Asymmetric Catalysis

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Asymmetric Simmons–Smith Reaction of Allylic Alcohols with Al Lewis Acid/N Lewis Base Bifunctional Al(Salalen) Catalyst**

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Optically active *trans*- and *cis*-disubstituted cyclopropylmethanol or cyclopropylester derivatives are useful building blocks for organic synthesis.[1,2] Asymmetric cyclopropanation of terminal olefins with an α-diazoacetate is an efficient method for synthesizing such esters, and many diastereo- and enantioselective reactions have been developed.[2] However, reactions with a satisfactory level (greater than 99 %) of *trans*- or *cis*-selectivity are limited.[2,3] Another useful method is the stereospecific asymmetric Simmons–Smith reaction of allylic alcohols.[2a,b] In 1992, Ukaji et al. reported a highly enantioselective method by using diethyl tartrate as a stoichiometric chiral auxiliary.[4a,c,5] Denmark and Edwards reported an efficient method that included a chiral amino alcohol.[4b] Subsequently, 2-butyl-1,3-dioxa-2-borolane-4,5-dicarboxamide[6] and 1,1′-bi-2-naphthol-3,3′-dicarboxamide[7] were reported to be efficient auxiliaries. Kobayashi and co-workers reported the first catalytic and satisfactorily enantioselective Simmons–Smith reaction by using a chiral disulfonamide/Et_2Zn/CH_2I_2 system at low temperatures.[8] Charette et al. reported a titanium(taddolate) complex that was an excellent catalyst, albeit under substoichiometric conditions.[9] Nevertheless, conducting asymmetric Simmons–Smith reactions of allylic alcohols in a catalytic and highly enantioselective manner at room temperature remains a challenge.[10,11]

Asymmetric Simmons–Smith reactions have been proposed to proceed through an in situ generated intermediate derived from an iodomethylzinc species and a chiral auxiliary.[2b,4,9] When the substrate is an allylic alcohol, the alcohol or the resulting alkoxyzinc species forms an aggregate with the iodomethylzinc species and the chiral auxiliary, and subsequently undergoes an asymmetric Simmons–Smith reaction. The aggregate can occur in one of three different modes (Figure 1 a–c): a) capture of an allyloxy(iodomethyl)zinc species by a Lewis acid catalyst derived from the chiral auxiliary,[8a,11c] b) capture of an allyloxyzinc and iodomethylzinc species by a bifunctional chiral auxiliary (in this case, the use of a C_2-symmetric auxiliary like diethyl tartrate[4a,c] should be important for obtaining high enantioselectivity if the two species are captured by two identical groups), and c) capture of the two species by a Lewis acid/base bifunctional catalyst.[12] Charette et al. proposed that the dioxaborolane having a Lewis acidic boron site and Lewis basic sites (the amide carbonyl group and the oxygen atom of the coordinated allylic oxide)[13] serves as a bifunctional catalyst, albeit under stoichiometric conditions.[6] It was expected that the efficiency of a bifunctional catalyst should be enhanced by strengthening the interaction between the iodomethylzinc species and a Lewis base site and the interaction between the alcohol (or alkoxyzinc species) and a Lewis acid site, respectively. We recently discovered that metal(salalen) complexes (salalen = salen/salan hybrid; salen = *N*,*N*′-bis(salicylidene)ethylenediamine); salan = *N*,*N*′-bis(*o*-hydroxybenzyl)-1,2-diaminoethane) show unique asymmetric catalysis.[14] Metal(salalen) complexes have an amine donor atom[15] and a Lewis acidic metal center and it is known that zinc ions and amines form stable complexes. Thus, we were intrigued by the bifunctional catalysis of metal(salalen) complexes. Taking into consideration the high oxophilicity of the aluminum ion, we expected an Al(salalen) complex to be a promising catalyst for the asymmetric Simmons–Smith reaction.[16,17]

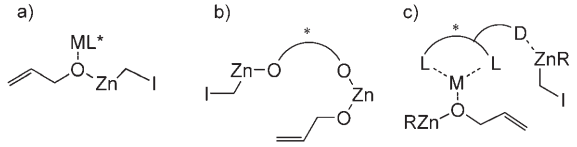

Figure 1. Formal classification of asymmetric Simmons–Smith reactions of allylic alcohols.

