A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are 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.

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.

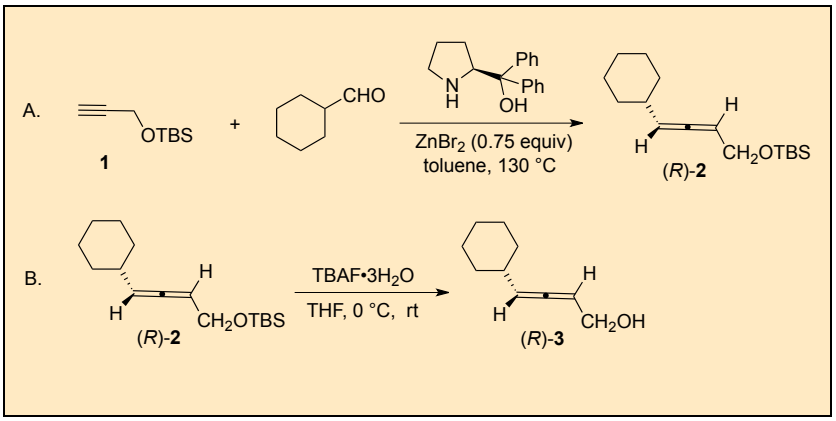
Organic Syntheses

Preparation of (*R*)-4-Cyclohexyl-2,3-butadien-1-ol

Juntao Ye and Shengming Ma*[1]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai, China

Checked by Mingyao Wu and Dawei Ma



Procedure

A. *(R)-tert-Butyldimethyl(4-cyclohexyl-2,3-butadien-1-yloxy)silane* ((*R*)-**2**). An oven-dried, three-necked 500-mL round-bottomed flask containing a magnetic stir bar (Notes 1 and 2) is connected to a vacuum line via a one-stopcock adapter in the left neck. A solid addition funnel is placed in the middle neck and a glass stopper is placed in the right neck. Zinc bromide ($ZnBr_2$) powder (17.3 g, 76.6 mmol) (Notes 3 and 4) is added to the flask via the solid addition funnel under argon atmosphere. After addition, the solid addition funnel is removed and replaced with a glass stopper. The flask is dried under vacuum (1 mmHg) with a heat gun for approximately 1 min. After cooling to room temperature, the middle neck is equipped with a Dean-Stark trap (Note 5). The glass stopper is removed and (*S*)-α,α-

DOI: 10.15227/orgsyn.091.0233 Published on the Web 7/14/2014

diphenylprolinol (25.9 g, 100 mmol, 1.00 equiv) (Notes 6 and 7) and *tert*-butyldimethyl(2-propynyloxy)silane (**1**)[2] (18.9 g, 110 mmol, 1.1 equiv) (Note 8) are added sequentially with stirring under argon atmosphere at room temperature. The suspension is allowed to stir for 5 min at room temperature (Note 9) before 150 mL of freshly distilled toluene (Note 7) is added via a 50-mL syringe under an argon atmosphere. Freshly distilled cyclohexanecarboxaldehyde (16.8 g, 150 mmol, 1.5 equiv) (Note 7) is added over the course of one min via a syringe. The flask containing the aldehyde is rinsed with 50 mL of toluene, which in turn is added to the reaction flask via syringe under the argon atmosphere. The resulting mixture is stirred for 3 min at room temperature, during which time 8 mL of freshly distilled toluene is added to fill the Dean-Stark trap. The trap is connected to an argon source under slight positive pressure, which is released via a bubbler to the atmosphere. The flask is then placed in a pre-heated oil bath of 130 °C for 11 h with stirring (Notes 10 and 11). After cooling to room temperature, the supernatant is transferred into a 500-mL flask and the precipitate is discarded after rinsing with 30 mL of ethyl ether. After concentration by rotary evaporation (15 mmHg with a water bath of 30 °C) (Note 12), flash chromatography on silica gel (eluent: petroleum ether/ethyl ether = 40:1) afforded 20.8 g of the crude product (*R*)-**2** as an orange-red liquid (Notes 13, 14, and 15).

B. *(R)-4-Cyclohexyl-2,3-butadien-1-ol (**(R)-3**).* The crude product (*R*)-**2** prepared above (20.80 g) is dissolved in 200 mL of THF (Note 7) in a 500-mL round-bottomed flask that contains a magnetic stir bar and is equipped with a solid addition funnel. The flask is placed in an ice-water bath and stirred while open to the atmosphere. To this solution is added TBAF·3H_2O (32.0 g, 101 mmol) (Note 7) in one portion via a solid addition funnel. After the addition is complete, the ice-water bath is removed and the resulting mixture is allowed to stir at room temperature. After 2 h, the reaction is complete as monitored by TLC (Note 10). The reaction mixture is poured into ice water (150 mL) in a 1-L beaker followed by addition of diethyl ether (300 mL). The mixture is transferred to a separatory funnel, the organic layer is separated, and the aqueous layer is extracted with ethyl ether (3 × 50 mL). The combined organic layer is washed with brine (100 mL) and dried over anhydrous Na_2SO_4 (15 g). After evaporation (15 mmHg with a water bath of 30 °C), the residue is purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20:1 → 15:1) (Note 16) to afford 9.42 g of (*R*)-**3** (62% combined yield over steps A and B) (Notes 17 and 18) as a light yellow liquid with 99% ee (Notes 19, 20, and 21).

