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Highly Diastereoselective Simmons–Smith Cyclopropanation of Allylic Amines

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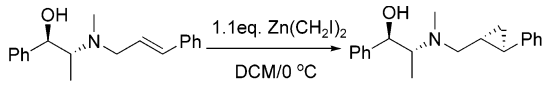
ABSTRACT



95% yield, >98:2 d.r.

Cyclopropanation of allylic tertiary amines using the Simmons–Smith reagent has been achieved by employing chelating groups in close proximity to the amine. The chelating groups promote cyclopropanation at the expense of *N*-ylide formation. Using pseudoephedrine as the chelating group, high diastereoselectivity is observed.

Simmons−Smith-type reagents[1] are widely used to cyclopropanate a range of alkenes.[2] Features that contribute to their popularity include broad substrate generality, tolerance of a variety of functional groups, stereospecificity with respect to alkene geometry, and the *syn*-directing/rate-enhancing effect observed with proximal oxygen atoms.

Much of the development of stereoselective cyclopropanation has relied on the directing effect of an allylic/homoallylic oxygen functional group, which provides an oxygen atom to chelate with the zinc reagent. Functional groups involved in substrate-controlled diastereoselective Simmons−Smith cyclopropanations include hydroxyl,[3] acetal,[4,5] amide,[6] and borate[7] groups. However, even though amines have the same potential for binding with the zinc reagent as oxygen functional groups, allylic amines have not been explored in Simmons−Smith cyclopropanation;[8] only enamines[9] and non-nucleophilic allylic amides[10] have been reported. The problem associated with the cyclopropanation of allylic amines (or olefins containing an amino group) is the competing ylide formation pathway. It has been reported that trimethylamine reacted with $Zn(CH_2Cl)_2$ generating a zinc-complexed ammonium ylide,[11] and our group also found that ylide formation was the predominant pathway when simple allylic amines were treated with $Zn(CH_2I)_2$. The resulting zinc-complexed ammonium ylides were rather stable but upon addition of ^{n}BuLi were converted into reactive zincate intermediates, which were capable of undergoing [2,3] sigmatropic rearrangements (Scheme 1).[12]

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(1) (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.

(2) For a review on Simmons−Smith cyclopropanation, see: Charette, A.; Beauchemin, A. *Org. React.* **2001**, *58*, 1.

(3) (a) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955. (b) Charette, A. B.; Côté, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166. (c) Charette, A. B.; Marcoux, J.-F. *Tetrahedron Lett.* **1993**, *34*, 7157.

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(8) Although a single example of the cyclopropanation of an allylic amine was reported, no details were provided. See: Perraud, R.; Arnaud, P. *Bull. Soc. Chim. Fr.* **1968**, 1540.

(9) (a) Kuehne, M. E.; DiVincenzo, G. *J. Org. Chem.* **1972**, *37*, 1023. (b) Kuehne, M. E.; King, J. C. *J. Org. Chem.* **1973**, *38*, 304.

(10) (a) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761. (b) Russ, P.; Ezzitouni, A.; Marquez, V. E. *Tetrahedron Lett.* **1997**, *38*, 723. (c) Ezzitouni, A.; Russ, P.; Marquez, V. E. *J. Org. Chem.* **1997**, *62*, 4870.

(11) Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* **1961**, *650*, 1.

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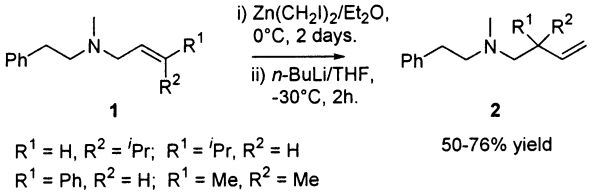
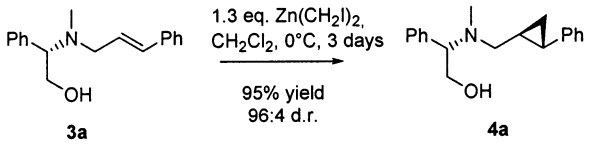
Scheme 1



To address the problem of cyclopropanation of allylic amines, we needed to inhibit ylide formation. We reasoned that by incorporating a hydroxyl group in close proximity to the amine, a stable zinc chelate would form, which might not readily undergo ring expansion to form an ammonium ylide. Indeed, stable chelates of $Zn(CH_2I)_2$ have been reported incorporating either nitrogen[13a] or oxygen[13b] ligands.

