# Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Enantioselective Alkylation of 2-[(4-Chlorobenzyliden)Amino]Propanoic Acid *tert*-Butyl Ester: Synthesis of (*R*)-2-Amino-2-Methyl-3-Phenylpropanoic Acid *tert*-Butyl Ester

(*S*)-**1** (Ar = 3,4,5-F$_3$-C$_6$H$_2$)
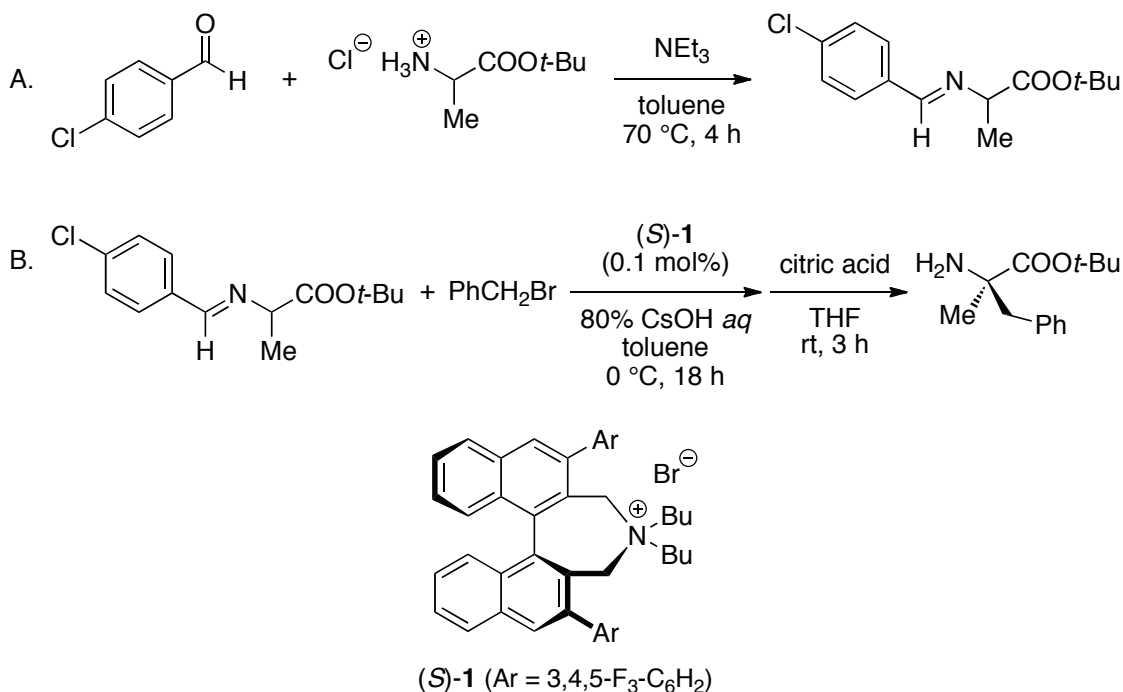
Submitted by Seiji Shirakawa, Kenichiro Yamamoto, Kun Liu, and Keiji Maruoka.[1]
Checked by Lindsey R. Cullen and Scott E. Denmark.

1. Procedure

A. 2-[(4-Chlorobenzyliden)amino]propanoic acid tert-butyl ester. A 200-mL, three-necked, round-bottomed flask, equipped with an overhead mechanical stirrer (Note 1), a 10-mL pressure-equalizing dropping funnel (attached to an argon inlet), and a thermometer fitted with a thermometer adapter, is charged with L-alanine *tert*-butyl ester hydrochloride (5.00 g, 27.5 mmol, 1.05 equiv) (Notes 2 and 3), 4-chlorobenzaldehyde (3.69 g, 26.2 mmol, 1.00 equiv) (Note 4) and toluene (25.0 mL). The mixture is stirred at 400 rpm and triethylamine (4.20 mL, 30.1 mmol, 1.15 equiv) (Note 5) is added dropwise over 5 min through the dropping funnel at ambient temperature (Note 6). The addition funnel is removed and replaced with a