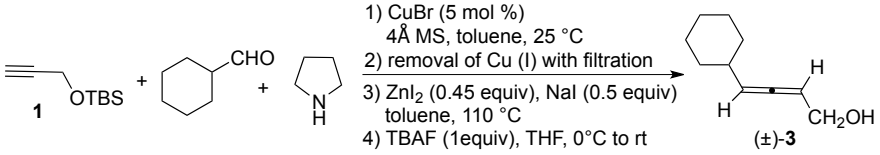
Notes

1. All glassware was thoroughly washed and dried in an oven at 120 °C. Teflon-coated magnetic stirring bars were washed with acetone and dried.
2. Efficient stirring is crucial for the reaction; the submitters used an oval-shaped (40 × 15 mm) magnetic stirring bar.
3. Anhydrous $ZnBr_2$ was stored under Ar or N_2 in a desiccator. While the material was weighed out open to the atmosphere, it should be transferred quickly into the flask using a solid addition funnel under argon atmosphere.
4. The submitters found that powder form of $ZnBr_2$ (>98%) purchased from TCI facilitated more efficient stirring. Granular crystal form of $ZnBr_2$ (99.9%), purchased from Alfa Aesar, was also used after being ground into powder with a mortar and pestle avoiding exposure to moisture by applying Ar or N_2 atmosphere.
5. Dean-Stark trap (205 × 130 mm, capacity: 5-mL) was purchased from Beijing Synthware Glass Co., Ltd, China. A larger size of Dean-Stark trap was found to be less efficient for water-removal. The outer surface of the Dean-Stark trap should be fully wrapped with cotton to improve the water-removing performance.
6. Since the starting materials are solid, the stirring apparatus should be turned on from the very beginning to ensure efficient stirring while the flask is in the oil bath.
7. (*S*)- α,α-Diphenylprolinol (98%) was purchased from Shanghai Darui Fine Chemical Co., Ltd., China. Toluene (≥99.5%) was purchased from Shanghai Experimental Reagent Co., Ltd., China and distilled over sodium wire with benzophenone under an atmosphere of argon before use. Tetrahydrofuran (≥99%) was purchased from Shanghai Experimental Reagent Co., Ltd, China; Ethyl acetate (≥99.5%), petroleum ether (60-90 °C, ≥99%), were purchased from Suzhou JIMCEL H&N Electronic Material Co., Ltd, China. $ZnBr_2$ (>98%) was purchased from TCI, Ltd. or Alfa Aesar. Cyclohexanecarboxaldehyde (≥98%) and tetrabutylammonium fluoride trihydrate (≥98%) were purchased from Shanghai Darui Fine Chemical Co., Ltd., China. Cyclohexanecarboxaldehyde was distilled before use while all other chemicals were used as received.

8. Butyldimethyl(2-propynyloxy)silane **1** (97%) is available from Sigma-Aldrich or can be prepared from the reaction of propargyl alcohol and TBSCl according to Radha's procedure.[2] When prepared, the submitters purified **1** by distillation under reduced pressure (68–74 °C/20 mmHg). Anhydrous Na_2SO_4 (1 g of Na_2SO_4/ 10 g of **1**) was added to the distillate to remove trace amounts of water, which is critical for the success of the reaction. The compound could be stored at 5-8 °C for >12 h before use.
9. The submitters found that stirring the suspension of $ZnBr_2$, (*S*)- α,α-diphenylprolinol, and *tert*-butyldimethyl(2-propynyloxy)silane **1** for 5 min at room temp is crucial for success of a larger scale reaction.
10. TLC analysis during the reaction: Step A: R_f of compound **1** = 0.61 (eluent : petroleum ether); R_f of compound **2** = 0.72 (eluent : petroleum ether); Step B: R_f of compound **3** = 0.41 (eluent : petroleum ether/EtOAc (10/1)). All samples were visualized using an aqueous solution of $KMnO_4$.
11. The solution in the flask boils vigorously within the first 1-2 h and refluxes gently thereafter. Approximately 2 mL of water were collected in the Dean-Stark trap when the reaction was complete. The color of the solution changed from light yellow to orange yellow and finally to dark brown over the course of the reaction.
12. After removing most of the toluene under vacuum (15 mmHg with a water bath of 30 °C) and cooling to room temperature, $CHCl_3$ (20 mL) was added to the mixture to dissolve some insoluble substances, Methylene bromide (CH_2Br_2) (1.74 g, 10 mmol) was then added via a syringe and mixed thoroughly to serve as the internal standard. Analysis of the crude reaction mixture by ^1H NMR showed that the NMR yields of the reaction ranged from 64-69% in different runs.
13. The purpose of this manipulation is to remove the polar imine by-product,[3] which may inhibit the efficient deprotection of the TBS group in the subsequent step. Therefore, after this operation, all the fractions containing the products can be collected together; minor impurities in these fractions will not affect its use in the next step.
14. After evaporation with a rotary evaporator (15 mmHg with a water bath of 30 °C), the remaining toluene can be removed under vacuum (1 mmHg) at room temperature before chromatography purification.
15. The column (diameter = 80 mm) was packed with 300 g of silica gel (10-40 μm): a mixture of 2.4 L of petroleum ether (60–90 °C) and 60 mL of ethyl ether was used as the eluent (~100 mL for each). The obtained

crude product was used directly in the next step without further treatment. Chromatographic separation on silica gel with an eluent of petroleum ether was used to obtain the relatively pure product (*R*)-**2**, which exhibits the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.08 (s, 6 H), 0.90 (s, 9 H), 1.05–1.29 (m, 5 H), 1.58–1.76 (m, 5 H), 1.97–2.00 (m, 1 H), 4.15–4.18 (m, 2 H), 5.15–5.25 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –5.11, –5.09, 18.3, 26.0, 26.1, 33.1, 37.1, 62.2, 92.5, 98.3, 202.3; MS (EI) *m*/*z* (%): 209 (M^+-^{t}Bu, 80.74), 127 (59.05), 75 (100); IR (neat): υ = 2927, 2854, 1962, 1448, 1362, 1255, 1092, 1005 cm^{-1}; HRMS calcd for $C_{10}H_{30}OSi$ [M^+]: 266.2066, found: 266.2064.

16. The column (diameter = 80 mm) was packed with 390 g of silica gel (10-40 μm): a mixture of 4.0 L of petroleum ether (60–90 °C) and 0.2 L of ethyl acetate was first used as the eluent (~400 mL for each fraction); then a mixture of 3.8 L of petroleum ether (60–90 °C) and 0.25 L of ethyl acetate was used (~100 mL for each fraction). After evaporation of the solvents, 9.42 g of the product (*R*)-**3** was obtained as a light yellow liquid.
17. The purity of the product (*R*)-4-cyclohexyl-2,3-butadien-1-ol ((*R*)-**3**) is 99% as determined by GC; GC conditions: hp-5 (30 m × 0.32 mm × 0.25 μm); oven: 50 °C for 2 min, then 20 °C/min, 250 °C for 10 min; inject: 320 °C; FID: 320 °C; split: 80:1; N_2: 20 mL/min.
18. The yield was calculated based on (*S*)-α,α-diphenylprolinol since it is the limiting reagent (1 equiv).
19. A second full-scale run provided 9.82 g (65%) for the two steps.
20. Determination of the enantiomeric excess of the product (*R*)-4-cyclohexyl-2,3-butadien-1-ol ((*R*)-**3**) required the synthesis of the corresponding racemic 4-cyclohexyl-2,3-butadien-1-ol (±)-**3** (Scheme 1).[4a]



Scheme 1. Preparation of racemic 4-cyclohexyl-2,3-butadien-1-ol (±)-3

To a flame-dried Schlenk tube that contained a stir bar were added CuBr (7.4 mg, 0.05 mmol) and activated 4 Å molecular sieves

