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Trifluoromethylated amino alcohol as chiral auxiliary for highly diastereoselective and fast Simmons–Smith cyclopropanation of allylic amine

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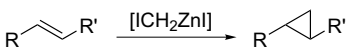
Received 31 March 2006; accepted 26 April 2006

Abstract—Three advantages of a trifluoromethylated amino alcohol auxiliary in the Simmons–Smith cyclopropanation of allylic amines are described. The trifluoromethylated amino alcohol auxiliary reduces unwanted side reactions induced by its acidic, and thus less nucleophilic, hydroxy group. The auxiliary accelerated the reaction rate by its electron-withdrawing effect, and promoted the reaction with excellent diastereoselectivity.

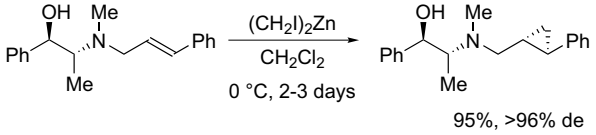
1. Introduction

The Simmons–Smith cyclopropanation with an organozinc species, such as $IZnCH_2I$ and $(ICH_2)_2Zn$, is one of the most widely used and popular tools for the conversion of olefins to cyclopropanes (Scheme 1).[1] Among various versions of this reaction, stereoselective cyclopropanations have been the focus of interest of many synthetic chemists and great progress has been made in recent years.[2] Efficient enantioselective cyclopropanations have been achieved using chiral ligands or catalysts.[3] Also, efficient diastereoselective cyclopropanations have been achieved using chiral auxiliaries.[4–9]

Recently, a highly diastereoselective Simmons–Smith cyclopropanation of allylic amines using the chelating pseudoephedrine moiety was attained by suppression of the possible side reactions (Scheme 2).[8] The product structure, aminomethyl cyclopropane, is the key structure of a series of irreversible inhibitors of monoamine



Scheme 1.



Scheme 2. (Ref. 8).

oxidase.[10] It is an accessory part of an opioid receptor antagonist,[11] and is a conformationally restricted histamine analogue[12] and γ-amino acid.[13] A drawback of the reaction is its slow reaction rate; the reaction requires 2–3 days for completion.[8]

In general, the slow reaction rates of Simmons–Smith cyclopropanation had been recognized as a synthetic drawback. Since the first report of Lewis acid acceleration of the reaction by Friedrich in 1989,[14] there have been a variety of accelerating methods developed for the reaction using an electron-withdrawing moiety to make the carbenoid species electrophilic.[15]

Recent computational studies on the reaction pathway suggested that the role of the Lewis acid is the push–pull of electrons by a Schlenk-type aggregation of a zinc carbenoid species.[16] A similar acceleration of the reaction rate of alkyl transfer process in a Grignard reaction by Schlenk-type aggregation of an organomagnesium species had been studied kinetically[17] as well as computationally.[18]

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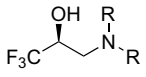
doi:10.1016/j.tetasy.2006.04.031

We found that a chiral α-trifluoromethyl-β-amino alcohol **1** promoted a highly diastereoselective ethylation of benzaldehyde and remarkable aggregation of a diethylzinc species at that time.[19] Of course, the trifluoromethyl group is a strong electron-withdrawing group. Thus, the utilization of the (chiral) α-trifluoromethyl-β-amino alcohol moiety should accelerate the Simmons–Smith cyclopropanation.



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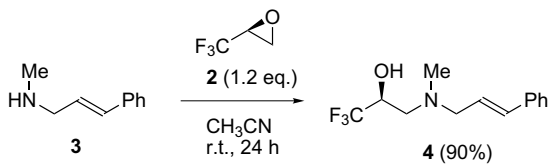
Herein, we succeeded in the improvement of the Simmons–Smith cyclopropanation as illustrated in Scheme 2[8] by the use of the chiral amino alcohol **1** instead of the pseudoephedrine moiety. This alteration caused, (1) an acceleration of the reaction, (2) high diastereoselectivity comparable to that of the original reaction,[21] and (3) destabilization of possible ammonium ylide[22] by the acidic hydroxy group to suppress the side reaction.[8,23]

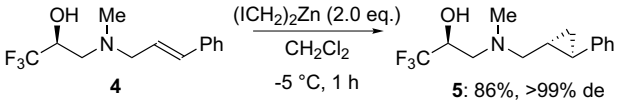
2. Results and discussion

The chiral auxiliary attached to the allylic amine was prepared by the reaction of allylic amine with enantiomerically pure 1,2-epoxy-3,3,3-trifluoropropane (TFPO) **2**[24] (Scheme 3). The enantiomerically pure TFPO is a compound with high availability and reliability; it can be prepared from commercially available optically active or racemic TFPO via Jacobsen's enantioselective hydrolysis procedure.[25] The TFPO can react smoothly with nucleophilic amines without a catalyst or a base. The epoxy ring is thus activated by the strong electron-withdrawing trifluoromethyl group meaning that it can react spontaneously with amines.[24] The reaction of amine **3** with the enantiomerically pure TFPO **2** in acetonitrile at room temperature, followed by recrystallization from hexane–ether, gave a chemically and enantiomerically pure allylic amine with chiral auxiliary **4** in 90% yield.