reflux condenser fitted with an argon inlet. The reaction mixture is heated to 70 °C in an oil bath and stirred at 400 rpm for 4 h (Note 7). After cooling to ambient temperature, the reaction mixture is diluted by the addition of water (50 mL). The reaction mixture is transferred to a 500-mL separatory funnel and toluene (50 mL) is added. The organic layer is separated and washed with brine (2 × 50 mL). The organic solution is dried over sodium sulfate (20 g), filtered, and concentrated on a rotary evaporator (15 mm Hg, 35 °C). The residue is dried by stirring under reduced pressure (0.2 mm Hg) at 23 °C for 2 h to afford the crude aldimine product (6.66 g, , 95% yield) (Note 8) as an amber oil (Note 9).

B. *(R)-2-Amino-2-methyl-3-phenylpropanoic acid tert-butyl ester*. A 300-mL, three-necked, round-bottomed flask, equipped with an overhead mechanical stirrer, 100-mL pressure-equalizing dropping funnel capped with an argon inlet, and a thermometer fitted with a thermometer adapter, is charged with crude 2-[(4-chlorobenzyliden)amino]propanoic acid *tert*-butyl ester (6.66 g, 24.9 mmol, 1.00 equiv) (Notes 8 and 10), (*S*)-4,4-dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepinium bromide (19.6 mg, 0.026 mmol, 0.001 equiv) (Note 11), benzyl bromide (3.74 mL, 31.4 mmol, 1.20 equiv) (Note 12) and toluene (52.4 mL). The mixture is stirred at 400 rpm and cooled to 0 °C in an ice-water bath. Aqueous cesium hydroxide solution (80 wt %, 24.5 g, 5.00 equiv) (Note 13) is added dropwise over 20 min through the dropping funnel (Note 14). The mixture is stirred for 18 h at 0 °C with constant stirring speed (400 rpm) under argon atmosphere (Note 15). The reaction mixture is diluted by the addition of water (100 mL) and the cooling bath is removed. After stirring for an additional 15 min at ambient temperature, the reaction mixture is transferred to a 500-mL separatory funnel and toluene (50 mL) is added. The organic layer is separated and washed with 10% aqueous sodium chloride solution (2 × 75 mL). The organic layer is dried over sodium sulfate (15 g), filtered, and concentrated on a rotary evaporator (15 mmHg, 35 °C). The pale yellow residue (10.4 g) is transferred to a 300-mL round-bottomed flask equipped with 3 cm egg-shaped stir bar and THF (50 mL) is added. Citric acid monohydrate (52.5 g, 250 mmol, 10 equiv) (Note 16) and water (150 mL) are added to the solution at ambient temperature. The cloudy, colorless mixture is stirred for 3 h at ambient temperature. The reaction mixture is transferred to a 500-mL separatory funnel and hexane (50 mL) is added. The water layer is separated and washed with hexane (2 × 50 mL). The aqueous solution is transferred to a 500-mL, three-necked, round-

bottomed flask equipped with a 3 cm egg-shaped stir bar, 100-mL pressure-equalizing dropping funnel, thermometer, septum, and is placed in a room temperature water bath. Aqueous sodium hydroxide solution (50 wt %, 39.3 g, 26.2 mL, 18.7 equiv) is added dropwise over 25 min (Note 17). The mixture is stirred for an additional 15 min at ambient temperature. The mixture is transferred to a 500-mL separatory funnel and *tert*-butyl methyl ether (150 mL) is added. The organic layer is separated and washed with 10% aqueous sodium chloride solution (2 × 75 mL). The organic layer is dried over sodium sulfate (15 g), filtered, and concentrated on a rotary evaporator (15 mm Hg, 23 °C). The residue is adsorbed onto Celite (8 g) and loaded as a solid onto a column (diameter: 5 cm, height: 10 cm) wet-packed with silica gel (100 g) (Note 18) in hexane/ethyl acetate, 4/1. Elution with a gradient of hexane/ethyl acetate (400 mL of each: 4:1 to 2:1 to 1:1 to 1:2) affords the product as a pale yellow oil [4.80 g, 78% yield (for 2 steps), 95–97% ee for the (*R*)-enantiomer] (Note 19 and 20).