(301.7 mg). Toluene (2 mL), *tert*-butyldimethyl(2-propynyloxy)silane **1** (170.5 mg, 1.0 mmol), cyclohexanecarboxaldehyde (124.0 mg, 1.1 mmol) and pyrrolidine (78.3 mg, 1.1 mmol) were then added sequentially under an argon atmosphere. The solution was then stirred at 25 °C until completion of the reaction as monitored by TLC (12 h). The crude reaction mixture was filtrated through a short pad of silica gel eluted with ether (20 mL). After evaporation, the crude product was used in the next step without further treatment. To another Schlenk tube that contained a stir bar were added anhydrous ground ZnI_2 (147.0 mg, 0.45 mmol) and NaI (75.2 mg, 0.5 mmol). The Schlenk tube was heated with a heating gun under vacuum (1 mmHg) for about 1 min, and the flask was refilled with argon. The above crude product was then dissolved in toluene (5 mL) and transferred to the Schlenk tube via a syringe under argon atmosphere. The Schlenk tube was then equipped with a condenser and placed in a pre-heated oil bath at 110 °C with stirring. After 6 h, the reaction was judged as complete by TLC, after which the crude reaction mixture was filtrated through a short pad of silica gel (diameter: 30 mm, height: 20 mm) with ether (20 mL) as the eluent. After evaporation, the crude product was then dissolved in THF (3 mL) and treated at 0 °C with TBAF·$3H_2O$ (316 mg, 1.0 mmol). The resulting mixture was allowed to warm to room temperature naturally with stirring. After 2 h, the reaction was complete, as determined by TLC, and H_2O (10 mL) and ether (10 mL) were then added. The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by flash chromatography (eluent: petroleum ether/ethyl acetate = 10/1) to afford 4-cyclohexyl-2,3-butadien-1-ol (±)-**3** (113.0 mg, 74%) as a liquid.

21. The enantiomeric excess was determined by chiral HPLC (conditions: Chiralcel AS-H column, eluent: hexane/*i*-PrOH = 98/2, flow rate: 0.7 mL/min). The peaks were visualized at 214 nm with retention times of 17.2 (major isomer) and 20.3 min (minor isomer). Enantioenriched (*R*)-4-cyclohexyl-2,3-butadien-1-ol ((*R*)-**3**) exhibits the following characteristics: $[\alpha]_D^{28} = -97.1$ (*c* = 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00–1.32 (m, 5 H), 1.62–1.77 (m, 6 H), 1.98–2.05 (m, 1 H), 4.10 (s, 2 H), 5.27–5.38 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.8, 25.9, 32.8, 32.9, 36.9, 60.7, 92.4, 99.4, 202.0; MS (EI) *m*/*z* (%): 152 (M^+, 0.70), 55 (100); IR (neat): υ = 3331, 2924, 2851, 1961, 1448, 1302, 1258, 1214, 1062, 1012 cm^{-1}; HRMS calcd for $C_{10}H_{16}O$ [M^+]: 152.1201, found: 152.1198.

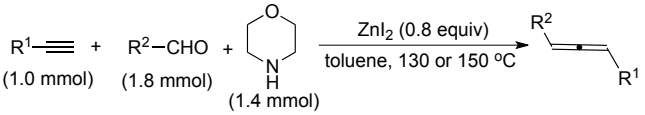
Handling and Disposal of Hazardous Chemicals

The procedures in this article are intended for use only by persons with prior 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 www.nap.edu). 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.

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.

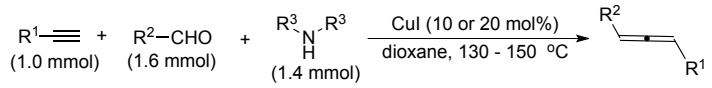
Discussion

Allenes have become an important class of compounds for the purposes of organic synthesis, medicinal chemistry, and materials science,[5] therefore, methods for the efficient synthesis of allenes from easily available starting materials are highly desirable.[6] In 1979, Crabbé *et al*. reported the first CuBr-mediated one-pot protocol for the synthesis of terminal allenes from terminal alkynes and formaldehyde in the presence of diisopropylamine.[3a] Based on this method, we have developed a modified procedure that proceeds in higher yields by utilizing CuI and dicyclohexylamine.[3b] However, it should be noted that the reaction is limited to paraformaldehyde: no allene is formed when other aldehydes are used. To address such a limitation, we have recently developed an efficient ZnI_2-mediated[3c] or CuI-catalyzed[3d] one-pot protocol for the synthesis of 1,3-disubstituted allenes from 1-alkynes, aldehydes, and morpholine (Scheme 2) or di(*n*-alkyl)amine (Scheme 3). Notably, functionalities such as halide, hydroxyl, and amine groups can all be tolerated in these transformations.



R^1 = *n*-C_8H_{17}, R^2 = Ph, 7.2 h, 65%
R^1 = *n*-C_8H_{17}, R^2 = *p*-ClC_6H_4, 6.7 h, 52%
R^1 = *p*-$O_2NC_6H_4CH_2OCH_2$, R^2 = *i*-Pr, 22 h, 56%
R^1 = *p*-$O_2NC_6H_4CH_2OCH_2$, R^2 = *n*-Bu, 6 h, 42%
R^1 = *p*-$O_2NC_6H_4CH_2O(CH_2)_2$, R^2 = Ph, 9.2 h, 51%
R^1 = *n*-$C_7H_{15}CH(OH)$, R^2 = Ph, 7.8 h, 62%
R^1 = *n*-$C_7H_{15}CH(NHTs)$, R^2 = Ph, 6.4 h, 59%
R^1 = *n*-$C_7H_{15}CH(NHTs)$, R^2 = *i*-Pr, 9.6 h, 49%

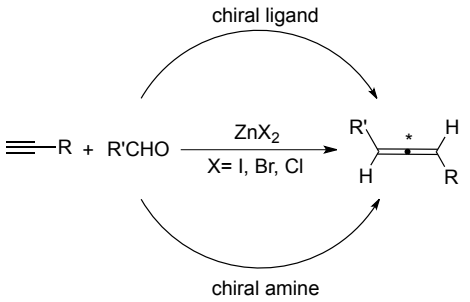
Scheme 2. ZnI_2-promoted one-pot synthesis of 1,3-disubstituted allenes



R^1 = PhCH(OH), R^2 = *n*-Pr, R^3 = *n*-Bu, 12 h, 73%
R^1 = *n*-$C_7H_{15}CH(OH)$, R^2 = *n*-Pr, R^3 = *n*-Bu, 36 h, 60%
R^1 = *n*-$C_7H_{15}CH(NHTs)$, R^2 = *n*-Pr, R^3 = *n*-Bu, 48 h, 54%
R^1 = $BnOCH_2$, R^2 = *n*-Pr, R^3 = *n*-Bu, 28 h, 55%
R^1 = PhCH(OH), R^2 = Et, R^3 = *i*-Bu, 18 h, 49%
R^1 = PhCH(OH), R^2 = Cy, R^3 = *i*-Bu, 18 h, 39%
R^1 = PhCH(OH), R^2 = *n*-C_5H_{11}, R^3 = *i*-Bu, 12 h, 55%
R^1 = $HOCH_2$, R^2 = *n*-C_7H_{15}, R^3 = *i*-Bu, 8 h, 41%

