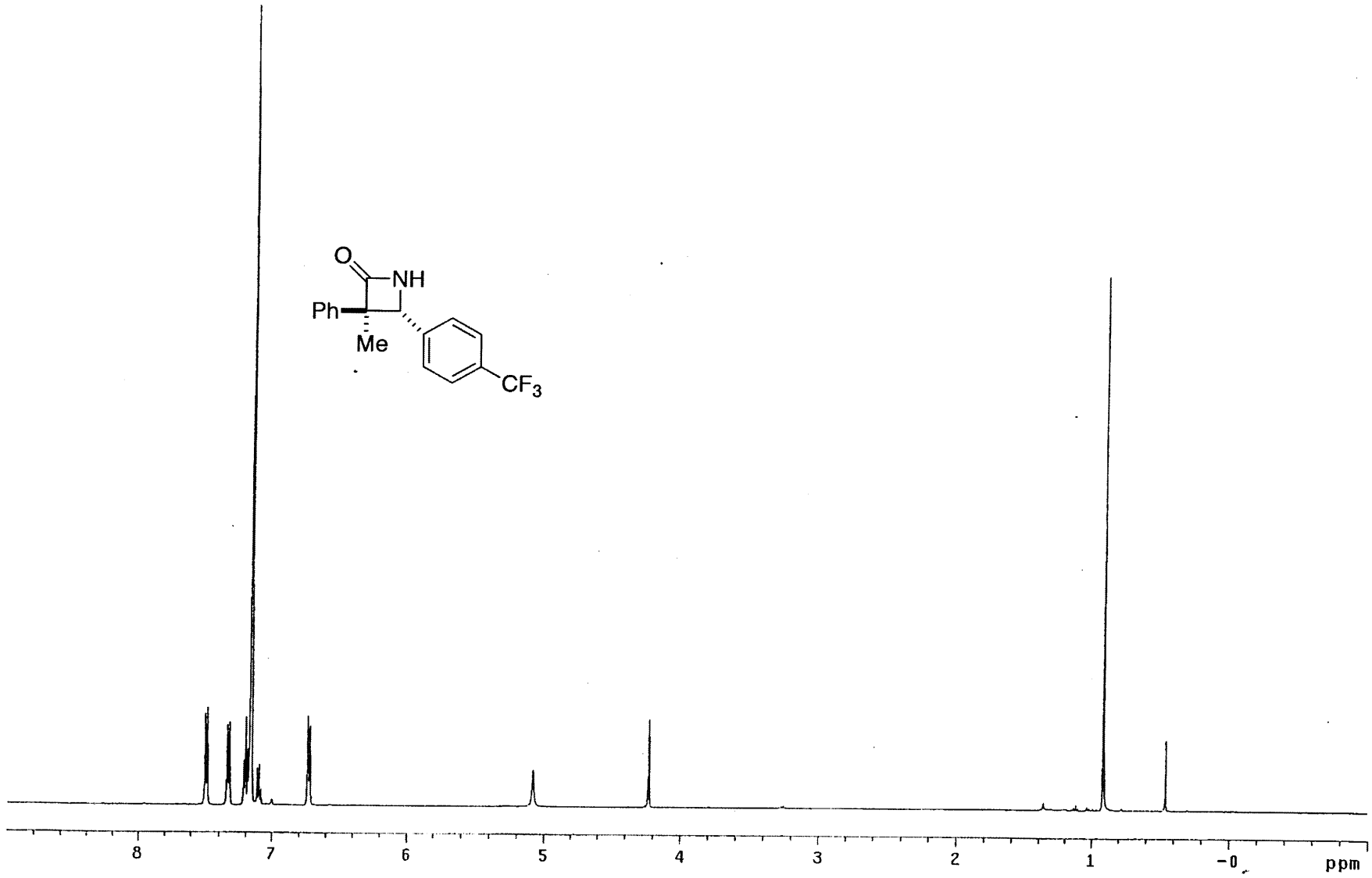
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# Chapter 3

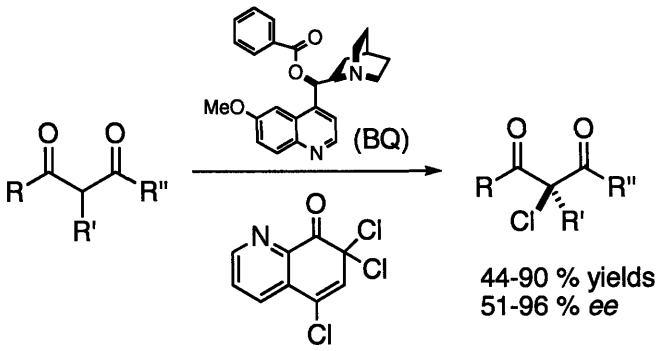
# Asymmetric Synthesis of Tertiary α-Chloroesters Catalyzed by a Planar-Chiral Nucleophilic Catalyst

## 3.1 Introduction

There has been rejuvenation in the use of chiral α-chlorocarbonyl containing compounds as building blocks in organic synthesis in recent years. This motif is attractive as subsequent derivatizations can yield a wide variety of chiral, carbonyl-containing targets.[1] Studies on developing novel methods to access compounds such as these via asymmetric catalysis have focused on three main areas: a) the α-halogenation of readily enolizable carbonyl compounds mediated by a chiral Lewis acid,[2] b) the α-halogenation of chiral zwitterionic enolates obtained from a nucleophile and a ketene,[3] c) organocatalytic α-halogenation via a chiral enamine intermediate.[4]

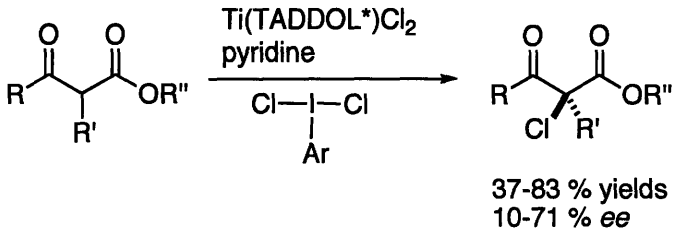
While these reports provide methods that allow access to various secondary α-chlorocarbonyl compounds, syntheses of tertiary α-chlorocarbonyl compounds are noticeably rare.[5] Tertiary α-chlorocarbonyl compounds are not only used as key intermediates in medicinal chemistry,[6] but are also found in potent pharmaceutical compounds.[7]

Previous examples of constructing tertiary α-chlorocarbonyl compound include a benzoylquinine (BQ) catalyzed method developed by Bartoli[9] where trichloroquinolinone is used as a chlorinating reagent (eq 1). However, this method is limited to diketones and ketoesters.



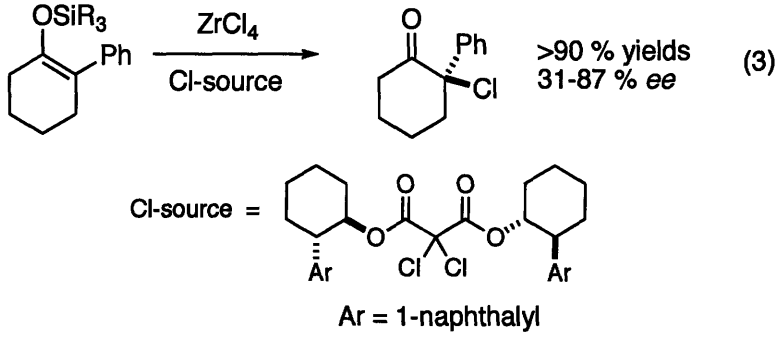

(1)

Another method that generates tertiary α-chloro β-ketoesters uses a Ti catalyst, developed by Togni (eq 2).[2a] Again this method is limited to a ketoester backbone, and only moderate stereochemical purity is observed.



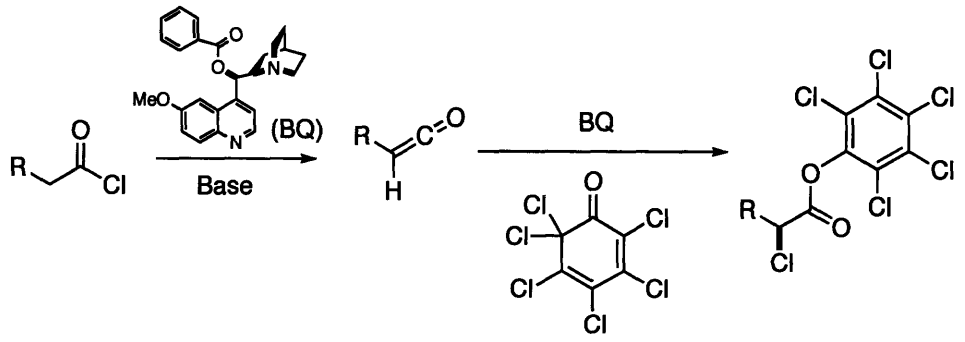

(2)

Yamamoto[2c] developed a Zr-mediated reaction that yields cyclic α-chloroketones. This method utilizes a novel chiral chlorinating reagent; however, a stoichiometric amount of the chiral chlorinating agent is used and superstoichimetric Zr is required and the method is limited to cyclic silyl enol ethers (eq 3).



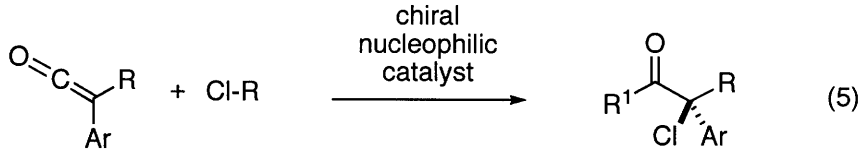

(3)

Analogous to our strategy, Lectka[3] has used ketene chemistry to install the chloro-substituent at the α-position of carbonyl-containing compounds in the presence of a chiral nucleophile (eq 4). This method uses perchlorinated quinone as a chlorinating agent and produces secondary α-chloroesters in good yields (40-81%) and excellent ee (80-99%).




(4)

Due to the limited existing methods for accessing tertiary α-chlorocarbonyl compounds, our aim was to create a general catalytic method for the synthesis of tertiary α-chlorocarbonyl compounds using chiral nucleophilic catalysis (eq 5).



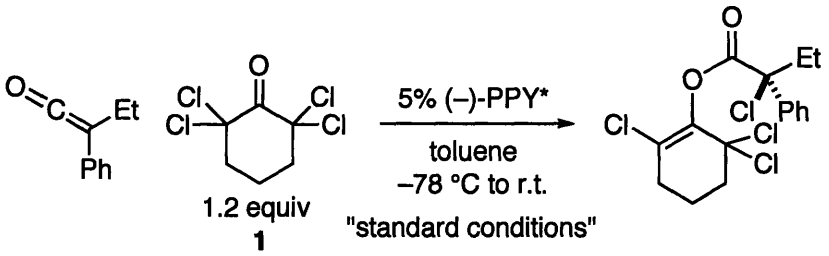

(5)

## 3.2 Results and Discussion

### *3.2.1. Reaction Optimization*

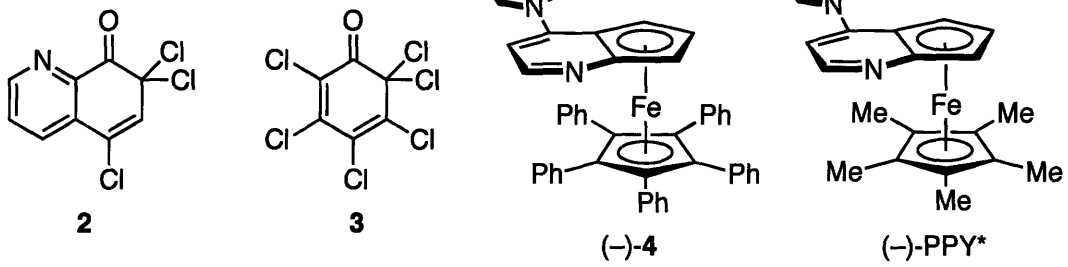
The initial reaction screening was performed by Dr. Kevin McCauley. In our early studies on the synthesis of α-chlorocarbonyl compounds via the reaction of a ketene and electrophilic chlorinating reagent, we examined the reaction of phenyl ethyl ketene with various chlorinating agents under a range of conditions (entries 1-4 of Table 1).[8] In the presence of PPY*, the use of reagents such as *N*-chlorosuccinimide,[4b] **2**,[9] and **3**[3a] provided the product in poor yield and/or ee (entries 1 and 2). On the other hand, the reaction of phenyl ethyl ketene with hexachloroacetone[10] cleanly furnished the desired enol ester with promising enantioselectivity (57% ee; entry 3). Hexachloroacetone is an inexpensive and commercially available chlorinating reagent that is relatively underutilized as an electrophilic chlorinating reagent.[10a,b] We hypothesized that using a similar chlorinating agent to hexachloroacetone, but with more rigidity built into the backbone, might improve the enantioselectively. This proved to be the case as demonstrated by the reaction of phenyl ethyl ketene with 2,2,6,6-tetrachlorocyclohexanone[11] catalyzed by PPY* (86% yield and 94% ee; entry 4). To the best of our knowledge, this is the first example of the use of 2,2,6,6-tetrachlorocyclohexanone as a chlorinating reagent in asymmetric catalysis.

***Table 1.*** Effect of Reaction Parameters on the Catalytic Asymmetric Synthesis of Tertiary α-Chloroesters.




| entry | change from the "standard conditions" | yield (%) | ee (%) |
|---|---|---|---|
| 1 | *N*-chlorosuccinimide or **2**, instead of **1** | <5 | – |
| 2 | **3**, instead of **1** | 40 | 8 |
| 3 | hexachloroacetone, instead of **1** | 96 | 57 |
| 4 | none | 86 | 94 |
| 5 | (–)-**4**, instead of (–)-PPY* | 46 | 88 |
| 6 | benzoylquinine, instead of (–)-PPY* | <5 | – |
| 7 | r.t., instead of –78 °C to r.t. | 45 | 26 |
| 8 | $CH_2Cl_2$, instead of toluene | 17 | 11 |
| 9 | THF, instead of toluene | <5 | – |

All data are the average of two runs.



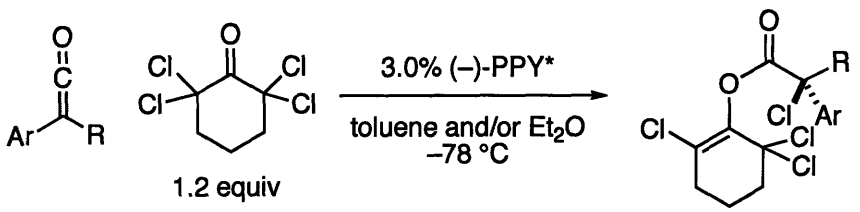

Other attempts to improve the yield and enantioselectivity included the use of (–)-**4**, which possesses a bulkier bottom ring relative to PPY*. However, in a reaction that utilized (–)-**4**, a lower yield and enantioselectivity were obtained (entry 5). Additionally, the use of benzoylquinine[12] afforded essentially none of the desired product (entry 6). Upon conducting the chlorinations at higher temperature (entry 7) or in other solvents (entries 8 and 9), poor yields and ee were observed. In the absence of a catalyst, no reaction between phenyl ethyl ketene and 2,2,6,6-tetrachlorocyclohexanone was observed.

*3.2.2. Asymmetric Synthesis of Tertiary α-Chloroesters Catalyzed by (–)-PPY**

After determining the best reaction conditions for the chlorination of phenyl ethyl ketene, we next examined the scope of this method, and we determined that the best enantioselectivities were obtained when the ketene substituents are unhindered (Table 2). It was found that a lower catalyst loading (3 mol%) could be employed relative to the initial screening conditions (5 mol%). Additionally, the reaction rate was rapid: most reactions were complete within 3 hours at -78 °C. It was also determined that the catalyst can be recovered during the purification step in approximately 60% yield.

Thus, reactions of phenyl alkyl ketenes in which the alkyl group was Me, Et, or *i*-Bu proceeded with good enantiomeric excess (entries 1-2, 4), whereas modest ee was observed in the case of α-branched alkyl substituents (entry 3 and 5). Similarly, if the aryl group was *ortho*-substituted, the chlorination occurred with only moderate enantioselectivity (entry 8). On the other hand, reactions of *meta*- and *para*-substituted aryl ketenes (entries 7, 9 and 10) and of a heteroaryl ketene (entry 6) as well as naphthalyl ketene (entry 11) generally proceeded with acceptable levels of asymmetric induction in the ranges of 72-95% ee.

***Table 2.*** Catalytic Asymmetric Synthesis of Tertiary α-Chlorocarbonyl Compounds



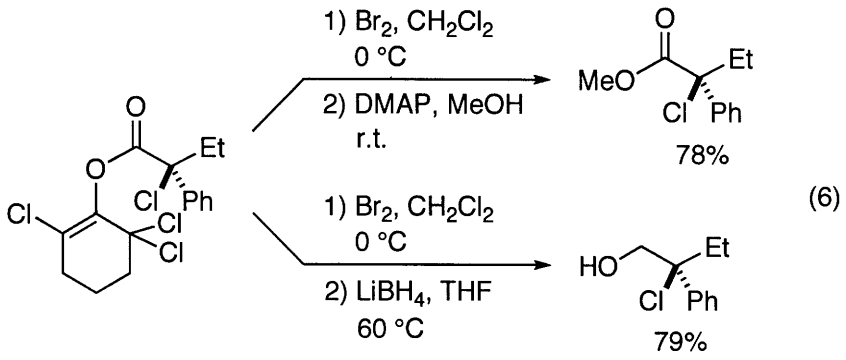

| entry | Ar | R | ee (%) | yield (%) |
|---|---|---|---|---|
| 1 | Ph | Me | 91 | 74 |
| 2 | Ph | Et | 94 | 86 |
| 3 | Ph | *i*-Pr | 47 | 83 |
| 4 | Ph | *i*-Bu | 85 | 76 |
| 5[c] | Ph | Cyp | 65 | 79 |
| 6 | 3-thiophenyl | *i*-Bu | 83 | 62 |
| 7 | 4-$ClC_6H_5$ | Et | 82 | 82 |
| 8 | *o*-tolyl | Et | 67 | 90 |
| 9 | *m*-tolyl | Et | 95 | 88 |
| 10 | 3-$OMeC_6H_5$ | Et | 86 | 82 |
| 11[b] | 6-OMe-2-Naphthyl | Me | 72 | 63 |

[a] All data are the average of two experiements. [b] 7.5% (–)-PPY* was used. [c] Reaction conducted at –78 °C.

The 4-chloro derivative (entry 7) can potentially be further functionalized by a cross-coupling reaction of the aryl chloride. In a similar fashion, the anisole derivatives (entries 10 and 11) can be functionalized by deprotection to the phenol and subsequently used as nucleophiles.

Fully aware that subsequent functionalization of these chlorinated enol esters was of importance, we explored transesterification conditions that would allow access to a more common and useful ester, e.g., a methyl ester. Numerous conditions were examined, including the use of $R_3SnOMe$ reagents that are known to induce transesterification with enol esters.[13] However, use of these types of reagents proved to be ineffective for our hindered enol esters. We have also investigated acid catalyzed transesterification mediated either by Lewis or protic acids, base catalyzed hydrolysis, or reduction conditions without any success. Subsequently, mild conditions were found that allowed for the transesterification to the methyl ester by use of methanol with $K_2CO_3$. Unfortunately, the long reaction time (3.5 days) and moderate yield (48%) prompted us to investigate other alternatives. Our next strategy was to oxidize the enol alkene to generate a more reactive ester (i.e., a hemiacetalate). However, numerous oxidizing conditions were attempted ($OsO_4$/NMO, $O_3$, DDQ etc.) without any success. Gratifyingly, an

acyl transfer reaction with the sterically demanding enol ester was accomplished through activation by bromine. Thus, treatment with $Br_2$ and then a nucleophile furnished a methyl ester or an alcohol (eq 6). Both reactions occurred without any erosion in stereochemical purity.




(6)

*3.2.3. Mechanistic Discussion*

A variety of mechanisms, two of which are illustrated in Figure 1, can be envisioned for the PPY*-catalyzed coupling of ketenes with 2,2,6,6-tetrachlorocyclohexanone to afford tertiary α-chlorocarbonyl compounds. In the top pathway, the key intermediate is a chiral chlorinating agent (*N*-chlorinated PPY*; ion pair **A**), which is formed by reaction of the catalyst with 2,2,6,6-tetrachlorocyclohexanone.[14] Subsequently, a new ion pair (**B**) is produced via addition of $RO^-$ to the ketene. Finally, Cl transfer occurs from the chiral *N*-chlorinated PPY* to the achiral enolate to furnish a new stereocenter with concurrent regeneration of the catalyst.[15]

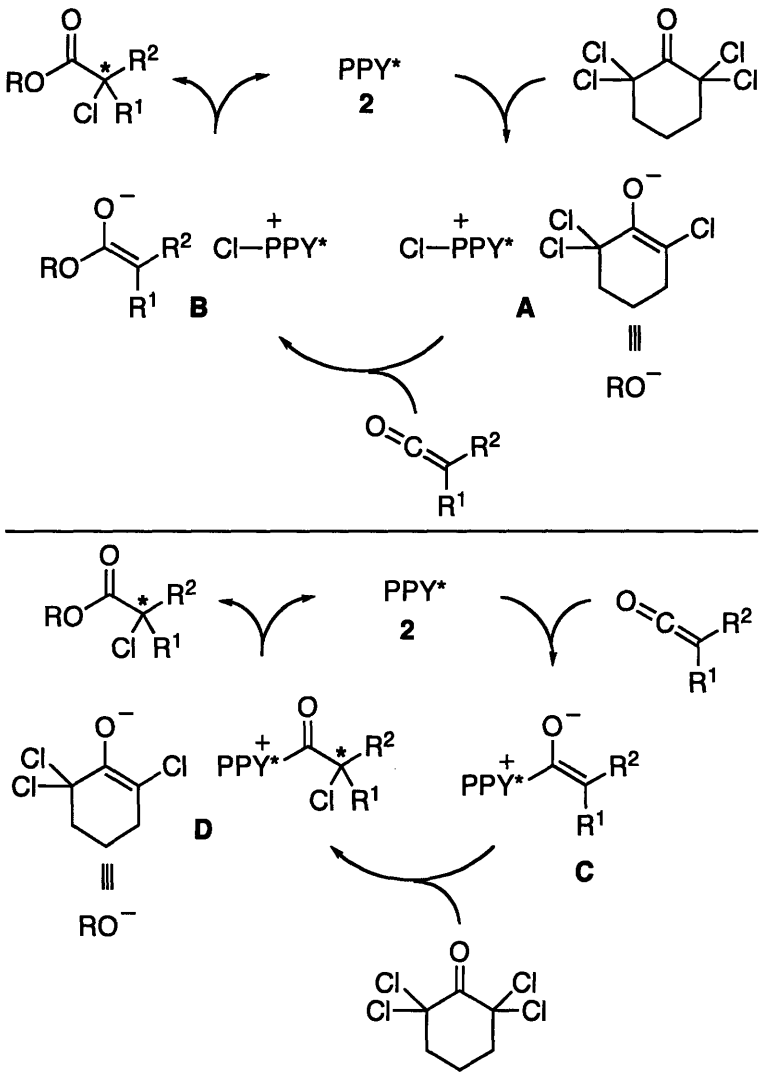



***Figure 1.*** Two of the possible mechanisms for asymmetric chlorinations catalyzed by PPY*: Top: via a chiral chlorinating agent; Bottom: via a chiral enolate.

In an alternative mechanism (bottom of Figure 1), PPY* adds to the ketene to afford a chiral enolate (**C**), which then reacts with the achiral chlorinating agent to furnish a new stereocenter (ion pair **D**). Acyl transfer can then occur to produce the tertiary α-chloroester with concurrent regeneration of the catalyst.[16,17]

Several observations have been made that may be relevant to understanding the mechanism. First, the $^{1}$H NMR spectrum of the reaction between phenyl cyclopentyl ketene and 2,2,6,6-tetrachlorocyclohexanone catalyzed by PPY* at –80 °C in toluene-$d_8$ shows that the resting state of the catalyst during the reaction is the unbound catalyst (i.e., not *N*-chlorinated or *N*-acylated PPY*) (Figure 2).

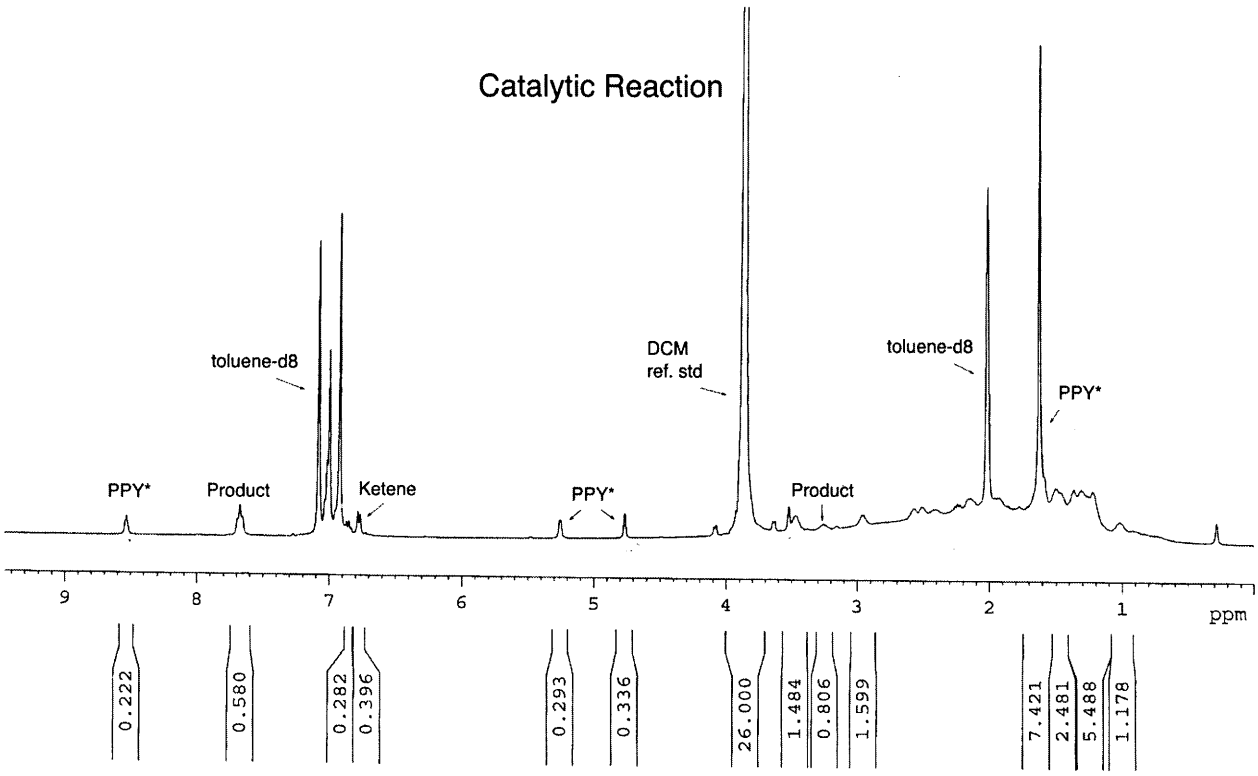
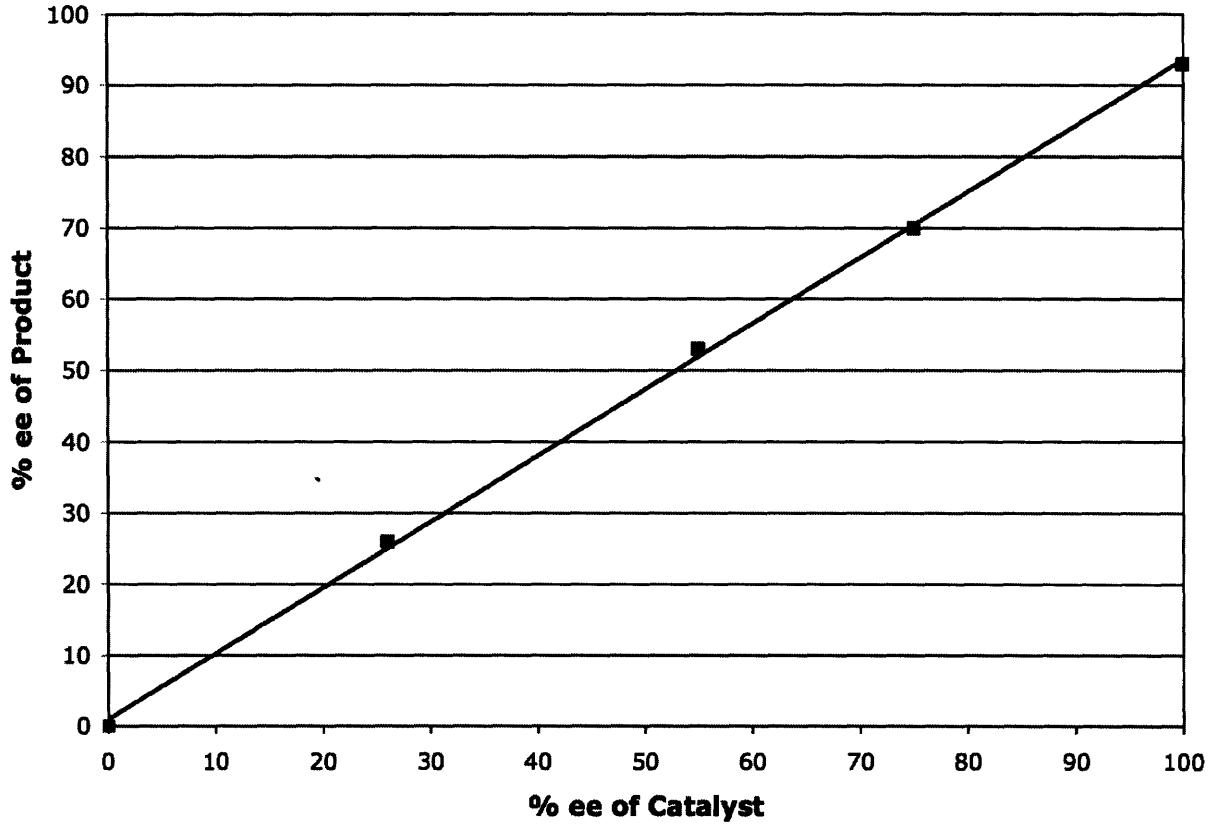



***Figure 2.*** $^1$H NMR spectrum to determine the resting-state of the catalyst. The reaction was performed as a reaction between phenyl cyclopentyl ketene, 2,2,6,6-tetrachlorocyclohexanone, and (–)-PPY* (10 mol%) at –80 to –82 °C in toluene-$d_8$ with DCM as a reference standard.

Second, when (–)-PPY* was mixed with 2,2,6,6-tetrachlorocyclohexanone at –78 °C or at room temperature (in the absence of a ketene), no reaction was observed by $^1$H NMR spectroscopy. Third, all attempts to trap the proposed enolate of the ion pair **A** failed: No reaction was observed upon addition of MeOTf, TMSOTf, TMSCl, isopropanol, or water during the stoichiometric reaction between PPY* and 2,2,6,6-tetrachlorocyclohexanone in toluene-$d_8$ at various different temperatures. Fourth, the enantioselectivity of the product correlated linearly with catalyst ee, which was consistent with the presence of one catalyst molecule in the stereochemistry-determining step of the reaction (Chart 1).[18]

*Chart 1.* Catalyst% ee vs Product% ee[a]




[a] This reaction was followed using *m*-tolyl ethyl ketene in Table 2, entry 9.

However, due to the rapid reaction rate, attempts to determine the rate law proved to be difficult either by $^1$H NMR or React-IR.

Although we have not ruled out reaction via a chiral chlorinating agent (top of Figure 1), on the basis of circumstantial evidence such as the stereochemical outcome and the reactivity profile, the chiral-enolate pathway is currently favored (bottom of Figure 1). Specifically, (1) The absolute stereochemistry at the α-center is the opposite of that predicted for a Brønsted acid catalyzed reactions.[15] (2) Unlike in reactions that involve Brønsted acid catalysis by protonated PPY*, the hindered ketenes are not useful substrates for our catalytic asymmetric chlorinations.

*3.2.4. Determination of Absolute Configuration*

The absolute configuration of the reaction product was established by x-ray crystallography of a representative compound (Table 2, entry 11) that was crystallized from ethanol at 0 °C.

## 3.3 Conclusions

We have developed a catalytic asymmetric method for the synthesis of tertiary α-chloroesters that complements recent progress in the generation of secondary α-halocarbonyl compounds. Additionally, we have demonstrated that commercially available 2,2,6,6-tetrachlorocyclohexanone is an efficient chlorinating reagent in our reaction conditions. It has been shown that the tertiary α-chloro enolesters are surprisingly robust; however, they can be derivatized into useful intermediates such as methyl esters and alcohols without erosion of enantioselectivity.

## 3.4 Experimental Procedures

*3.4.1. General*

All air- or moisture-sensitive manipulations were carried out under nitrogen with standard syringe/Schlenk techniques or in a glovebox.

Prior to use, toluene, $CH_2Cl_2$, and $Et_2O$ were purified by passage through a neutral alumina column under argon. 2,2,6,6-Tetrachlorocyclohexanone (Aldrich) was recrystallized from pentane/$CH_2Cl_2$. Bromine (Alfa Aesar), methanol (anhydrous; Aldrich), lithium borohydride (Aldrich), and DMAP (Aldrich) were used as received. PPY* was prepared and resolved as previously reported.[19] The ketenes were prepared according to literature procedures.[20]

$^1H$ NMR spectra were recorded on either Varian Mercury 300 or INOVA 500 spectrometer (300 or 500 MHz) at ambient temperature. $^{13}C$ NMR spectra were obtained with complete proton decoupling on a Varian INOVA 501 spectrometer (126 MHz) at ambient temperature.

Infrared spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. Optical rotations were measured on a Perkin Elmer Model 241 polarimeter.