2. Notes

1. The Teflon paddle of the mechanical stirrer is 6.5 cm in length and 1.8 cm in height.
2. L-Alanine *tert*-butyl ester hydrochloride (99%) was purchased from Acros Organics and used as received. This reagent is also available from Watanabe Chemical Industries, Ltd. and Sigma-Aldrich Co.
3. D-Alanine and DL-alanine *tert*-butyl ester hydrochloride can be also used as starting materials instead of L-alanine *tert*-butyl ester hydrochloride.
4. 4-Chlorobenzaldehyde (>98.5%) was purchased from Acros Organics and used as received. This reagent is also available from Wako Pure Chemical Industries, Ltd.
5. Triethylamine (>99%) was purchased from Sigma-Aldrich Co. and used as received. This reagent is also available from Kanto Chemical Co., Inc.
6. The internal temperature was kept below 30 °C during the addition of triethylamine.
7. ^{1}H NMR analysis of the reaction mixture indicated nearly complete consumption of the starting materials. An aliquot of the reaction mixture (30 µL) was diluted with DMSO-d_6 (0.7 mL), and analyzed by ^{1}H NMR [4-chlorobenzaldehyde: δ 10.00 (ArC*H*O, s, 1H), aldimine product: δ

8.39 (ArC*H*=N, s, 1H)]. A residual amount of 4-chlorobenzaldehyde (1%) was observed after 4 h.

8. The crude aldimine product includes 1mol % of 4-chlorobenzaldehyde (determined by ^{1}H NMR analysis).

9. The product gradually decomposes in air at room temperature. The compound should be kept in a refrigerator under an inert atmosphere where it is stable for at least 2 weeks. The product solidifies to a low-melting, white solid upon storage at –20 °C. ^{1}H NMR (500 MHz, DMSO-*d₆*) δ: 1.34 (d, *J* = 6.8 Hz, 3 H), 1.39 (s, 9 H), 4.09 (q, *J* = 6.6 Hz, 1 H), 7.53 (d, *J* = 8.3 Hz, 2 H), 7.78 (d, *J* = 8.6 Hz, 2 H), 8.39 (s, 1 H); ^{13}C NMR (125 MHz, DMSO-*d₆*) δ: 19.0, 27.6, 67.1, 80.3, 128.8, 129.7, 134.6, 135.5, 161.4, 170.9; ^{1}H NMR (500 MHz, CDCl₃) δ: 1.47 (s, 9 H), 1.48 (d, *J* = 7.1 Hz, 3 H), 4.04 (q, *J* = 6.9 Hz, 1 H), 7.38 (d, *J* = 8.6 Hz, 2 H), 7.71 (d, *J* = 8.6 Hz, 2 H), 8.25 (s, 1 H); ^{13}C NMR (125 MHz, CDCl₃) δ: 19.5, 28.2, 68.5, 81.4, 128.7, 129.8, 134.6, 137.0, 161.3, 171.8; IR (neat) 2975, 2926, 2871, 1732, 1642, 1365, 1153, 1125, 1087, 844, 824 cm^{-1}. HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{19}ClNO_2^+$: 268.1104 ([M + H]$^+$). Found: 268.1108.

10. The full amount of crude aldimine product in procedure A was used for the next step (procedure B). Reagent equivalents in procedure B were based upon amount of 4-chlorobenzaldehyde (26.2 mmol).

11. (*S*)-4,4-Dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepinium bromide (Nagase purity) was purchased from Sigma-Aldrich Co. and used as received. This catalyst is also available from Kanto Chemical Co., Inc. and Strem Chemicals, Inc.

12. Benzyl bromide (98%) was purchased from Sigma-Aldrich Co. and used as received.

13. Cesium hydroxide solution (80 wt %) was prepared from cesium hydroxide monohydrate (96%) purchased from Alfa-Aesar Co. as follows: Cesium hydroxide monohydrate (44.81 g) was weighed into a neoprene bottle. The neoprene bottle was then cooled in an ice bath, followed by addition of distilled water (5.2 mL). The solution was shaken to incorporate solid into solution and allowed to stand for 2 h to ensure dissolution. The homogenous, colorless solution was stored in a neoprene bottle. [Caution: Cooling with an ice bath is necessary for preparation of 80 wt % cesium hydroxide solution. The dissolution of cesium hydroxide in water is very exothermic.] Cesium hydroxide monohydrate (>95%) is also available from Sigma-Aldrich Co.