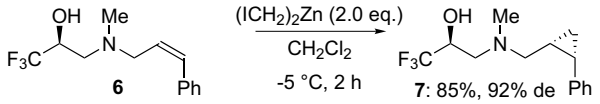
A Simmons–Smith cyclopropanation of the *trans*-allylic amine **4** with the trifluoromethylated chiral auxiliary is illustrated in Scheme 4. It took only 1 h to complete the reaction; conversion of the reaction was found to be >99% and the yield of the sole product **5** analyzed by NMR was 98%. Crude reaction mixtures were submitted to HPLC equipped with a chiral column (Daicel Chiralcel OD-H, hexane–*i*-PrOH = 40:1). The mean diastereoselectivity of the products of three runs was >99%. The isolated yield of product **5** via silica-gel column chromatography was 86%.



Scheme 3.



Scheme 4.

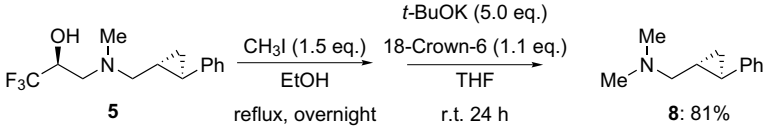


Scheme 5.

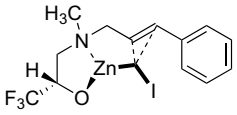
Similar to that of *trans*-allylic amine, a Simmons–Smith cyclopropanation of *cis*-allylic amine **6** gave cyclopropane **7**, as illustrated in Scheme 5. The isolated yield of product **7** was 85% with 92% de. The stereochemistry of the major diastereomer **7** was confirmed to be (*R*,*S*) by X-ray crystallographic analysis.[26]

The chiral auxiliary within **5** was removed from the cyclopropyl moiety via quarternization with MeI followed by treatment with *t*-BuOK, as shown in Scheme 6.[8] The isolated yield of the product, 2-phenyl-1-(*N*,*N*-dimethylamino)methyl-cyclopropane **8**, was 81%. The stereochemistry of compound **8** was assigned by comparison of the specific rotation to that of the literature;[8] the specific rotation was found to be $[\alpha]_D^{25} = -116$ {lit., $[\alpha]_D^{20} = -109$ (96% ee)[8]}.

It is noteworthy that the induced stereochemistry of the cyclopropane unit of **8** was (*R*,*R*) from the (*S*)-trifluoromethylated chiral auxiliary, which is similar to the results achieved by Meek et al. using the pseudoephedrine auxiliary (Scheme 2).[8] Similarly, the chiral auxiliary, trifluoromethylated amino alcohol moiety, tightly held the zinc carbenoid species, which would result in high diastereoselectivity of the product (Scheme 7). This stereochemical result is consistent with Meek's suggestion that 'large groups attached to the oxygen center play a dominant role.' We suggest that the trifluoromethyl group works as a large group in the stereocontrolled Simmons–Smith cyclopropanation, and its effective size is comparable to that of the phenyl group.



Scheme 6.



Scheme 7.

3. Conclusion

In conclusion, we have found three remarkable advantages of the trifluoromethylated amino alcohol reduced in the Simmons–Smith cyclopropanation of allylic amines; (1) the trifluoromethylated amino alcohol auxiliary depressed unwanted side reactions with its acidic hydroxy group; (2) it accelerated the reaction rate remarkably, and (3) it promoted excellent diastereoselectivity by the bulkiness of its trifluoromethyl group. Easy introduction and removal of this trifluoromethylated chiral auxiliary would be an additional synthetic advantage. We are currently eager to find further applications of the trifluoromethylated amino alcohol ligands and auxiliaries for the stereoselective reactions.[19,20]

Acknowledgments

We thank the SC-NMR Laboratory of Okayama University for ^{19}F and ^{1}H NMR analyses and the Venture Business Laboratory of Graduate School of Okayama University for the single-crystal X-ray diffraction analysis.