Initial studies employing allylic amine **3a** derived from (*S*)-2-phenylglycinol under the same conditions as shown in Scheme 1 were not encouraging, as only starting material was recovered. However, when CH_2Cl_2 was used instead of Et_2O, a mixture of starting material and cyclopropanation product **4a** was obtained in a 4:1 ratio. Complete conversion was achieved by treating amine **3a** with 1.3 equiv of the zinc reagent at 0 °C for 3 days, and the cyclopropanation product **4a** was obtained in 95% yield and as a 96:4 mixture of diastereoisomers (Scheme 2).

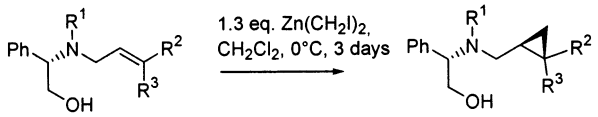
Scheme 2



Further investigation revealed that the substituent on the nitrogen atom had a significant effect on the reaction (Table 1). When R^1 = H (**3b**), no cyclopropanation occurred and an inseparable mixture of products was obtained.[14] When R^1 = Bn (**3c**), the cyclopropanation product was obtained in 87% yield but the diastereoselectivity was reduced to 92:8. Interestingly, *trans* allylic amine **3e** gave higher diastereoselectivity than the corresponding *cis* isomer **3d**. Both alkyl and aryl substituents on the alkene were tolerated (entries 1, 3−6), although substrates containing additional basic functional groups (entry 7 and 8) did not form the cyclopropanated products.

Pseudoephedrine is a very inexpensive commodity chemical and was therefore also tested as an alternative auxiliary in the same reaction. We were pleased to find it was even more effective than the phenylglycinol substrate in many cases (Table 2). The need for both a tertiary amine and free hydroxyl group to achieve good yield and high diastereoselectivity was also established (Table 2, entry 1 and Table 1, entry 1).

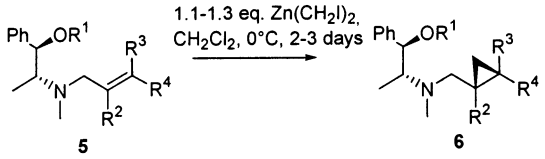
Table 1. Diastereoselective Cyclopropanation of Allylic Amines Derived from (*S*)-Phenylglycinol



entry	substrate	R^1	R^2	R^3	yield (%)[a]	dr[b]
1	**3a**	Me	Ph	H	95	96:4
2	**3b**	H	Ph	H	*c*	–
3	**3c**	Bn	Ph	H	87	92:8
4	**3d**	Me	H	^{n}Pr	92	95:5
5	**3e**	Me	^{n}Pr	H	96	>98:2
6	**3f**	Me	Me	Me	94	92:8
7	**3g**	Me	CH_2OH	H	*c*	–
8	**3h**	Me	CH_2CO_2Me	H	*c*	–

[a] Isolated yield. [b] The diastereoselectivity was determined by ^{1}H NMR of the crude product. [c] No cyclopropane was observed.