*3.4.2. Catalytic Asymmetric Synthesis of Tertiary α-Chloroesters*

**General.** Three solutions were prepared in a glovebox: the ketene (1.0 equiv) in a flask, (+)-PPY* (3 mol%) in a vial, and 2,2,6,6-tetrachlorocyclohexanone (1.2 equiv) in a vial. All other manipulations were conducted outside of a glovebox. Two solvent systems were employed: toluene only (entries 2, 9, 10, and 11) and ~17:1 $Et_2O$:toluene (entries 1, 3-8).

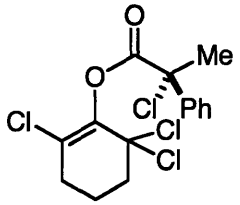



**Table 2, entry 1.** A solution of phenyl methyl ketene (50.0 mg, 0.38 mmol) in $Et_2O$ (8.0 mL) was cooled to –78 °C. A solution of 2,2,6,6-tetrachlorocyclohexanone (107 mg, 0.45 mmol) in $Et_2O$ (1.0 mL) was added in one portion, followed by the rapid (~15 seconds) dropwise addition of a solution of (+)-PPY* (4.3 mg, 11 μmol) in a 1:1 mixture of $Et_2O$ and toluene (1.0 mL). The reaction mixture was stirred at –78 °C for 45 min, and then the solvent was removed, and the desired product was isolated by flash chromatography (5% EtOAc/hexanes). Yield: 105 mg (76%) of a colorless oil. HPLC analysis: 90% ee [Daicel CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 29.4 min (minor), 47.0 min (major)].

Second run with (–)-PPY* (same scale as above). Yield: 100 mg (72%), 91% ee.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.70-7.69 (m, 2H), 7.43-7.34 (m, 3H), 2.72-2.70 (m, 2H), 2.59 (t, J=6.0 Hz, 2H), 2.31 (s, 3H), 2.01-1.96 (m, 2H).

$^{13}$C NMR (76 MHz, $CDCl_3$) δ 166.6, 140.5, 139.6, 128.9, 128.8, 128.5(x2), 126.7(x2), 83.9, 69.6, 45.5, 32.8, 29.7, 20.4. FTIR (NaCl) 3063, 2942, 1772, 1447, 1130, 756, 695 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{15}H_{14}Cl_4NaO_2$ (M+Na) 388.9640, found 388.9650. $[\alpha]^{20}_D$ +22 (*c* 0.0040, $CH_2Cl_2$; 91% ee from (–)-PPY*).

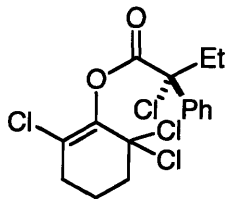



**Table 2, entry 2.** A solution of phenyl ethyl ketene (70.0 mg, 0.48 mmol) in toluene (23 mL) was cooled to –78 °C. A solution of 2,2,6,6-tetrachlorocyclohexanone (136 mg, 0.58 mmol) in toluene (2.0 mL) was added in one portion, followed by the rapid (~15 seconds) dropwise addition of a solution of (+)-PPY* (5.4 mg, 14 μmol) in toluene (2.0 mL). The reaction mixture was

stirred at –78 °C for 45 min, and then the solvent was removed, and the desired product was isolated by flash chromatography (5% EtOAc/hexanes). Yield: 160 mg (87%) of a colorless oil. HPLC analysis: 94% ee [Daicel CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 27.9 min (major), 50.6 min (minor)].

Second run with (–)-PPY* (same scale as above). Yield: 156 mg (85%), 94% ee.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 2H), 7.42-7.38 (m, 2H), 7.36-7.33 (m, 1H), 2.73-2.64 (m, 2H), 2.59 (t, J=6.0 Hz, 2H), 2.52 (qq, J=7.0, 7.5 Hz, 2H), 2.04-1.92 (m, 2H), 1.10 (t, J=7.0 Hz, 3H). $^{13}$C NMR (76 MHz, $CDCl_3$) δ 166.2, 140.4, 138.1, 128.8, 128.6, 128.4(x2), 127.1(x2), 83.9, 75.4, 45.6, 34.4, 32.9, 20.4, 9.3. FTIR (NaCl) 3029, 2942, 1772, 1657, 1448, 1161, 696 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{16}H_{16}Cl_4NaO_2$ (M+Na) 402.9797, found 402.9806. $[\alpha]^{20}_D$ –36 (*c* 0.0027, $CH_2Cl_2$; 94% ee from (+)-PPY*).

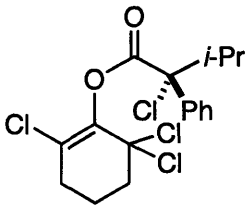



**Table 2, entry 3.** phenyl isopropyl ketene (50.0 mg, 0.38 mmol) was dissolved in $Et_2O$ (8.0 mL) and tetrachlorocyclohexanone (106 mg, 0.45 mmol) was in $Et_2O$ (1.0 mL). (+)-PPY* (4.30 mg, 11.3 μmol) was dissolved in a 1:1 mixture of $Et_2O$ and toluene (1.0 mL). The reaction mixture was stirred at -78 °C to room temperature over 20 hrs. The desired product was purified and isolated by flash silica column chromatography (5.0% EtOAc / hexanes). Yield: 120 mg (81%) of a colorless oil. HPLC analysis: 45% ee [Daicel CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 20.8 min (minor), 34.5 min (major)].

Second run with (–)-PPY*: same scale as above. Yield: 125 mg (84%), 49% ee.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 3.17 (septet, J=6.5 Hz, 1H) 2.68 (m, 2H), 2.54 (m, 2H), 1.97 (m, 2H), 1.27 (d, J=8.0 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H). $^{13}$C NMR (76 MHz, $CDCl_3$) δ 166.2, 140.5, 137.3, 128.7, 128.6, 128.3(x2), 127.7(x2), 83.9, 81.4, 45.7, 36.9, 33.0, 20.5, 19.1, 17.3. FTIR (NaCl) 3061, 2942, 1771, 1655, 1447, 1158, 697 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{18}Cl_4O_2$ (M+Na) 416.9961, found 416.9954. $[\alpha]^{20}_D$ – 20.8 (*c* 0.0041, $CH_2Cl_2$, 44% ee with (+)-PPY*).

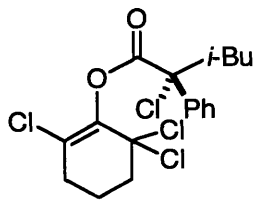



**Table 2, entry 4.** A solution of phenyl isobutyl ketene (60.0 mg, 0.34 mmol) in $Et_2O$ (7.1 mL) was cooled to –78 °C. A solution of 2,2,6,6-tetrachlorocyclohexanone (97.4 mg, 0.41 mmol) in $Et_2O$ (1.0 mL) was

added in one portion, followed by the rapid (~15 seconds) dropwise addition of a solution of (+)-PPY* (3.9 mg, 10 μmol) in a 1:1 mixture of $Et_2O$ and toluene (1.0 mL). The reaction mixture was stirred at –78 °C for 2 h, and then the solvent was removed, and the desired product was isolated by flash chromatography (5% EtOAc/hexanes). Yield: 110 mg (78%) of a colorless oil. HPLC analysis: 84% ee [Daicel CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 7.10 min (major), 10.3 min (minor)].

Second run with (–)-PPY* (same scale as above). Yield: 105 mg (74%), 85% ee.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.70-7.69 (m, 2H), 7.41-7.32 (m, 3H), 2.74-2.64 (m, 2H), 2.62-2.56 (m, 2H), 2.55 (dd, J=5.0, 10.0 Hz, 1H), 2.42 (dd, J=5.5, 9.5 Hz, 1H), 2.10-1.94 (m, 2H), 1.87 (septet, J=5.0 Hz, 1H), 0.99 (d, J=7.0 Hz, 3H), 0.78 (d, J=6.5 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.5, 140.5, 138.3, 128.7, 128.5, 128.3(x2), 127.2(x2), 83.9, 74.4, 49.5, 45.7, 33.0, 25.5, 24.6, 24.4, 20.5. FTIR (NaCl) 3029, 2958, 1770, 1699, 1447, 1182, 697 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{18}H_{20}Cl_4NaO_2$ (M+Na) 431.0115, found 431.0131. $[\alpha]^{20}_D$ –12 (*c* 0.0045, $CH_2Cl_2$; 84% ee from (+)-PPY*).

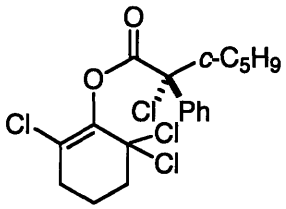



**Table 2, entry 5.** A solution of phenyl cyclopentyl ketene (60.0 mg, 0.32 mmol) in $Et_2O$ (6.5 mL) was cooled to –78 °C. A solution of 2,2,6,6-tetrachlorocyclohexanone (91.2 mg, 0.39 mmol) in $Et_2O$ (1.0 mL) was added in one portion, followed by the rapid (~15 seconds) dropwise addition of a solution of (+)-PPY* (6.1 mg, 16 μmol) in a 1:1 mixture of $Et_2O$ and toluene (1.0 mL). The reaction mixture was allowed to slowly warm to r.t. overnight (total reaction time: 20 h). The solvent was removed, and the desired product was isolated by flash chromatography (5% EtOAc/hexanes). Yield: 111 mg (82%) of a colorless oil. HPLC analysis: 68% ee [Daicel CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 15.6 min (major), 29.7 min (minor)].

Second run with (–)-PPY* (same scale as above). Yield: 104 mg (76%), 62% ee.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.75-7.73 (m, 2H), 7.39-7.35 (m, 2H), 7.34-7.30 (m, 1H), 3.40 (q, J=8.0 Hz, 1H), 2.73-2.63 (m, 2H), 2.55 (t, J=6.0 Hz, 2H), 2.14-2.09 (m, 1H), 2.01-1.93 (m, 2H), 1.92-1.83 (m, 1H), 1.75-1.44 (m, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.2, 140.5, 138.4, 128.7, 128.5, 128.3(x2), 127.6(x2), 83.9, 80.2, 47.8, 45.6, 32.9, 29.4, 28.5, 26.6, 26.3, 20.5. FTIR (NaCl) 2960, 2870, 1770, 1657, 1447, 1155, 699 cm$^{-1}$. HRMS (ESI, m/e) calcd for

$C_{19}H_{20}Cl_4NaO_2$ (M+Na) 443.0115, found 443.0129. $[\alpha]^{20}_D$ +23 (*c* 0.0042, $CH_2Cl_2$; 62% ee from (–)-PPY*).

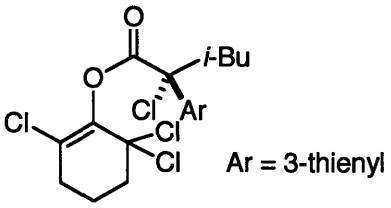



**Table 2, entry 6.** A solution of 3-thienyl isobutyl ketene (50.0 mg, 0.28 mmol) in $Et_2O$ (5.2 mL) was cooled to –78 °C. A solution of 2,2,6,6-tetrachlorocyclohexanone (78.0 mg, 0.33 mmol) in $Et_2O$ (1.0 mL) was added in one portion, followed by the rapid (~15 seconds) dropwise addition of a solution of (+)-PPY* (3.1 mg, 8.3 μmol) in a 1:1 mixture of $Et_2O$ and toluene (1.0 mL). The reaction mixture was stirred at –78 °C for 2 h, and then the solvent was removed, and the desired product was isolated by flash chromatography (5% EtOAc/hexanes). Yield: 70 mg (61%) of a colorless oil. HPLC analysis: 84% ee [Daicel CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 12.8 min (major), 17.3 min (minor)].

Second run with (–)-PPY* (same scale as above). Yield: 72 mg (63%), 81% ee.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J=0.5, 1.5 Hz, 1H), 7.31 (dd, J=3.0, 2.0 Hz, 1H), 7.26 (dd, J=0.5, 4.0 Hz, 1H), 2.73-2.70 (m, 2H), 2.59 (t, J=6.0 Hz, 2H), 2.55 (dd, J=5.5, 9.5 Hz, 1H), 2.40 (dd, J=6.0, 9.0 Hz, 1H), 2.02-1.98 (m, 2H), 1.96-1.91 (m, 1H), 1.00 (d, J=7.0 Hz, 3H), 0.88 (d, J=6.5 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.9, 140.5, 140.1, 128.7, 127.3, 126.0, 124.2, 83.9, 71.5, 49.3, 45.6, 33.0, 25.8, 24.4, 24.3, 20.5. FTIR (NaCl) 3116, 2958, 1772, 1658, 1440 1160, 743 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{16}H_{18}Cl_4NaO_2S$ (M+Na) 436.9782, found 436.9674. $[\alpha]^{20}_D$ –15 (*c* 0.0025, $CH_2Cl_2$; 84% ee from (+)-PPY*).

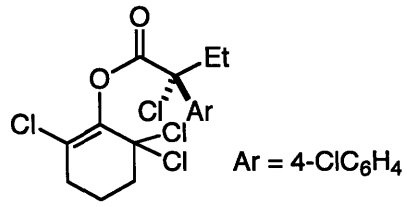



**Table 2, entry 7.** A solution of 4-chlorophenyl ethyl ketene (60.0 mg, 0.33 mmol) in $Et_2O$ (7.3 mL) was cooled to –78 °C. A solution of 2,2,6,6-tetrachlorocyclohexanone (94.0 mg, 0.40 mmol) in $Et_2O$ (1.0 mL) was added in one portion, followed by the rapid (~15 seconds) dropwise addition of a solution of (+)-PPY* (3.7 mg, 10 μmol) in a 1:1 mixture of $Et_2O$ and toluene (1.0 mL). The reaction mixture was stirred at –78 °C for 2 h, and then the solvent was removed, and the desired product was isolated by flash chromatography (5% EtOAc/hexanes). Yield: 110 mg (80%) of a colorless oil. HPLC analysis: 82% ee [Daicel

CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 15.1 min (major), 49.6 min (minor)].

Second run with (–)-PPY* (same scale as above). Yield: 115 mg (83%), 82% ee.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.63-7.60 (m, 2H), 7.38-7.36 (m, 2H), 2.75-2.58 (m, 3H), 2.60 (t, J=6.5 Hz, 2H), 2.47 (qq, J=7.5, 7.0 Hz, 1H), 2.03-1.94 (m, 2H), 1.08 (t, J=7.5 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.8, 140.4, 136.8, 134.7, 128.9, 128.7(x2), 128.6(x2), 83.9, 74.7, 45.6, 34.3, 32.9, 20.4, 9.2. FTIR (NaCl) 2941, 1773, 1658, 1491, 1161, 750 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{16}H_{15}Cl_5NaO_2$ (M+Na) 436.9407, found 436.9427. $[\alpha]^{20}_D$ –27 (*c* 0.0039, $CH_2Cl_2$; 82% ee from (+)-PPY*).

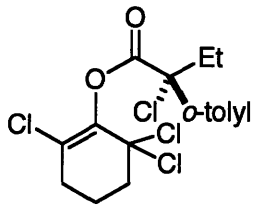



**Table 2, entry 8.** A solution of *o*-tolyl ethyl ketene (50.0 mg, 0.31 mmol) in $Et_2O$ (6.7 mL) was cooled to –78 °C. A solution of 2,2,6,6-tetrachlorocyclohexanone (88.0 mg, 0.38 mmol) in $Et_2O$ (1.0 mL) was added in one portion, followed by a solution of (+)-PPY* (3.5 mg, 9.4 μmol) in a 1:1 mixture of $Et_2O$ and toluene (1.0 mL). The reaction mixture was stirred at –78 °C for 3 h, and then the solvent was removed, and the desired product was isolated by flash chromatography (5% EtOAc/hexanes). Yield: 110 mg (89%) of a colorless oil. HPLC analysis: 68% ee [Daicel CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 19.7 min (major), 37.7 min (minor)].

Second run with (–)-PPY* (same scale as above). Yield: 112 mg (90%), 65% ee.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.73-7.71 (m, 1H), 7.27-7.20 (m, 3H), 2.80-2.63 (m, 4H), 2.57 (t, J=6.5 Hz, 2H), 2.52 (s, 3H), 2.06-1.94 (m, 2H), 1.11 (t, J=7.0 Hz, 3H).
$^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.1, 140.3, 137.1, 136.0, 132.5, 128.7, 127.5, 125.9(x2), 84.1, 75.6, 45.9, 33.2, 33.1, 22.2, 20.3, 9.35. FTIR (NaCl) 2942, 1771, 1656, 1453, 1127, 740 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{18}Cl_4O_2$ (M+Na) 416.9959, found 416.9961. $[\alpha]^{20}_D$ +30 (*c* 0.0033, $CH_2Cl_2$; 65% ee from (–)-PPY*).

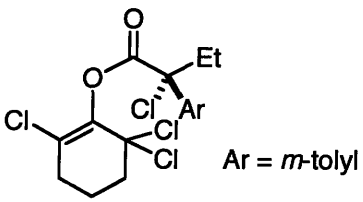
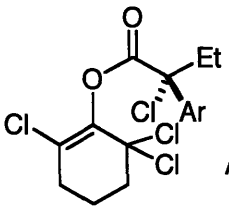



**Table 2, entry 9.** A solution of *m*-tolyl ethyl ketene (50.0 mg, 0.31 mmol) in toluene (13.4 mL) was cooled to –78 °C. A solution of

2,2,6,6-tetrachlorocyclohexanone (88.0 mg, 0.38 mmol) in toluene (2.0 mL) was added in one portion, followed by the rapid (~15 seconds) dropwise addition of a solution of (+)-PPY* (3.5 mg, 9.4 μmol) in toluene (2.0 mL). The reaction mixture was stirred at –78 °C for 3 h, and then the solvent was removed, and the desired product was isolated by flash chromatography (5% EtOAc/hexanes). Yield: 113 mg (91%) of a colorless oil. HPLC analysis: 95% ee [Daicel CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 14.3 min (major), 23.0 min (minor)].

Second run with (–)-PPY* (same scale as above). Yield: 105 mg (85%), 94% ee.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.49-7.45 (m, 2H), 7.29-7.25 (m, 1H), 7.16-7.14 (m, 1H), 2.75-2.64 (m, 3H), 2.58 (t, J=6.0 Hz, 2H), 2.48 (qq, J=7.0, 7.5 Hz, 1H), 2.37 (s, 3H), 2.03-1.94 (m, 2H), 1.09 (t, J=7.5 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.3, 140.4, 138.0, 129.3, 128.8, 128.2, 127.9(x2), 124.1, 84.0, 75.5, 45.7, 34.5, 33.0, 21.7, 20.5, 9.3. FTIR (NaCl) 3055, 2944, 1771, 1440, 1265, 1161, 739 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{18}Cl_4NaO_2$ (M+Na) 416.9954, found 416.9971. $[\alpha]^{20}_D$ –35 (*c* 0.0011, $CH_2Cl_2$; 95% ee from (+)-PPY*).



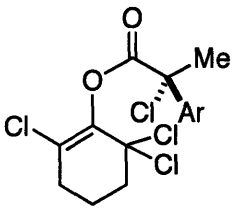
Ar = 3-(MeO)$C_6H_4$

**Table 2, entry 10.** A solution of *m*-methoxyphenyl ethyl ketene (50.0 mg, 0.28 mmol) in toluene (11.7 mL) was cooled to –78 °C. A solution of 2,2,6,6-tetrachlorocyclohexanone (80.0 mg, 0.34 mmol) in toluene (2.0 mL) was added in one portion, followed by the rapid (~15 seconds) dropwise addition of a solution of (+)-PPY* (3.2 mg, 8.5 μmol) in toluene (2.0 mL). The reaction mixture was stirred at –78 °C for 3 h, and then the solvent was removed, and the desired product was isolated by flash chromatography (5% EtOAc/hexanes). Yield: 96 mg (82%) of a colorless oil. HPLC analysis: 87% ee [Daicel CHIRALCEL OJ column; 0.9 mL/min; solvent system: 15% *iso*-propanol/hexanes; retention times: 24.8 min (major), 48.7 min (minor)].

Second run with (–)-PPY* (same scale as above). Yield: 95 mg (81%), 85% ee.

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 3H), 6.89-6.87 (m, 1H), 3.83 (s, 3H), 2.73-2.64 (m, 3H), 2.58 (t, J=6.3 Hz, 2H), 2.53-2.47 (m, 1H), 2.20-1.94 (m, 2H), 1.09 (t, J=7.2 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.2, 159.6, 140.4, 139.6, 129.4, 128.8, 119.4, 114.2, 113.2, 83.9, 75.2, 55.6, 45.6, 34.5, 33.0, 20.4, 9.3. FTIR (NaCl) 2942, 1771, 1601, 1433, 1161,

697 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{17}H_{18}Cl_4NaO_3$ (M+Na) 432.9908, found 432.9917. $[\alpha]^{20}_D$ +20 (*c* 0.0025, $CH_2Cl_2$; 85% ee from (–)-PPY*).

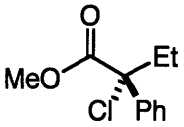


Ar = 6-OMe-2-naphthyl

**Table 2, entry 11.** 6-methoxy-2-naphthyl methyl ketene (60.0 mg, 0.28 mmol) was dissolved in toluene (11.7 mL) and tetrachlorocyclohexanone (80.0 mg, 0.34 mmol) was in toluene (2.0 mL). (+)-PPY* (8.00 mg, 21.2 μmol) was dissolved in toluene (2.0 mL). The reaction mixture was stirred at -78 °C to room temperature over 20 hrs. The desired product was purified and isolated by flash silica column chromatography (100% $CH_2Cl_2$). Yield: 81 mg (64%) of colorless oil. HPLC analysis: 73% ee [Daicel CHIRALCEL AS-H column; 1.0 mL/min; solvent system: 1% *iso*-propanol/hexanes; retention times: 12.9 min (major), 19.1 min (minor)].

Second run with (–)-PPY*: same scale as above. Yield: 78 mg (61%), 70% ee.

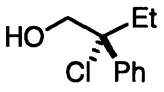
$^1H$ NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J=2.0 Hz, 1H), 7.79-7.72 (m, 3H), 7.18 (dd, J=2.5, J=6.5 Hz, 1H), 7.14 (d, J=2.5 Hz, 1H), 3.84 (s, 3H), 2.70 (m, 2H), 2.59 (m, 2H), 2.41 (s, 3H), 1.99 (m, 2H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 166.7, 158.6, 140.6, 134.8, 134.5, 130.2, 128.9, 128.3, 127.2, 125.5, 125.4, 119.5, 105.7, 83.9, 70.0, 55.6, 45.6, 32.9, 29.6, 20.5. FTIR (NaCl) 3055, 2987, 1712, 1266, 896, 742 $cm^{-1}$. HRMS (ESI, m/e) calcd for $C_{20}H_{18}Cl_4O_3$ (M+Na) 468.9902, found 468.9896. $[\alpha]^{20}_D$ –7.2 (*c* 0.00050, $CH_2Cl_2$, 70% ee (–)-PPY*).




**Eq 5, transesterification.** The enol ester (39.0 mg, 0.10 mmol; 94% ee) was dissolved in $CH_2Cl_2$ (2.0 mL), and the resulting solution was cooled to 0 °C. Bromine (5.2 μL, 0.10 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h. The solvent was removed, and then the residue was dissolved in MeOH (1.5 mL). DMAP (37.0 mg, 0.31 mmol) was added, and the mixture was stirred for 20 h at r.t. The desired product was purified by flash chromatography (10% EtOAc/hexanes). Yield: 17 mg (78%) of a colorless oil. GC analysis: 93% ee [CP-Chirasil-Dex CB column; 100 °C (2 min), 1.0 °C/min to 120 °C; 12.62 psi He; retention times: 20.2 min (major), 20.5 min (minor)].

Second run: same scale as above. Yield: 17 mg (78%), 94% ee.

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.48-7.36 (m, 3H), 3.78 (s, 3H), 2.51 (sextet, J=6.9 Hz, 1H), 2.39 (sextet, J=6.9 Hz, 1H), 0.99 (t, J=7.5 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.3, 139.6, 128.6(x2), 128.5, 126.4(x2), 75.8, 53.6, 34.9, 9.4. FTIR (NaCl) 2953, 1738, 1447, 1248, 697 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{11}H_{13}ClNaO_2$ (M+Na) 235.0496, found 235.0504. $[\alpha]^{20}_D$ –23 (*c* 0.00050, $CH_2Cl_2$; 93% ee).




**Eq. 5, reduction.** The enol ester (50.0 mg, 0.13 mmol; 93% ee) was dissolved in $CH_2Cl_2$ (2.5 mL), and the resulting solution was cooled to 0 °C. Bromine (6.7 μL, 0.13 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h. The solvent was removed, and then the residue was dissolved in THF (2.5 mL). $LiBH_4$ (29.0 mg, 1.31 mmol) was added, and the mixture was stirred for 5 h at 60 °C. The reaction mixture was cooled to 0 °C, and then water (1 mL) was added. The product was extracted with EtOAc (3 x 30 mL), and the combined extracts were dried over $MgSO_4$. The desired product was isolated by flash chromatography (25% EtOAc/hexanes). Yield: 19 mg (79%) of a colorless oil. HPLC analysis: 92% ee [Daicel CHIRALCEL OD-H column; 1.0 mL/min; solvent system: 1% hexanes/hexanes; retention times: 17.0 min (minor), 18.8 min (major)].

Second run: same scale as above. Yield: 19 mg (79%), 94% ee.

$^1$H NMR (300 MHz, $C_6D_6$) δ 7.38-7.35 (m, 2H), 7.11-6.99 (m, 3H), 3.70 (dd, J=6.0, 5.7 Hz, 1H), 3.61 (dd, J=6.0, 7.2 Hz, 1H), 2.09 (sextet, J=7.2 Hz, 1H), 1.97 (sextet, J=7.2 Hz, 1H), 1.52 (t, J=6.6 Hz, 1H), 0.79 (t, J=7.2 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 140.3, 128.6(x2), 128.0, 127.1(x2), 71.4, 66.1, 33.2, 9.1. FTIR (NaCl) 3398, 2974, 1494, 1445, 1055, 698 cm$^{-1}$. HRMS (ESI, m/e) calcd for $C_{10}H_{13}ClNaO$ (M+Na) 207.0547, found 207.0554. $[\alpha]^{20}_D$ –7.1 (*c* 0.0015, $CH_2Cl_2$; 92% ee).

**Chart 1. Product% ee vs Catalyst% ee.**

The procedure was followed for *m*-tolyl ethyl ketene. Catalyst with 26% ee furnished α-chloroester with 26% ee (85% yield). Catalyst with 55% ee furnished α-chloroester with 53% ee (81% yield). Catalyst with 75% ee furnished α-chloroester with 70% ee (87% yield).

## 3.5 References and Notes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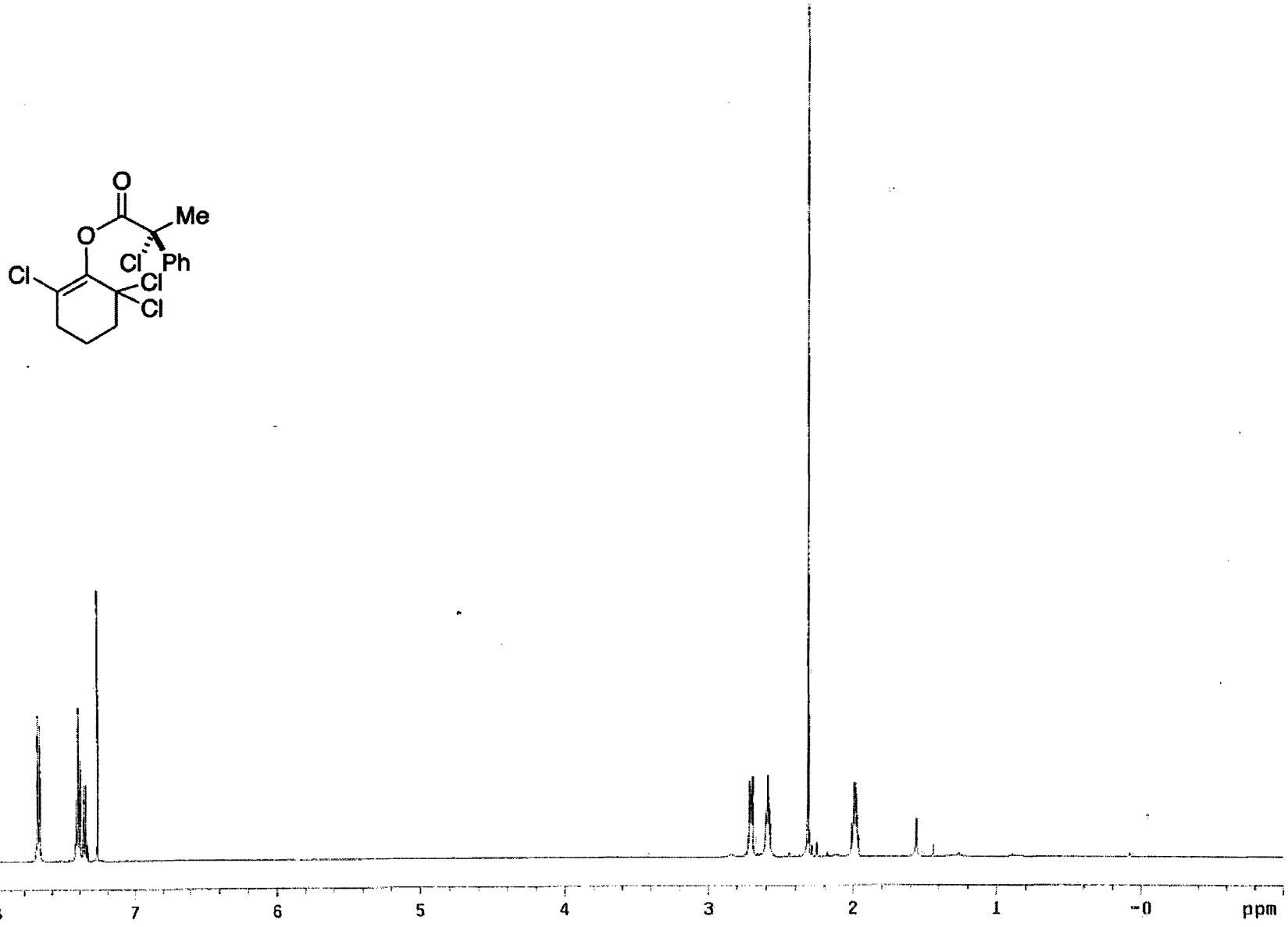
7. (a) McMorris, T. C.; Staake, M. D.; Kelner, M. J. *J. Org. Chem.* **2004**, *69*, 619-623. (b) Jung, M. E.; Parker, M. H. *J. Org. Chem.* **1997**, *62*, 7094-7095.
8. The initial reaction screening was done by Dr. Kevin McCauley.
9. Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 2-5.
10. (a) Laskovics, F. M.; Schulman, E. M. *J. Am. Chem. Soc.* **1977**, *99*, 6672-6677. (b) Laskovics, F. M.; Schulman, E. M. *Tetrahdron Lett.* **1977**, *18*, 759-762. (c) Hexachloroacetone is available from Aldrich ($13.80/50g).
11. 2,2,6,6,-Tetrachlorocyclohexanone is available from Aldrich ($55.00/5g).
12. See Reference 3. When we apply Lectka's method to the chlorination of phenyl ethyl ketene, the desired ester is produced in 30% yield and 5% ee.
13. Otera, J. *Chem. Rev.* **1993**, *93*, 1449-1470. (b) Orita, A.; Mitsutome, A.; Otera, J. *J. Org. Chem.* **1998**, *63*, 2420-2421. (c) Yanagisawa, A.; Goudu, R.; Arai, T. *Org. Lett.* **2004**, *6*, 4281-4283.
14. N-chloropyridines are known. For example, see: Smith, J. R. L.; McKeer, L. C.; Taylor, J. M. J. *Chem. Soc., Perkin Trans. II* **1987**, 1533-1537.
15. This mechanism resembles the Brønsted-acid pathway that we have proposed for certain asymmetric additions to ketenes that are catalyzed by PPY* (i.e., Cl takes the place of H). For example, see: Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176-6177.
16. We have suggested that PPY* and related compounds serve as nucleophilic catalysts for several reactions that involve ketenes. For leading references, see: Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542–547.
17. Lectka favors a chiral-enolate pathway for his benzoylquinine-catalyzed asymmetric synthesis of secondary α-chloroesters from ketenes (see reference 3).

18. For a review of nonlinear effects in asymmetric catalysis, see: Kagan, H. B.; Luukas, T. O. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 4.1.
19. Ruble, J. C.; Fu. G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532-11533.
20. (a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006-10007. Allen, A. D.; Baigrie, L. M.; Gong, L.; Tidwell, T. T. *Can. J. Chem.* **1991**, *69*, 138-145. (b) Ruble, J. C.; Fu. G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532-11533.