Scheme 3. CuI-catalyzed one-pot synthesis of 1,3-disubstituted allenes

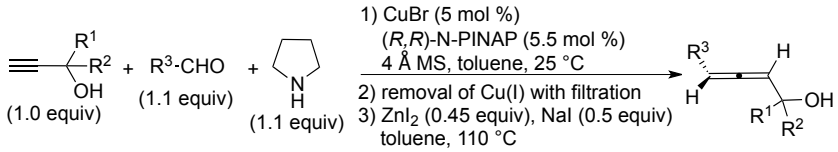
After numerous unsuccessful attempts, we have recently developed the synthesis of optically active allenes via two different strategies involving a) the utilization of a chiral amines, and b) the utilization of chiral ligands (Scheme 4).[4]



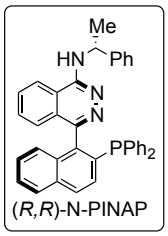
Scheme 4. Two approaches for the synthesis of optically active allenes

Among the allene family, axially chiral α-allenols are of particular interest as they are not only versatile building blocks for the synthesis of different types of heterocycles with a central chirality, but they are also the most basic starting materials for the synthesis of allenyl amines, malonates, thiols, aldehydes or ketones, and carboxylic acids with an axial chirality.[7] However, enantioselective synthesis of α-allenols is still challenging due to the fact that such an axial chirality spreads over three carbon atoms and there is a free hydroxyl group. Traditionally, a tedious, low-yielding route to axially chiral primary α-allenols from optically active propargylic alcohols using inconvenient and potentially hazardous chemicals such as *n*-BuLi and $LiAlH_4$ has been used.[8] Thus, a highly efficient approach to such primary α-allenols is in great demand.

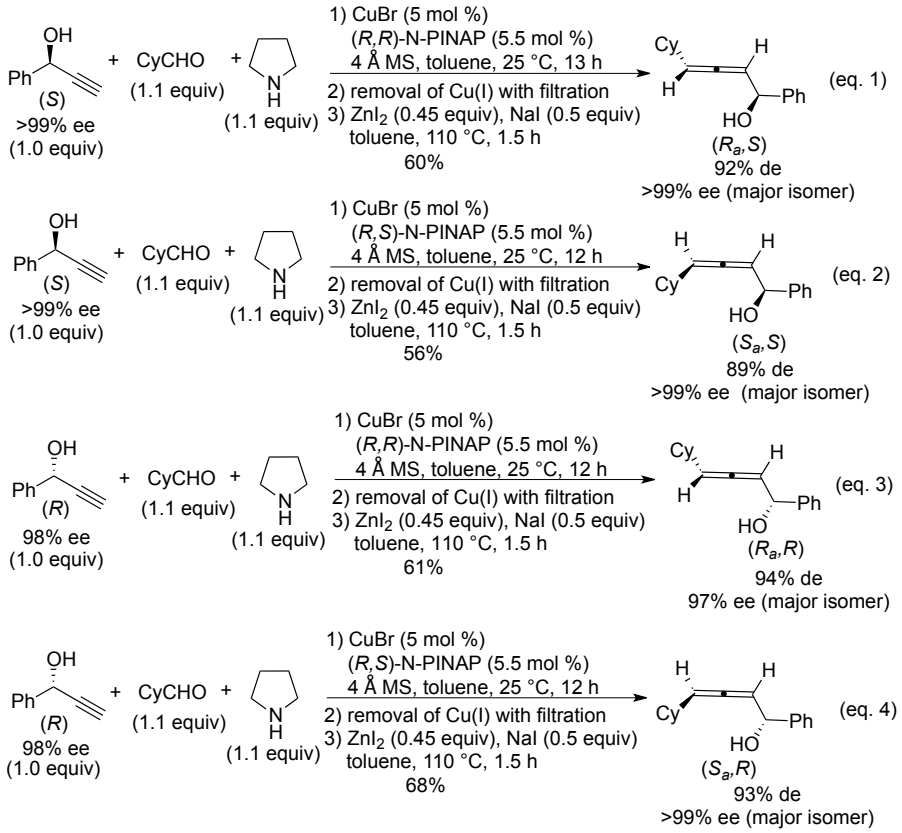
Tertiary and secondary α-allenols may be prepared via the catalytic formation of optically active propargylic amines (Scheme 5 and 6).[4a] However, this approach is not suitable for the synthesis of such primary alcohols in high ees and yields.



R^1, R^2 = -$(CH_2)_5$-, R^3 = Cy, 68%, 96% ee
R^1, R^2 = -$(CH_2)_4$-, R^3 = Cy, 69%, 95% ee
R^1, R^2 = Me, Me, R^3 = Cy, 71%, 95% ee
R^1, R^2 = Et, Et, R^3 = Cy, 77%, 96% ee
R^1, R^2 = -$(CH_2)_5$-, R^3 = *i*-Pr, 50%, 95% ee
R^1, R^2 = -$(CH_2)_5$-, R^3 = *i*-Bu, 75%, 90% ee
R^1, R^2 = -$(CH_2)_5$-, R^3 = *n*-C_7H_{15}, 54%, 92% ee
R^1, R^2 = -$(CH_2)_5$-, R^3 = Ph, 78%, 93% ee

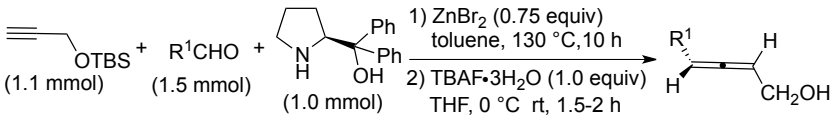


Scheme 5. Chiral ligand approach for the synthesis of tertiary α-allenols



Scheme 6. Chiral ligand approach for the synthesis of four diastereoisomers of axially chiral secondary α-allenols

This submission details the procedure based on the second approach shown in Scheme 4: a highly efficient $ZnBr_2$-mediated[4,9] multi-gram synthesis of highly enantioenriched axially chiral α-allenols from TBS-protected propargylic alcohols, aldehydes, and the inexpensive commercially available secondary amine (*S*)-α,α-diphenylprolinol followed by desilylation. By utilizing this strategy, axially chiral primary and secondary α-allenols may all be prepared efficiently in moderate to good yields with 96-99% ee or de (Scheme 7).