Table 2. Diastereoselective Cyclopropanation of Allylic Amines Derived from (1*R*,2*R*)-Pseudoephedrine



entry	substrate	R^1	R^2	R^3	R^4	yield (%)[a]	dr[b]
1	**5a**[c]	H	H	H	Ph	95	>98:2
2	**5b**[c]	Me	H	H	Ph	93	75:25
3	**5c**[c]	H	H	H	^{n}Pr	96	>98:2
4	**5d**[d]	H	H	^{n}Pr	H	95	89:11
5	**5e**[d]	H	H	Me	Me	94	93:7
6	**5f**[c]	H	Me	H	H	93	–

[a] Isolated yield. [b] The diastereoselectivity was determined by ^{1}H NMR of the crude product. [c] 1.1 equiv of $Zn(CH_2I)_2$, 2 days. [d] 1.3 equiv of $Zn(CH_2I)_2$, 3 days.

Ephedrine was also tested, and under identical conditions as described in Table **2,** allylic amine **7** was converted into the corresponding cyclopropane derivative **8** in 95% yield and >98% diastereoselectivity (Scheme 3).

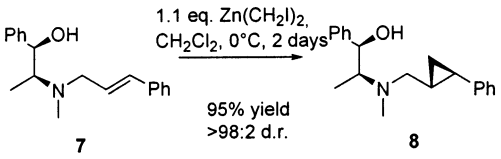
The relative stereochemistry of the cyclopropanation product **6a** was determined by independent synthesis. (2-Phenylcyclopropanyl)-methanol **9** was prepared in 78% ee following an established procedure (Scheme 4) in which the stereochemistry of the major isomer was determined as (1*R*,2*R*).[15] Swern oxidation of the cyclopropanyl methanol

(12) Aggarwal, V. K.; Fang, G. Y.; Charmant, J. P. H.; Meek, G. *Org. Lett.* **2003**, *5*, 1757.

(13) (a) Charette, A. B.; Marcoux, J.-F.; Molinaro, C.; Beauchemin, A.; Brochu, C.; Isabel, E. *J. Am. Chem. Soc.* **2000**, *122*, 4508. (b) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1991,** *113*, 723.

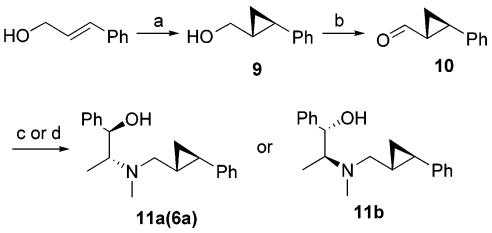
(14) No signals were found in the crude ^{1}H NMR that were diagnostic for the cyclopropane unit.

Scheme 3



7 yielded the corresponding aldehyde **10** in 84% yield. Aldehyde **10** was condensed with (1*R*,2*R*)-pseudoephedrine and (1*S*,2*S*)-pseudoephedrine in the presence of $NaBH_3CN$ to obtain compound **11a** and its diastereoisomer **11b (**Scheme 4). The ^1H NMR spectrum of compound **6a** was identical to the ^1H NMR spectrum of compound **11a**, which showed significant differences from the ^1H NMR spectrum of compound **11b**. Thus, the stereochemistry of the cyclopropane unit in compound **6a** was unambiguously assigned as (1*R*,2*R*) (Scheme 4).

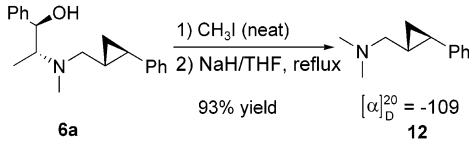
Scheme 4[a]



[a] Conditions: (a) (i) 1.1 equiv $ZnEt_2$/0.1 equiv *N*-{(1*R*,2*R*)-2-[methylsulfonyl)amino]cyclohexyl}methanesulfonamide/CH_2Cl_2, 0 °C; (ii) 1.0 equiv $Zn(CH_2I)_2$, CH_2Cl_2 0 °C. (b) DMSO-$(COCl)_2$, *i*-Pr_2EtN, CH_2Cl_2, −78 °C. (c) (1*R*,2*R*)-pseudoephedrine, $NaBH_3CN$-AcOH, MeOH, rt. (d) (1*S*,2*S*)-pseudoephedrine, $NaBH_3CH$-AcOH, MeOH, rt.