## 3.6. $^{1}$H NMR for Selected Compounds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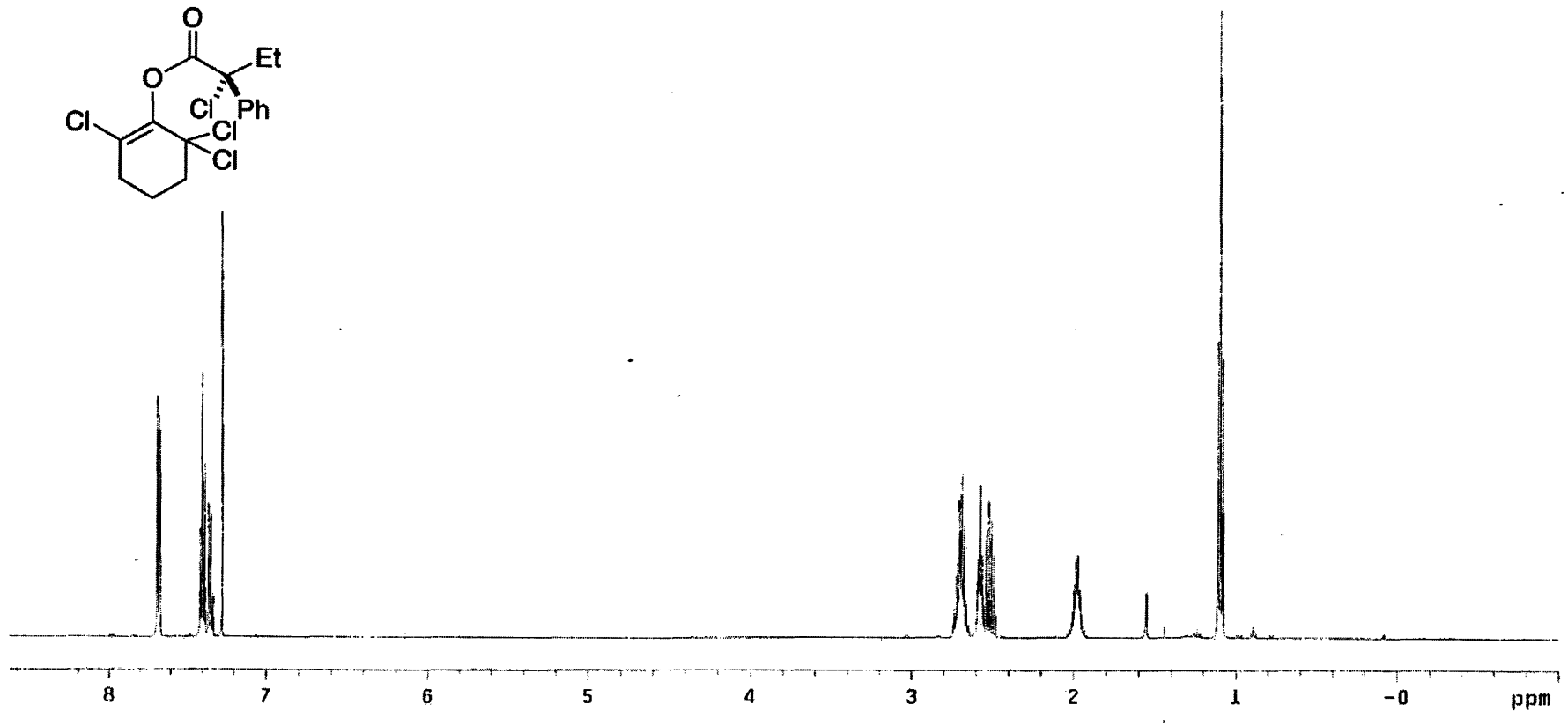
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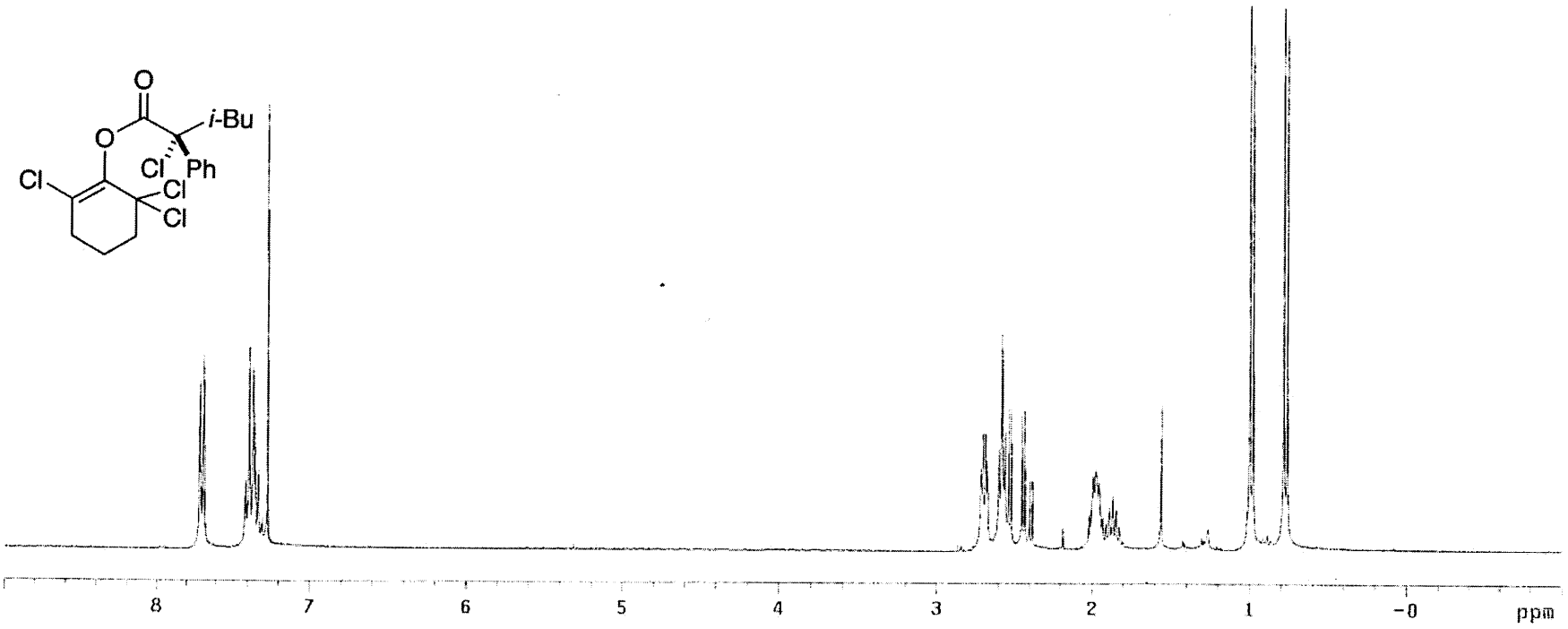
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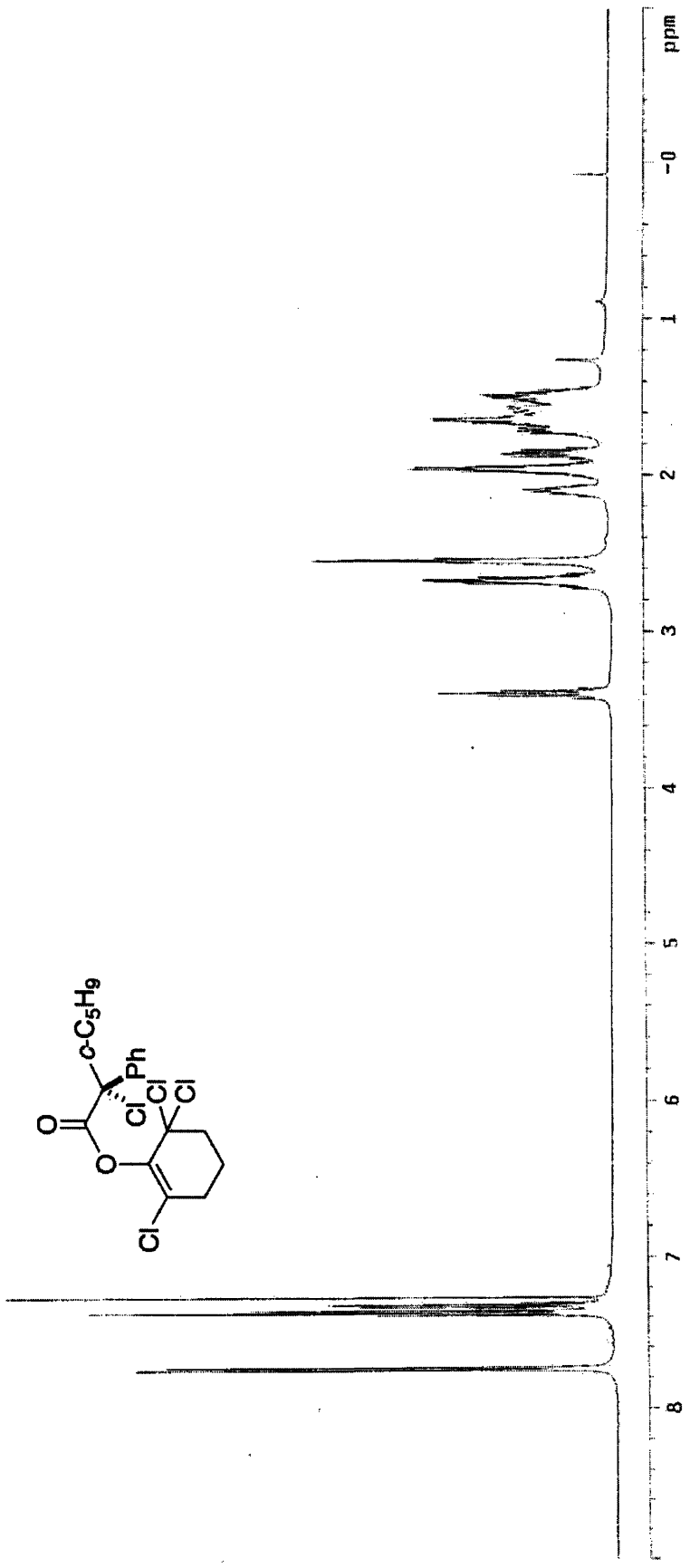
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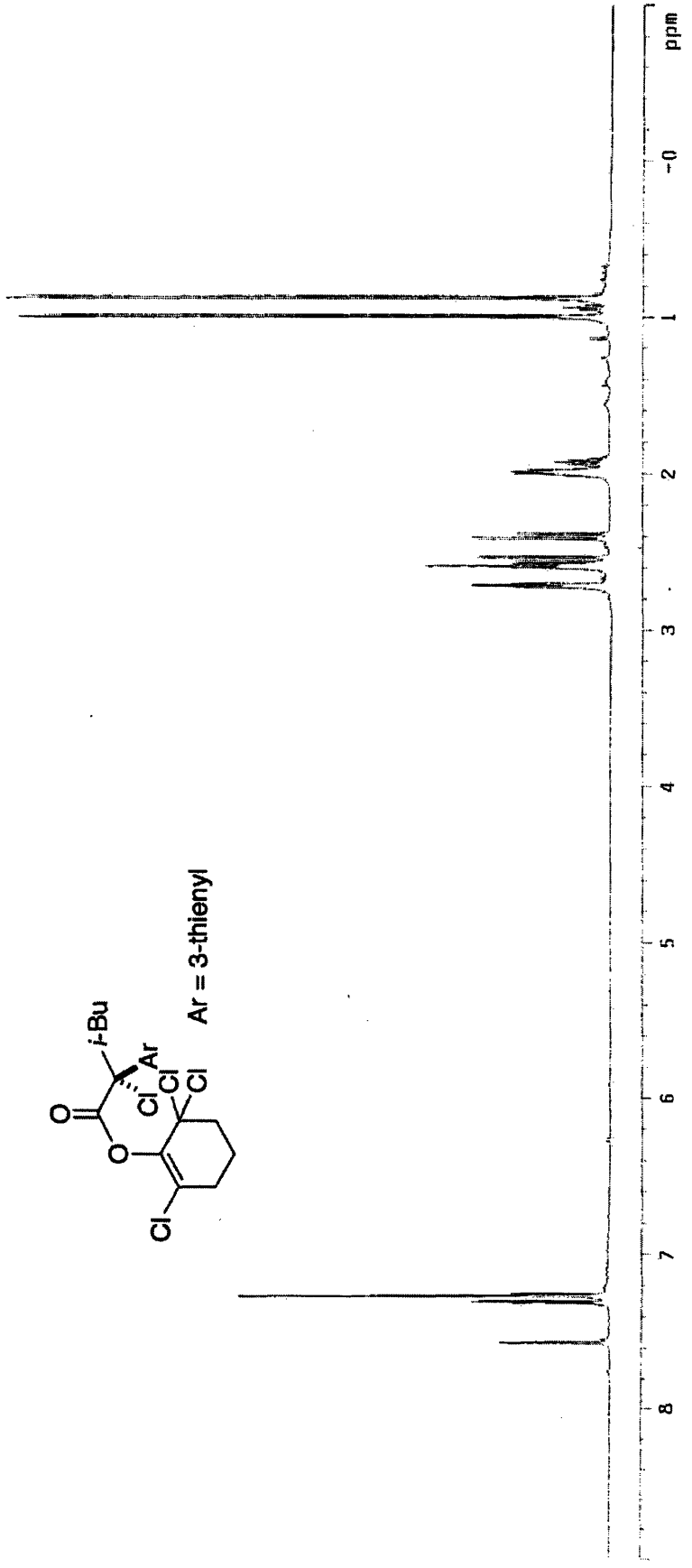
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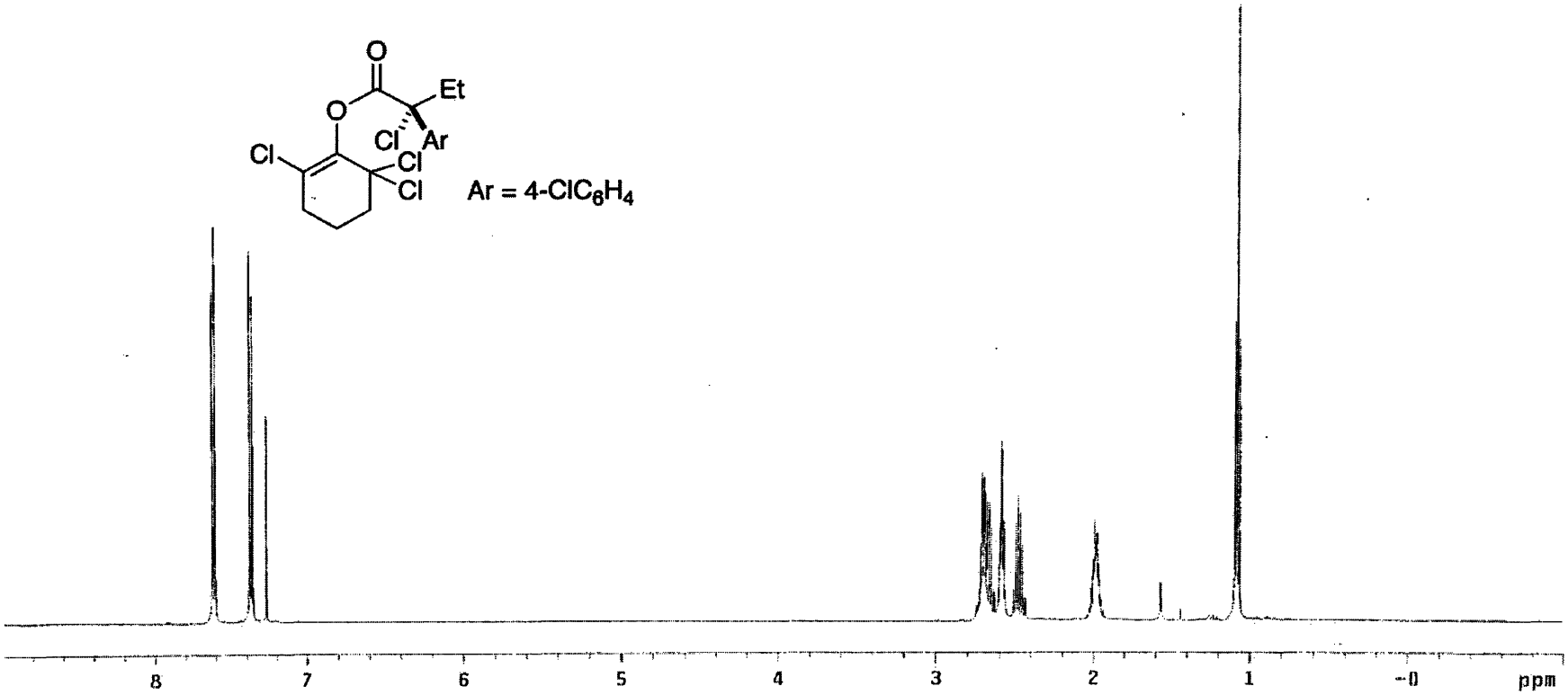
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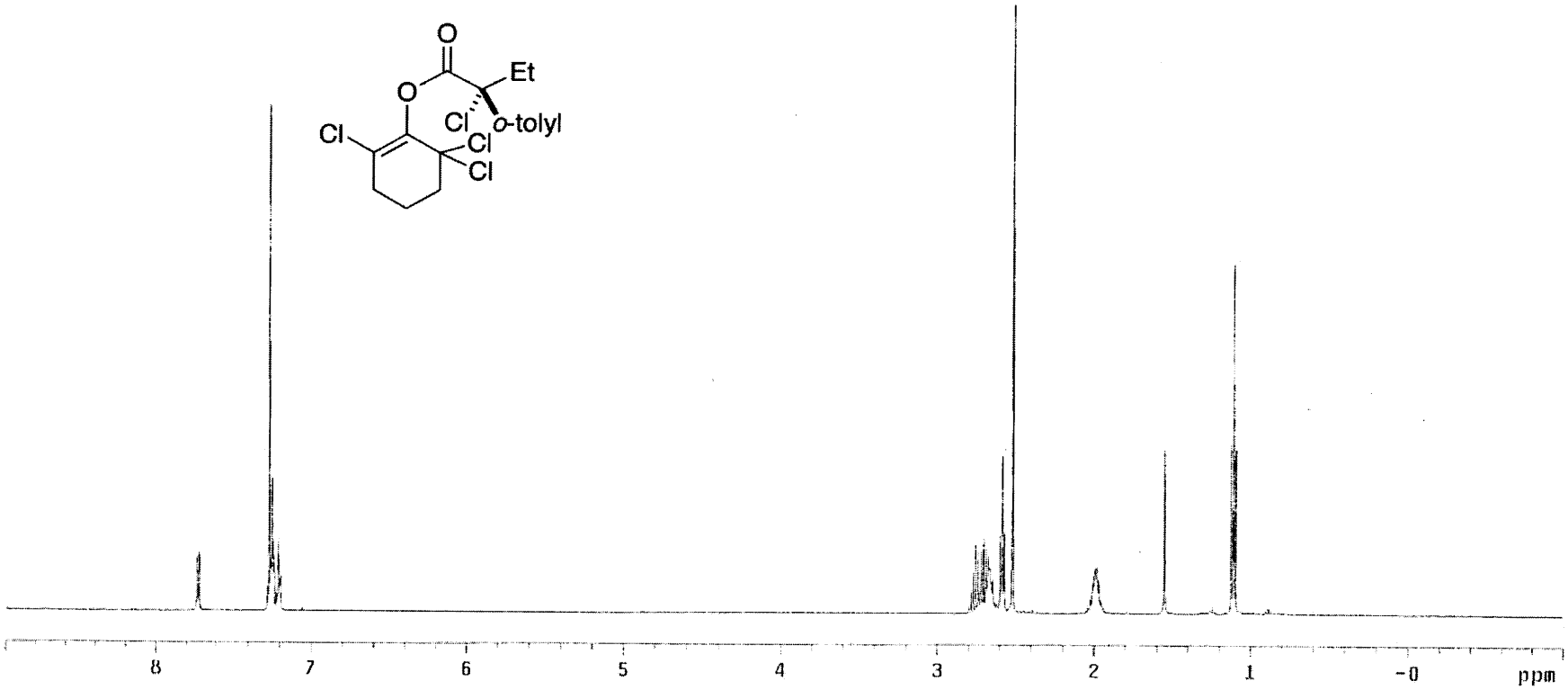
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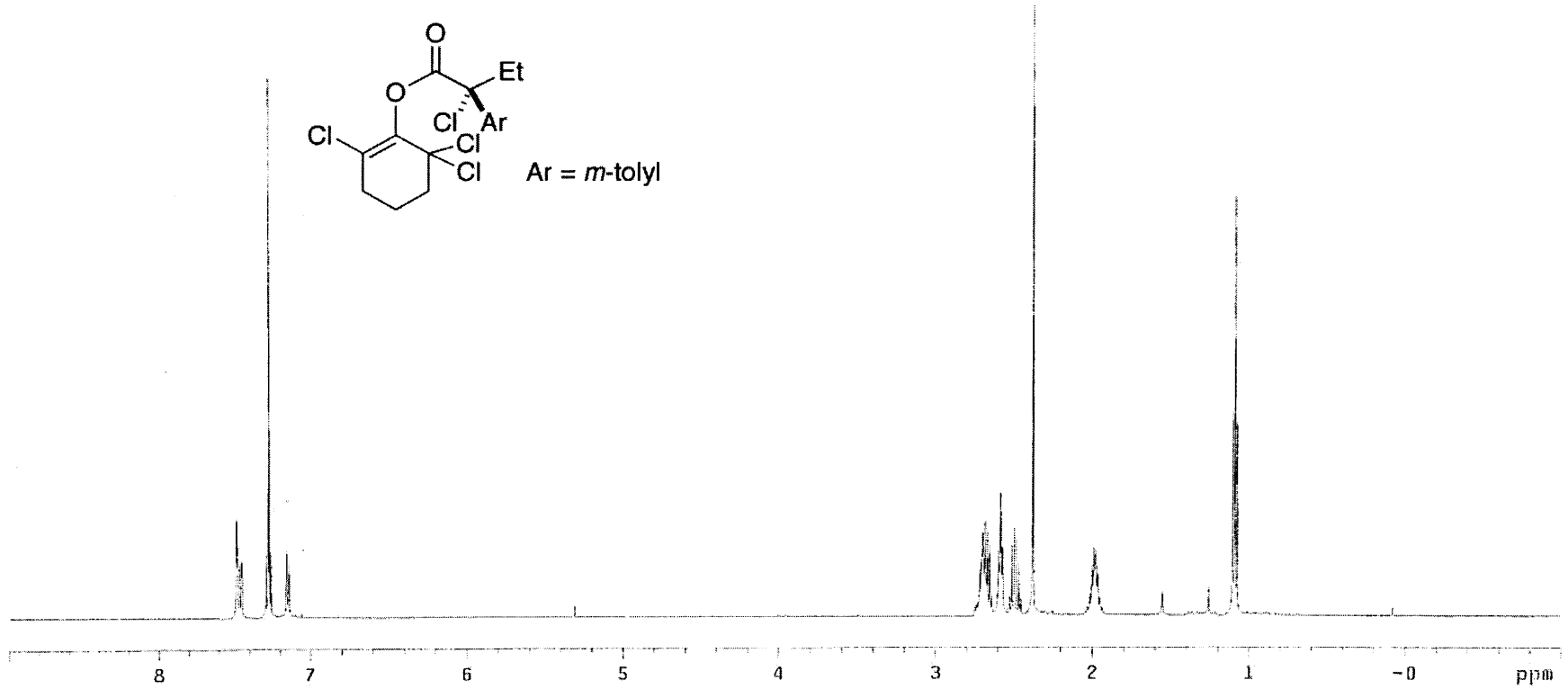
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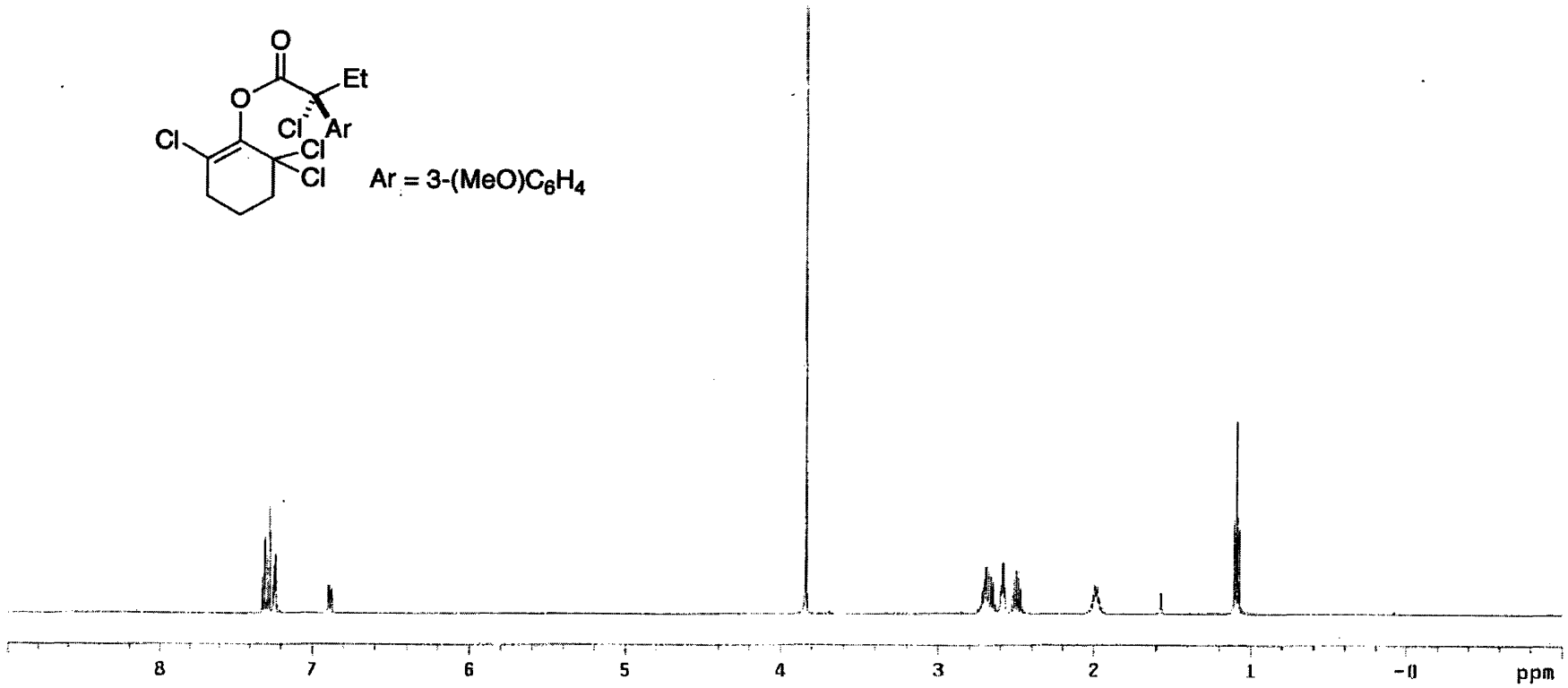
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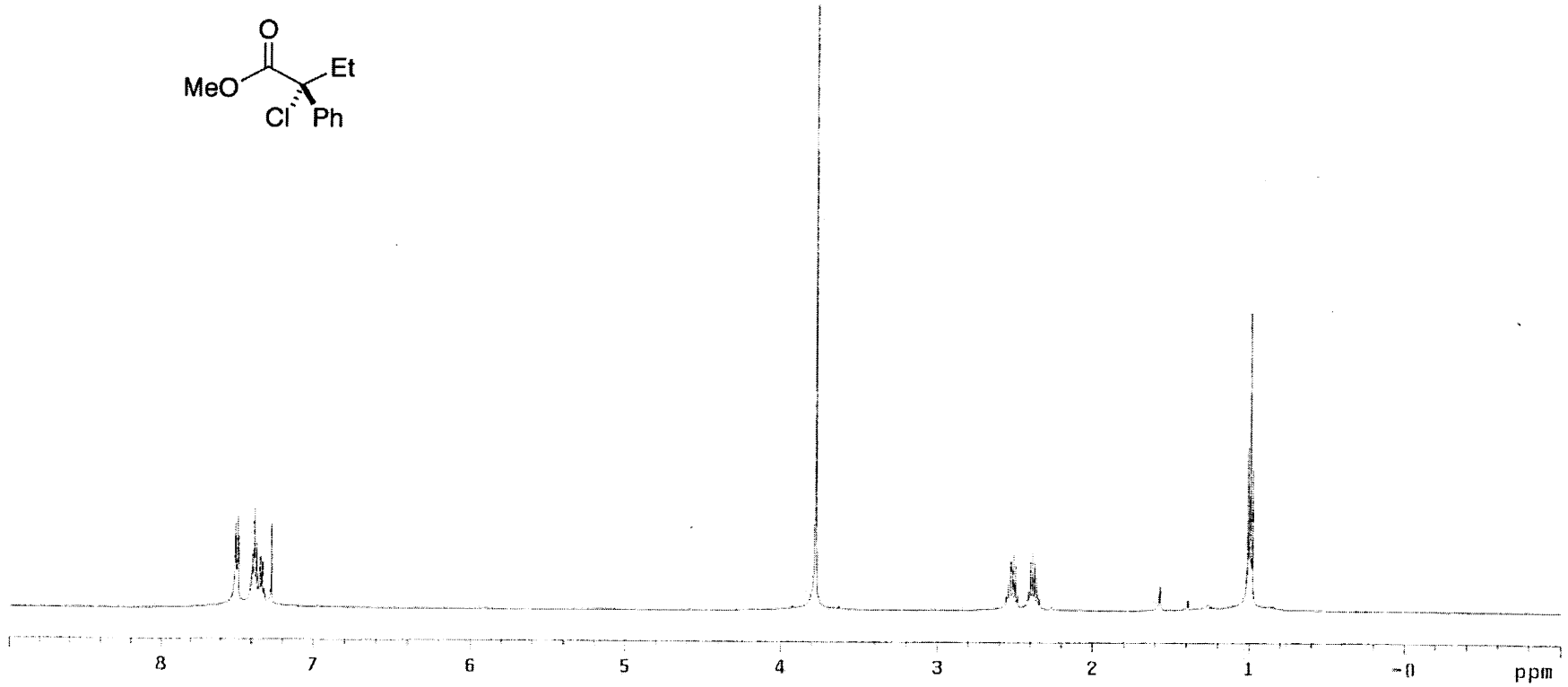
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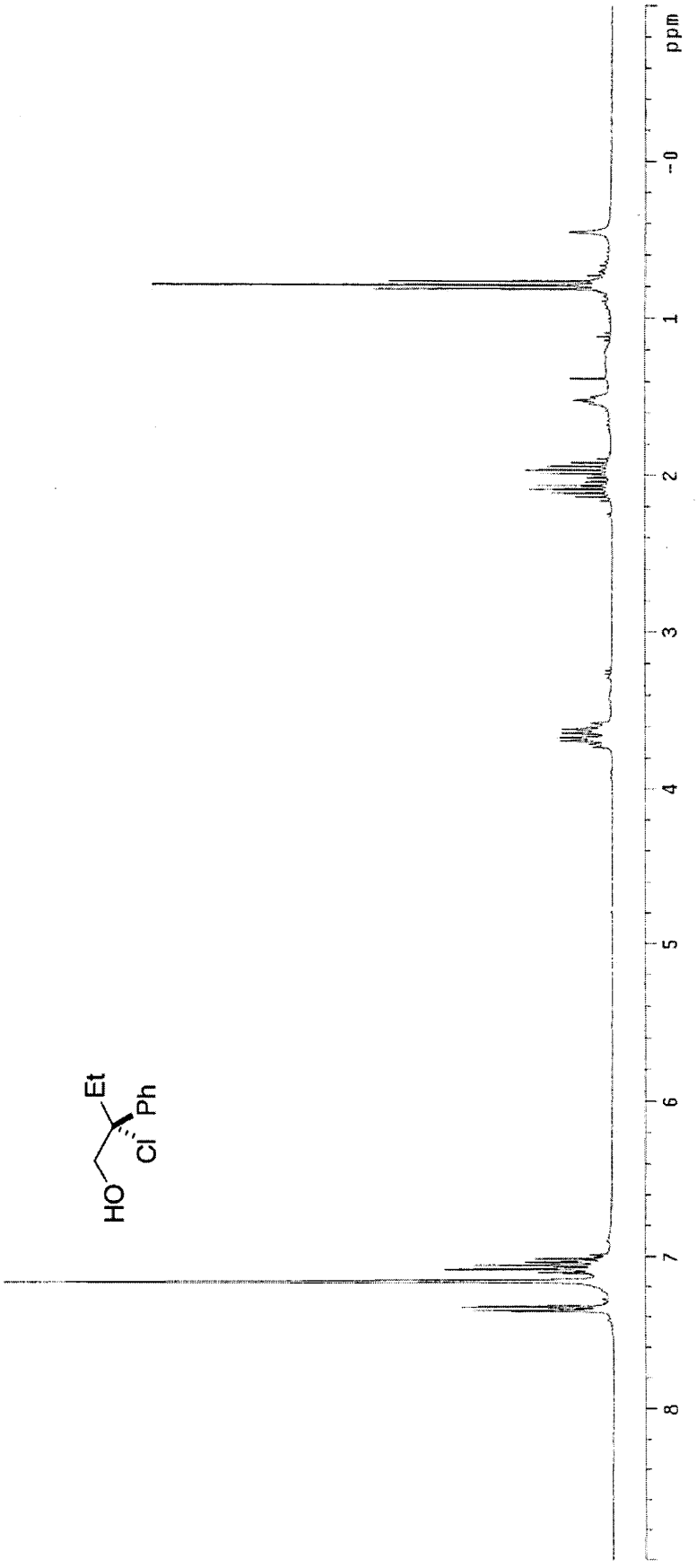
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# Chapter 4

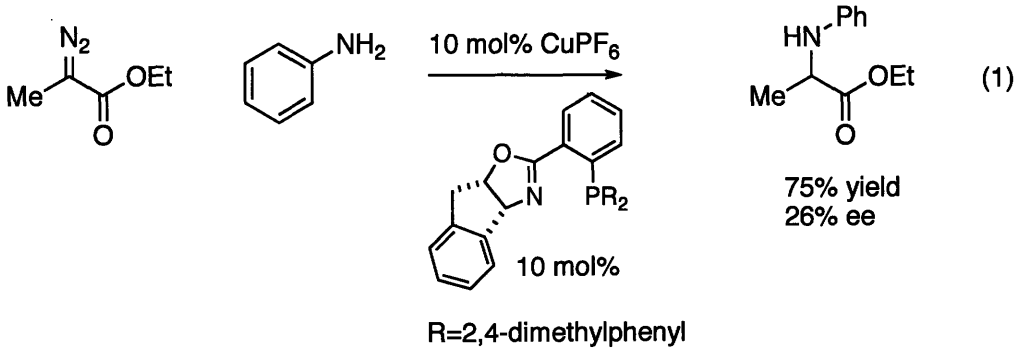
# Catalytic Asymmetric Synthesis of α-Aminoesters via Copper-Catalyzed N-H Insertion Reactions

## 4.1 Introduction

Developing efficient methods for the synthesis of optically active α-amino carboxylic acid derivatives is of considerable importance in organic chemistry and biology.[1] Optically active phenylglycine and its derivatives are not only versatile chiral building blocks in organic synthesis, but they are also fundamental to peptide and protein synthesis. Moreover, optically active *unnatural* α-amino acids are now routinely incorporated into protein synthesis to understand the mechanism of biological processes.[2] As a result, a great deal of effort has been devoted to the preparation of α- and β-amino acids in enantiomerically pure form of either configuration.[3]

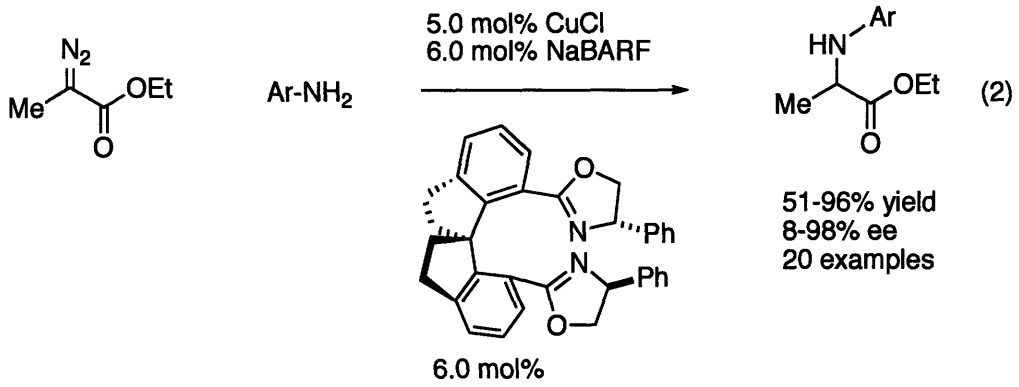
In recent decades, metal-mediated carbenoid reactions have gained wide application in synthetic organic chemistry. Many of these studies focused on cyclopropanation reactions, X-H (X= C, N, O, Si, S) insertion reactions, and ylide formation followed by subsequent rearrangement reactions to afford a diverse set of products.[4] Although remarkable advances have been made in the area of asymmetric C-H insertion reactions,[5] relatively few advances have been made in the area of asymmetric insertion into N-H bonds.[6]

Following the first report on the catalytic N-H insertion reaction in the presence of copper by Yates,[7] a diasteroselective copper-catalyzed N-H insertion reaction has been reported.[6a] The first example of a catalytic asymmetric N-H insertion catalyzed by copper was reported by Jorgensen (eq 1),[6f] where in the presence of ethyl α-diazoester and aniline, the product was generated in moderate yield (75%) and poor ee (26%). This method lacks generality since only one example (i.e., ethyl α-diazoester and aniline) was reported.