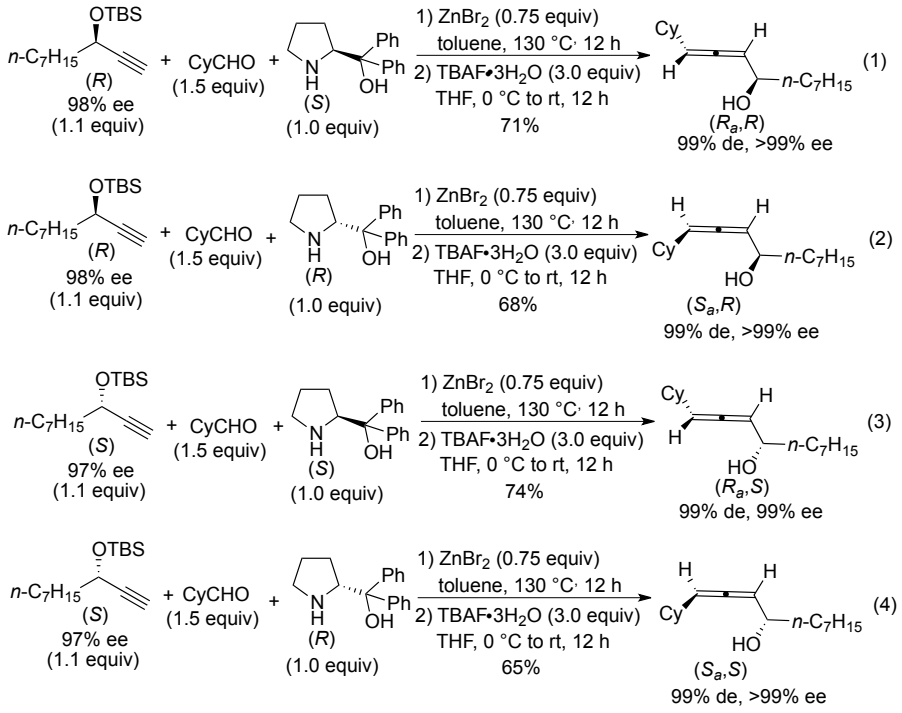
R_1 = Cy, 68%, 99% ee
Cy, 70%, 99% ee (10 mmol scale)
^{i}Bu, 45%, 98% ee (3 mmol scale)
n-C_5H_{11}, 59%, 98% ee

R_1 = *c*-C_5H_9, 59%, 98% ee
n-C_7H_{15}, 65%, 97% ee
$Ph(CH_2)_2$, 60%, 96% ee
Et_2CH, 63%, 98% ee

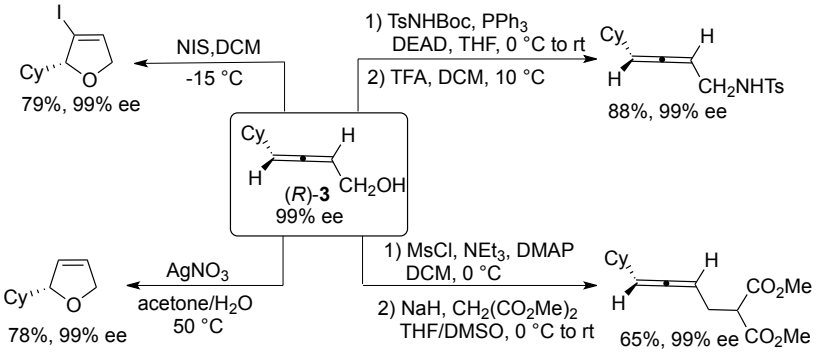
Scheme 7. Chiral amine approach for the synthesis of axially chiral primary α-allenols

When (*R*)-α,α-diphenylprolinol is used as the chiral amine, the corresponding (*S*)-α-allenols are conveniently prepared with the same level of enantioselectivity. Therefore, all four diastereoisomers of axially chiral secondary α-allenols can be prepared with high stereoselectively by simply adjusting the absolute configurations of the central chiralities in the TBS-protected propargylic alcohols and α,α-diphenylprolinol (eq. 1-4, Scheme 8).

The primary enantioenriched α-allenols obtained through this method are very useful and may be transformed into a wide variety of not-readily-available, yet synthetically useful, optically active heterocyclic compounds with central chirality or into functionalized allenes with axial chirality without loss of enantiomeric purity (Scheme 9).



Scheme 8. Chiral amine approach for the synthesis of four diastereoisomers of axially chiral secondary α-allenols



Scheme 9. Transformations of axially chiral α–allenol (*R*)-3

References

1. State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai, China. E-mail: masm@sioc.ac.cn.
2. Falck, J. R.; He, A.; Fukui, H.; Tsutsui, H.; Radha, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4527.
3. (a) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun*. **1979**, 859. (b) Kuang, J.; Ma, S. *J. Org. Chem*. **2009,** *74*, 1763. (c) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786. (d) Kuang, J.; Luo, H.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 933.
4. (a) Ye, J.; Li, S.; Chen, B.; Fan, W.; Kuang, J.; Liu, J.; Liu, Y.; Miao, B.; Wan, B.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Ma, S. *Org. Lett.* **2012**, *14*, 1346. Recently, Periasamy, *et al*. reported a "two-step" procedure of $ZnBr_2$-promoted synthesis of axially chiral 1,3-disubstituted allenes: (b) Periasamy, M.; Sanjeevakumar, N.; Dalai, M.; Gurubrahamam, R.; Reddy, P. O. *Org. Lett.* **2012**, *14*, 2932. In their paper, they reported that stirring the solution of $ZnBr_2$, (*S*)-α,α-diphenylprolinol, and terminal alkynes in toluene for 10 min at 120 °C followed by the addition of aldehydes at room temperature and then gradually heating the solution to 120 °C are very important for the high ees and yields for 1-aryl substituted allenes. However, we have not been able to reproduce their results in terms of ee and yield: the calibrated specific optical rotations of the same allenes with similar ee values from our study and the data in their report are different.
5. For most recent reviews on the chemistry of allenes, see: (a) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (b) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91. (c) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (d) Ma, S. A*cc. Chem. Res.* **2009**, *42*, 1679. (e) Alcaide, B.; Almendros, P.; Campo, T. M. d. *Chem. Eur. J.* **2010**, *16*, 5836. (f)Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev*. **2011**, *111*, 1954; (g) Inagaki, F.; Kitagaki, S.; Mukai, C. *Synlett* **2011**, 594. (h) López, F.; Mascareñas, J. L. *Chem. Eur. J.* **2011**, *17*, 418. (i) Yu, S.; Ma, S. *Angew. Chem., Int. Ed*. **2012**, *51*, 3074.
6. For reviews on the synthesis of allenes, see: (a) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133. (b) Krause, N. Hashmi, A. S. K., Eds.; *Modern Allene Chemistry;* Wiley-VCH: Weinheim, Germany, 2004; Vol. 1 and 2. (c) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671. (d)

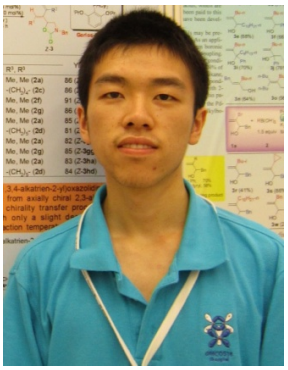
Brummond, K. M.; Deforrest, J. E. *Synthesis* **2007**, 795. (e) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259. (f) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384.