14. During the addition of the cesium hydroxide solution, the internal temperature was kept under 5 °C.

15. ^{1}H NMR analysis of the reaction mixture indicates complete consumption of the starting materials. An aliquot of the reaction mixture (30 µL) was diluted with d_6-DMSO (0.7 mL), and analyzed by ^{1}H NMR [starting aldimine substrate: δ 8.39 (ArC*H*=N, s, 1H), alkylation product: δ 8.25 (ArC*H*=N, s, 1H)]. The checkers observed highly variable reaction times ranging from 18 h to 48 h to reach full conversion.

16. Citric acid monohydrate (>99.0%) was purchased from Sigma-Aldrich Co. and used as received. This reagent is also available from Kanto Chemical Co., Inc.

17. Sodium hydroxide solution (50 wt %) was purchased from Acros Organics and used as received. This reagent is also available from Kanto Chemical Co., Inc. During the addition of 50 wt % sodium hydroxide solution, the internal temperature was kept under 37 °C. A room temperature water bath was necessary to control the internal temperature.

18. Silica gel was purchased from SiliCycle., Inc. (SiliaFlash F-60–40/63). TLC: R_f 0.11 (hexane/EtOAc, 1:1, visualized using ninhydrin stain).

19. Column chromatography was performed without collecting a forecut and 20 mL fractions were collected using 16 mm × 150 mm test tubes. The desired product tailed significantly and was isolated from fractions 13 through 64 using rotary evaporation (15 mmHg, 35 °C).

20. The final product was obtained as a pale yellow oil but did not show the presence of an impurity by ^{1}H NMR. The colored impurity was removed from a portion of the final product (1.0 mL) by Kugelrohr distillation at 70 °C under reduced pressure (4.3×10^{-5} mmHg) to afford a colorless oil (956 mg) prior to elemental analysis and further characterization. Characterization data for the product: $[\alpha]^{24}_D$ = 15.3 (c = 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.34 (s, 3 H), 1.46 (s, 9 H), 1.51 (br s, 2 H), 2.77 (d, J = 13.2 Hz, 1 H), 3.11 (d, J = 13.2 Hz, 1 H), 7.21–7.29 (m, 5 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 27.1, 28.1, 46.6, 58.9, 81.2, 126.9, 128.3, 130.3, 137.0, 176.4; IR 3372, 3310, 2975, 2926, 1722, 1365, 1153, 1105, 848, 737, 699 cm^{-1}. HRMS (ESI-TOF) *m/z* calcd for C$_{14}$H$_{22}$NO$_2$$^+$: 236.1651 ([M + H]$^+$); Found: 236.1657. Calcd. for C$_{14}$H$_{21}$NO$_2$: C; 71.46, H; 8.99, N; 5.95. Found: C; 71.50, H; 9.14, N; 6.17. The enantioselectivity was determined by chiral stationary phase HPLC analysis [Daicel Chiralcel AD-H column, 3.3% 2-propanol/hexane, 0.50 mL/min, λ = 220 nm, 5.0 mg/mL, retention times: (*R*)-enantiomer (major): 13.1 min, (*S*)-enantiomer (minor):

22.4 min]. The racemate was prepared for comparison following the above procedure by substituting tetrabutylammonium bromide as the catalyst.

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These procedures must be conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

3. Discussion

Nonproteinogenic α,α-dialkyl-α-amino acids have played a special role in the design of peptides with enhanced properties. This is not only because they possess stereochemically stable quaternary carbon centers, but also their incorporation into peptides results in the significant influence on the conformational preferences, which eventually provides useful information for the elucidation of enzymatic mechanisms. Furthermore, α,α-dialkyl-α-amino acids themselves are often effective enzyme inhibitors and also constitute a series of interesting building blocks for the synthesis of various biologically active compounds. Accordingly, numerous studies have been conducted to develop truly efficient methods for their preparation,[2] and phase-transfer catalysis has made unique contributions.[3] In 1992, O'Donnell reported the first chiral phase-transfer-catalyzed alkylations of an alanine derivative by using an *N*-benzylcinchonium chloride with moderate enantioselectivity.[4] Lygo improved the enantioselectivity for the reaction by using an *N*-9-anthracenylmethyl substituted cinchona alkaloid-derived catalyst.[5] Highly enantioselective alkylation of an alanine derivative with broad generality of alkyl halides was achieved by using a binaphthyl-