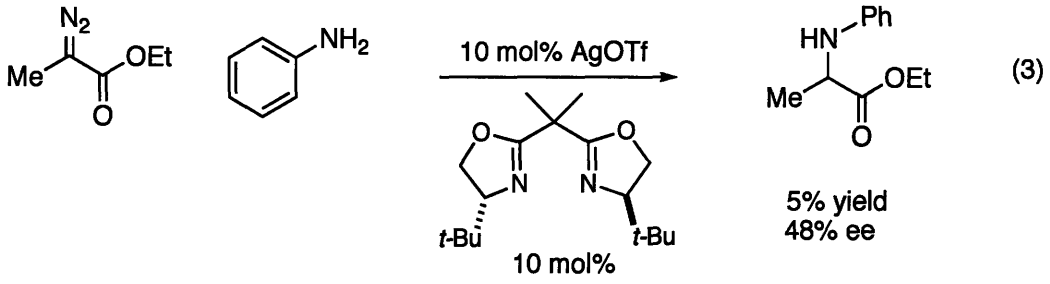

More recently, a significant improvement of this method was demonstrated by Zhou (eq 2).[6g] In this report, a diverse set of aniline derivatives were inserted into ethyl α-diazoester,

catalyzed by a copper/chiral bisoxazoline complex. Products were generated in good yield (51-96%) and excellent ee (8-98%, where most of the examples were >90% ee).




(2)

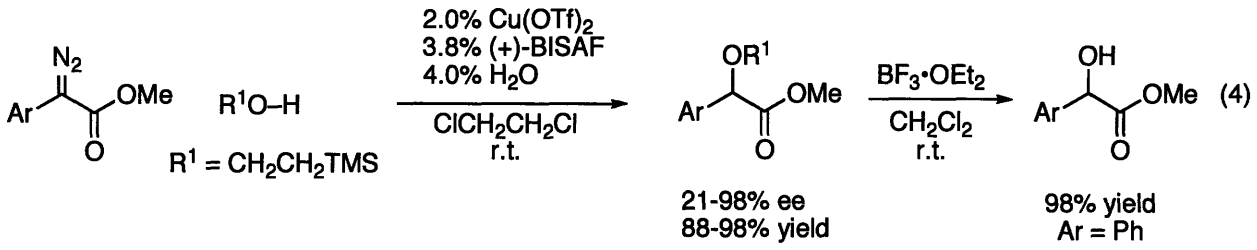
In addition, diastereoselective N-H insertion reactions using rhodium have also been documented.[6b-e] Finally, Jorgensen reported a silver-catalyzed asymmetric N-H insertion reaction (eq 3).[6f] This method afforded product in poor yield (5%) and moderate ee (48%). Again, a single example was described.



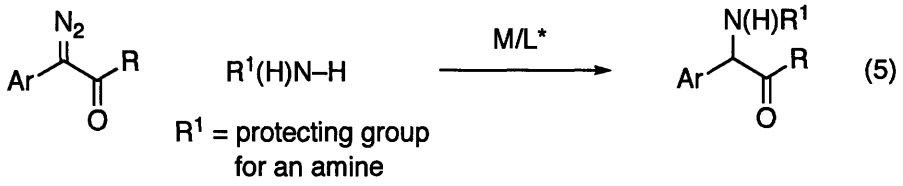

(3)

Although these examples show a tremendous advance toward the synthesis of optically active α-amino carbonyl containing compounds, these methodologies are limited to aniline based amine insertions. Hence, obtaining free α-amino carbonyl compounds from these sets of products is challenging.[8]

More recently, our laboratory has developed the first effective method for catalytic enantioselective insertion into O-H bonds using a copper/(+)-BISAF catalyst (eq 4).[9] This reaction afforded products in high yield (88-98%) and good ee (21-98%). Furthermore, the insertion product was deprotected to provide the α-hydroxy ester in high yield without racemization.



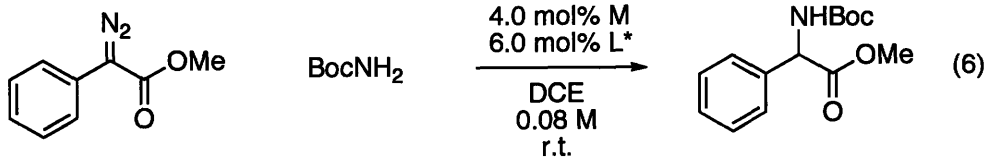

Our aim was to develop a general catalytic system for the synthesis of α-amino carbonyl compounds using an α-diazoester and a protected amine source (that can readily be deprotected) in the presence of a metal and a chiral ligand (eq 5).




## 4.2 Results and Discussion

### *4.2.1. Reaction Optimization*

Initially, we examined several reaction parameters including various metals, chiral ligands and different protected amines. These parameters were varied simultaneously in order to determine the optimal conditions for the reaction of a protected amine with a diazoester species. We chose methyl α-diazo-α-phenyl-ester and *tert*-butyl carbamate ($BocNH_2$) as model substrates for the optimization screening (eq 6). The choice of methyl α-diazo-α-phenyl-ester is based upon the fact that it lacks a β-proton, which is known to lead to unwanted side products in certain metal-catalyzed processes.[6f] $BocNH_2$ was chosen for its ability to be readily cleaved with acid to afford free α-amino acids.



We began our investigation by screening metal/chiral ligand systems such as Cu, Ag, and Rh in combination with chiral ligands such as diphosphines, diamines, diimines, amino alcohols, Pybox, P-N ligands, semicorrins and bisoxazoline ligands.

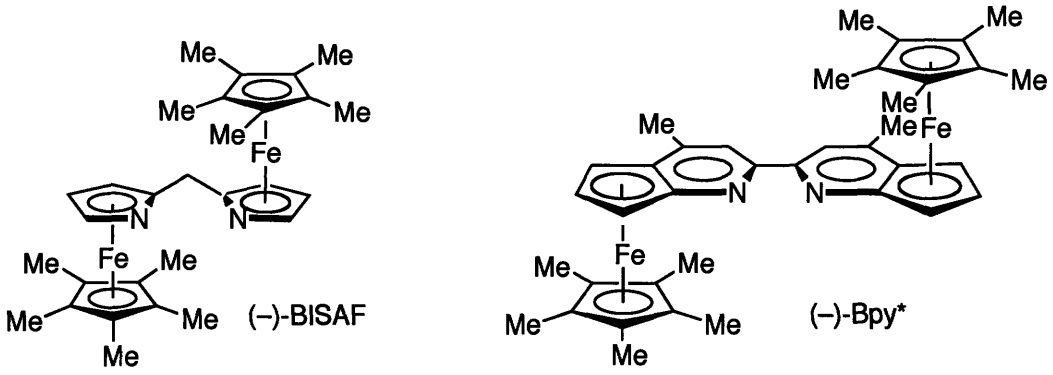
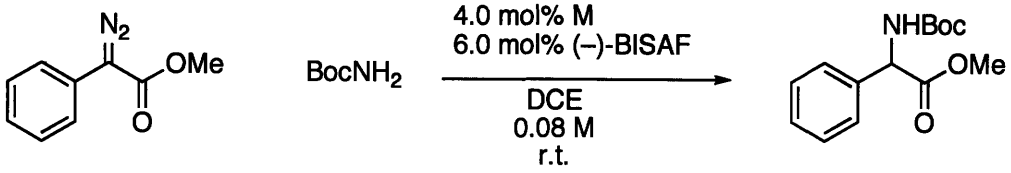



*Figure 1*. Planar-chiral ligands used in the synthesis of α-aminoesters.

In the presence of rhodium(I) and a variety of different ligands, acceptable yields of product (>70%) were observed; however, enantioselectivities were <5%. After screening various copper and ligand combinations, an initial promising result (Table 1) was obtained with $CuPF_6(CH_3CN)_4$ and a planar-chiral bisazaferrocene ligand (BISAF, Figure 1), where 67% ee was observed (entry 1). Additionally, the effect of copper(I) counter anion appeared to play an important role in this reaction. Copper complexes that contained strongly coordinating anions yielded inferior enantioselectivities (entries 2-6); however, the use of $CuPF_6$/(–)-BISAF provided product in 67% ee. Interestingly, (–)-BISAF was also compatible with silver(I) salts, generating the product in 73% ee (entries 7-9). As indicated before, there is only a single example in the literature of a catalytic asymmetric N-H insertion reaction that is mediated by silver, and the product was generated in moderate ee (48%) and poor yield (5%).[6f] We decided to screen copper salts with other non-coordinating anions. The use of CuCl or $CuCl_2$ in conjunction with $AgSbF_6$ gave an improvement in ee to 79% (entries 11-12). However, further optimization of this reaction proved to be difficult. In most cases, the reaction seemed to be extremely rapid at room temperature, i.e., the reaction was completed in <30 min.

***Table 1.*** Initial Screening of Metals with (–)-BISAF



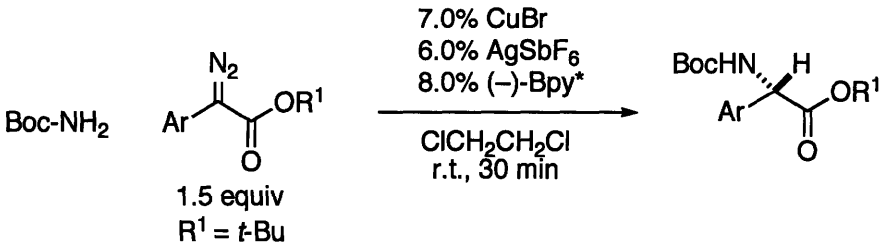

| entry | M | ee (%) |
|---|---|---|
| 1 | $CuPF_6(CH_3CN)_4$ | 67 |
| 2 | $Cu(OTf)_2$ | 11 |
| 3 | CuOTf•benzene | 5 |
| 4 | CuOAc | – |
| 5 | CuCl | 0 |
| 6 | $CuCl_2$ | 0 |
| 7 | $AgSbF_6$ | 69 |
| 8 | $AgPF_6$ | 73 |
| 9 | $AgAsF_6$ | 70 |
| 10 | AgCl | – |
| [a]11 | $CuCl_2/AgSbF_6$ | 79 |
| [b]12 | $CuCl/AgSbF_6$ | 73 |

[a] Cu/Ag ratio was 1:2. [b] Cu/Ag ratio was 1:1.

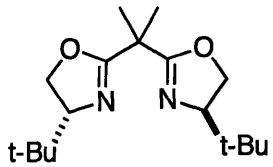
Subsequently, we postulated that the use of a more rigid ligand would help in improving enantioselectivity. Hence, the use of a 2,2'-bipyridyl based planar-chiral ligand (Bpy*, Figure 1) under the same reaction conditions as described in Table 1, entry 12 provided desired product in 80% ee and 75% yield. Again, we examined several metal sources (CuCl, CuBr, or CuI in conjunction with $AgSbF_6$, $AgAsF_6$, or $AgPF_6$) along with the (–)-Bpy* ligand and determined that the combination of CuBr and AgSbF6 with (–)-Bpy* as the ligand provided the most consistent results.

In order to improve upon the yield and ee of our preliminary lead, we examined the dependence of the insertion reaction on the steric nature of the diazoester (Table 2). A general increase in stereoselectivity was observed when the ester group was increased in size (Table 2, entries 2-4), with the tert-butyl ester furnishing the highest yield and ee. In addition, 1.5 equivalents of diazoester was necessary to generate the products in acceptable yield (>70%).

***Table 2.*** Copper–Catalytic N-H Insertions: Reaction Parameters.




| entry | change from standard condition | yield (%)[a,b] | ee (%)[a] |
|---|---|---|---|
| 1 | none | 74 | 94 |
| 2 | $R^1$ = Me instead of *t*-Bu | 70 | 70 |
| 3 | $R^1$ = *i*-Pr instead of *t*-Bu | 69 | 84 |
| 4 | $R^1$ = Bn instead of *t*-Bu | 81 | 77 |
| 5 | no BPy* | 72 | 0 |
| 6 | 7.0% CuBr alone instead of | NR | - |
| 7 | 7.0% $AgSbF_6$ alone instead of | 15 | 86 |
| 8 | 7.0% $CuPF_6(CH_3CN)_4$ alone intead of | 51 | 39 |
| 9 | 6.0% AgOTf instead of $AgSbF_6$ | 78 | 87 |
| 10 | 8.0% of **1** instead of BPy* | 72 | 0 |
| 11 | 8.0% of BISAF instead of BPy* | 63 | <6 |
| 12 | 0 °C o/n instead of r.t. | 46 | 76 |
| 13 | THF instead of $ClCH_2CH_2Cl$ | 59 | 69 |
| 14 | Benzene instead of $ClCH_2CH_2Cl$ | NR | - |




**1**

[a] Average of two experiments. [b] Isolated yields.

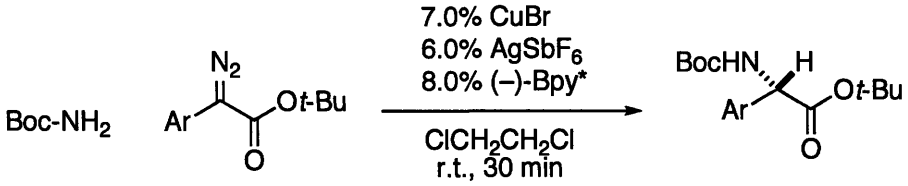
The effect of further modification of the reaction parameters on the yield and ee for the copper catalyzed coupling of $BocNH_2$ with *tert*-butyl α-diazo-α-phenyl-ester were investigated (Table 2). In the absence of the (–)-Bpy* ligand, we observed a significant background reaction, in which 0% ee was observed (entry 5). Under the standard reaction conditions, but in the absence of $AgSbF_6$ (i.e., reaction catalyzed only by CuBr and (–)-Bpy* ligand), there was no product formation (entry 6). Finally, in the absence of CuBr (i.e., reaction catalyzed only by $AgSbF_6$ and (–)-Bpy* ligand), a significant decrease in yield (15%), yet a high ee (86%) was observed (entry 7). These results highlight the importance of the use of two metals in our optimized reaction condition. It is our hypothesis that the actual metal species that is catalyzing the reaction is the "CuSbF6". In contrast, when $CuPF_6(CH_3CN)_4$ was used instead of the CuBr and $AgSbF_6$ combination, an unsatisfactory yield and ee were observed (entry 8). In the presence of CuBr and AgOTf, product was obtained with inferior stereoselectivity, and no stereoselectivity was observed by the use of chiral bisoxazoline (**1**) or (–)-BISAF ligands (entries

10-11). Insertion reactions that were conducted either at lower temperature (entry 12) or in other solvents, i.e., THF or benzene, afforded either low ee or no product (entries 13-14).

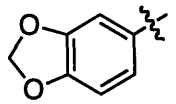
*4.2.2. Copper/(–)-Bpy*–Catalyzed Asymmetric Synthesis of α–Aminoesters*

Copper/(–)-Bpy*-catalyzed insertions into the N-H bond of $BocNH_2$ proceeded in good yield (48-89%) and ee (80-95%) with range of *tert*-butyl α-diazoesters (Table 3).

**Table 3.** Copper-Catalyzed N-H Insertions: Reaction Scope



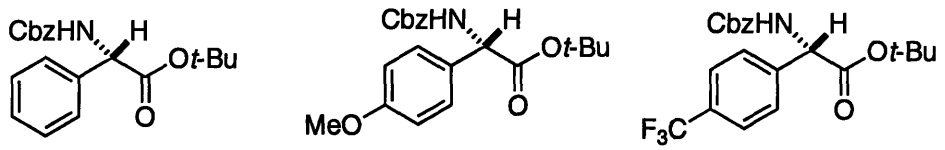

1.5 equiv

| entry | Ar | yield (%)[a,b] | ee (%)[a] |
|---|---|---|---|
| 1 | Ph | 75 | 94 |
| 2 | (2-Me)$C_6H_4$ | 71 | 81 |
| 3 | (3-Me)$C_6H_4$ | 75 | 88 |
| 4 | (4-OMe)$C_6H_4$ | 61 | 95 |
| 5 | (4-Br)$C_6H_4$ | 86 | 85 |
| 6 | (4-$CF_3$)$C_6H_4$ | 89 | 85 |
| 7 | 2-naphthyl | 73 | 91 |
| 8 |  | 74 | 90 |
| 9 | 3-thienyl | 48 | 80 |

[a] Average of two experiments. [b] Isolated yield.

Thus, substitution on the aromatic ring was tolerated at the ortho, meta, and para positions (entries 2-6). Additionally, the aromatic ring of the diazoester can be electronically diverse (entries 4-6), while still providing high ee's of product (> 85%). Furthermore, bicyclic substituents also reacted well to generate product in good ee (entries 7-8) and a thiophene derivative reacted to afford 80% ee with a modest yield (48%, entry 9).

In addition to the use of $BocNH_2$, we were able to demonstrate that another carbamate derivative was tolerated using our reaction conditions. Specifically, we were able to show that benzyl carbamate ($CbzNH_2$) is also an effective coupling partner. Thus, this method now provides direct access to highly useful Cbz-protected α-aminoesters. Several examples of the reaction of $CbzNH_2$ with *tert*-butyl-α-diazoesters are included in Figure 2. Electron-rich, -poor, and -neutral diazoesters generated products in good ee (82-95%) and yield (49-78%).




**2**
95% ee, 76%y

**3**
90% ee, 49%y

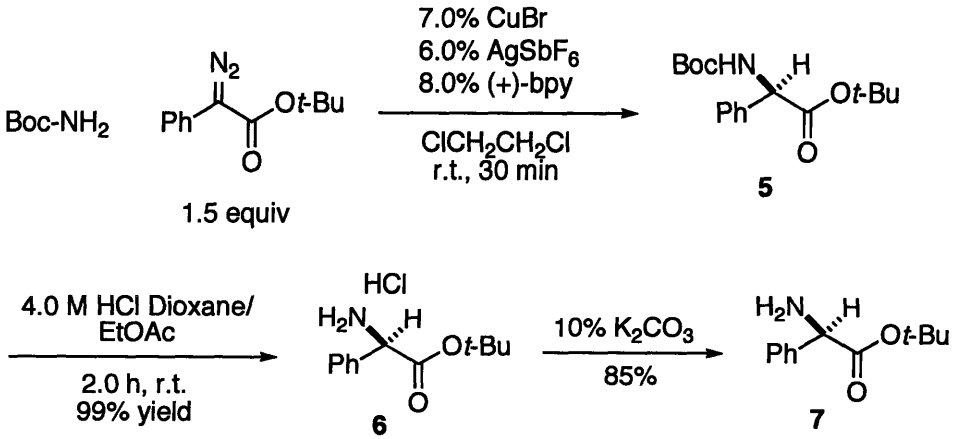
**4**
82% ee, 78%y

***Figure 2.*** The scope of the N-H insertion reaction involving $CbzNH_2$ with Cu/(–)-Bpy*.

*4.2.3. Determination of Absolute Configuration*

The absolute stereochemistry of *tert*-butyl α-(*tert*-butoxycarbonylamino)-α-diazoesters (**5**) was determined by correlation with (*R*)-*tert*-butyl α-(*tert*-butoxycarbonylamino)-α-diazoester reported in the literature.[10] (*R*)-*tert*-Butyl α-amino-α-phenyl-ester (**7**) was prepared as shown in Scheme 1. All relevant data were consistent with the reported values.[10]

***Scheme 1.***



## 4.3 Conclusions

We have developed an efficient method for catalytic enantioselective insertion into N-H bonds. Thus, a copper/Bpy* catalyst system is effective in coupling carbamates such as $BocNH_2$ and $CbzNH_2$ with α-aryl-α-diazoesters in good yield (48-89%) and ee (81-95%), after which the Boc- or Cbz-group can be cleaved to generate a free α-amino-α-diazoester.

## 4.4 Experimental Procedures

*4.4.1. General*

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. $BocNH_2$ was recrystallized from dichloromethane and pentane. All other chemicals were purchased from commercial suppliers and used as received, unless noted otherwise. Dichloroethane (anhydrous; Fluka), CuBr (Strem), $AgSbF_6$ (Strem), $CbzNH_2$ (Aldrich) were used as received. Bpy* ligand was prepared and resolved as previously reported.[11]

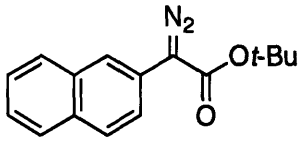
HPLC analyses were carried out on an Agilent 1100 series system with Daicel Chiralpak® columns in hexane/isopropanol mixtures. GC analysis were carried out on an Agilent 6850 series system with CP-Chirasil-Dex CB column; 140 °C (5 min), 1.0 °C/min to 160 °C; 14.37 psi He or Astec G-TA column; 140 °C (1 min), 1.0 °C/min to 180 °C; 14.89 psi He

Melting points were measured on a Hoover melting point apparatus and are uncorrected.

*4.4.2. Preparation of Diazo Compounds*

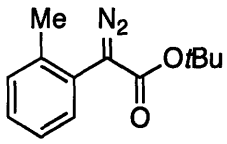
**GP 1.** All of the α–diazoesters were prepared via direct diazo transfer as previously reported using either tosyl azide or *p*-ABSA.[9]

The following diazo compounds have been previously reported: *tert*-butyl α–diazo–α–phenyl-ester (CAS 72410-67-4) and *tert*-butyl α–diazo–α–4-methoxyphenyl-ester (CAS 76530-00-2).



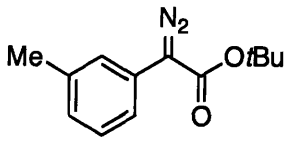
***tert*-Butyl α–diazo–α–2-naphthalenyl-ester.** The compound was prepared according to GP 1 using *tert*-butyl 2-naphthalenyl-ester (843 mg, 3.48 mmol), MeCN (14 mL), DBU (0.78 mL, 5.22 mmol), and tosyl azide (870 mg, 4.52 mmol). Product: 695 mg (74%); orange solid.

$^1$H NMR ($CDCl_3$, 300 MHz) δ 8.04 (s, 1H), 7.86-7.79 (m, 3H), 7.52-7.43 (m, 3H), 1.60 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 164.9, 133.8, 131.5, 128.7, 127.8, 127.7, 126.7, 125.8, 123.5, 122.6, 122.1, 82.4, 28.6 (x3), the resonance of the carbon that bears the diazo group was not detected;
IR (film) cm$^{-1}$ 3055, 2987, 2306, 2088, 1696, 1422, 1266, 1148, 896, 739, 705.



***tert*-Butyl α–diazo–α–*o*-tolyl-ester.** The compound was prepared according to GP 1 using *tert*-butyl *o*-tolyl-ester (3.10 g, 15.0 mmol), MeCN (53 mL), DBU (4.50 mL, 30.0 mmol), and *p*-ABSA (5.40 g, 22.5 mmol). Product: 1.02 g (29%); orange oil.

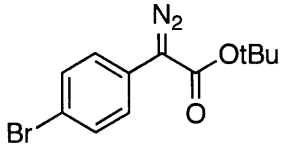
$^1$H NMR ($CDCl_3$, 300 MHz) δ 7.51-7.47 (m, 1H), 7.37-7.32 (m, 3H), 2.47 (s, 3H), 1.63 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 165.5, 137.6, 130.9, 130.88, 128.7, 126.5, 124.8, 81.9, 28.6 (x3), 20.2, the resonance of the carbon that bears the diazo group was not detected;
IR (film) cm$^{-1}$ 2979, 2932, 2084, 1699, 1491, 1368, 1295, 1253, 1149, 1006, .



***tert*-Butyl α–diazo–α–*m*-tolyl-ester.** The compound was prepared according to GP 1 using *tert*-butyl *m*-tolyl-ester (2.44 g, 11.8 mmol), MeCN (42 mL), DBU (2.70 mL, 17.8 mmol), and *p*-ABSA (3.70 g, 15.4 mmol). Product: 1.33 g (47%); orange oil.

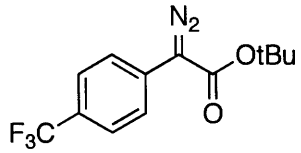
$^1$H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.34 (m, 1H), 7.29-7.27 (m, 2H), 7.02-6.99 (m, 1H), 2.38 (s, 3H), 1.58 (s, 9H);

$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 164.9, 138.8, 128.9, 126.6, 126.1, 124.8, 121.2, 82.1, 28.6 (x3), 21.8, the resonance of the carbon that bears the diazo group was not detected;
IR (film) cm$^{-1}$ 2979, 2931, 2084, 1701, 1605, 1492, 1369, 1344, 1290, 1249, 1143, 1055, 779.



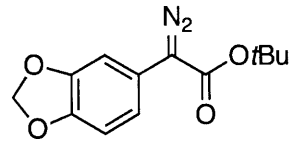

***tert*-Butyl α-diazo-α-4-bromophenyl-ester**. The compound was prepared according to GP 1 using *tert*-butyl 4-bromophenyl-ester (1.67 g, 6.15 mmol), MeCN (28 mL), DBU (1.38 mL, 9.23 mmol), and tosyl azide (1.54 g, 8.00 mmol). Product: 1.40 g (77%); orange solid.

$^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.48 (d, $J$ = 9.0 Hz, 2H), 7.35 (d, $J$ = 8.7 Hz, 2H), 1.55 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 164.3, 132.1 (x2), 125.5 (x2), 125.5, 119.2, 82.6, 28.6 (x3), the resonance of the carbon that bears the diazo group was not detected;
IR (film) cm$^{-1}$ 3055, 2984, 2088, 1696, 1491, 1347, 1266, 1148, 1003, 740, 705.



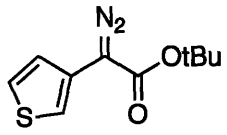

***tert*-Butyl α-diazo-α-4-trifluoromethylphenyl-ester**. The compound was prepared according to GP 1 using *tert*-butyl 4-trifluoromethylphenyl-ester (3.46 g, 13.3 mmol), MeCN (60 mL), DBU (2.90 mL, 20.0 mmol), and *p*-ABSA (4.20 g, 17.3 mmol). Product: 1.45 g (38%); orange solid.

$^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 4H), 1.55 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 163.9, 130.9, 127.4 (q, $^{2}J_{CF}$ = 33.0 Hz), 125.9 (q, $^{3}J_{CF}$ = 3.8 Hz), 123.6, 122.5, 82.9, 28.5 (x3), the resonance of the carbon that bears the diazo group was not detected;
IR (film) cm$^{-1}$ 3055, 2987, 2094, 1699, 1422, 1328, 1266, 1148, 896, 740, 705.




***tert*-Butyl α-diazo-α-1,3-dioxol-5-yl-phenyl-ester**. The compound was prepared according to GP 1 using *tert*-butyl 1,3-dioxol-5-yl-phenyl-ester (1.64 g, 6.94 mmol), MeCN (28 mL), DBU (1.56 mL, 10.4 mmol), and tosyl azide (1.73 g, 9.02 mmol). Product: 489 mg (27%); orange solid.

$^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.06-7.05 (m, 1H), 6.85-6.83 (m, 2H), 5.96 (s, 2H), 1.54 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 165.1, 148.5, 146.0, 127.8, 117.9, 109.0, 105.9, 101.4, 82.2, 28.5 (x3), the resonance of the carbon that bears the diazo group was not detected;
IR (film) cm$^{-1}$ 3055, 2984, 2087, 1694, 1505, 1493, 1370, 1266, 1235, 1041, 740, 705.




***tert*-Butyl α–diazo–α–3-thiophenyl-ester**. The compound was prepared according to GP 1 using *tert*-butyl 3-thiophenyl-ester (4.34 g, 21.9 mmol), MeCN (69 mL), DBU (4.90 mL, 32.8 mmol), and tosyl azide (6.80 g, 28.5 mmol). Product: 829 mg (17%); orange solid.

$^1$H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.36 (m, 2H), 7.03-7.01 (m, 1H), 5.96 (s, 2H), 1.56 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 165.0, 126.4, 124.6, 123.9, 117.6, 82.3, 28.6 (x3), the resonance of the carbon that bears the diazo group was not detected;
IR (film) cm$^{-1}$ 3055, 2986, 2306, 2085, 1695, 1422, 1318, 1266, 1139, 896, 740, 705.

*4.4.3. Preparation of α-Aryl-α-diazoesters*

**GP 2: Table 1 and 2**

All enantioselectivities and isolated yields that are reported in Table 1 are the average of two runs, with (+)-Bpy*.

All enantioselectivities and isolated yields that are reported in Table 2 are the average of two runs, first one with (-)-Bpy* and second one with the other enantiomer.

**General Procedure A**

In a glovebox, the catalyst was prepared by mixing CuBr (1.23 mg, 8.54 mmoles), (–)-Bpy* (6.30 mg, 9.76 mmoles), $AgSbF_6$ (2.52 mg, 7.32 mmoles) and dichloroethane (1.1 mL) in an amber vial. The resulting mixture was stirred for 45 min. In a separate vial, *tert*-butyl α–diazo–α–phenyl-ester (49.1 mg, 0.183 mmoles) and $BocNH_2$ (14.3 mg, 0.122 mmoles) were dissolved in dichloroethane (0.8 mL) and added into a vial containing the catalyst mixture via syringe over 3 min and rinsed vial with dichloroethane (0.1 mL). The reaction mixture was stirred at room temperature for 30 min, concentrated to dryness and purified via flash column chromatography.

**General Procedure B**

In a glovebox, the catalyst was prepared by mixing CuBr (1.02 mg, 7.14 mmoles), (–)-Bpy* (5.20 mg, 8.16 mmoles), $AgSbF_6$ (2.10 mg, 6.12 mmoles) and dichloroethane (2.8 mL) in an amber vial. The resulting mixture was stirred for 45 min. From this mixture, 0.90 mL was withdrawn and reserved in a separate amber vial. In another separate vial, *tert*-butyl α–diazo–

α–phenyl-ester (22.3 mg, 0.102 mmoles) and $CbzNH_2$ (16.0 mg, 0.102 mmoles) were dissolved in dichloroethane (0.56 mL) and added into a vial containing the catalyst mixture via syringe over 3 min. Dichloroethane (0.10 mL) was used to rinse the vial. This reaction mixture was allowed to stir for 5 min, and then the reserved catalyst mixture was added all at once. Subsequently, phenyl diazo *tert*-butylester (11.1 mg, 0.051 mmoles) in dichloroethane (0.56 mL) was added dropwise over 30 sec, and rinsed the vial with dichloroethane (0.10 mL). The reaction mixture was stirred at room temperature for 30 min, concentrated to dryness and purified via flash column chromatography.

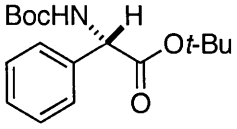



**Table 3, entry 1**. The compound was prepared according to GP A with (-)-Bpy* from 154 mg *tert*-butyl α–diazo–α–phenyl-ester (0.704 mmol) and 55.0 mg $BocNH_2$ (0.469 mmol). After chromatography on silica gel (1% ethylether in $CH_2Cl_2$), the title compound was isolated as a white solid: run 1, 105 mg (73%, 93% ee); run 2, 110 mg (76%, 95% ee). The ee was determined on a CP-Chirasil-Dex CB column with $t_r$(major) 21.6 min., $t_r$(minor) 22.0 min.