References

1. (a) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1–131; (b) Edrik, E. *Organozinc Reagents in Organic Synthesis*; CRC: Boca Raton, 1996; pp 95–105; (c) Taguchi, T.; Okada, M. *J. Fluorine Chem.* **2000**, *105*, 279–283; (d) Charette, A. B.; Beuchemin, A. *Org. React.* **2001**, *58*, 1–415; (e) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347.
2. (a) Inomata, K.; Ukaji, Y. *Rev. Heteroatom Chem.* **1998**, *18*, 119–140; (b) Schuppan, J.; Koert, U. Stereocontrolled Simmons–Smith cyclopropanation. In *Organic Synthesis Highlights IV*; Schmalz, H. G., Ed.; Wiley-VCH: Weinheim, 2000; pp 3–10; (c) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
3. (a) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575–2578; (b) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, 61–64; (c) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Lett.* **1993**, 1227–1230; (d) Imai, N.; Takahashi, H.; Kobayashi, S. *Chem. Lett.* **1994**, 177–180; (e) Imai, N.; Sakamoto, K.; Takahashi, H.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 7045–7048; (f) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651–2652; (g) Kitajima, H.; Aoki, Y.; Ito, K.; Katsuki, T. *Chem. Lett.* **1995**, 1113–1114; (h) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081–1083; (i) Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013–12026; (j) Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367–11368; (k) Denmark, S. E.; Christenson, B. L.; Coe, D. M.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2215–2218; (l) Denmark, S. E.; Christenson, B. L.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2219–2222; (m) Charette, A. B.; Juteau, H.; Lebel, H.; Deschenes, D. *Tetrahedron Lett.* **1996**, *37*, 7925–7928; (n) Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett.* **1997**, *38*, 1423–1426; (o) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207–217; (p) Charette, A. B.; Lemay, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 1090–1092; (q) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584–594; (r) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 3390–3401; (s) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621–8624; (t) Denmark, S. E.; O'Connor, S. P.; Wilson, R. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1149–1151; (u) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952; (v) Balsells, J.; Walsh, P. J. *J. Org. Chem.* **2000**, *65*, 5005–5008; (w) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168–12175; (x) Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13632–13633; (y) Ukaji, Y.; Inomata, K. *Synlett* **2003**, 1075–1087; (z) Long, J.; Du, H.; Li, K.; Shi, Y. *Tetrahedron Lett.* **2005**, *46*, 2737–2740; Charette, A. B.; Lacasse, M.-C. *J. Am. Chem. Soc.* **2005**, *127*, 12440–12441.
4. Diastereoselective Simmons–Smith cyclopropanation with a sugar auxiliary: (a) Charette, A. B.; Cote, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166–8167; (b) Charette, A. B.; Côté, B. *J. Org. Chem.* **1993**, *58*, 933–936; (c) Charette, A. B.; Marcoux, J. F. *Tetrahedron Lett.* **1993**, *34*, 7157–7160; (d) Charette, A. B.; Turcotte, N.; Marcoux, J.-F. *Tetrahedron Lett.* **1994**, *35*, 513–516; (e) Charette, A. B.; Juteau, H.; Lebel, H.; Deschenes, D. *Tetrahedron Lett.* **1996**, *37*, 7925–7928; (f) Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721–12732; (g) Kang, J.; Lim, G. J.; Yoon, S. K.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564–577.
5. Diastereoselective Simmons–Smith cyclopropanation with a chiral diol auxiliary: (a) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254–8256; (b) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256–8258; (c) Mori, A.; Arai, I.; Yamamoto, H.; Nakai, H.; Arai, Y. *Tetrahedron* **1986**, *42*, 6447–6458; (d) Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775–5778; (e) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Tai, A. *Tetrahedron Lett.* **1989**, *30*, 3807–3810; (f) Sugimura, T.; Koguro, K.; Tai, A. *Tetrahedron Lett.* **1993**, *34*, 509–512; (g) Yeh, S.; Huang, L.; Luh, T. *J. Org. Chem.* **1996**, *61*, 3906–3908; (h) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Katagiri, T.; Miyashige, R.; Mizuguchi, M.; Nagano, S.; Sugimori, S.; Tai, A.; Tei, T.; Okumura, T. *Tetrahedron* **2001**, *52*, 7495–7499; (i) Tei, T.; Sugimura, T.; Katagiri, T.; Tai, A.; Okuyama, T. *Tetrahedron: Asymmetry* **2001**, *12*, 2727–2730.
6. Diastereoselective Simmons–Smith cyclopropanation with camphor auxiliary: Kaye, P. T.; Molema, W. E. *Chem. Commun.* **1998**, 2479–2480.
7. Diastereoselective Simmons–Smith cyclopropanation with a chiral boronic acid ester auxiliary: (a) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986–4988; (b) Luithle, J. E. A.; Pietruszka, J. *Liebigs Ann. Recl.* **1997**, 2297–2302.
8. Diastereoselective Simmons–Smith cyclopropanation with an ephedrine auxiliary: Aggarwal, V. K.; Fang, G. Y.; Meek, G. *Org. Lett.* **2003**, *5*, 4417–4430.
9. Diastereoselective Simmons–Smith cyclopropanation: Corsaro, A.; Chiacchio, U.; Adamo, R.; Pistara, V.; Rescifina, A.; Romeo, R.; Catelani, G.; D'Andrea, F.; Mariani, M.; Attolino, E. *Tetrahedron* **2004**, *60*, 3787–3795.
10. (a) Gnad, F.; Reizer, O. *Chem. Rev.* **2003**, *103*, 1603–1623; (b) Silverman, R. B.; Ding, C. Z.; Borrillo, J. L.; Chang, J. T. *J. Am. Chem. Soc.* **1993**, *115*, 2982–2983; (c) Silverman, R. B.; Lu, X.; Blomquist, G. D.; Ding, C. Z.; Yang, S. *Bioorg. Med. Chem.* **1997**, *5*, 297–304.