The chiral auxiliary was easily removed by quarternization with MeI followed by treatment with NaH in THF,[16] giving 2-phenyl-cyclopropylmethylamine **12** in 93% yield (Scheme 5).

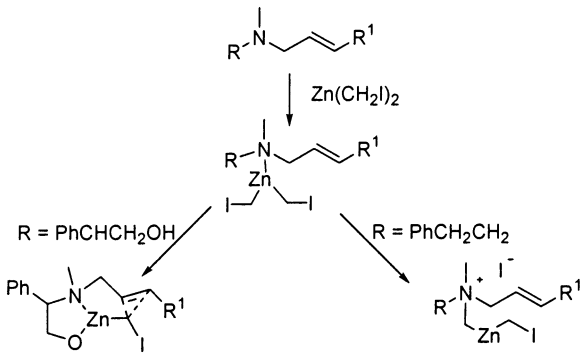
Scheme 5



The stereochemistry of the cyclopropane units in compounds **4a** and **8** was assigned by removal of the auxiliaries following the same procedure as described above and comparison of the optical rotations of the cyclopropanes with that of compound **12**. We were surprised to find that the stereochemistry of the cyclopropane unit in compound **8** was (1*R*,2*R*), the same as compound **6a**. This result means that of the two stereogenic centers in the auxiliary, it is the center adjacent to the remote hydroxyl group that controlled and dominated the stereochemistry of the cyclopropanation. As the two diastereomers **5a** and **7** give similarly high diastereoselectivity for the same major cyclopropane isomer, it means that the stereochemistry of the amino group does not influence the stereochemistry of the product. However, when there is no stereochemistry at the hydroxyl group (**3a**), the stereogenic center bearing the amino group is able to strongly influence the stereochemical outcome of the cyclopropanation process. The unusual absence of matched and mismatched stereocontrol with substrates **5a** and **7** could be a consequence of the size of the groups at the stereogenic centers: small groups at nitrogen play a very small role, whereas large groups attached to the oxygen center play a dominant role. This could then account for the high selectivity observed with **3a**, which bears a large group at the amino stereogenic center.

The divergent behavior of allylic amines and those bearing additional chelating groups can be readily accounted for. In both cases the reaction is initiated by complexation of the amine with the zinc reagent. In the case of the simple allyl substituted amine (R = $PhCH_2CH_2$), this species undergoes 1,2-shift to furnish a zinc-complexed ammonium ylide. In the case of the amino alcohol (R = $PhCHCH_2OH$), we believe that a more stable chelated zinc complex is formed that does not readily undergo the 1,2-shift.[17] However, because of the proximity of the olefin to the tightly held zinc carbenoid, cyclopropanation occurs instead (Scheme 6).

Scheme 6



At this stage, we do not have a persuasive model to account for the high diastereoselectivity observed.

In conclusion, we have demonstrated the first diastereoselective cyclopropanation of allylic amines with the Simmons−Smith reagent. The success of the cyclopropanation was attributed to the formation of a chelating complex between the zinc reagent and the chiral amino alcohol of

(15) Denmark, S. E.; O'Connor, S. P.; Wilson, S. R. *Angew. Chem., Int. Ed.* **1998,** *37,* 1149.

(16) García-Valverde, M.; Nieto, J.; Pedrosa, R.; Vicente, M. *Tetrahedron* **1999**, *55*, 2755.

(17) Ylide formation of *N*-methyl-ephedrine is possible in the absence of neighboring allylic groups. See: Denmark, S. E.; Edwards, J. *Synlett* **1992**, 229.

the allylic amines. All of the chiral amino alcohol tested (phenylglycinol, pseudoephedrine, ephedrine) gave very high diastereoselectivity in the cyclopropanation process.

Acknowledgment. We thank Chirotech for financial support.

Supporting Information Available: Spectroscopic data and experimental procedures for compounds **3a**−**h**, **4b**−**f**, **5a**−**f**, **6a**−**f**, **7**−**10**, **11a,b**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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