MP: $^{o}C$;

$[\alpha]^{20}_{D} = -120$ (c = 0.950, $CH_2Cl_2$), 95% ee, with (+)-Bpy*;

$^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.29-7.21 (m, 5H), 5.53 (d, *J* = 6.5 Hz, 1H), 5.13 (d, *J* = 7.5 Hz, 1H), 1.36 (s, 9H), 1.31 (s, 9H);

$^{13}C$ NMR ($CDCl_3$, 126 MHz) δ 170.4, 155.0, 137.0, 128.8, 128.2(x2), 127.1(x2), 82.5, 78.0, 58.2, 28.5(x3), 27.9(x3);

IR (film) $cm^{-1}$ 3055, 2987, 2306, 1422, 1266, 896, 740, 705;

HRMS (ESI) calcd for $C_{17}H_{25}NO_4$ ($M + Na^+$) 330.1676, found 330.1679.

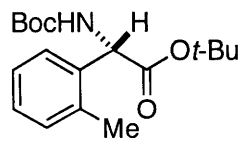



**Table 3, entry 2.** The compound was prepared according to GP A with (-)-Bpy* from 119 mg *tert*-Butyl α–diazo–α–*o*-tolyl-ester (0.512 mmol) and 40.0 mg $BocNH_2$ (0.341 mmol). After chromatography on silica gel (1% ethylether in $CH_2Cl_2$), the title compound was isolated as a colorless oil: run 1, 74.0 mg (68%, 77% ee); run 2, 81.0 mg (74%, 81% ee). The ee was determined on a Astec G-TA column with $t_r$(major) 37.1 min., $t_r$(minor) 37.6 min.

$[\alpha]^{20}_{D} = +85.6$ (c = 1.25, $CH_2Cl_2$), 77% ee, with (–)-Bpy*;

$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.27-7.16 (m, 4H), 5.52 (d, $J$ = 7.0 Hz, 1H), 5.44 (d, $J$ = 7.5 Hz, 1H), 1.43 (s, 9H), 1.37 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 170.9, 155.1, 136.8, 136.5, 130.9, 128.1, 126.4, 126.1, 82.3, 79.9, 54.7, 28.5(x3), 28.0(x3), 19.7;
IR (film) cm$^{-1}$ 3055, 2985, 2306, 1712, 1492, 1369, 1266, 1154, 896, 740, 705;
HRMS (ESI) calcd for $C_{18}H_{27}NO_4$ (M + $Na^+$) 344.1832, found 344.1838.

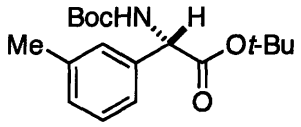



**Table 3, entry 3.** The compound was prepared according to GP A with (-)-Bpy* from 163 mg *tert*-Butyl α–diazo–α–*m*-tolyl-ester (0.704 mmol) and 55.0 mg $BocNH_2$ (0.469 mmol). After chromatography on silica gel (1% ethylether in $CH_2Cl_2$), the title compound was isolated as a colorless oil: run 1, 114 mg (76%, 88% ee); run 2 with $BocNH_2$ (0.427 mmol), 100 mg (73%, 87% ee). The ee was determined on AD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min.) with $t_r$(minor) 6.53 min., $t_r$(major) 10.4 min.

$[\alpha]^{20}_D$ = +87.5 (c =1.50, $CH_2Cl_2$), 88% ee, with (–)-Bpy*;
$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.22 (dd, $J$ = 15, 7.5 Hz, 1H), 7.16-7.09 (m, 3H), 5.55 (d, $J$ = 7.5 Hz, 1H), 5.16 (d, $J$ = 7.5 Hz, 1H), 2.34 (s, 3H), 1.44 (s, 9H), 1.40 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 126 MHz) δ 170.5, 155.0, 138.5, 137.7 129.0, 128.7, 127.9, 124.1, 82.4, 80.0, 58.2, 28.5(x3), 28.0(x3), 21.6;
IR (film) cm$^{-1}$ 3055, 2984, 2306, 1712, 1494, 1266, 1155, 1052, 740, 705;
HRMS (ESI) calcd for $C_{18}H_{27}NO_4$ (M + $Na^+$) 344.1832, found 344.1833.

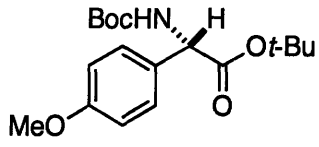



**Table 3, entry 4.** The compound was prepared according to GP A with (-)-Bpy* from 159 mg *tert*-Butyl α–diazo–α–4-methoxyphenyl-ester (0.640 mmol) and 50.0 mg $BocNH_2$ (0.427 mmol). After chromatography on silica gel (1% ethylether in $CH_2Cl_2$), the title compound was isolated as a colorless oil: run 1, 89.0 mg (62%, 94% ee); run 2, 86.0 mg (60%, 95% ee). The ee was determined on AD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min.) with $t_r$(minor) 9.40 min., $t_r$(major) 11.1min.

$[\alpha]^{20}_D$ = +106 (c = 1.20, $CH_2Cl_2$), 94% ee, with (–)-Bpy*;
$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, $J$ = 8.0 Hz, 2H), 6.87 (d, $J$ = 9.0 Hz, 2H), 5.56 (d, $J$ = 7.0 Hz, 1H), 5.14 (d, $J$ = 7.5 Hz, 1H), 3.78 (s, 3H), 2.34 (s, 3H), 1.44 (s, 9H), 1.40 (s, 9H);

$^{13}$C NMR ($CDCl_3$, 126 MHz) δ 170.6, 159.4, 154.9, 130.0, 128.3(x2), 114.3(x2), 82.3, 79.9, 57.6, 55.3, 28.5(x3), 27.9(x3);

IR (film) $cm^{-1}$ 3055, 2987, 2306, 1422, 1266, 896, 740, 705;

HRMS (ESI) calcd for $C_{18}H_{27}NO_5$ (M + $Na^+$) 360.1781, found 360.1772.

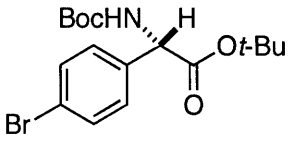



**Table 3, entry 5.** The compound was prepared according to GP A with (-)-Bpy* from 152 mg *tert*-Butyl α–diazo–α–4-bromophenyl-ester (0.512 mmol) and 40.0 mg $BocNH_2$ (0.341 mmol). After chromatography on silica gel (2% ethylether in $CH_2Cl_2$), the title compound was isolated as a colorless oil: run 1, 113 mg (86%, 85% ee); run 2, 113 mg (86%, 85% ee). The ee was determined on AD-H column (hexanes/*iso*-propanol 99:1, flow 1.0 mL/min.) with $t_r$(minor) 25.1 min., $t_r$(major) 26.7 min.

$[\alpha]^{20}_D$ = +72.2 (c = 1.65, $CH_2Cl_2$), 85% ee, with (–)-Bpy*;

$^1$H NMR ($CDCl_3$, 300 MHz) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.65 (d, *J* = 6.9 Hz, 1H), 5.15 (d, *J* = 7.2 Hz, 1H), 1.42 (s, 9H), 1.38 (s, 9H);

$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 169.8, 154.9, 137.2, 131.9(x2), 128.8(x2), 122.2, 83.0, 80.3, 57.7, 28.5(x3), 27.9(x3);

IR (film) $cm^{-1}$ 3055, 2987, 2306, 1712, 1422, 1266, 1156, 896, 706, 736;

HRMS (ESI) calcd for $C_{17}H_{24}BrNO_4$ (M + $Na^+$) 408.0781, found 408.0789.

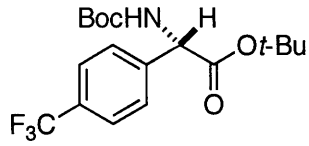



**Table 3, entry 6**. The compound was prepared according to GP A with (-)-Bpy* from 146 mg *tert*-Butyl α–diazo–α–4-trifluoromethylphenyl-ester (0.512 mmol) and 40.0 mg $BocNH_2$ (0.341 mmol). After chromatography on silica gel (1% ethylether in $CH_2Cl_2$), the title compound was isolated as a colorless oil: run 1, 113 mg (88%, 85% ee); run 2, 115 mg (90%, 84% ee). The ee was determined on AD-H column (hexanes/*iso*-propanol 99:1, flow 1.0 mL/min.) with $t_r$(major) 17.2 min., $t_r$(minor) 19.1 min.

$[\alpha]^{20}_D$ = +77.2 (c = 1.25, $CH_2Cl_2$), 85% ee, with (–)-Bpy*);

$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 5.76 (d, *J* = 7.0 Hz, 1H), 5.26 (d, *J* = 7.0 Hz, 1H), 1.42 (s, 9H), 1.39 (s, 9H);

$^{13}$C NMR ($CDCl_3$, 126 MHz) δ 169.5, 154.9, 142.2, 130.4 (q, $^2J_{CF}$ = 32.2 Hz), 127.4(x2), 125.8 (q, $^3J_{CF}$ = 3.4 Hz), 125.77, 124.2 (q, $J_{CF}$ = 272 Hz), 83.2, 80.4, 57.9, 28.5(x3), 27.9(x3);

IR (film) $cm^{-1}$ 3055, 2987, 2306, 1713, 1422, 1326, 1266, 1156, 896, 736, 706;
HRMS (ESI) calcd for $C_{18}H_{24}F_3NO_4$ ($M + Na^+$) 398.1550, found 398.1559.

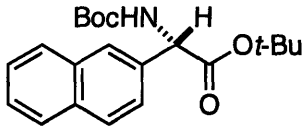



**Table 3, entry 7.** The compound was prepared according to GP A with (-)-Bpy* from 155 mg *tert*-Butyl α–diazo–α–2-naphthalenyl-ester (0.578 mmol) and 45.1 mg $BocNH_2$ (0.385 mmol). After chromatography on silica gel (1% ethylether in $CH_2Cl_2$), the title compound was isolated as a white solid: run 1, 96.0 mg (70%, 89% ee); run 2, 103 mg (75%, 92% ee). The ee was determined on AD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min.) with $t_r$(minor) 7.43 min., $t_r$(major) 10.3 min.

MP: $^oC$;
$[\alpha]^{20}_D$ = +106 (c = 1.20, $CH_2Cl_2$), 89% ee, with (–)-Bpy*;
$^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.85-7.83 (m, 4H), 7.50-7.47 (m, 3H), 5.73 (d, *J* = 7.0 Hz, 1H), 5.38 (d, *J* = 7.5 Hz, 1H), 1.45 (s, 9H), 1.39 (s, 9H);
$^{13}C$ NMR ($CDCl_3$, 126 MHz) δ 170.4, 155.0, 135.4, 133.5, 133.2, 128.7, 128.3, 127.9(x2), 126.4(x2), 124.9, 82.7, 80.1, 58.4, 28.5(x3), 28.0(x3);
IR (film) $cm^{-1}$ 3055, 2986, 2306, 1712, 1422, 1266, 1155, 896, 739, 705;
HRMS (ESI) calcd for $C_{21}H_{27}NO_4$ ($M + Na^+$) 380.1832, found 380.1831.

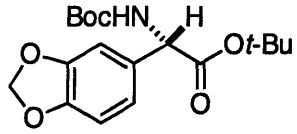



**Table 3, entry 8.** The compound was prepared according to GP A with (-)-Bpy* from 120 mg *tert*-Butyl α–diazo–α–1,3-dioxol-5-yl-phenyl-ester (0.458 mmol) and 35.7 mg $BocNH_2$ (0.305 mmol). After chromatography on silica gel (2% ethylether in $CH_2Cl_2$), the title compound was isolated as a colorless oil: run 1, 80.0 mg (75%, 89% ee); run 2, 77.0 mg (72%, 91% ee). The ee was determined on AD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min.) with $t_r$(minor) 9.17 min., $t_r$(major) 13.2 min.

$[\alpha]^{20}_D$ = +79.6 (c = 1.80, $CH_2Cl_2$), 89% ee, with (–)-Bpy*;
$^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.83-6.75 (m, 3H), 5.95 (s, 2H), 5.56 (d, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 7.5 Hz, 1H), 1.43 (s, 9H), 1.40 (s, 9H);
$^{13}C$ NMR ($CDCl_3$, 75.5 MHz) δ 170.4, 154.9, 148.0, 147.6, 131.8, 120.7, 108.6, 107.6, 101.3, 82.6, 80.1, 57.9, 28.5(x3), 27.9(x3);
IR (film) $cm^{-1}$ 3055, 2987, 2306, 1715, 1422, 1266, 1155, 896, 740, 705;

HRMS (ESI) calcd for $C_{18}H_{25}NO_6$ (M + $Na^+$) 374.1574, found 374.1572.

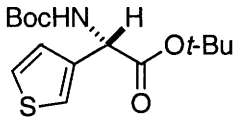
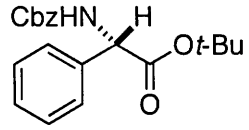


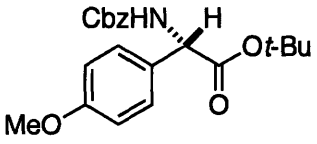

**Table 3, entry 9.** The compound was prepared according to GP A with (-)-Bpy* from 172 mg *tert*-Butyl α–diazo–α–3-thiophenyl-ester (0.768 mmol) and 60.0 mg $BocNH_2$ (0.512 mmol). After chromatography on silica gel (1% ethylether in $CH_2Cl_2$), the title compound was isolated as a yellow oil: run 1, 84.0 mg (51%, 82% ee); run 2, 77.0 mg (46%, 77% ee). The ee was determined on IA column (hexanes/*iso*-propanol 95:5, flow 1.0 mL/min.) with $t_r$(minor) 11.3 min., $t_r$(major) 14.3 min.

$[\alpha]^{20}_D$ = –51.5 (c = 1.70, $CH_2Cl_2$), 82% ee, with (+)-Bpy*;
$^1$H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.28 (m, 1H), 7.24-7.23 (m, 1H), 7.08 (dd, *J* = 3.6, 1.2 Hz, 1H), 5.95 (s, 2H), 5.46 (d, *J* = 7.5 Hz, 1H), 5.32 (d, *J* = 8.4 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 170.1, 153.6, 138.2, 126.5, 126.4, 122.5, 82.7, 80.2, 54.3, 28.5(x3), 28.1(x3);
IR (film) $cm^{-1}$ 3430, 30054, 2983, 2306, 1714, 1493, 1369, 1265, 1154, 1055, 744, 705;
HRMS (ESI) calcd for $C_{15}H_{23}NO_4$ (M + $Na^+$) 336.1240, found 336.1246.




**2.** The compound was prepared according to GP B with (-)-Bpy* from 83.4 mg *tert*-Butyl α–diazo–α–phenyl-ester (0.383 mmol) and 60.0 mg $CbzNH_2$ (0.383 mmol) and 41.7 mg diazo *tert*-butylester (0.191 mmol) as a second portion. After chromatography on silica gel (0.5% ethylether in $CH_2Cl_2$), the title compound was isolated as a colorless oil: run 1, 100 mg (77%, 88% ee); run 2, 110 mg (77%, 94% ee). The ee was determined on AD-H column (hexanes/*iso*-propanol 95:5, flow 1.0 mL/min.) with $t_r$(minor) 19.5 min., $t_r$(major) 25.5 min.

$[\alpha]^{20}_D$ = –70.6 (c = 2.35, $CH_2Cl_2$), 94% ee, with (+)-Bpy*;
$^1$H NMR ($CDCl_3$, 300 MHz) δ 7.36 (broad s, 10H), 5.89 (d, *J* = 6.9 Hz, 1H), 5.28 (d, *J* = 7.5 Hz, 1H), 5.11 (dt, J = 8.7 Hz, 12 Hz, 2H), 1.40 (s, 9H);
$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 175.7, 155.5, 137.5, 136.4, 128.9(x2), 128.7(x2), 128.4(x2), 128.3 (x2), 127.1(x2), 82.8, 67.1, 58.5, 27.9(x3);
IR (film) $cm^{-1}$ 3424, 3055, 2984, 2306, 1722, 1498, 1266, 1153, 1051, 739, 704;
HRMS (ESI) calcd for $C_{20}H_{23}NO_4$ (M + $Na^+$) 364.1519, found 364.1520.




3. The compound was prepared according to GP B with (-)-Bpy* from 86.9 mg *tert*-Butyl α–diazo–α–4-methoxyphenyl-ester (0.350 mmol) and 55.0 mg $CbzNH_2$ (0.350 mmol) and 43.4 mg diazo *tert*-butylester (0.175 mmol) as a second portion. After chromatography on silica gel (100% $CH_2Cl_2$), the title compound was isolated as colorless oil: run 1, 62 mg (48%, 90% ee); run 2, 110 mg (49%, 90% ee). The ee was determined on AD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min.) with $t_r$(minor) 22.1 min., $t_r$(major) 24.5 min.

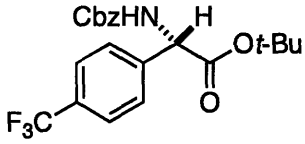
$[\alpha]^{20}_D$ = –92.4 (c = 1.30, $CH_2Cl_2$), 90% ee, with (+)-Bpy*;

$^1$H NMR ($CDCl_3$, 300 MHz) δ 7.27 (broad s, 5H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.76 (d, *J* = 7.2 Hz, 1H), 5.12 (d, *J* = 7.5 Hz, 1H), 5.02 (dt, J = 7.8 Hz, 12 Hz, 2H), 3.72 (s, 3H), 1.32 (s, 9H);

$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 170.2, 159.6, 155.5, 136.4, 129.7, 128.7(x2), 128.4(x5), 114.3 (x2), 82.6, 67.1, 58.0, 55.4, 28.0(x3);

IR (film) $cm^{-1}$ 3055, 2987, 2306, 1719, 1512, 1421, 1266, 1154, 896, 740, 705;

HRMS (ESI) calcd for $C_{21}H_{25}NO_5$ ($M + Na^+$) 394.1625, found 394.1619.




4. The compound was prepared according to GP B with (-)-Bpy* from 91.0 mg *tert*-Butyl α–diazo–α–4-trifluoromethylphenyl-ester (0.318 mmol) and 50.0 mg $CbzNH_2$ (0.318 mmol) and 50.0 mg diazo *tert*-butylester (0.159 mmol) as a second portion. After chromatography on silica gel (1.0% ethylether in $CH_2Cl_2$), the title compound was isolated as white residue: run 1, 105 mg (81%, 81% ee); run 2, 96.0 mg (74%, 83% ee). The ee was determined on AD-H column (hexanes/*iso*-propanol 95:5, flow 1.0 mL/min.) with $t_r$(minor) 16.2 min., $t_r$(major) 18.0 min.

$[\alpha]^{20}_D$ = – 92.7 (c = 1.20, $CH_2Cl_2$), 83% ee, with (+)-Bpy*;

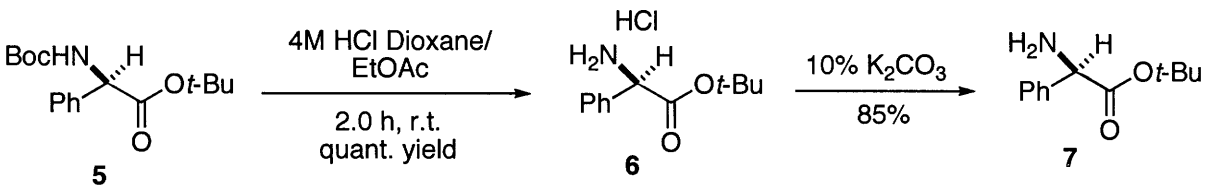
$^1$H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.36 (broad s, 5H), 6.06 (d, *J* = 6.6 Hz, 1H), 5.33 (d, *J* = 6.9 Hz, 1H), 5.10 (dt, J = 11.4 Hz, 12.3 Hz, 2H), 1.40 (s, 9H);

$^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 169.1, 155.5, 141.7, 136.2, 130.6 (q, $^2J_{CF}$ = 32.5 Hz), 128.7 (x2), 128.5, 128.4, 127.5(x2), 125.9 (q, $^3J_{CF}$ = 3.9 Hz), 122.3, 83.6, 67.3, 58.2, 27.9(x3);

IR (film) $cm^{-1}$ 3055, 2987, 2306, 1719, 1422, 1266, 1167, 896, 740, 705;

HRMS (ESI) calcd for $C_{21}H_{22}F_3NO_4$ ($M + Na^+$) 432.1393, found 432.1397.

*4.4.4. Determination of Absolute Configuration*




Into a vial containing *tert*-butyl α-(*tert*-butoxycarbonylamino)-α-diazoesters (**5**) (53.0 mg, 0.172 mmol) in ethyl acetate (0.5 mL) was added 4.0 M dioxane (0.2 mL) at room temperature. Resulting mixture was stirred for 2 hrs and evaporated down to dryness to obtain **6**. Resulting white residue was stirred in diethyl ether (2.0 mL) and 10% $K_2CO_3$ (1.0 mL) until all the solids dissolved. Separation of layers, extraction of the product with diethyl ether (1.0 mL x2) followed by brine wash, and dried over $MgSO_4$. After chromatography on silica gel (5% MeOH in EtOAc), (**7**) was isolated as crystalline residue (30.3mg, 85%y).

$[\alpha]^{20}_D$ = – 97.5 (c = 1.61, $CHCl_3$), from **5** (94% ee, with (+)-Bpy*) compared to the literature reported value of $[\alpha]^{20}_D$ = – 108 (c = 1.61, $CHCl_3$) for **7**;

$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.27 (m, 5H), 4.49 (s, 1H), 1.92 (s, 2H), 1.40 (s, 9H);

$^{13}$C NMR ($CDCl_3$, 126 MHz) δ 173.4, 141.1, 128.8, 127.9, 126.8, 81.7, 59.5, 29.9, 28.1.

## 4.5 References and Notes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## 4.6 $^{1}$H NMR for Selected Compounds