11. Black, S. L.; Chauvignac, C.; Grundt, P.; Miller, C. N.; Wood, S.; Traynor, J. R.; Lewis, J. W.; Husbands, S. M. *J. Med. Chem.* **2003**, *46*, 5505–5511.
12. Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669–1677.
13. Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2005**, *7*, 1137–1140.
14. Friedrich, E. C.; Lunetta, S. E.; Lewis, E. J. *J. Org. Chem.* **1989**, *54*, 2388–2390.
15. (a) Charette, A. B.; Beauchemin, A.; Marcoux, J. F. *Tetrahedron Lett.* **1999**, *40*, 33–36; (b) Charette, A. B.; Francoeur, S.; Martel, J.; Wilb, N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4539–4542; (c) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12160–12167; (d) Zhao, C.; Wang, D.; Phillips, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 12903–12914; (e) Fournier, J. F.; Charette, A. B. *Eur. J. Org. Chem.* **2004**, 1401–1404; (f) Lorenz, J. C.; Long, J.; Yang, Z.; Xue, S.; Xie, Y.; Shi, Y. *J. Org. Chem.* **2004**, *69*, 327–334; (g) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974–6981.
16. (a) Nakamura, E.; Hirai, A.; Nakamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5844–5845; (b) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 2341–2350.
17. (a) Maruyama, K.; Hayami, J.; Katagiri, T. *Chem. Lett.* **1986**, 601–604; (b) Maruyama, K.; Katagiri, T. *J. Am. Chem. Soc.* **1986**, *108*, 6263–6270; (c) Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* **1989**, *2*, 205–213; (d) Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* **1991**, *4*, 381–386.
18. Yamazaki, S.; Yamabe, S. *J. Org. Chem.* **2002**, *67*, 9346–9353.
19. Katagiri, T.; Fujiwara, Y.; Takahashi, S.; Ozaki, N.; Uneyama, K. *Chem. Commun.* **2002**, 986–987.
20. Fujiwara, Y.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6161–6163.
21. The bulkiness of the trifluoromethyl group in the stereoselective reductions was sometimes comparable to that of a phenyl group, see: Katagiri, T.; Uneyama, K. Functional group transformations at α-carbon to trifluoromethyl group. In *Fluorine-Containing Synthons*; Soloshonok, V., Ed.; ACS Symposium Series 911; ACS: Washington, DC, 2005; pp 318–341.
22. Aggarwal, V. K.; Fang, G. Y.; Charmant, J. P. H.; Meek, G. *Org. Lett.* **2003**, *5*, 1757–1760.
23. The acidity of 2,2,2-trifluoroethanol (TFE: $pK_a = 11.4$) is comparable to the alkanethiols ($pK_a = 10$–11): (a) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; PTR Prentice Hall: New York, 1992; p 550; (b) Begue, J. P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18–29.
24. (a) Katagiri, T. Synthesis of stereochemically defined trifluoromethyl-containing compounds through (*S*)-3,3,3-trifluoropropene oxide. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999; pp 161–178; (b) Katagiri, T.; Uneyama, K. *J. Fluorine Chem.* **2000**, *105*, 285–293.
25. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.
26. Major diastereomer **7** was isolated, recrystallized, then submitted to X-ray diffraction measurement. Colorless needles, mp: 59 °C, crystal data for **7**: $C_{14}H_{18}F_3NO$, $M = 273.29$, monoclinic, space group $P2_1$, $a = 8.4633(17)$ Å, $b = 5.8574(7)$ Å, $c = 14.280(3)$ Å, $\alpha = 90°$, $\beta = 94.606(2)°$, $\gamma = 90°$, $V = 705.6(2)$ Å^3, $Z = 2$, $D_x = 1.286$ g cm^{-3}, wave length (Mo-Kα) = 0.71069 Å, $F(0\,0\,0) = 288$, 1646 reflections were collected. Full-matrix least squares refinement based on F^2 with anisotropic thermal parameters for the non-hydrogen atoms led to agreement factors $R_1 = 0.0657$ for 1593 reflections and $wR_2 = 0.1772$ for all reflections. Crystallographic data for the structure herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 602550. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].