7. For selected reports on the reactions of α-allenols, see: (a) Olsson, L.-I.; Claesson, A. *Synthesis* **1979**, 743. (b) Nikam, S. S.; Chu, K. H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 745. (c) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1990**, *55*, 2995. (d) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180. (e) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966. (f) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933. (g) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. (h) Friesen, R. W.; Blouin, M. *J. Org. Chem.* **1993**, *58*, 1653. (i) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943. (j) Fu, C.; Li, J.; Ma, S. *Chem. Commun.* **2005**, 4119. (k) Li, J.; Fu, C.; Chen, G.; Chai, G.; Ma, S. *Adv. Synth. Catal.* **2008**, *350*, 1376. (l) Deng, Y.; Jin, X.; Ma, S. *J. Org. Chem.* **2007**, *72*, 5901. (m) Deng, Y.; Yu, Y.; Ma, S. *J. Org. Chem.* **2008**, *73*, 585.
8. For early leading references, see: (a) Olsson, L.-I.; Claesson, A. *Acta Chem. Scand.* **1977**, *B31*, 614. (b) Claesson, A.; Olsson, L.-I. *J. Am. Chem.Soc.* **1979**, *101*, 7302. (c) Smith, R. A.; White, R. L.; Krantz, A. *J. Med. Chem.* **1988**, *31*, 1558. For an alternative eight-step approach, see: (d) Stichler-Bonaparte, J.; Kruth, H.; Lunkwitz, R.; Tschierske, C. *Liebigs Ann.* **1996**, 1375.
9. Ye, J.; Fan, W.; Ma, S. *Chem. Eur. J.* **2013**, *19*, 716.

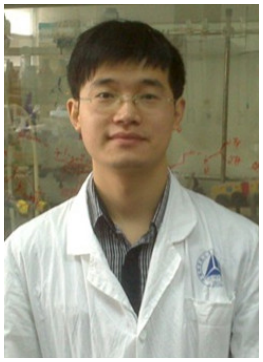
Appendix
Chemical Abstracts Nomenclature (Registry Number)

2-Propyn-1-ol; (107-19-7)
Silane, chloro(1,1-dimethylethyl)dimethyl-; (18162-48-6)
1*H*-Imidazole; (288-32-4)
Silane, (1,1-dimethylethyl)dimethyl(2-propyn-1-yloxy)-; (76782-82-6)
Zinc bromide; (7699-45-8)
Cyclohexanecarboxaldehyde; (2043-61-0)
2-Pyrrolidinemethanol, α,α-diphenyl-, (2S)-; (112068-01-6)
Butanaminium, *N*,*N*,*N*-tributyl-, fluoride, hydrate (1:1:3) **(**87749-50-6**)**
Pyrrolidine; (123-75-1)
Copper(I) bromide; (7787-70-4)
Zinc iodide; (10139-47-6)
Sodium iodide; (7681-82-5)
(±)-2,3-Butadien-1-ol, 4-cyclohexyl-; (153489-62-4)

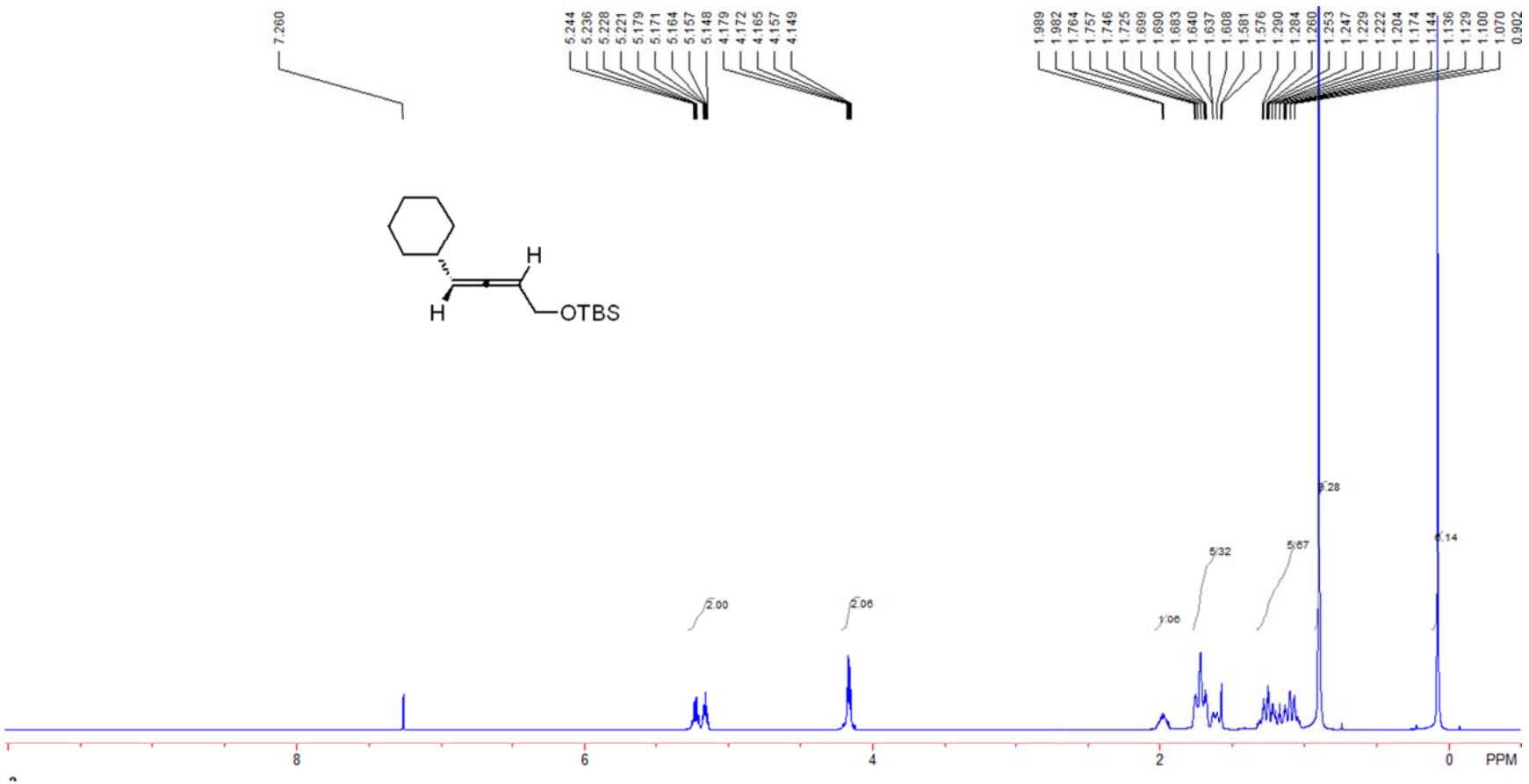
Prof. Shengming Ma was born in 1965 in Zhejiang, China. He graduated from Hangzhou University (1986) and received his Ph.D. degree from Shanghai Institute of Organic Chemistry (1990). He became an assistant professor of SIOC in 1991. After his postdoctoral appointments at ETH with Prof. Venanzi and Purdue University with Prof. Negishi from 1992–1997, he joined the faculty of SIOC in 1997. From February 2003 to September 2007, he was jointly appointed by SIOC and Zhejiang University. He works for East China Normal University and SIOC since October 2007.