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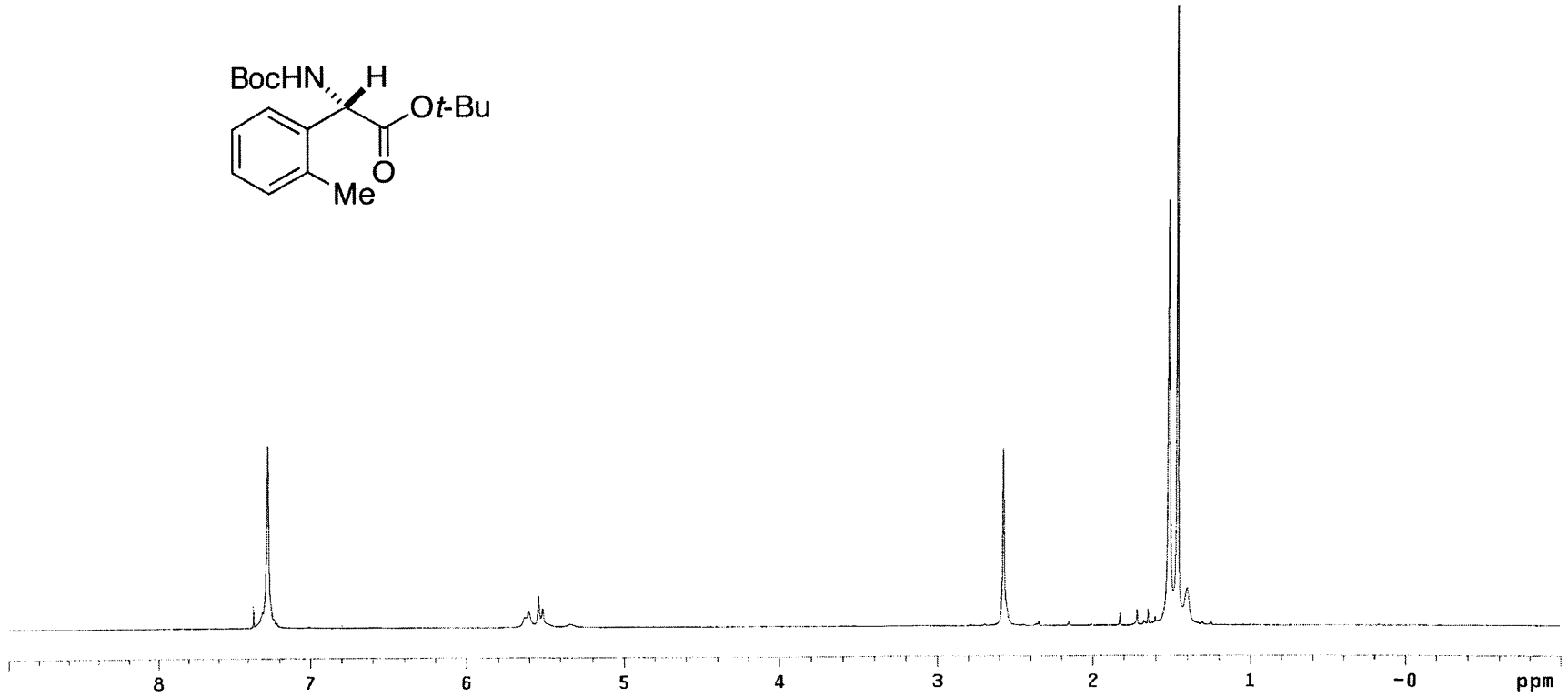
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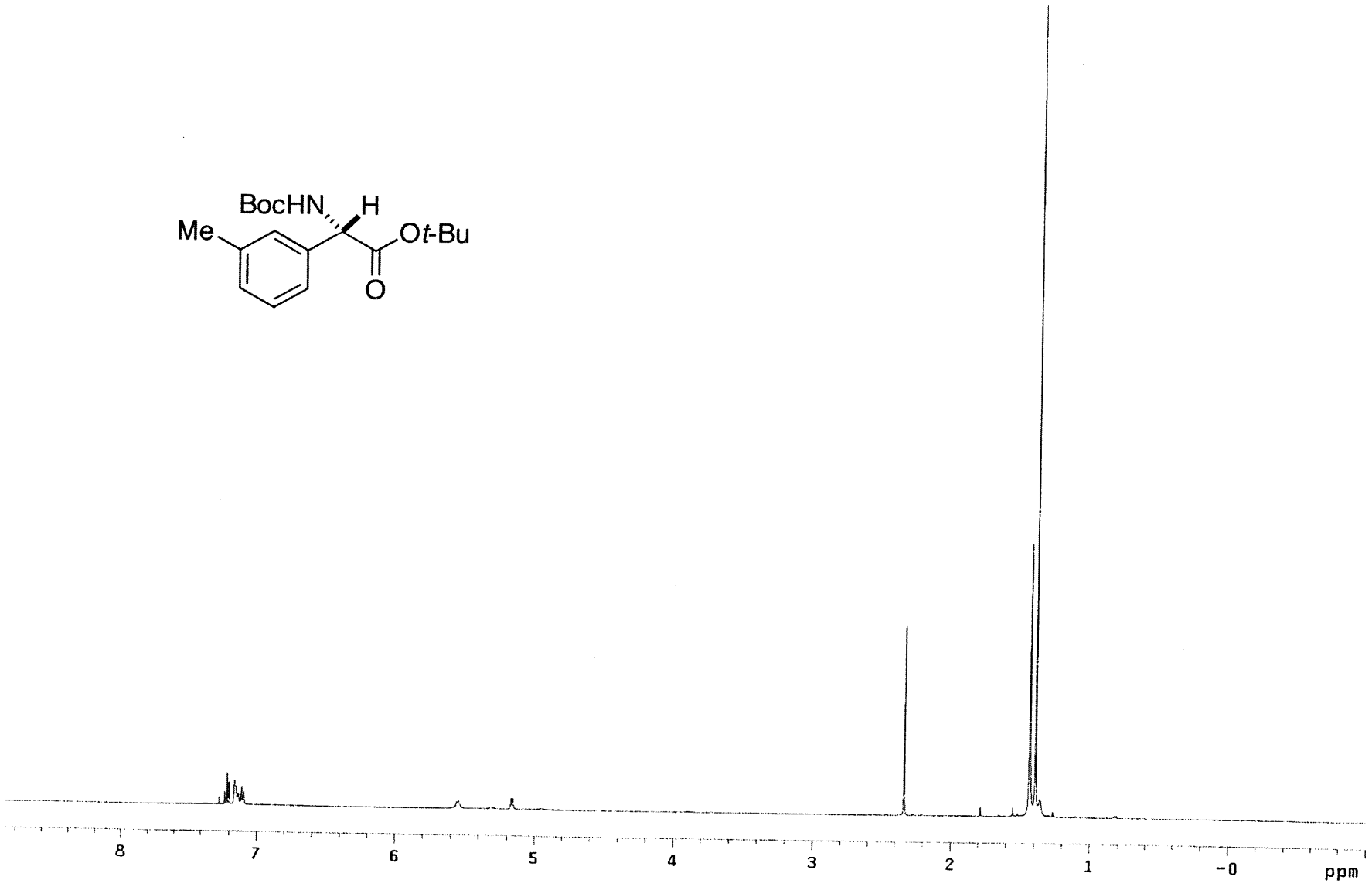
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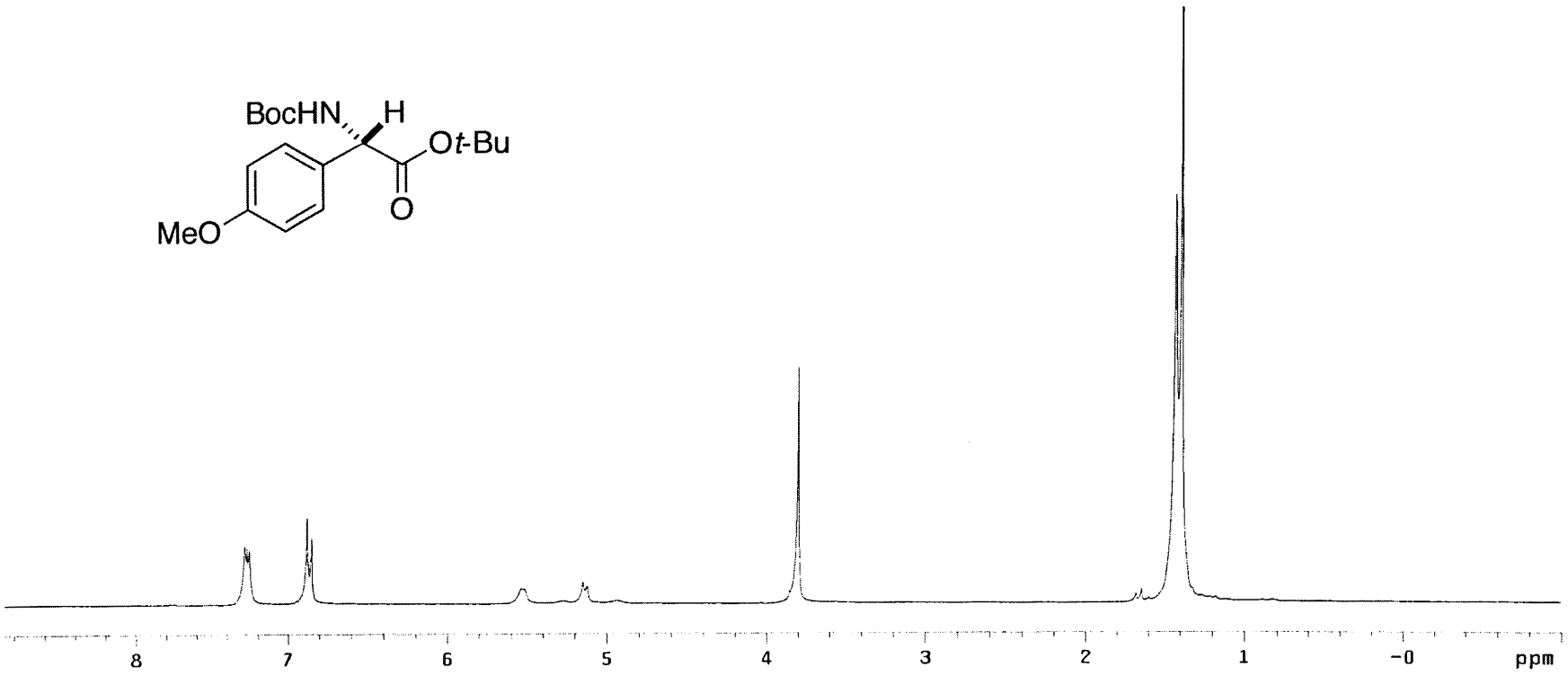
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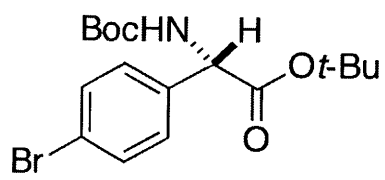
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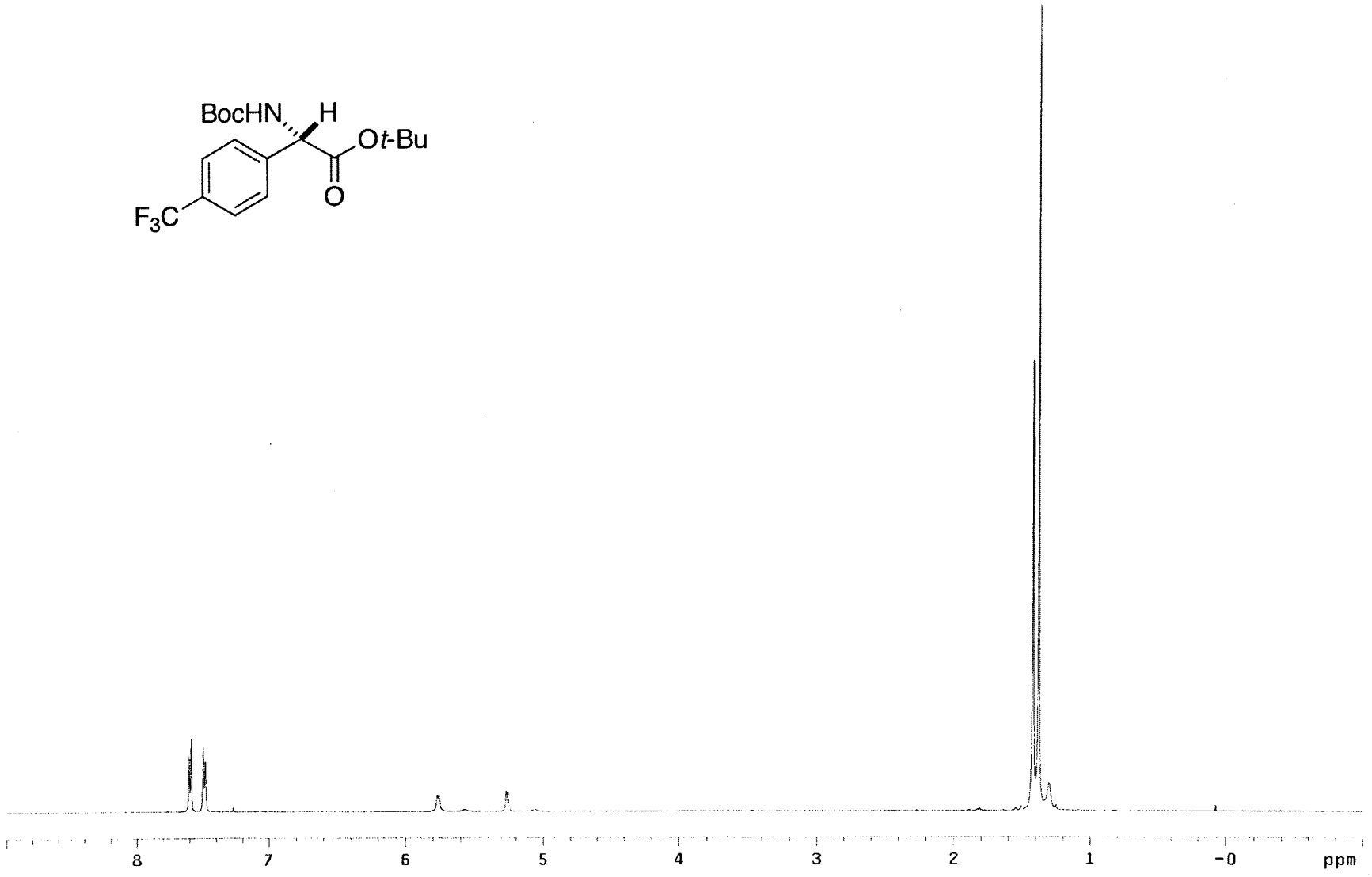
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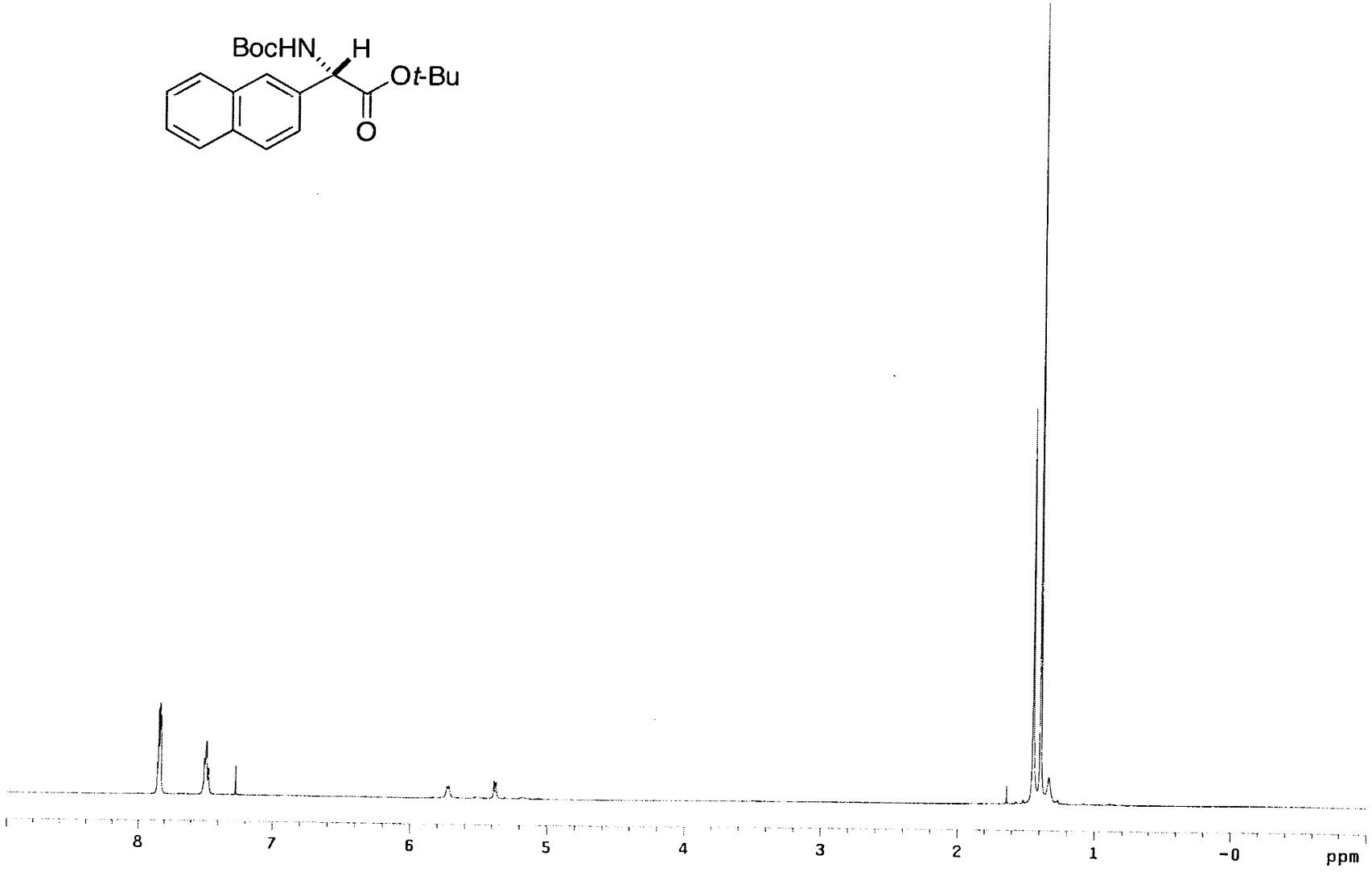
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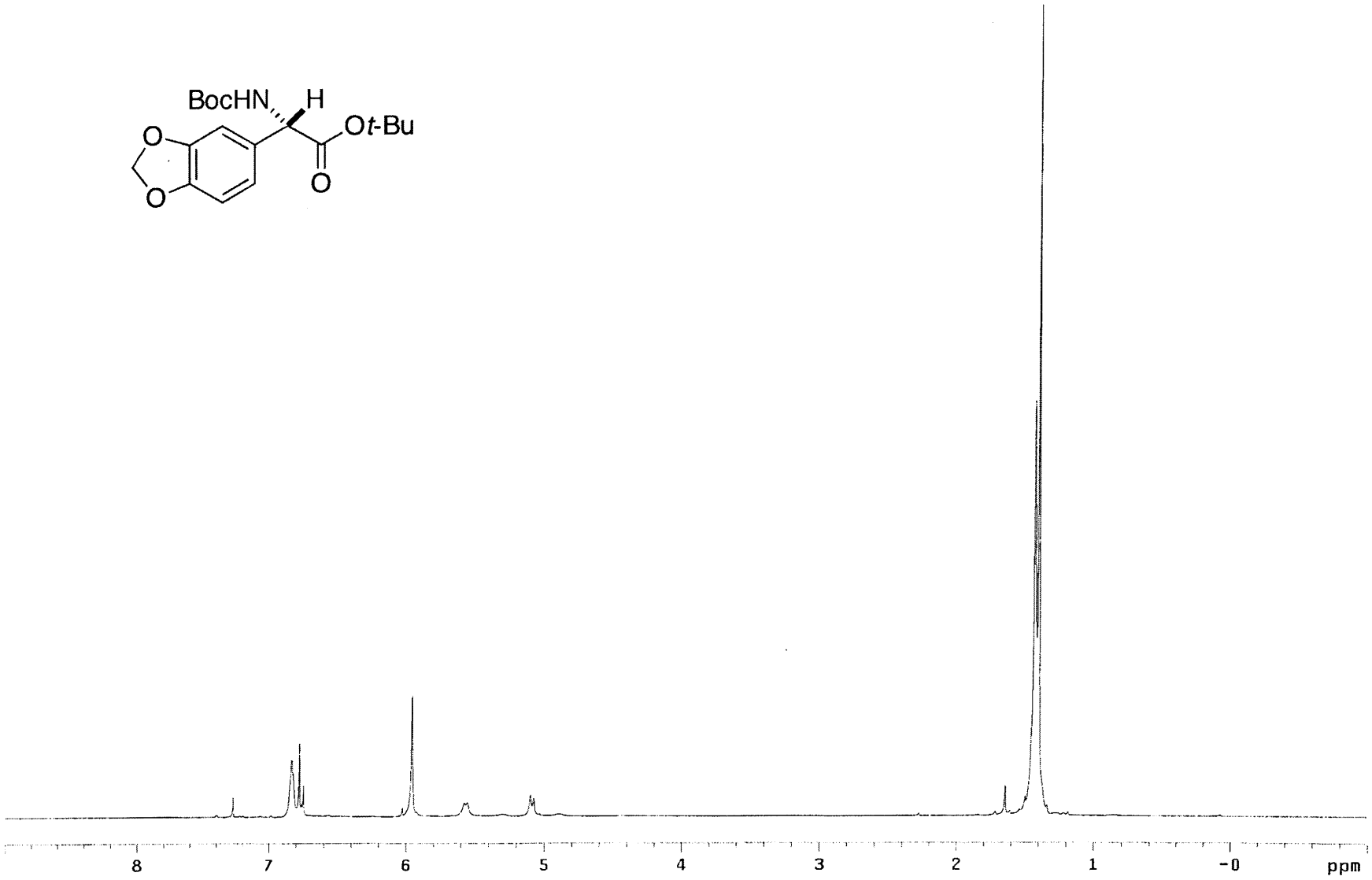
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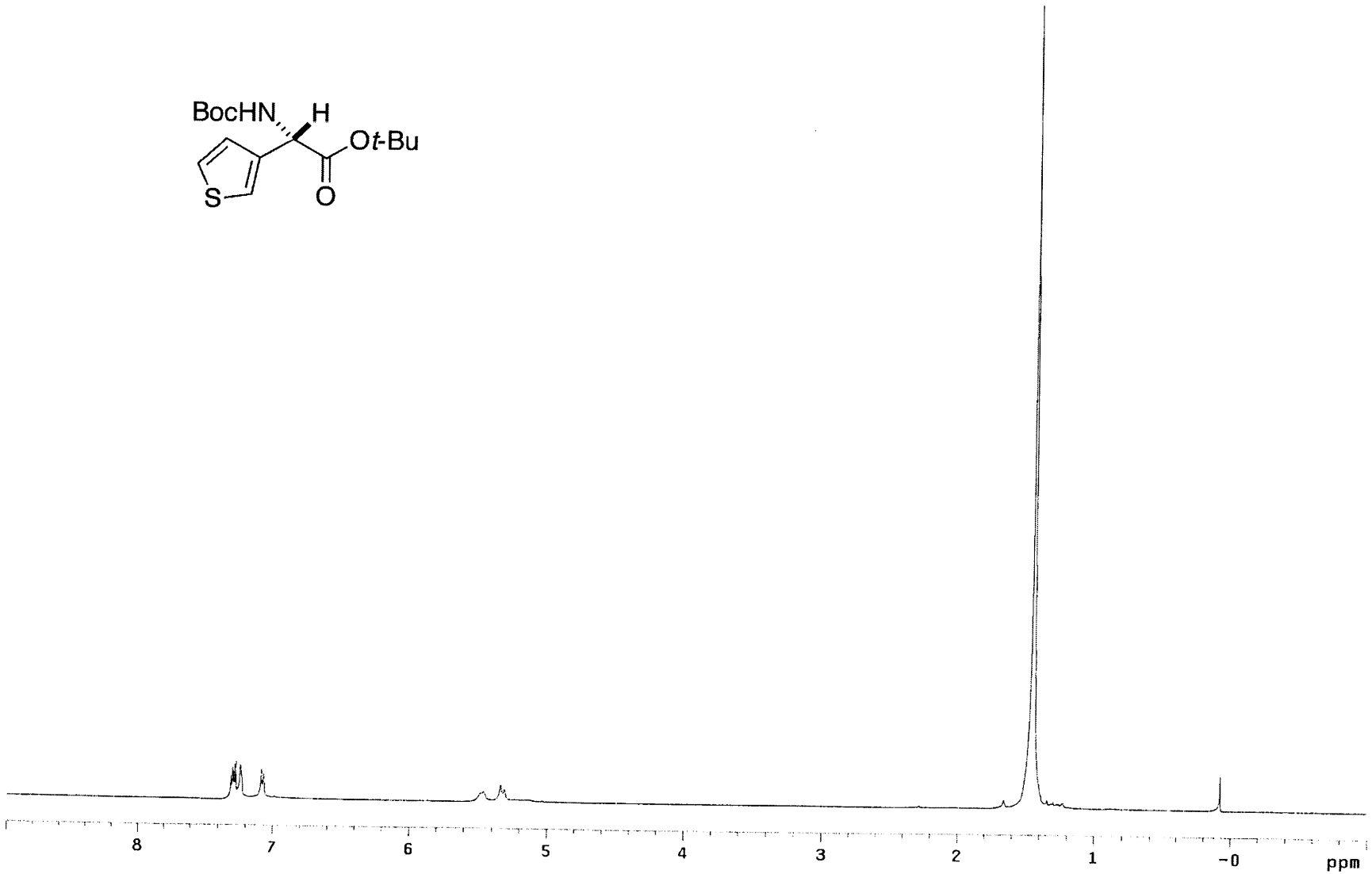
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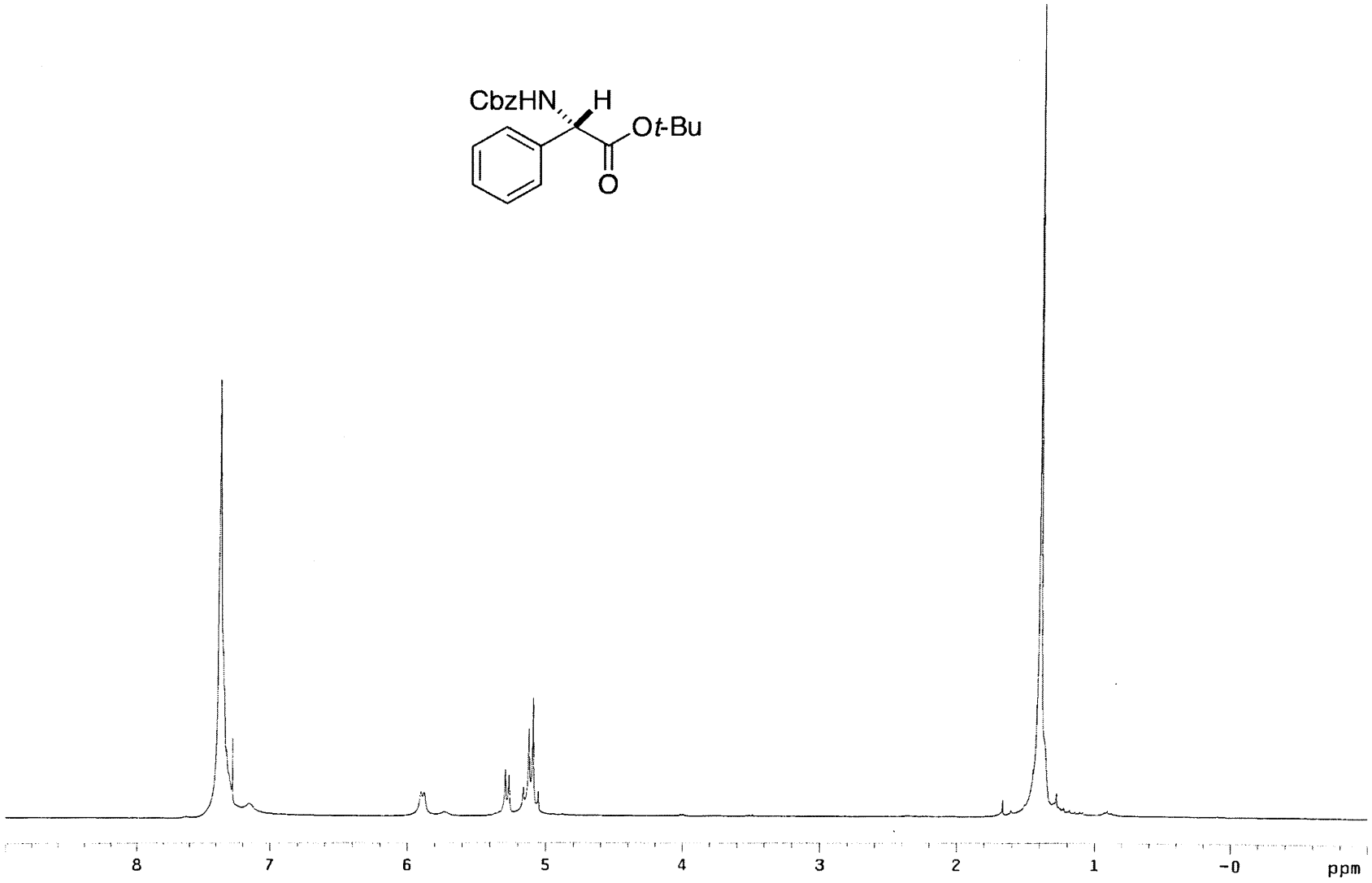
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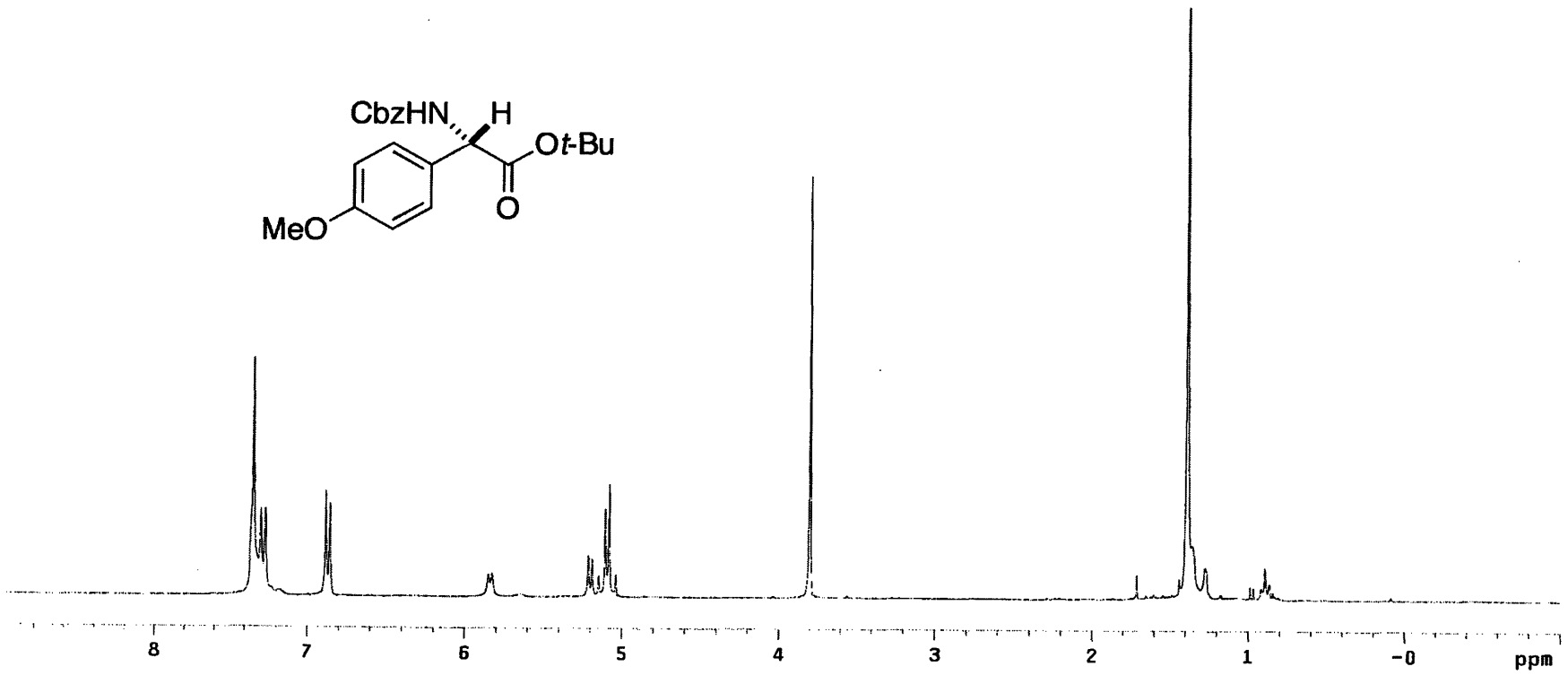
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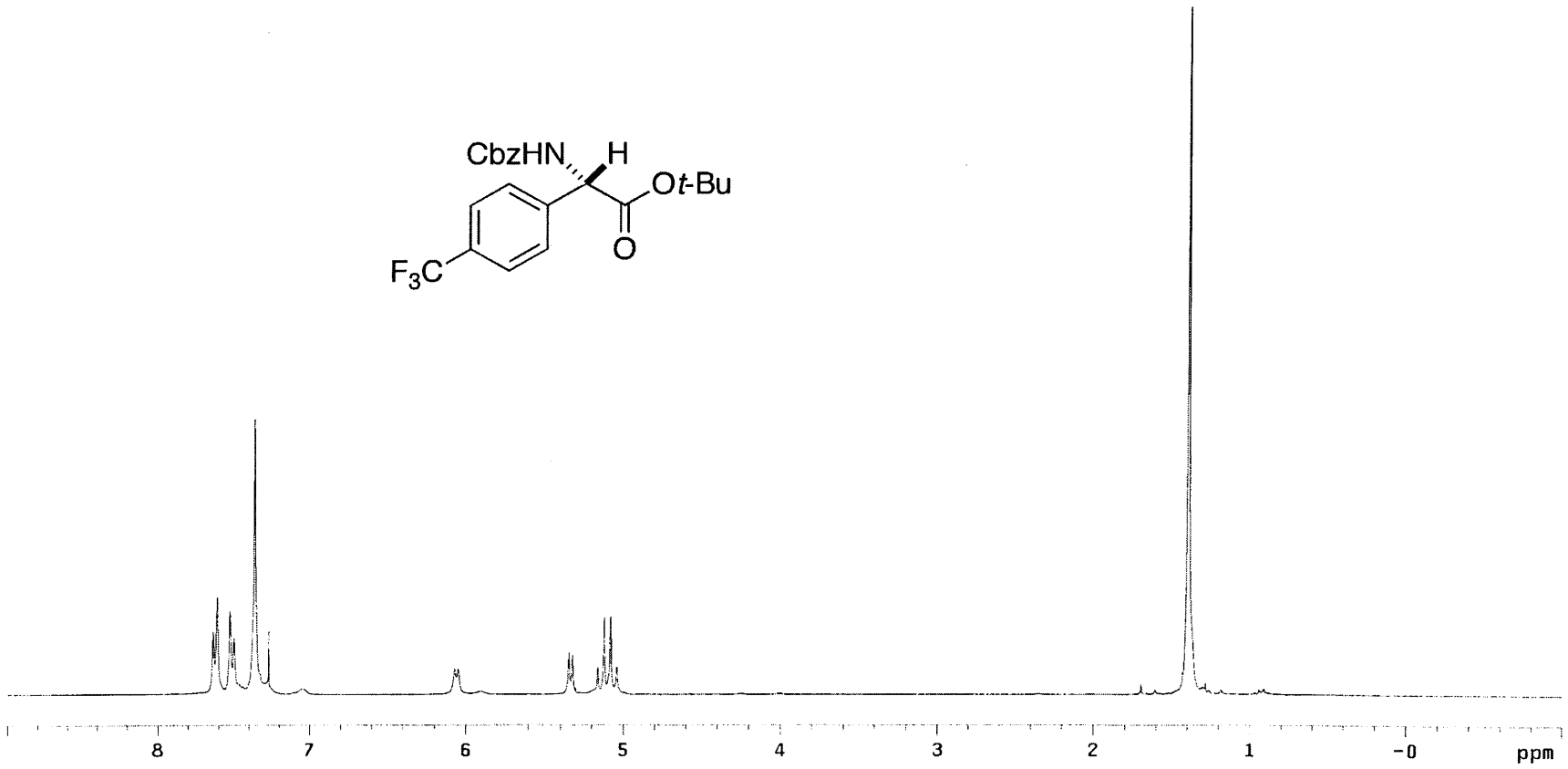
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3
2
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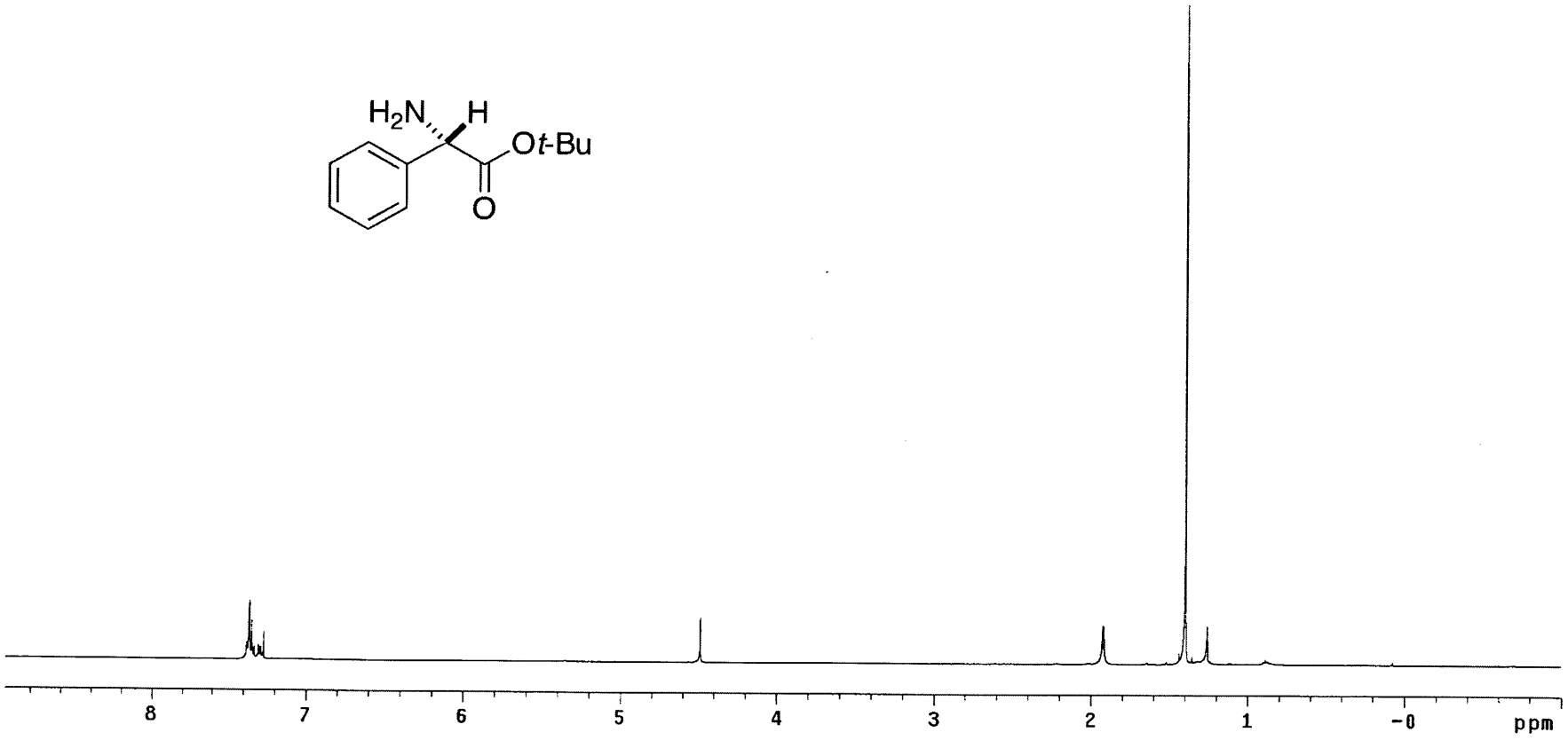
ppm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O
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ppm

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Massachusetts Institute of Technology, Ph.D., Chemistry, 2007
Loyola University of Chicago, B.S., Chemistry, 1991

**Massachusetts Institute of Technology** 2002 - 2007
*Graduate Student with Professor Gregory C. Fu*

- Currently investigating catalytic asymmetric N-H insertion reactions of α-diazoesters
- Developed first catalytic asymmetric methodology for constructing tertiary alkyl α-chloroesters
- Developed first catalytic asymmetric methodology for constructing *trans*-selective β-lactams via the Staudinger reaction
- Designed and developed a more efficient synthesis of the PPY* (4-(pyrrolidino)pyridine) catalyst
- Synthesized and examined a variety of borabenzenes and derivatives for potential use as chiral Lewis acids

*Teaching Assistant* 2002 - 2003

- Led discussion sections for two semesters of sophomore organic chemistry

**20th IUPAC Symposium on the Chemistry of Natural Products** 1996
*Associate Editor*

**Abbott Laboratories, GPRD, Process Research and Development** 1992 - 2002
*Research Scientist*

- Designed and developed efficient synthetic routes towards clinically active anti-epileptic, anti-Alzheimer, anti-bacterial and anti-mitotic compounds
- Collaborated efforts with medicinal, analytical, chemical engineering, and formulation departments for the development of drug candidates for Phase I/II clinical trials
- Performed scale-up reactions in accordance with cGMP protocol
- Collaborated on development of a new program for the biomimetic synthesis of drug metabolites by utilizing metalloporphyrins

**G.D. Searle, CNS Drug Research** 1989, 1990
*Summer Intern*

- Synthesized potent cyclic peptide intermediates

**Loyola University of Chicago** 1988 - 1990
*Undergraduate Researcher with Professor Charles M. Thompson*

- Synthesized chiral intermediates for further incorporation into heterocyclic natural products, such as Castanospermine

Abbott Laboratories, Associate Scientist of the Year, 1994
Technical Achievements in Organic Chemistry, ACS Organic Chemistry Division, 208th National Meeting, 1994

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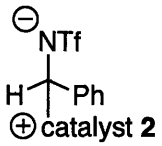
# Appendix A. X-ray Crystal Structure Data

X-ray Crystal Structure of Adduct **3** from Chapter 2, Eq 14.




**3**

Crystals suitable for X-ray structural analysis were obtained by crystallizing adduct **3** from acetonitrile at –30 °C.