modified *N*-spiro-type chiral phase-transfer catalyst.[6] Based on the design of binaphthyl-modified *N*-spiro-type catalysts, the very reactive high-performance catalyst (*S*)-**1** was developed.[7] Most notably, the reaction proceeded smoothly under mild phase-transfer conditions in the presence of only 0.05–0.1 mol% of (*S*)-**1** to afford the corresponding alkylation products with excellent enantioselectivities (Scheme 1).

Scheme 1. Enantioselective Alkylation of Alanine Derivative

63% yield, 98% ee
(at –20 °C)

66% yield, 98% ee
(at 0 °C)

60% yield, 96% ee
(at 0 °C)
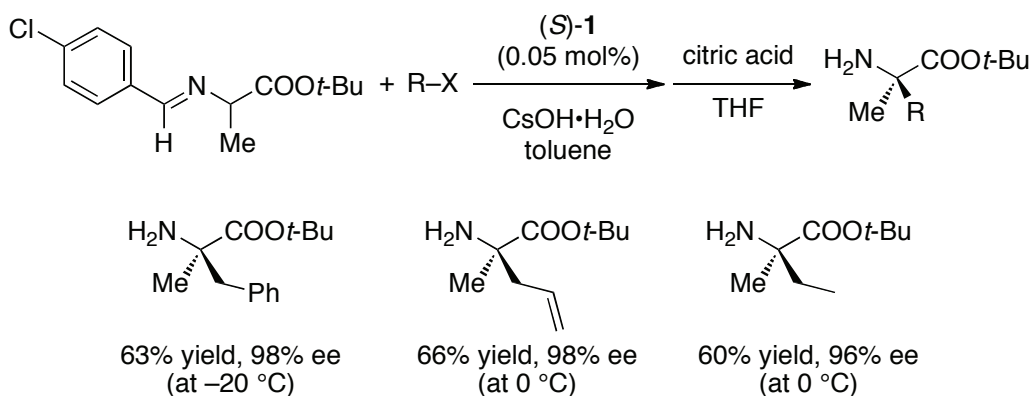
1. Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto, 606-8502, Japan. E-mail: maruoka@kuchem.kyoto-u.ac.jp
2. (a) Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65-84. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (c) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127. (d) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406.
3. (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (d) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (e) Ooi, T.; Maruoka, K. *Aldrichimica Acta* **2007**, *40*, 77. (f) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (g) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679. (h) Maruoka, K., Ed. *Asymmetric Phase Transfer Catalysis*; Willy-VCH: Weinheim, 2008. (i) Shirakawa, S.; Maruoka, K. In *Catalytic Asymmetric Synthesis, 3rd Ed*; Ojima, I., Ed.; John Wiley & Sons: New Jersey, 2010; Chapter 2C, p 95.
4. O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3,* 591.
5. Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671.

6. Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

7. (a) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44,* 1549. (b) Kitamura, M.; Shirakawa, S.; Arimura, Y.; Wang, X.; Maruoka, K. *Chem. Asian J.* **2008**, *3*, 1702.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

2-[(4-Chlorobenzyliden)amino]propanoic acid tert-butyl ester; (142274-97-3)

L-Alanine *tert*-butyl ester hydrochloride; (13404-22-3)

4-Chlorobenzaldehyde; (104-88-1)

Triethylamine; (121-44-8)

(R)-2-Amino-2-methyl-3-phenylpropanoic acid tert-butyl ester; (147714-90-7)

(*S*)-4,4-Dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepinium bromide; (851942-89-7)

Benzyl bromide; (100-39-0)

Cesium hydroxide monohydrate; (35103-79-8)

Keiji Maruoka was born in 1953 in Mie, Japan. He graduated from Kyoto University (1976) and received his Ph.D. (1980) from University of Hawaii (Thesis Director: Professor Hisashi Yamamoto). He became an assistant professor of Nagoya University (1980) and was promoted to a lecturer (1985) and an associate professor (1990) there. He moved to Hokkaido University as a full professor (1995−2001), and he currently is a professor of chemistry in Kyoto University since 2000. His research interests are the design of high-performance organocatalysts and bidentate Lewis acid chemistry.