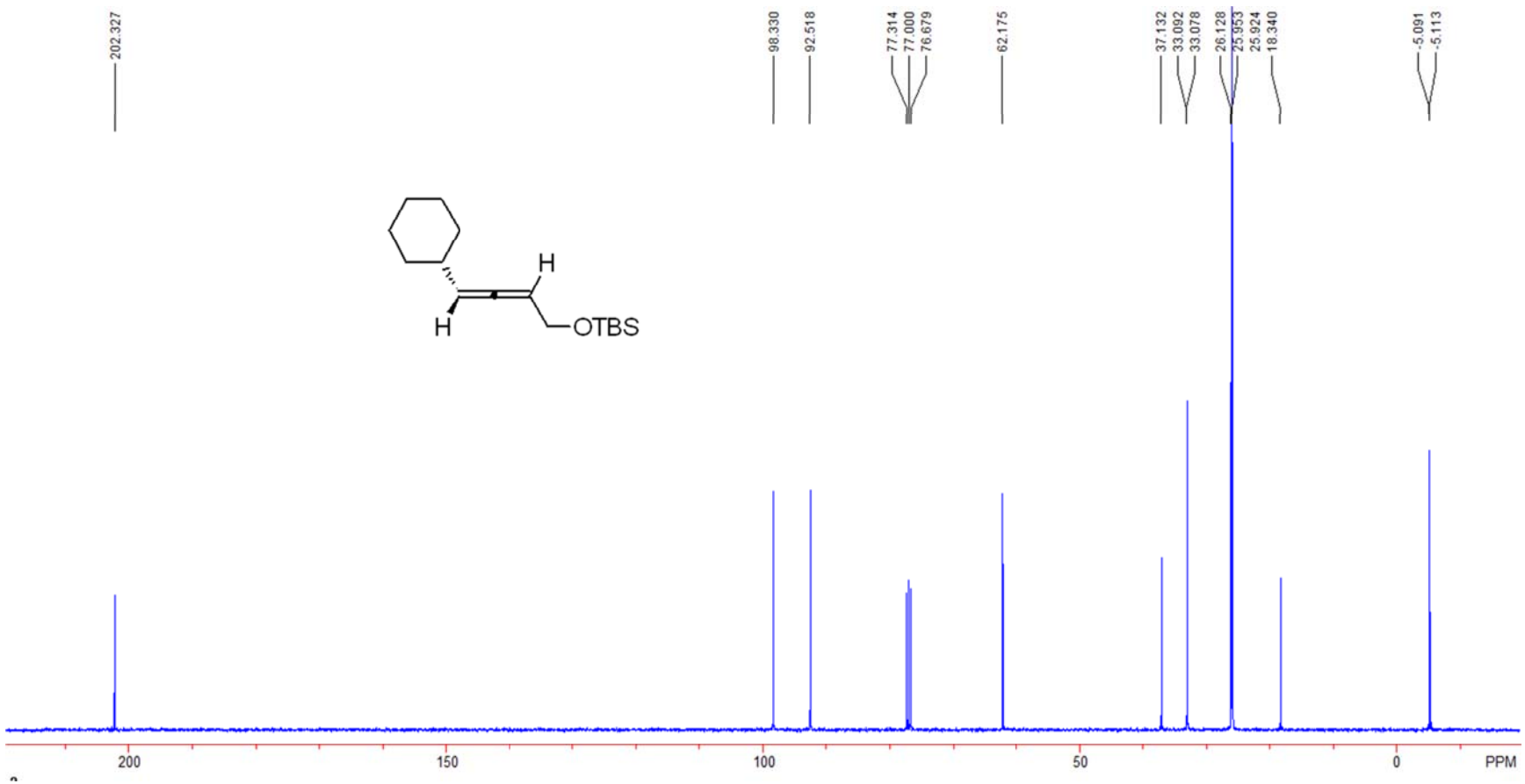


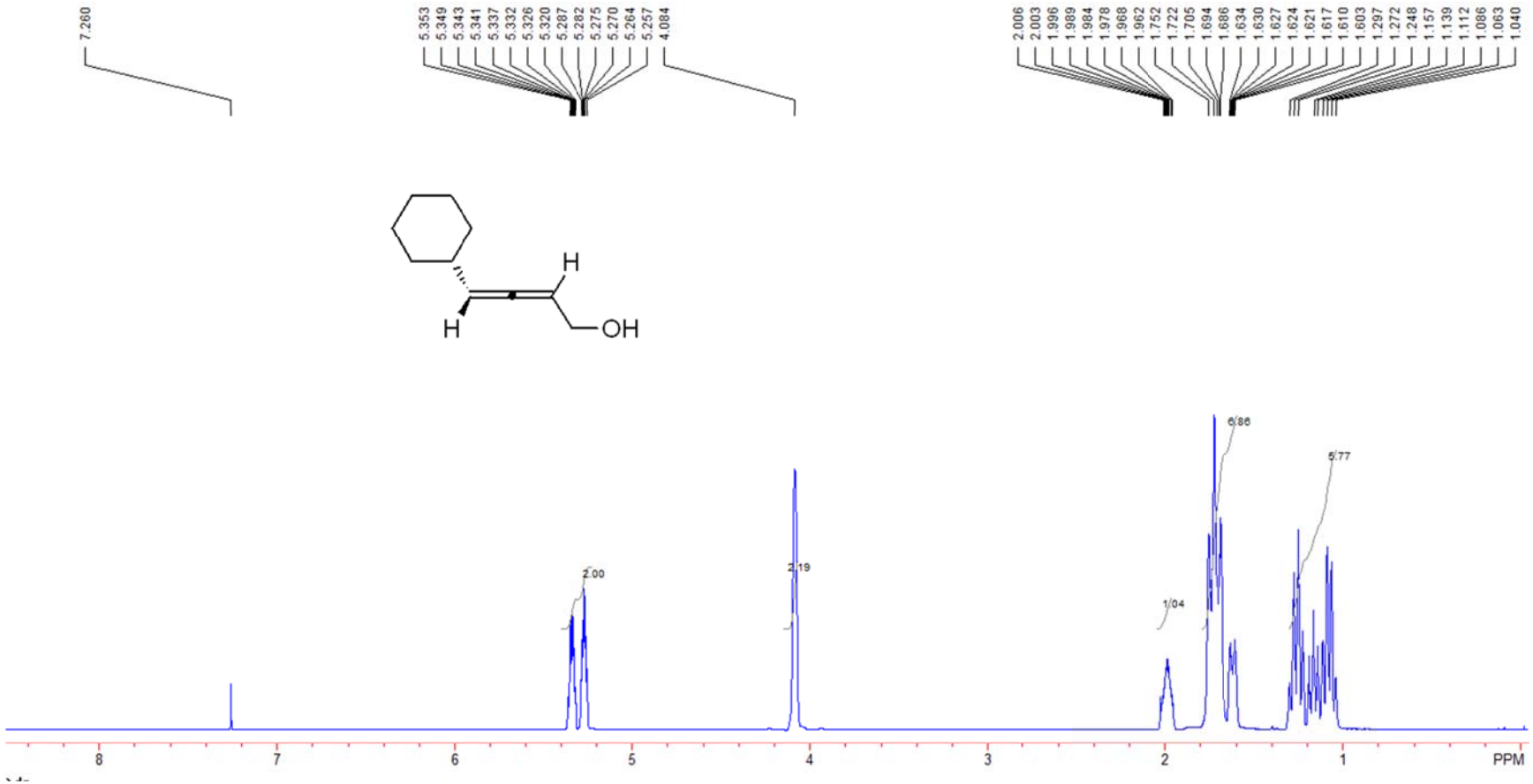
Juntao Ye was born in Hubei, China. He received his B.S. degree in chemistry from Huazhong University of Science and Technology (HUST) in 2008. He obtained his Ph.D. degree in 2013 under the supervision of Prof. Shengming Ma. His doctoral research was focused on the synthesis and cyclization reactions of allenes. Currently, he is a postdoctoral fellow in Prof. Mark Lautens' group at the University of Toronto.