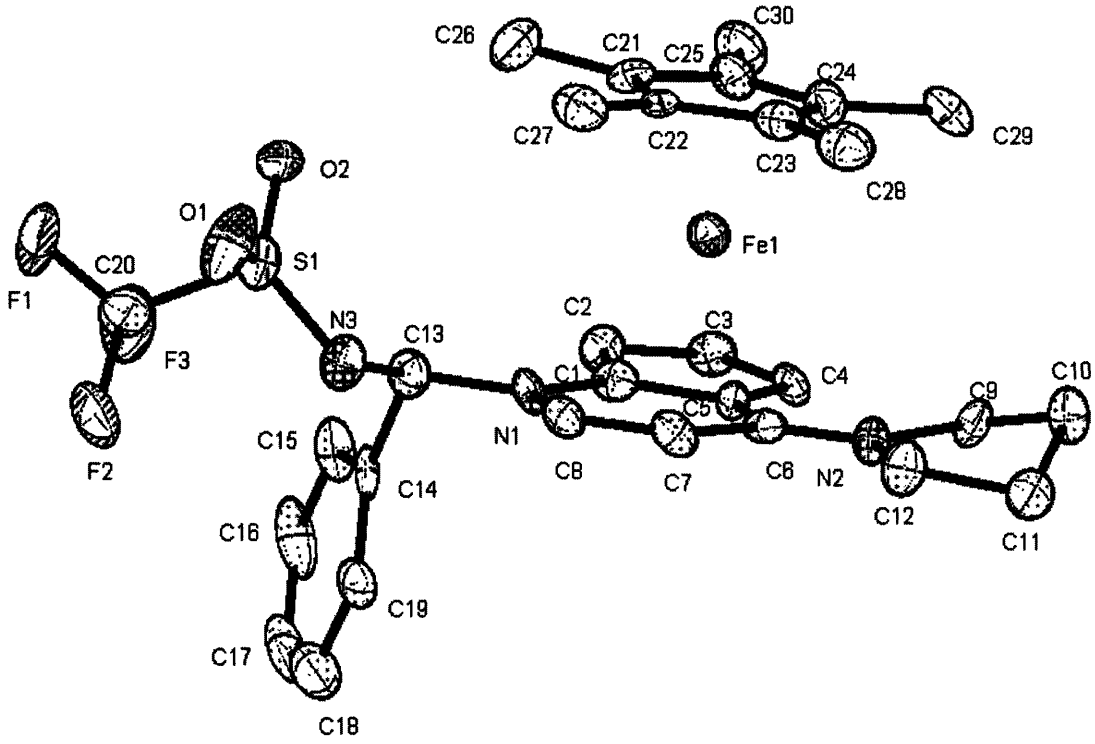


Table 1. Crystal data and structure refinement for **3**.

| | |
|---|---|
| Identification code | **3** |
| Empirical formula | $C_{33}H_{38.5}F_3FeN_{4.5}O_2S$ |
| Formula weight | 675.09 |
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | P2(1) |
| Unit cell dimensions | a = 12.9446(11) Å α= 90°.<br>b = 13.3261(12) Å β= 94.617(3)°.<br>c = 18.8459(16) Å γ = 90°. |
| Volume | 3240.4(5) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.384 $Mg/m^3$ |
| Absorption coefficient | 0.584 $mm^{-1}$ |
| F(000) | 1412 |
| Crystal size | 0.10 x 0.10 x 0.03 $mm^3$ |
| Theta range for data collection | 1.58 to 22.49°. |
| Index ranges | -13<=h<=13, -14<=k<=14, 0<=l<=20 |
| Reflections collected | 34504 |
| Independent reflections | 8451 [R(int) = 0.0992] |
| Completeness to theta = 22.49° | 100.0 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9827 and 0.9439 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 8451 / 1 / 815 |
| Goodness-of-fit on $F^2$ | 1.033 |
| Final R indices [I>2sigma(I)] | R1 = 0.0485, wR2 = 0.0835 |
| R indices (all data) | R1 = 0.0721, wR2 = 0.0923 |
| Absolute structure parameter | 0.014(17) |
| Largest diff. peak and hole | 0.419 and -0.266 $e.Å^{-3}$ |

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

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Fe(1) | -1138(1) | -8011(1) | -3462(1) | 20(1) |
| S(1) | -5338(1) | -9437(1) | -4163(1) | 27(1) |
| F(1) | -6715(3) | -10864(3) | -3984(2) | 46(1) |
| F(2) | -7008(3) | -9486(3) | -3462(2) | 71(1) |
| F(3) | -5795(3) | -10454(3) | -3031(2) | 51(1) |
| O(1) | -5982(3) | -9237(3) | -4802(2) | 47(1) |
| O(2) | -4537(3) | -10179(3) | -4199(2) | 37(1) |
| N(1) | -3495(3) | -7595(3) | -3393(2) | 17(1) |
| N(2) | -1560(3) | -5145(3) | -3810(2) | 19(1) |
| N(3) | -5044(3) | -8465(3) | -3778(2) | 25(1) |
| C(1) | -2481(4) | -7537(4) | -3054(3) | 20(1) |
| C(2) | -1978(4) | -8244(4) | -2589(3) | 21(1) |
| C(3) | -993(4) | -7831(4) | -2370(3) | 22(1) |
| C(4) | -878(4) | -6905(4) | -2709(3) | 18(1) |
| C(5) | -1805(4) | -6698(4) | -3156(3) | 16(1) |
| C(6) | -2149(4) | -5919(4) | -3660(3) | 16(1) |
| C(7) | -3164(4) | -6042(4) | -3991(3) | 21(1) |
| C(8) | -3775(4) | -6849(4) | -3848(3) | 18(1) |
| C(9) | -457(4) | -4998(4) | -3555(3) | 22(1) |
| C(10) | -90(4) | -4200(4) | -4052(3) | 27(2) |
| C(11) | -1058(4) | -3568(4) | -4224(3) | 26(2) |
| C(12) | -1917(4) | -4353(4) | -4311(3) | 27(2) |
| C(13) | -4170(4) | -8465(4) | -3246(3) | 22(1) |
| C(14) | -4519(4) | -8414(4) | -2492(3) | 19(1) |
| C(15) | -4200(4) | -9159(5) | -2003(3) | 33(2) |
| C(16) | -4517(5) | -9127(6) | -1322(3) | 42(2) |
| C(17) | -5168(5) | -8373(6) | -1123(3) | 43(2) |
| C(18) | -5504(5) | -7652(5) | -1617(3) | 39(2) |
| C(19) | -5175(4) | -7660(5) | -2296(3) | 27(2) |
| C(20) | -6251(5) | -10085(5) | -3636(4) | 38(2) |
| C(21) | -1101(4) | -9360(4) | -3981(3) | 26(2) |
| C(22) | -1470(4) | -8604(4) | -4461(3) | 23(2) |
| C(23) | -690(4) | -7849(4) | -4482(3) | 24(2) |
| C(24) | 169(4) | -8140(5) | -4001(3) | 24(1) |
| C(25) | -84(4) | -9082(5) | -3694(3) | 25(2) |
| C(26) | -1648(5) | -10331(5) | -3824(3) | 39(2) |
| C(27) | -2489(4) | -8592(5) | -4922(3) | 35(2) |
| C(28) | -748(5) | -6924(4) | -4950(3) | 31(2) |
| C(29) | 1193(4) | -7598(5) | -3845(3) | 29(2) |
| C(30) | 587(4) | -9696(5) | -3177(3) | 35(2) |
| Fe(2) | -3227(1) | -4738(1) | -1139(1) | 22(1) |

| | | | |
|---|---|---|---|
| S(101) 696(1) | -3023(1) | -176(1) | 28(1) |
| F(101) 2715(2) | -3297(3) | -228(2) | 48(1) |
| F(102) 1893(3) | -4596(3) | 112(2) | 43(1) |
| F(103) 2185(2) | -3348(3) | 830(2) | 46(1) |
| O(101) 26(3) | -3370(3) | 345(2) | 31(1) |
| O(102) 961(3) | -1976(3) | -158(2) | 32(1) |
| N(101) -1051(3) | -4097(3) | -1582(2) | 22(1) |
| N(102) -3651(3) | -3475(3) | -3001(2) | 22(1) |
| N(103) 449(4) | -3371(3) | -945(2) | 26(1) |
| C(101) -1854(4) | -4795(5) | -1645(3) | 22(1) |
| C(102) -2001(4) | -5686(4) | -1273(3) | 21(1) |
| C(103) -2932(4) | -6132(4) | -1556(3) | 22(1) |
| C(104) -3408(4) | -5496(4) | -2083(3) | 23(2) |
| C(105) -2755(4) | -4642(4) | -2154(3) | 18(1) |
| C(106) -2833(4) | -3723(4) | -2553(3) | 21(1) |
| C(107) -1977(4) | -3056(5) | -2447(3) | 26(1) |
| C(108) -1136(4) | -3266(4) | -1979(3) | 25(2) |
| C(109) -4642(4) | -4045(4) | -3092(3) | 29(2) |
| C(110) -5392(5) | -3279(4) | -3448(3) | 39(2) |
| C(111) -4719(5) | -2659(5) | -3891(3) | 38(2) |
| C(112) -3729(5) | -2526(5) | -3406(3) | 33(2) |
| C(113) -94(4) | -4309(4) | -1074(3) | 23(1) |
| C(114) 579(4) | -5085(4) | -1400(3) | 23(2) |
| C(115) 1140(4) | -4825(5) | -1982(3) | 27(2) |
| C(116) 1791(4) | -5521(5) | -2266(3) | 32(2) |
| C(117) 1869(5) | -6483(5) | -1983(3) | 33(2) |
| C(118) 1332(5) | -6738(5) | -1411(3) | 32(2) |
| C(119) 679(4) | -6048(4) | -1121(3) | 24(2) |
| C(120) 1934(5) | -3595(5) | 148(3) | 33(2) |
| C(121) -3214(4) | -3516(4) | -477(3) | 25(2) |
| C(122) -3161(4) | -4409(4) | -74(3) | 23(1) |
| C(123) -4057(5) | -5005(4) | -282(3) | 29(2) |
| C(124) -4679(4) | -4456(5) | -807(3) | 31(2) |
| C(125) -4159(4) | -3538(5) | -942(3) | 27(2) |
| C(126) -2470(5) | -2646(4) | -429(3) | 31(2) |
| C(127) -2322(4) | -4686(5) | 495(3) | 35(2) |
| C(128) -4292(5) | -6005(5) | 34(3) | 47(2) |
| C(129) -5721(4) | -4773(6) | -1160(3) | 46(2) |
| C(130) -4544(4) | -2701(5) | -1426(3) | 36(2) |
| N(1S) 983(6) | -12262(5) | -2878(4) | 74(2) |
| C(1S) 1615(6) | -12158(5) | -2436(4) | 55(2) |
| C(2S) 2368(6) | -12018(6) | -1839(4) | 64(2) |
| N(2S) -6420(4) | -5717(5) | -3484(3) | 51(2) |
| C(3S) -6521(5) | -6128(5) | -4021(4) | 35(2) |
| C(4S) -6611(5) | -6644(5) | -4705(3) | 39(2) |
| N(3S) -2049(5) | -10695(4) | -1949(3) | 56(2) |

| | | | | |
|---|---|---|---|---|
| C(5S) | -1255(7) | -10604(5) | -1636(4) | 50(2) |
| C(6S) | -223(6) | -10463(6) | -1270(3) | 61(2) |

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

| | |
|---|---|
| Fe(1)-C(25) | 2.045(6) |
| Fe(1)-C(21) | 2.049(6) |
| Fe(1)-C(24) | 2.049(5) |
| Fe(1)-C(22) | 2.054(5) |
| Fe(1)-C(5) | 2.055(5) |
| Fe(1)-C(4) | 2.056(5) |
| Fe(1)-C(1) | 2.058(6) |
| Fe(1)-C(23) | 2.062(5) |
| Fe(1)-C(3) | 2.066(5) |
| Fe(1)-C(2) | 2.068(5) |
| S(1)-O(1) | 1.434(4) |
| S(1)-O(2) | 1.439(4) |
| S(1)-N(3) | 1.517(5) |
| S(1)-C(20) | 1.822(7) |
| F(1)-C(20) | 1.343(7) |
| F(2)-C(20) | 1.325(7) |
| F(3)-C(20) | 1.336(7) |
| N(1)-C(8) | 1.344(6) |
| N(1)-C(1) | 1.415(6) |
| N(1)-C(13) | 1.491(7) |
| N(2)-C(6) | 1.326(6) |
| N(2)-C(12) | 1.466(6) |
| N(2)-C(9) | 1.482(6) |
| N(3)-C(13) | 1.451(6) |
| C(1)-C(2) | 1.410(7) |
| C(1)-C(5) | 1.443(7) |
| C(2)-C(3) | 1.419(7) |
| C(3)-C(4) | 1.403(7) |
| C(4)-C(5) | 1.437(7) |
| C(5)-C(6) | 1.452(7) |
| C(6)-C(7) | 1.418(7) |
| C(7)-C(8) | 1.374(7) |
| C(9)-C(10) | 1.518(7) |
| C(10)-C(11) | 1.523(7) |
| C(11)-C(12) | 1.527(7) |
| C(13)-C(14) | 1.527(7) |
| C(14)-C(19) | 1.384(7) |
| C(14)-C(15) | 1.394(7) |
| C(15)-C(16) | 1.380(8) |
| C(16)-C(17) | 1.382(9) |
| C(17)-C(18) | 1.383(8) |
| C(18)-C(19) | 1.382(8) |
| C(21)-C(22) | 1.410(8) |
| C(21)-C(25) | 1.432(7) |

| | |
|---|---|
| C(21)-C(26) | 1.516(8) |
| C(22)-C(23) | 1.428(8) |
| C(22)-C(27) | 1.520(7) |
| C(23)-C(24) | 1.431(7) |
| C(23)-C(28) | 1.515(8) |
| C(24)-C(25) | 1.431(8) |
| C(24)-C(29) | 1.517(7) |
| C(25)-C(30) | 1.495(7) |
| Fe(2)-C(123) | 2.042(5) |
| Fe(2)-C(104) | 2.043(6) |
| Fe(2)-C(122) | 2.048(5) |
| Fe(2)-C(121) | 2.051(6) |
| Fe(2)-C(125) | 2.055(6) |
| Fe(2)-C(105) | 2.059(5) |
| Fe(2)-C(102) | 2.060(6) |
| Fe(2)-C(124) | 2.062(6) |
| Fe(2)-C(103) | 2.065(6) |
| Fe(2)-C(101) | 2.085(5) |
| S(101)-O(102) | 1.437(4) |
| S(101)-O(101) | 1.438(4) |
| S(101)-N(103) | 1.531(4) |
| S(101)-C(120) | 1.834(6) |
| F(101)-C(120) | 1.340(7) |
| F(102)-C(120) | 1.336(7) |
| F(103)-C(120) | 1.341(6) |
| N(101)-C(108) | 1.336(7) |
| N(101)-C(101) | 1.394(7) |
| N(101)-C(113) | 1.529(6) |
| N(102)-C(106) | 1.341(6) |
| N(102)-C(112) | 1.477(7) |
| N(102)-C(109) | 1.488(7) |
| N(103)-C(113) | 1.445(7) |
| C(101)-C(102) | 1.398(8) |
| C(101)-C(105) | 1.463(7) |
| C(102)-C(103) | 1.410(7) |
| C(103)-C(104) | 1.408(7) |
| C(104)-C(105) | 1.431(8) |
| C(105)-C(106) | 1.437(7) |
| C(106)-C(107) | 1.423(7) |
| C(107)-C(108) | 1.374(7) |
| C(109)-C(110) | 1.526(7) |
| C(110)-C(111) | 1.502(8) |
| C(111)-C(112) | 1.523(7) |
| C(113)-C(114) | 1.513(8) |
| C(114)-C(119) | 1.389(7) |
| C(114)-C(115) | 1.407(7) |

| | |
|---|---|
| C(115)-C(116) | 1.389(8) |
| C(116)-C(117) | 1.389(8) |
| C(117)-C(118) | 1.372(8) |
| C(118)-C(119) | 1.390(8) |
| C(121)-C(122) | 1.410(8) |
| C(121)-C(125) | 1.446(8) |
| C(121)-C(126) | 1.505(8) |
| C(122)-C(123) | 1.434(8) |
| C(122)-C(127) | 1.509(7) |
| C(123)-C(124) | 1.425(8) |
| C(123)-C(128) | 1.501(8) |
| C(124)-C(125) | 1.429(8) |
| C(124)-C(129) | 1.516(8) |
| C(125)-C(130) | 1.500(8) |
| N(1S)-C(1S) | 1.129(8) |
| C(1S)-C(2S) | 1.441(9) |
| N(2S)-C(3S) | 1.150(8) |
| C(3S)-C(4S) | 1.456(9) |
| N(3S)-C(5S) | 1.150(8) |
| C(5S)-C(6S) | 1.465(10) |

| | |
|---|---|
| C(25)-Fe(1)-C(21) | 40.9(2) |
| C(25)-Fe(1)-C(24) | 40.9(2) |
| C(21)-Fe(1)-C(24) | 68.8(2) |
| C(25)-Fe(1)-C(22) | 68.3(2) |
| C(21)-Fe(1)-C(22) | 40.2(2) |
| C(24)-Fe(1)-C(22) | 68.6(2) |
| C(25)-Fe(1)-C(5) | 163.1(2) |
| C(21)-Fe(1)-C(5) | 155.2(2) |
| C(24)-Fe(1)-C(5) | 126.4(2) |
| C(22)-Fe(1)-C(5) | 121.5(2) |
| C(25)-Fe(1)-C(4) | 125.0(2) |
| C(21)-Fe(1)-C(4) | 161.9(2) |
| C(24)-Fe(1)-C(4) | 107.9(2) |
| C(22)-Fe(1)-C(4) | 156.8(2) |
| C(5)-Fe(1)-C(4) | 40.91(19) |
| C(25)-Fe(1)-C(1) | 153.2(2) |
| C(21)-Fe(1)-C(1) | 120.0(2) |
| C(24)-Fe(1)-C(1) | 165.4(2) |
| C(22)-Fe(1)-C(1) | 109.9(2) |
| C(5)-Fe(1)-C(1) | 41.1(2) |
| C(4)-Fe(1)-C(1) | 67.5(2) |
| C(25)-Fe(1)-C(23) | 68.4(2) |
| C(21)-Fe(1)-C(23) | 68.2(2) |
| C(24)-Fe(1)-C(23) | 40.7(2) |
| C(22)-Fe(1)-C(23) | 40.6(2) |

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|---|---|
| C(5)-Fe(1)-C(23) | 109.2(2) |
| C(4)-Fe(1)-C(23) | 121.7(2) |
| C(1)-Fe(1)-C(23) | 128.7(2) |
| C(25)-Fe(1)-C(3) | 106.6(2) |
| C(21)-Fe(1)-C(3) | 125.0(2) |
| C(24)-Fe(1)-C(3) | 119.4(2) |
| C(22)-Fe(1)-C(3) | 162.3(2) |
| C(5)-Fe(1)-C(3) | 68.1(2) |
| C(4)-Fe(1)-C(3) | 39.8(2) |
| C(1)-Fe(1)-C(3) | 66.6(2) |
| C(23)-Fe(1)-C(3) | 155.0(2) |
| C(25)-Fe(1)-C(2) | 117.9(2) |
| C(21)-Fe(1)-C(2) | 106.4(2) |
| C(24)-Fe(1)-C(2) | 152.8(2) |
| C(22)-Fe(1)-C(2) | 125.9(2) |
| C(5)-Fe(1)-C(2) | 69.2(2) |
| C(4)-Fe(1)-C(2) | 68.0(2) |
| C(1)-Fe(1)-C(2) | 40.0(2) |
| C(23)-Fe(1)-C(2) | 164.2(2) |
| C(3)-Fe(1)-C(2) | 40.16(19) |
| O(1)-S(1)-O(2) | 117.5(3) |
| O(1)-S(1)-N(3) | 110.4(3) |
| O(2)-S(1)-N(3) | 117.1(2) |
| O(1)-S(1)-C(20) | 100.8(3) |
| O(2)-S(1)-C(20) | 101.6(3) |
| N(3)-S(1)-C(20) | 107.0(3) |
| C(8)-N(1)-C(1) | 116.1(5) |
| C(8)-N(1)-C(13) | 124.2(4) |
| C(1)-N(1)-C(13) | 119.7(4) |
| C(6)-N(2)-C(12) | 122.7(4) |
| C(6)-N(2)-C(9) | 126.0(4) |
| C(12)-N(2)-C(9) | 111.1(4) |
| C(13)-N(3)-S(1) | 118.8(4) |
| C(2)-C(1)-N(1) | 127.5(5) |
| C(2)-C(1)-C(5) | 110.3(5) |
| N(1)-C(1)-C(5) | 122.2(5) |
| C(2)-C(1)-Fe(1) | 70.4(3) |
| N(1)-C(1)-Fe(1) | 126.5(4) |
| C(5)-C(1)-Fe(1) | 69.4(3) |
| C(1)-C(2)-C(3) | 106.3(5) |
| C(1)-C(2)-Fe(1) | 69.6(3) |
| C(3)-C(2)-Fe(1) | 69.8(3) |
| C(4)-C(3)-C(2) | 109.6(5) |
| C(4)-C(3)-Fe(1) | 69.7(3) |
| C(2)-C(3)-Fe(1) | 70.0(3) |
| C(3)-C(4)-C(5) | 108.7(5) |

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|---|---|
| C(3)-C(4)-Fe(1) | 70.5(3) |
| C(5)-C(4)-Fe(1) | 69.5(3) |
| C(4)-C(5)-C(1) | 105.1(5) |
| C(4)-C(5)-C(6) | 135.9(5) |
| C(1)-C(5)-C(6) | 118.9(5) |
| C(4)-C(5)-Fe(1) | 69.6(3) |
| C(1)-C(5)-Fe(1) | 69.6(3) |
| C(6)-C(5)-Fe(1) | 122.6(4) |
| N(2)-C(6)-C(7) | 121.6(5) |
| N(2)-C(6)-C(5) | 123.0(5) |
| C(7)-C(6)-C(5) | 115.4(5) |
| C(8)-C(7)-C(6) | 122.2(5) |
| N(1)-C(8)-C(7) | 125.0(5) |
| N(2)-C(9)-C(10) | 103.5(4) |
| C(9)-C(10)-C(11) | 103.1(4) |
| C(10)-C(11)-C(12) | 102.9(5) |
| N(2)-C(12)-C(11) | 103.6(4) |
| N(3)-C(13)-N(1) | 107.9(4) |
| N(3)-C(13)-C(14) | 111.8(4) |
| N(1)-C(13)-C(14) | 111.1(4) |
| C(19)-C(14)-C(15) | 119.8(5) |
| C(19)-C(14)-C(13) | 120.9(5) |
| C(15)-C(14)-C(13) | 119.3(5) |
| C(16)-C(15)-C(14) | 119.9(6) |
| C(15)-C(16)-C(17) | 120.5(6) |
| C(16)-C(17)-C(18) | 119.3(6) |
| C(19)-C(18)-C(17) | 120.9(6) |
| C(18)-C(19)-C(14) | 119.6(6) |
| F(2)-C(20)-F(3) | 107.2(6) |
| F(2)-C(20)-F(1) | 106.0(5) |
| F(3)-C(20)-F(1) | 106.4(5) |
| F(2)-C(20)-S(1) | 112.0(5) |
| F(3)-C(20)-S(1) | 112.2(4) |
| F(1)-C(20)-S(1) | 112.6(5) |
| C(22)-C(21)-C(25) | 108.2(5) |
| C(22)-C(21)-C(26) | 126.6(5) |
| C(25)-C(21)-C(26) | 125.2(5) |
| C(22)-C(21)-Fe(1) | 70.1(3) |
| C(25)-C(21)-Fe(1) | 69.4(3) |
| C(26)-C(21)-Fe(1) | 128.8(4) |
| C(21)-C(22)-C(23) | 108.5(5) |
| C(21)-C(22)-C(27) | 127.4(6) |
| C(23)-C(22)-C(27) | 124.1(5) |
| C(21)-C(22)-Fe(1) | 69.7(3) |
| C(23)-C(22)-Fe(1) | 70.0(3) |
| C(27)-C(22)-Fe(1) | 128.9(4) |

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|---|---|
| C(22)-C(23)-C(24) | 107.9(5) |
| C(22)-C(23)-C(28) | 126.0(5) |
| C(24)-C(23)-C(28) | 126.1(5) |
| C(22)-C(23)-Fe(1) | 69.4(3) |
| C(24)-C(23)-Fe(1) | 69.1(3) |
| C(28)-C(23)-Fe(1) | 128.6(4) |
| C(23)-C(24)-C(25) | 107.6(5) |
| C(23)-C(24)-C(29) | 128.0(6) |
| C(25)-C(24)-C(29) | 124.4(5) |
| C(23)-C(24)-Fe(1) | 70.1(3) |
| C(25)-C(24)-Fe(1) | 69.4(3) |
| C(29)-C(24)-Fe(1) | 127.4(4) |
| C(24)-C(25)-C(21) | 107.9(5) |
| C(24)-C(25)-C(30) | 127.1(5) |
| C(21)-C(25)-C(30) | 125.0(5) |
| C(24)-C(25)-Fe(1) | 69.7(3) |
| C(21)-C(25)-Fe(1) | 69.7(3) |
| C(30)-C(25)-Fe(1) | 127.3(4) |
| C(123)-Fe(2)-C(104) | 124.9(2) |
| C(123)-Fe(2)-C(122) | 41.1(2) |
| C(104)-Fe(2)-C(122) | 162.1(2) |
| C(123)-Fe(2)-C(121) | 68.7(2) |
| C(104)-Fe(2)-C(121) | 156.5(2) |
| C(122)-Fe(2)-C(121) | 40.2(2) |
| C(123)-Fe(2)-C(125) | 68.8(2) |
| C(104)-Fe(2)-C(125) | 120.9(2) |
| C(122)-Fe(2)-C(125) | 68.6(2) |
| C(121)-Fe(2)-C(125) | 41.3(2) |
| C(123)-Fe(2)-C(105) | 163.8(2) |
| C(104)-Fe(2)-C(105) | 40.8(2) |
| C(122)-Fe(2)-C(105) | 154.8(2) |
| C(121)-Fe(2)-C(105) | 121.8(2) |
| C(125)-Fe(2)-C(105) | 110.0(2) |
| C(123)-Fe(2)-C(102) | 116.8(2) |
| C(104)-Fe(2)-C(102) | 68.0(2) |
| C(122)-Fe(2)-C(102) | 106.2(2) |
| C(121)-Fe(2)-C(102) | 126.4(2) |
| C(125)-Fe(2)-C(102) | 165.6(2) |
| C(105)-Fe(2)-C(102) | 68.5(2) |
| C(123)-Fe(2)-C(124) | 40.6(2) |
| C(104)-Fe(2)-C(124) | 108.1(2) |
| C(122)-Fe(2)-C(124) | 68.4(2) |
| C(121)-Fe(2)-C(124) | 68.5(2) |
| C(125)-Fe(2)-C(124) | 40.6(2) |
| C(105)-Fe(2)-C(124) | 128.1(2) |
| C(102)-Fe(2)-C(124) | 151.5(2) |

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|---|---|
| C(123)-Fe(2)-C(103) | 105.7(2) |
| C(104)-Fe(2)-C(103) | 40.1(2) |
| C(122)-Fe(2)-C(103) | 124.9(2) |
| C(121)-Fe(2)-C(103) | 162.5(2) |
| C(125)-Fe(2)-C(103) | 153.9(2) |
| C(105)-Fe(2)-C(103) | 67.9(2) |
| C(102)-Fe(2)-C(103) | 40.0(2) |
| C(124)-Fe(2)-C(103) | 118.7(2) |
| C(123)-Fe(2)-C(101) | 151.4(2) |
| C(104)-Fe(2)-C(101) | 68.0(2) |
| C(122)-Fe(2)-C(101) | 119.1(2) |
| C(121)-Fe(2)-C(101) | 110.0(2) |
| C(125)-Fe(2)-C(101) | 130.2(2) |
| C(105)-Fe(2)-C(101) | 41.34(19) |
| C(102)-Fe(2)-C(101) | 39.4(2) |
| C(124)-Fe(2)-C(101) | 167.6(2) |
| C(103)-Fe(2)-C(101) | 66.5(2) |
| O(102)-S(101)-O(101) | 116.9(2) |
| O(102)-S(101)-N(103) | 110.3(2) |
| O(101)-S(101)-N(103) | 117.2(2) |
| O(102)-S(101)-C(120) | 101.3(3) |
| O(101)-S(101)-C(120) | 101.5(3) |
| N(103)-S(101)-C(120) | 107.4(3) |
| C(108)-N(101)-C(101) | 118.6(5) |
| C(108)-N(101)-C(113) | 122.0(5) |
| C(101)-N(101)-C(113) | 119.4(5) |
| C(106)-N(102)-C(112) | 123.6(5) |
| C(106)-N(102)-C(109) | 125.2(5) |
| C(112)-N(102)-C(109) | 110.8(4) |
| C(113)-N(103)-S(101) | 118.9(4) |
| N(101)-C(101)-C(102) | 130.9(5) |
| N(101)-C(101)-C(105) | 120.8(5) |
| C(102)-C(101)-C(105) | 108.3(5) |
| N(101)-C(101)-Fe(2) | 126.4(4) |
| C(102)-C(101)-Fe(2) | 69.3(3) |
| C(105)-C(101)-Fe(2) | 68.4(3) |
| C(101)-C(102)-C(103) | 108.3(5) |
| C(101)-C(102)-Fe(2) | 71.2(3) |
| C(103)-C(102)-Fe(2) | 70.2(3) |
| C(104)-C(103)-C(102) | 109.0(5) |
| C(104)-C(103)-Fe(2) | 69.1(3) |
| C(102)-C(103)-Fe(2) | 69.8(3) |
| C(103)-C(104)-C(105) | 108.4(5) |
| C(103)-C(104)-Fe(2) | 70.8(3) |
| C(105)-C(104)-Fe(2) | 70.2(3) |
| C(104)-C(105)-C(106) | 135.2(5) |

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|---|---|
| C(104)-C(105)-C(101) | 105.9(5) |
| C(106)-C(105)-C(101) | 118.8(5) |
| C(104)-C(105)-Fe(2) | 69.0(3) |
| C(106)-C(105)-Fe(2) | 121.7(4) |
| C(101)-C(105)-Fe(2) | 70.3(3) |
| N(102)-C(106)-C(107) | 120.1(5) |
| N(102)-C(106)-C(105) | 124.0(5) |
| C(107)-C(106)-C(105) | 116.0(5) |
| C(108)-C(107)-C(106) | 122.1(6) |
| N(101)-C(108)-C(107) | 123.6(5) |
| N(102)-C(109)-C(110) | 102.8(5) |
| C(111)-C(110)-C(109) | 103.6(5) |
| C(110)-C(111)-C(112) | 103.3(5) |
| N(102)-C(112)-C(111) | 103.3(5) |
| N(103)-C(113)-C(114) | 111.7(4) |
| N(103)-C(113)-N(101) | 107.7(4) |
| C(114)-C(113)-N(101) | 109.7(4) |
| C(119)-C(114)-C(115) | 118.9(6) |
| C(119)-C(114)-C(113) | 121.2(5) |
| C(115)-C(114)-C(113) | 119.9(5) |
| C(116)-C(115)-C(114) | 120.2(6) |
| C(117)-C(116)-C(115) | 119.7(6) |
| C(118)-C(117)-C(116) | 120.3(6) |
| C(117)-C(118)-C(119) | 120.5(6) |
| C(114)-C(119)-C(118) | 120.3(6) |
| F(102)-C(120)-F(101) | 107.3(5) |
| F(102)-C(120)-F(103) | 107.4(5) |
| F(101)-C(120)-F(103) | 107.4(5) |
| F(102)-C(120)-S(101) | 111.6(4) |
| F(101)-C(120)-S(101) | 112.1(4) |
| F(103)-C(120)-S(101) | 110.7(4) |
| C(122)-C(121)-C(125) | 108.1(5) |
| C(122)-C(121)-C(126) | 127.9(5) |
| C(125)-C(121)-C(126) | 123.9(5) |
| C(122)-C(121)-Fe(2) | 69.8(3) |
| C(125)-C(121)-Fe(2) | 69.5(3) |
| C(126)-C(121)-Fe(2) | 128.5(4) |
| C(121)-C(122)-C(123) | 108.5(5) |
| C(121)-C(122)-C(127) | 126.2(5) |
| C(123)-C(122)-C(127) | 125.3(5) |
| C(121)-C(122)-Fe(2) | 70.0(3) |
| C(123)-C(122)-Fe(2) | 69.2(3) |
| C(127)-C(122)-Fe(2) | 127.9(4) |
| C(124)-C(123)-C(122) | 107.7(5) |
| C(124)-C(123)-C(128) | 127.6(6) |
| C(122)-C(123)-C(128) | 124.7(5) |