Seiji Shirakawa was born in 1974 in Ehime, Japan. He graduated from Nihon University (1997) and received his Ph.D. (2004) from Kyoto University (Thesis Director: Professor Keiji Maruoka). He worked with Professor James L. Leighton at Columbia University (2004–2005) and Professor Shu Kobayashi at University of Tokyo (2005–2007) as a postdoctoral fellow. He was appointed as an assistant professor at Nihon University in 2007, and he currently is an associate professor in Kyoto University since 2009.

Kenichiro Yamamoto was born in Madison, Wisconsin, USA, in 1978 and raised in Yamaguchi, Japan. He obtained his M.S. degree from Kyoto University in 2004 under the direction of Professor Keiji Maruoka. Since 2004, he has been working as process chemist in the Research & Development Center of NAGASE & CO., LTD. (Kobe, Japan). From 2009, he has been doing postgraduate studies in Kyoto University under the direction of Professor Keiji Maruoka.

Kun Liu was born in 1984 in Shandong Province, China. He graduated from Tianjin University (2006) and received his Masters degree from the same university under supervision of Professor Jun-An Ma (2008). Currently he is a doctoral student at Kyoto University under the supervision of Professor Keiji Maruoka.

Lindsey R. Cullen received her bachelor's degree in Chemistry from the University of Detroit Mercy. During this time she performed research with Professor Matthew J. Mio on Cu(I)-catalyzed cross coupling reactions of aryl alkynes. In 2009 she began her graduate studies in Organic Chemistry at the University of Illinois, under the mentorship of Professor Scott E. Denmark. The focus of her research is the application of chiral quaternary ammonium salt catalysts in enantioselective reactions, specifically conjugate addition of nucleophiles via fluorodesilylation and phase transfer catalyzed rearrangements.

¹H NMR (500 MHz, CDCl₃)

¹H NMR (500 MHz, (CD₃)₂SO)

10.00

8.38

7.78
7.76
7.53
7.51

4.11
4.10
4.08
4.07

1.40
1.35
1.34

0.02

1.00

2.07
2.10

1.21

9.11
2.96

11.5   10.5   9.5   8.5   7.5   6.5   5.5   4.5   3.5   2.5   1.5   0.5   −0.5
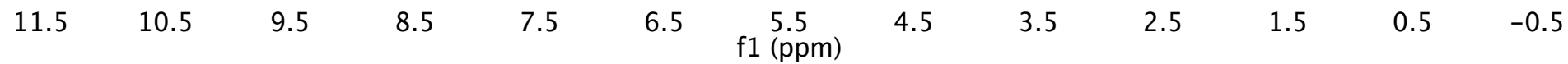
f1 (ppm)

^{13}C NMR (125 MHz, CDCl$_3$)
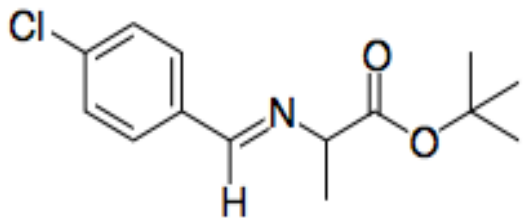
171.77
161.25
137.03
134.55
129.76
128.96
81.37
68.52
28.17
19.53

^{13}C NMR (125 MHz, (CD$_3$)$_2$SO)
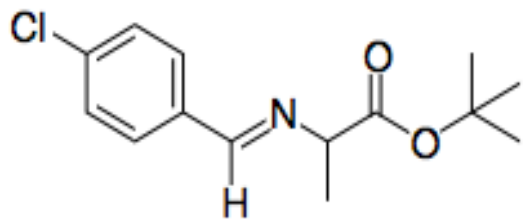
170.94
161.43
135.53
134.61
129.65
128.77
80.34
67.10
27.61
19.04