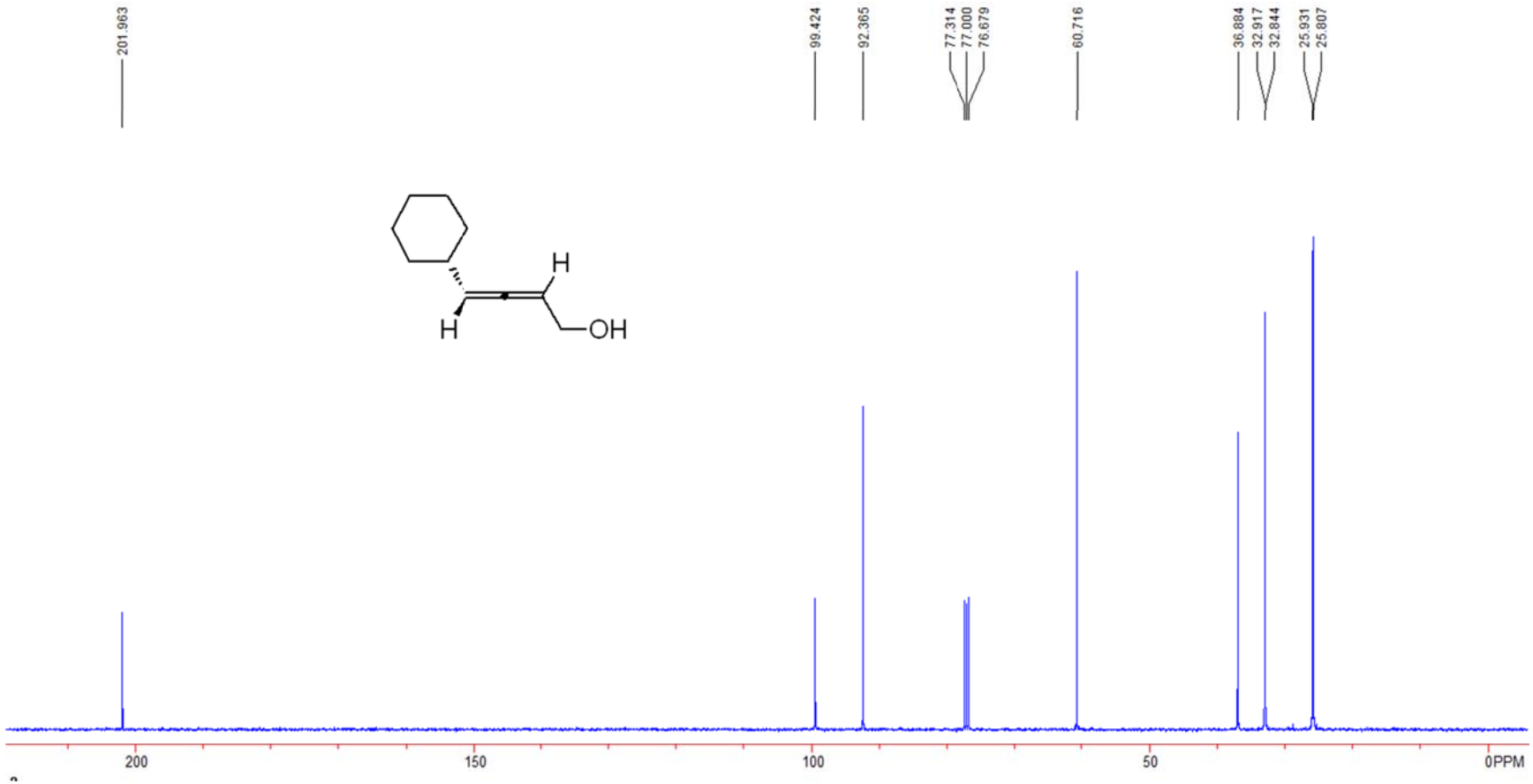


Mingyao Wu was born in Hubei, China. He received his B.S. degree in chemistry from Wuhan University in 2008. He earned his Ph.D. in Shanghai Institute of Organic Chemistry (SIOC) in 2013 under the supervision of Prof. Dawei Ma, working on total synthesis of complex natural products.


7.260
5.244
5.236
5.228
5.221
5.179
5.171
5.164
5.157
5.148
4.179
4.172
4.165
4.157
4.149
1.989
1.982
1.764
1.757
1.746
1.725
1.699
1.690
1.683
1.640
1.637
1.608
1.581
1.576
1.290
1.284
1.260
1.253
1.247
1.229
1.222
1.204
1.174
1.144
1.136
1.129
1.100
1.070
0.902
H
H
OTBS
2.00
2.06
1.06
5.32
5.67
9.28
6.14
8
6
4
2
0
PPM


202.327
98.330
92.518
77.314
77.000
76.679
62.175
37.132
33.092
33.078
26.128
25.953
25.924
18.340
-5.091
-5.113
H
H
OTBS
200
150
100
50
0
PPM


7.260
5.353
5.349
5.343
5.341
5.337
5.332
5.326
5.320
5.287
5.282
5.275
5.270
5.264
5.257
4.084
2.006
2.003
1.996
1.989
1.984
1.978
1.968
1.962
1.752
1.722
1.705
1.694
1.686
1.634
1.630
1.627
1.624
1.621
1.617
1.610
1.603
1.297
1.272
1.248
1.157
1.139
1.112
1.086
1.063
1.040
H
H
OH
2.00
2.19
1.04
6.86
5.77
8
7
6
5
4
3
2
1
PPM


201.963
99.424
92.365
77.314
77.000
76.679
60.716
36.884
32.917
32.844
25.931
25.807
H
H
OH
200
150
100
50
0PPM