| | |
|---|---|
| C(124)-C(123)-Fe(2) | 70.5(3) |
| C(122)-C(123)-Fe(2) | 69.7(3) |
| C(128)-C(123)-Fe(2) | 127.2(4) |
| C(123)-C(124)-C(125) | 108.4(5) |
| C(123)-C(124)-C(129) | 126.5(6) |
| C(125)-C(124)-C(129) | 125.1(6) |
| C(123)-C(124)-Fe(2) | 68.9(3) |
| C(125)-C(124)-Fe(2) | 69.4(3) |
| C(129)-C(124)-Fe(2) | 128.0(4) |
| C(124)-C(125)-C(121) | 107.3(5) |
| C(124)-C(125)-C(130) | 127.4(5) |
| C(121)-C(125)-C(130) | 125.2(6) |
| C(124)-C(125)-Fe(2) | 70.0(3) |
| C(121)-C(125)-Fe(2) | 69.2(3) |
| C(130)-C(125)-Fe(2) | 129.9(4) |
| N(1S)-C(1S)-C(2S) | 176.1(9) |
| N(2S)-C(3S)-C(4S) | 178.0(7) |
| N(3S)-C(5S)-C(6S) | 177.0(8) |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **3**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12} ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Fe(1) | 16(1) | 22(1) | 22(1) | -2(1) | 1(1) | 1(1) |
| S(1) | 24(1) | 27(1) | 29(1) | -1(1) | -1(1) | -6(1) |
| F(1) | 37(2) | 34(2) | 65(3) | -1(2) | -4(2) | -17(2) |
| F(2) | 33(2) | 45(3) | 139(4) | -10(3) | 41(2) | -3(2) |
| F(3) | 60(3) | 51(3) | 41(2) | 9(2) | 3(2) | -21(2) |
| O(1) | 58(3) | 44(3) | 34(3) | 3(2) | -23(2) | -21(3) |
| O(2) | 26(3) | 31(3) | 57(3) | -20(2) | 12(2) | -2(2) |
| N(1) | 9(3) | 19(3) | 21(2) | 6(2) | 2(2) | 1(2) |
| N(2) | 19(3) | 19(3) | 19(3) | 2(2) | 1(2) | -4(2) |
| N(3) | 23(3) | 24(3) | 26(3) | 4(2) | -6(2) | -1(2) |
| C(1) | 19(4) | 24(4) | 17(3) | -3(3) | -2(3) | 2(3) |
| C(2) | 27(4) | 20(4) | 16(3) | 3(3) | 2(3) | -2(3) |
| C(3) | 20(3) | 23(4) | 23(3) | -1(3) | -2(2) | 5(3) |
| C(4) | 10(3) | 21(4) | 24(3) | 0(3) | 3(3) | 1(3) |
| C(5) | 16(3) | 16(3) | 16(3) | -3(3) | 3(2) | -5(3) |
| C(6) | 15(3) | 18(3) | 15(3) | -4(3) | -1(2) | 4(3) |
| C(7) | 20(3) | 25(4) | 19(3) | 8(3) | 5(3) | 5(3) |
| C(8) | 14(3) | 23(4) | 17(3) | 1(3) | 1(2) | 3(3) |
| C(9) | 20(3) | 16(4) | 30(3) | -3(3) | -4(3) | -4(3) |
| C(10) | 23(4) | 27(4) | 31(3) | 7(3) | 1(3) | -4(3) |
| C(11) | 32(4) | 27(4) | 18(3) | 2(3) | 3(3) | -4(3) |
| C(12) | 29(4) | 23(4) | 27(3) | 7(3) | -1(3) | -3(3) |
| C(13) | 18(3) | 23(3) | 24(3) | 0(3) | -1(3) | -1(3) |
| C(14) | 15(3) | 22(3) | 20(3) | 6(3) | 0(2) | -11(3) |
| C(15) | 23(4) | 34(4) | 40(4) | 10(3) | 3(3) | -7(3) |
| C(16) | 31(4) | 62(5) | 31(4) | 26(4) | -1(3) | -19(4) |
| C(17) | 31(4) | 71(6) | 27(4) | -2(4) | 11(3) | -23(4) |
| C(18) | 28(4) | 55(5) | 33(4) | -9(4) | 7(3) | -7(3) |
| C(19) | 14(3) | 37(4) | 31(4) | -7(3) | 1(3) | -6(3) |
| C(20) | 22(4) | 31(4) | 61(5) | -10(4) | 3(4) | 7(4) |
| C(21) | 30(4) | 14(3) | 33(3) | -7(3) | 10(3) | 3(3) |
| C(22) | 22(4) | 26(4) | 22(3) | -18(3) | 9(3) | -7(3) |
| C(23) | 24(4) | 24(4) | 23(3) | -4(3) | 5(3) | 4(3) |
| C(24) | 24(4) | 27(4) | 22(3) | 0(3) | 4(3) | -5(3) |
| C(25) | 15(3) | 29(4) | 30(3) | -2(3) | 2(3) | 3(3) |
| C(26) | 36(4) | 28(4) | 54(4) | -13(4) | 3(3) | -4(3) |
| C(27) | 23(4) | 53(5) | 27(3) | -17(3) | -2(3) | 0(3) |
| C(28) | 31(4) | 39(4) | 24(3) | -4(3) | 1(3) | 4(3) |
| C(29) | 20(4) | 37(4) | 31(3) | 3(3) | 10(3) | 4(3) |
| C(30) | 25(3) | 33(4) | 48(4) | 5(4) | 8(3) | 6(3) |
| Fe(2) | 23(1) | 24(1) | 21(1) | -2(1) | 4(1) | 2(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| S(101) | 30(1) | 28(1) | 24(1) | -3(1) | -3(1) | -1(1) |
| F(101) | 28(2) | 63(3) | 53(2) | -6(2) | 3(2) | -2(2) |
| F(102) | 49(2) | 34(2) | 44(2) | -6(2) | -13(2) | 6(2) |
| F(103) | 45(2) | 54(3) | 36(2) | -8(2) | -17(2) | 1(2) |
| O(101) | 35(2) | 39(3) | 20(2) | -3(2) | 5(2) | -2(2) |
| O(102) | 42(3) | 24(3) | 29(2) | 0(2) | -7(2) | -3(2) |
| N(101) | 26(3) | 23(3) | 17(3) | 2(2) | 1(2) | -1(3) |
| N(102) | 25(3) | 20(3) | 22(3) | 6(2) | -1(2) | 1(2) |
| N(103) | 31(3) | 30(3) | 17(2) | 0(2) | -3(2) | -4(3) |
| C(101) | 27(4) | 24(4) | 17(3) | -7(3) | 8(3) | -7(3) |
| C(102) | 20(4) | 29(4) | 14(3) | 7(3) | 0(3) | 4(3) |
| C(103) | 25(4) | 17(4) | 27(3) | 1(3) | 10(3) | -1(3) |
| C(104) | 25(4) | 23(4) | 21(3) | 4(3) | 3(3) | 2(3) |
| C(105) | 20(3) | 20(4) | 16(3) | 0(3) | 4(2) | 7(3) |
| C(106) | 20(3) | 28(4) | 16(3) | -8(3) | 3(3) | 1(3) |
| C(107) | 38(4) | 22(3) | 18(3) | 0(3) | 6(3) | -3(4) |
| C(108) | 27(4) | 27(4) | 21(3) | -6(3) | 3(3) | -4(3) |
| C(109) | 29(4) | 24(4) | 33(4) | 0(3) | 0(3) | 2(3) |
| C(110) | 41(4) | 30(4) | 42(4) | 2(3) | -7(3) | 5(3) |
| C(111) | 45(4) | 37(4) | 30(4) | 3(3) | -6(3) | 15(3) |
| C(112) | 34(4) | 32(4) | 30(4) | -1(3) | -7(3) | 7(3) |
| C(113) | 24(4) | 23(4) | 22(3) | 8(3) | -1(3) | -3(3) |
| C(114) | 18(3) | 34(4) | 15(3) | -2(3) | -7(3) | -1(3) |
| C(115) | 24(4) | 35(4) | 22(3) | 1(3) | -3(3) | -6(3) |
| C(116) | 18(4) | 54(5) | 26(4) | -10(4) | 5(3) | 3(4) |
| C(117) | 26(4) | 42(5) | 31(4) | -19(3) | -10(3) | 9(3) |
| C(118) | 26(4) | 35(4) | 32(4) | -4(3) | -11(3) | 6(3) |
| C(119) | 19(4) | 31(4) | 23(3) | 0(3) | -3(3) | 3(3) |
| C(120) | 37(4) | 35(4) | 28(4) | -9(3) | 0(3) | 0(4) |
| C(121) | 31(4) | 25(4) | 19(3) | -3(3) | 6(3) | 3(3) |
| C(122) | 30(4) | 20(4) | 21(3) | -6(3) | 11(3) | 7(3) |
| C(123) | 41(4) | 24(4) | 24(3) | 1(3) | 16(3) | 4(3) |
| C(124) | 27(4) | 33(5) | 35(4) | -6(3) | 15(3) | 2(3) |
| C(125) | 29(4) | 28(4) | 26(3) | -4(3) | 10(3) | 10(3) |
| C(126) | 45(4) | 25(4) | 24(3) | -5(3) | 4(3) | 4(3) |
| C(127) | 41(4) | 40(4) | 25(3) | -4(3) | 2(3) | 7(4) |
| C(128) | 57(5) | 42(5) | 45(4) | 4(4) | 26(4) | -11(4) |
| C(129) | 26(4) | 55(5) | 58(4) | -23(4) | 14(3) | -1(4) |
| C(130) | 33(4) | 41(5) | 34(4) | -9(3) | 4(3) | 15(3) |
| N(1S) | 97(6) | 50(5) | 70(5) | 20(4) | -20(4) | -21(4) |
| C(1S) | 64(6) | 37(5) | 61(5) | 0(4) | -10(5) | -8(4) |
| C(2S) | 63(6) | 71(6) | 59(5) | -9(5) | 5(4) | -4(5) |
| N(2S) | 43(4) | 56(5) | 57(4) | -3(4) | 22(3) | -6(3) |
| C(3S) | 22(4) | 39(5) | 45(5) | 11(4) | 10(3) | 2(3) |
| C(4S) | 33(4) | 45(5) | 40(4) | 11(4) | 4(3) | 0(3) |
| N(3S) | 77(5) | 33(4) | 55(4) | -3(3) | -11(4) | 11(4) |

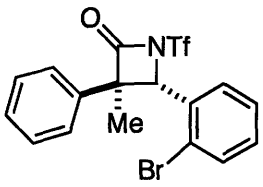
| | | | | | | |
|---|---|---|---|---|---|---|
| C(5S) | 85(7) | 28(4) | 36(5) | 1(4) | -2(4) | 20(4) |
| C(6S) | 82(6) | 56(5) | 39(4) | -9(4) | -27(4) | 34(5) |

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

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | -2245 | -8872 | -2451 | 26 |
| H(3) | -490 | -8134 | -2044 | 27 |
| H(4) | -285 | -6484 | -2651 | 22 |
| H(7) | -3430 | -5552 | -4322 | 25 |
| H(8) | -4448 | -6880 | -4089 | 22 |
| H(9A) | -59 | -5628 | -3592 | 27 |
| H(9B) | -389 | -4765 | -3055 | 27 |
| H(10A) | 153 | -4504 | -4488 | 32 |
| H(10B) | 477 | -3794 | -3814 | 32 |
| H(11A) | -1009 | -3181 | -4669 | 31 |
| H(11B) | -1173 | -3098 | -3831 | 31 |
| H(12A) | -2587 | -4071 | -4188 | 32 |
| H(12B) | -1997 | -4611 | -4805 | 32 |
| H(13) | -3766 | -9098 | -3295 | 26 |
| H(15) | -3764 | -9687 | -2139 | 39 |
| H(16) | -4286 | -9628 | -987 | 50 |
| H(17) | -5382 | -8351 | -653 | 51 |
| H(18) | -5968 | -7144 | -1487 | 47 |
| H(19) - | 5397 | -7152 | -2627 | 33 |
| H(26A) | -2397 | -10248 | -3931 | 59 |
| H(26B) | -1504 | -10502 | -3320 | 59 |
| H(26C) | -1397 | -10870 | -4119 | 59 |
| H(27A) | -2394 | -8912 | -5380 | 52 |
| H(27B) | -2717 | -7897 | -5001 | 52 |
| H(27C) | -3015 | -8961 | -4681 | 52 |
| H(28A) | -217 | -6442 | -4772 | 47 |
| H(28B) | -1434 | -6617 | -4943 | 47 |
| H(28C) | -629 | -7114 | -5439 | 47 |
| H(29A) | 1727 | -7920 | -4107 | 43 |
| H(29B) | 1397 | -7628 | -3333 | 43 |
| H(29C) | 1117 | -6895 | -3993 | 43 |
| H(30A) | 1000 | -10165 | -3438 | 53 |
| H(30B) | 150 | -10073 | -2870 | 53 |
| H(30C) | 1050 | -9252 | -2885 | 53 |
| H(102) | -1550 | -5945 | -895 | 25 |
| H(103) | -3195 | -6760 | -1415 | 27 |
| H(104) | -4054 | -5615 | -2346 | 28 |
| H(107) | -1987 | -2446 | -2708 | 31 |
| H(108) | -584 | -2794 | -1935 | 30 |
| H(10C) | -4868 | -4263 | -2627 | 35 |
| H(10D) | -4575 | -4641 | -3398 | 35 |

| | | | | |
|---|---|---|---|---|
| H(11C) | -5950 | -3616 | -3750 | 46 |
| H(11D) | -5708 | -2861 | -3089 | 46 |
| H(11E) | -5045 | -2003 | -4014 | 46 |
| H(11F) | -4579 | -3014 | -4335 | 46 |
| H(11G) | -3122 | -2433 | -3687 | 39 |
| H(11H) | -3783 | -1944 | -3085 | 39 |
| H(113) | -320 | -4572 | -614 | 28 |
| H(115) | 1072 | -4171 | -2182 | 33 |
| H(116) | 2182 | -5339 | -2652 | 39 |
| H(117) | 2296 | -6966 | -2186 | 40 |
| H(118) | 1406 | -7391 | -1211 | 38 |
| H(119) | 300 | -6236 | -731 | 29 |
| H(12A) | -2712 | -2139 | -105 | 47 |
| H(12B) | -2431 | -2351 | -903 | 47 |
| H(12C) | -1781 | -2883 | -249 | 47 |
| H(12D) | -1689 | -4312 | 418 | 53 |
| H(12E) | -2183 | -5408 | 472 | 53 |
| H(12F) | -2551 | -4518 | 964 | 53 |
| H(12G) | -4602 | -5904 | 486 | 70 |
| H(12H) | -3649 | -6391 | 118 | 70 |
| H(12I) | -4778 | -6373 | -296 | 70 |
| H(12J) | -5729 | -5503 | -1228 | 69 |
| H(12K) | -5837 | -4441 | -1623 | 69 |
| H(12L) | -6270 | -4582 | -858 | 69 |
| H(13A) | -5028 | -2969 | -1805 | 54 |
| H(13B) | -3957 | -2385 | -1635 | 54 |
| H(13C) | -4900 | -2201 | -1152 | 54 |
| H(2S1) | 2029 | -12092 | -1395 | 96 |
| H(2S2) | 2669 | -11345 | -1860 | 96 |
| H(2S3) | 2917 | -12522 | -1855 | 96 |
| H(4S1) | -6168 | -6311 | -5031 | 59 |
| H(4S2) | -7333 | -6623 | -4905 | 59 |
| H(4S3) | -6391 | -7344 | -4638 | 59 |
| H(6S1) | 299 | -10483 | -1618 | 91 |
| H(6S2) | -85 | -11000 | -920 | 91 |
| H(6S3) | -193 | -9813 | -1027 | 91 |

Determination of Absolute Configuration




**Chapter 2, Table 6, Entry 8.** Crystals of the β-lactam product were suitable for X-ray structural analysis were obtained by dissolving the b-lactam in benzene and adding pentane at 0 °C.

A colorless needle of dimensions 0.4 x 0.19 x 0.16 $mm^3$ was mounted under STP and transferred to a Bruker AXS/CCD three-circle diffractometer equipped with a cold stream of $N_2$ gas. An initial unit cell was determined with monochromated Mo Kα radiation (l = 0.71073 Å). The cell thus determined was triclinic.

The raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. The data that were collected (4966 total reflections, 4073 unique, $R_{int}$ = 0.0266) had the following Miller index ranges: –9 to 8 in h, –12 to 13 in k, and –13 to 10 in l. SADABS absorption correction was performed, and the maximum and minimum effective transmissions were 0.808038 and 0.251115, respectively.

All aspects of the solution and refinement were handled by SHELXTL NT version 5.10. The structure was solved by direct methods in the triclinic space group P1, a = 8.7897(7) Å; b = 12.2246(9) Å; c = 12.4432(9) Å; α= 93.8300(10)°; β = 108.5630(10)°; γ = 100.5330(10)°, and refined using standard difference Fourier techniques. Final, full-matrix least-squares refinement (4073 data for 616 parameters) on $F^2$ yielded residuals of R1 and wR2 of 0.0558 and 0.1485 for data I > 2s(I), and 0.0577 and 0.1508, 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 riding model. No extinction coefficient was used in the refinement. Residual electron density amounted to a maximum of 0.871 e/$Å^3$ and a minimum of –0.562 e/$Å^3$.

The absolute structure (Flack) parameter for the correct enantiomer is 0.060(12). The structure was inverted and refined in order to confirm the initial assignment of absolute stereochemistry.

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

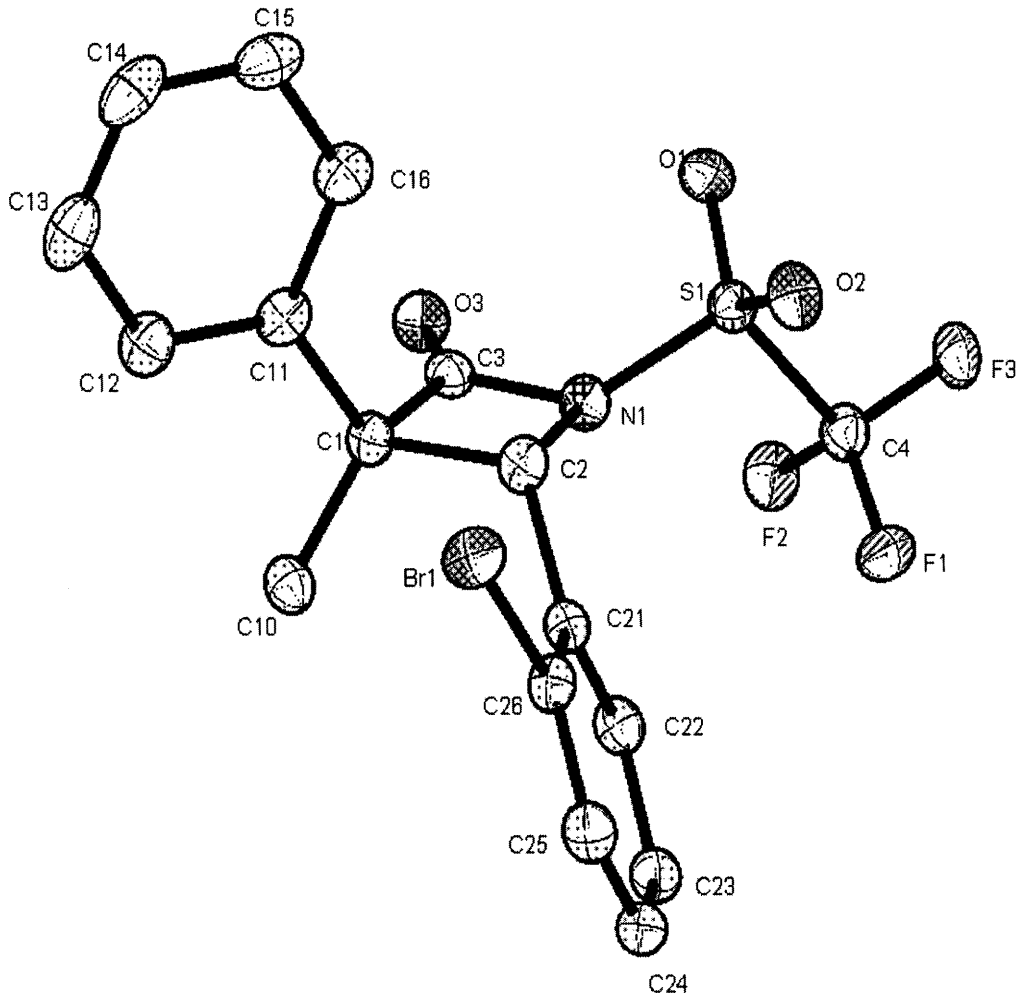

C15
C14
C16
C13
O1
S1
O2
O3
C3
F3
C12
C11
N1
C1
C2
C4
F2
F1
Br1
C10
C21
C26
C22
C25
C23
C24

Table 1. Crystal data and structure refinement for **Chapter 2, Table 6, Entry 8.**

| | |
|---|---|
| Identification code | **Chapter 2, Table 6, Entry 8** |
| Empirical formula | $C_{17}H_{13}BrF_3NO_3S$ |
| Formula weight | 448.25 |
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions | a = 7.2080(3) Å α= 90°.<br>b = 8.7647(3) Å β= 90°.<br>c = 27.1374(11) Å γ = 90°. |
| Volume | 1714.43(12) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.737 $Mg/m^3$ |
| Absorption coefficient | 2.568 $mm^{-1}$ |
| F(000) | 896 |
| Crystal size | 0.20 x 0.20 x 0.10 $mm^3$ |
| Theta range for data collection | 2.44 to 26.37°. |
| Index ranges | -8<=h<=9, 0<=k<=10, 0<=l<=33 |
| Reflections collected | 26769 |
| Independent reflections | 3480 [R(int) = 0.0329] |
| Completeness to theta = 26.37° | 99.9 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7833 and 0.6276 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3480 / 0 / 236 |
| Goodness-of-fit on $F^2$ | 1.059 |
| Final R indices [I>2sigma(I)] | R1 = 0.0260, wR2 = 0.0653 |
| R indices (all data) | R1 = 0.0272, wR2 = 0.0657 |
| Absolute structure parameter | 0.024(6) |
| Largest diff. peak and hole | 0.691 and -0.276 $e.Å^{-3}$ |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **Chapter 2, Table 6, Entry 8**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | -4399(3) | -4545(2) | 1849(1) | 18(1) |
| S(1) | -2700(1) | -5527(1) | 2099(1) | 17(1) |
| O(1) | -3468(3) | -6760(2) | 2373(1) | 23(1) |
| O(2) | -1314(3) | -5738(2) | 1735(1) | 24(1) |
| C(4) | -1777(4) | -4213(3) | 2568(1) | 20(1) |
| F(1) | -888(2) | -3063(2) | 2362(1) | 26(1) |
| F(2) | -3176(2) | -3681(2) | 2837(1) | 26(1) |
| F(3) | -634(2) | -4977(2) | 2858(1) | 25(1) |
| C(1) | -6718(4) | -4183(3) | 1371(1) | 16(1) |
| C(10) | -7810(4) | -2692(3) | 1359(1) | 20(1) |
| C(11) | -7465(4) | -5436(3) | 1036(1) | 19(1) |
| C(12) | -8898(4) | -5168(3) | 706(1) | 23(1) |
| C(13) | -9524(4) | -6322(3) | 399(1) | 29(1) |
| C(14) | -8730(4) | -7752(3) | 412(1) | 30(1) |
| C(15) | -7311(4) | -8046(3) | 743(1) | 28(1) |
| C(16) | -6684(4) | -6893(3) | 1055(1) | 23(1) |
| C(2) | -4516(4) | -4008(3) | 1328(1) | 17(1) |
| C(21) | -3748(4) | -2432(3) | 1235(1) | 17(1) |
| C(22) | -3550(4) | -1377(3) | 1618(1) | 19(1) |
| C(23) | -2897(4) | 88(3) | 1530(1) | 21(1) |
| C(24) | -2411(4) | 525(3) | 1057(1) | 22(1) |
| C(25) | -2598(4) | -500(3) | 666(1) | 22(1) |
| C(26) | -3280(4) | -1955(3) | 763(1) | 18(1) |
| Br(1) | -3610(1) | -3295(1) | 214(1) | 24(1) |
| C(3) | -6367(4) | -4755(3) | 1899(1) | 17(1) |
| O(3) | -7253(3) | -5202(2) | 2237(1) | 21(1) |

Table 3. Bond lengths [Å] and angles [°] for **Chapter 2, Table 6, Entry 8**.

| | |
|---|---|
| N(1)-C(3) | 1.437(4) |
| N(1)-C(2) | 1.494(3) |
| N(1)-S(1) | 1.642(2) |
| S(1)-O(2) | 1.417(2) |
| S(1)-O(1) | 1.4250(18) |
| S(1)-C(4) | 1.842(3) |
| C(4)-F(1) | 1.319(3) |
| C(4)-F(3) | 1.322(3) |
| C(4)-F(2) | 1.329(3) |
| C(1)-C(11) | 1.524(3) |
| C(1)-C(10) | 1.526(3) |
| C(1)-C(3) | 1.537(3) |
| C(1)-C(2) | 1.599(4) |
| C(11)-C(12) | 1.387(4) |
| C(11)-C(16) | 1.396(4) |
| C(12)-C(13) | 1.386(4) |
| C(13)-C(14) | 1.377(4) |
| C(14)-C(15) | 1.386(4) |
| C(15)-C(16) | 1.394(4) |
| C(2)-C(21) | 1.509(3) |
| C(21)-C(26) | 1.391(3) |
| C(21)-C(22) | 1.397(3) |
| C(22)-C(23) | 1.388(4) |
| C(23)-C(24) | 1.384(4) |
| C(24)-C(25) | 1.399(4) |
| C(25)-C(26) | 1.391(4) |
| C(26)-Br(1) | 1.911(2) |
| C(3)-O(3) | 1.185(3) |

| | |
|---|---|
| C(3)-N(1)-C(2) | 94.17(19) |
| C(3)-N(1)-S(1) | 129.08(17) |
| C(2)-N(1)-S(1) | 126.68(18) |
| O(2)-S(1)-O(1) | 122.66(11) |
| O(2)-S(1)-N(1) | 107.88(11) |
| O(1)-S(1)-N(1) | 108.90(11) |
| O(2)-S(1)-C(4) | 107.99(12) |
| O(1)-S(1)-C(4) | 104.62(11) |
| N(1)-S(1)-C(4) | 103.08(11) |
| F(1)-C(4)-F(3) | 109.7(2) |
| F(1)-C(4)-F(2) | 109.5(2) |
| F(3)-C(4)-F(2) | 108.9(2) |
| F(1)-C(4)-S(1) | 111.06(18) |
| F(3)-C(4)-S(1) | 108.68(16) |
| F(2)-C(4)-S(1) | 108.97(17) |

| | |
|---|---|
| C(11)-C(1)-C(10) | 115.0(2) |
| C(11)-C(1)-C(3) | 112.23(19) |
| C(10)-C(1)-C(3) | 112.6(2) |
| C(11)-C(1)-C(2) | 112.1(2) |
| C(10)-C(1)-C(2) | 115.4(2) |
| C(3)-C(1)-C(2) | 86.37(18) |
| C(12)-C(11)-C(16) | 118.6(2) |
| C(12)-C(11)-C(1) | 121.7(2) |
| C(16)-C(11)-C(1) | 119.6(2) |
| C(13)-C(12)-C(11) | 120.4(3) |
| C(14)-C(13)-C(12) | 120.9(3) |
| C(13)-C(14)-C(15) | 119.5(3) |
| C(14)-C(15)-C(16) | 119.9(3) |
| C(15)-C(16)-C(11) | 120.6(3) |
| N(1)-C(2)-C(21) | 115.2(2) |
| N(1)-C(2)-C(1) | 87.47(19) |
| C(21)-C(2)-C(1) | 117.7(2) |
| C(26)-C(21)-C(22) | 117.4(2) |
| C(26)-C(21)-C(2) | 121.2(2) |
| C(22)-C(21)-C(2) | 121.3(2) |
| C(23)-C(22)-C(21) | 121.4(2) |
| C(24)-C(23)-C(22) | 120.0(2) |
| C(23)-C(24)-C(25) | 120.2(2) |
| C(26)-C(25)-C(24) | 118.6(2) |
| C(21)-C(26)-C(25) | 122.4(2) |
| C(21)-C(26)-Br(1) | 120.19(18) |
| C(25)-C(26)-Br(1) | 117.37(19) |
| O(3)-C(3)-N(1) | 130.3(2) |
| O(3)-C(3)-C(1) | 137.8(3) |
| N(1)-C(3)-C(1) | 91.95(19) |

Symmetry transformations used to generate equivalent atoms:

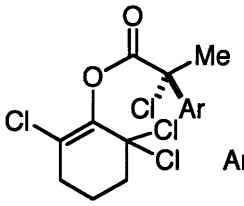
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **Chapter 2, Table 6, Entry 8.** The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12} ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| N(1) | 20(1) | 20(1) | 12(1) | 3(1) | -1(1) | -1(1) |
| S(1) | 18(1) | 17(1) | 17(1) | 0(1) | -1(1) | 1(1) |
| O(1) | 25(1) | 19(1) | 23(1) | 4(1) | -3(1) | 0(1) |
| O(2) | 22(1) | 30(1) | 20(1) | -2(1) | 1(1) | 4(1) |
| C(4) | 19(1) | 21(1) | 18(1) | -2(1) | -3(1) | 1(1) |
| F(1) | 27(1) | 21(1) | 31(1) | 3(1) | -3(1) | -6(1) |
| F(2) | 23(1) | 31(1) | 24(1) | -9(1) | 2(1) | 3(1) |
| F(3) | 23(1) | 29(1) | 23(1) | 2(1) | -8(1) | 1(1) |
| C(1) | 18(1) | 19(1) | 13(1) | 0(1) | -1(1) | 0(1) |
| C(10) | 20(1) | 22(1) | 18(1) | 0(1) | -2(1) | 2(1) |
| C(11) | 20(1) | 22(1) | 14(1) | -1(1) | 4(1) | -4(1) |
| C(12) | 26(2) | 28(1) | 17(1) | 0(1) | -2(1) | -2(1) |
| C(13) | 27(2) | 41(2) | 18(1) | -2(1) | -3(1) | -11(1) |
| C(14) | 30(2) | 35(1) | 25(1) | -14(1) | 7(1) | -14(1) |
| C(15) | 31(2) | 21(1) | 33(2) | -6(1) | 9(1) | -4(1) |
| C(16) | 24(1) | 24(1) | 22(1) | -4(1) | 2(1) | -1(1) |
| C(2) | 20(1) | 22(1) | 9(1) | 0(1) | 0(1) | -2(1) |
| C(21) | 16(1) | 18(1) | 18(1) | 1(1) | -2(1) | 1(1) |
| C(22) | 21(1) | 22(1) | 15(1) | 1(1) | -1(1) | 2(1) |
| C(23) | 21(1) | 20(1) | 23(1) | -4(1) | -2(1) | 2(1) |
| C(24) | 20(1) | 19(1) | 28(1) | 2(1) | -2(1) | 0(1) |
| C(25) | 22(1) | 25(1) | 17(1) | 5(1) | 1(1) | 0(1) |
| C(26) | 17(1) | 21(1) | 16(1) | -3(1) | 0(1) | 0(1) |
| Br(1) | 33(1) | 26(1) | 14(1) | -1(1) | 0(1) | -4(1) |
| C(3) | 20(1) | 14(1) | 17(1) | -2(1) | -2(1) | 2(1) |
| O(3) | 22(1) | 24(1) | 17(1) | 1(1) | 3(1) | -1(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **Chapter 2, Table 6, Entry 8.**

| | x | y | z | U(eq) | |
|---|---|---|---|---|---|
| H(10A) | | -7694 | -2225 | 1033 | 30 |
| H(10B) | | -7318 | -1994 | 1609 | 30 |
| H(10C) | | -9121 | -2901 | 1428 | 30 |
| H(12) | -9455 | -4187 | 691 | 28 | |
| H(13) | -10513 | -6125 | 177 | 34 | |
| H(14) | -9153 | -8530 | 196 | 36 | |
| H(15) | -6765 | -9032 | 757 | 34 | |
| H(16) | -5717 | -7101 | 1283 | 28 | |
| H(2) | -3979 | -4773 | 1095 | 20 | |
| H(22) | -3870 | -1668 | 1944 | 23 | |
| H(23) | -2783 | 791 | 1795 | 25 | |
| H(24) | -1949 | 1524 | 999 | 27 | |
| H(25) | -2267 | -209 | 340 | 26 | |

Determination of Absolute Configuration:




Ar = 6-OMe-2-naphthyl

**Chapter 3, Table 2, Entry 11.** Crystals of an a-chloroester (derived from a reaction catalyzed by (+)-PPY*) that were suitable for X-ray analysis were obtained by dissolving the ester in ethanol (200 proof) and crystallizing at 0 °C.

Low-temperature diffraction data were collected on a Siemens Platform three-circle diffractometer coupled to a Bruker-AXS Apex CCD detector with graphite monochromated Mo Kα radiation (λ = 0.71073Å), performing ϕ- and ϕ-scans. Raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. All structures were solved by direct methods using SHELXS and refined against $F^2$ on all data by full-matrix least squares with SHELXL-97 (Sheldrick, G. M. *SHELXL 97*, Universität Göttingen, Göttingen, Germany, 1997). SADABS absorption correction was performed. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of the hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups).

A colorless needle of dimensions 0.20 x 0.15 x 0.05 $mm^3$ was mounted under STP and transferred to a Siemens Platform three-circle diffractometer equipped with a cold stream of $N_2$ gas. The data that were collected (43730 total reflections, 5535 unique, Rint = 0.0472) had the following Miller index ranges: (-9 to 9 in h, -10 to 10 in k, and -51 to 51 in l). The structure was solved in the triclinic space group *P2(1)2(1)2(1)*, *a* = 6.7317(10) Å, *b* = 7.9098(11) Å, *c* = 37.107(6) Å, α = 90°; β = 90°; γ = 90°, and refined using standard difference Fourier techniques. Final, full-matrix least squares refinement (5535 data for 258 parameters) on $F^2$ yielded residuals of R1 and wR2 of 0.042 and 0.1000 for data I > 2σ(I), and 0.0457 and 0.1015, respectively, for all data. Residual electron density amounted to a maximum of 0.553 e/Å$^3$ and a minimum of -0.435 e/Å$^3$. The absolute structure (Flack) parameter for the correct enantiomer is 0.05(6), thus confirming the absolute stereochemistry.

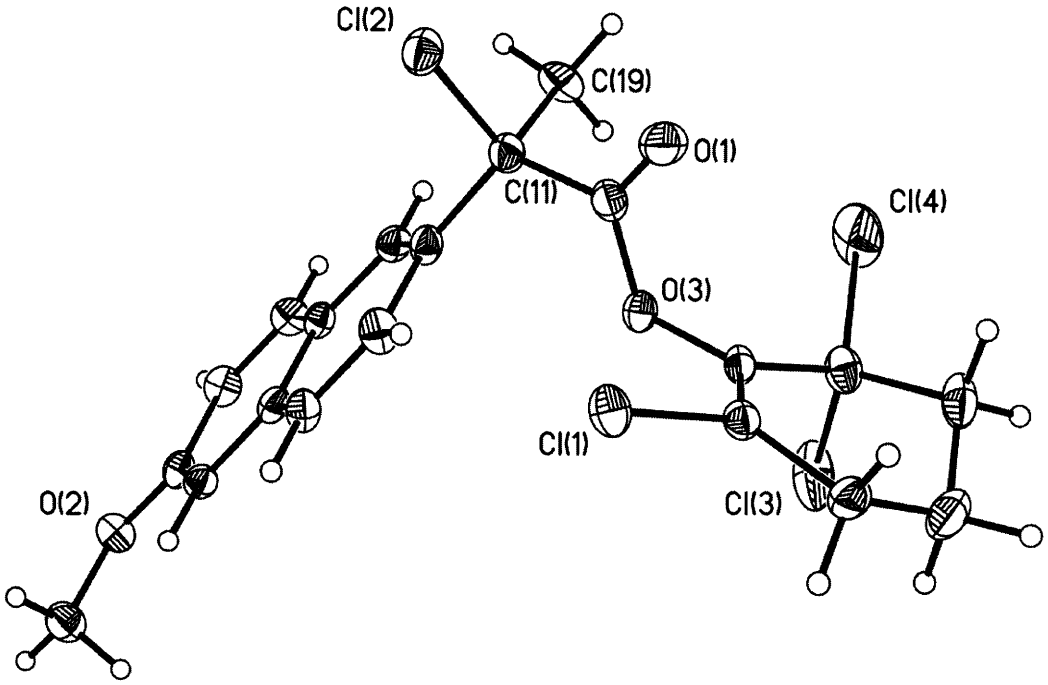

Cl(2)
C(19)
O(1)
C(11)
Cl(4)
O(3)
Cl(1)
O(2)
Cl(3)

Table 1. Crystal data and structure refinement for Chapter 3, Table 2, Entry 11.

| | | |
|---|---|---|
| Identification code | Chapter 3, Table 2, Entry 11 | |
| Empirical formula | C20 H18 Cl4 O3 | |
| Formula weight | 448.14 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P2(1)2(1)2(1) | |
| Unit cell dimensions | a = 6.7317(10) Å | a= 90°. |
| | b = 7.9098(11) Å | b= 90°. |
| | c = 37.107(6) Å | g = 90°. |
| Volume | 1975.8(5) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.507 $Mg/m^3$ | |
| Absorption coefficient | 0.618 $mm^{-1}$ | |
| F(000) | 920 | |
| Crystal size | 0.20 x 0.15 x 0.05 $mm^3$ | |
| Theta range for data collection | 2.20 to 29.56°. | |
| Index ranges | -9<=h<=9, -10<=k<=10, -51<=l<=51 | |
| Reflections collected | 43730 | |
| Independent reflections | 5535 [R(int) = 0.0472] | |
| Completeness to theta = 29.56° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9698 and 0.8864 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 5535 / 37 / 258 | |
| Goodness-of-fit on $F^2$ | 1.161 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0422, wR2 = 0.1000 | |
| R indices (all data) | R1 = 0.0457, wR2 = 0.1015 | |
| Absolute structure parameter | 0.05(6) | |
| Largest diff. peak and hole | 0.553 and -0.435 $e.Å^{-3}$ | |