We first examined the cyclopropanation of cinnamyl alcohol (**1**), a widely used substrate for asymmetric Simmons–Smith reactions, in dichloromethane for 1 hour with 2 equivalents of Et_2Zn and 3 equivalents of CH_2I_2 in the presence of 10 mol % Al complex prepared in situ from a salalen ligand and DIBAL (Table 1). To our delight, the reaction with ligand **2**[18] was complete within 1 hour at room temperature and gave the product in quantitative yield with 91 % *ee* (Table 1, entry 1). The diastereomeric complex prepared in situ from **4** was a far less efficient catalyst (Table 1, entry 3), and the complex derived from **6** was a poor catalyst (Table 1, entry 5). Notably, both N-methylated complexes **3** and **5**, in which the amine group does not have a proton that can be abstracted and cannot serve as Lewis base, were poor asymmetric catalysts irrespective of their stereochemistry (Table 1, entries 2 and 4). This suggested that the NH group plays an

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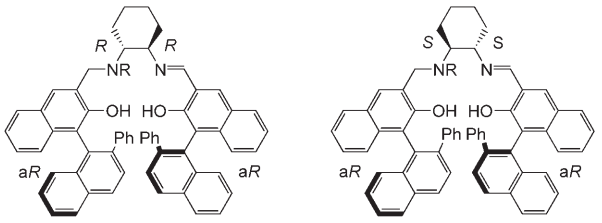
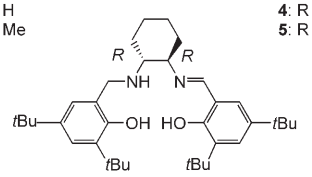


2: R = H
3: R = Me

4: R = H
5: R = Me



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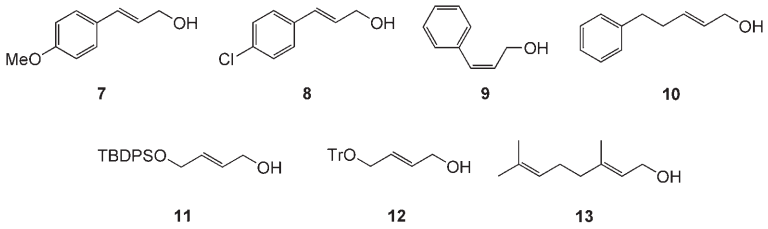
important role in the asymmetric induction by the salalen complex. Moreover, the less Lewis acidic zinc complex of **2** (not reported) showed poor enantioselectivity (8% *ee*). Thus, we examined several Al(salalen) complexes derived from **2** and different Al sources, and found that the complex prepared from diethylaluminum chloride was the best; it generated the product in 95% *ee*, the highest value obtained by either stoichiometric or catalytic asymmetric Simmons–Smith reactions of **1** (Table 1, entry 8). Moreover, the same reaction was conducted by using 2 equivalents of Et_2Zn and 1.2 equivalents of CH_2I_2 without eroding the enantioselectivity (Table 1, entry 9). Although the reactions that were run in halogenated and aromatic solvents, such as dichloromethane, chloroform, dichloroethane, 1,1,2,2-tetrachloroethane, and toluene, proceeded with high enantioselectivity (90–95% *ee*), the best results were obtained in dichloromethane or 1,1,2,2-tetrachloroethane (Table 1, entries 9 and 10). The reaction in THF was slow and the product had a significantly reduced enantioselectivity (Table 1, entry 11). When the catalyst loading was reduced to 5 mol% the reaction proceeded smoothly, but the enantioselectivity was diminished to 93% *ee* (Table 1, entry 12).

The scope of the reaction was examined under the optimized conditions (Table 1, entry 9). The reactions of *p*-substituted (*E*)-cinnamyl alcohols **7** and **8** proceeded with high enantioselectivities, irrespective of the electronic nature of the substituents (Table 2, entries 1 and 2), whereas the enantioselectivity of the reaction of the (*Z*)-cinnamyl alcohol (**9**) was moderate (Table 2, entry 3). The reaction of nonconjugated *E* allylic alcohols proceeded with high enantioselectivities (greater than 86% *ee*) and in quantitative yields (Table 2, entries 4–6). However, the reaction of trisubstituted allylic alcohol **13**, which has a *Z* substituent, was moderately enantioselective (Table 2, entry 7). Lowering the reaction temperature increased the enantioselectivity to 70% *ee*, but the reaction slowed down (Table 2, entry 8).

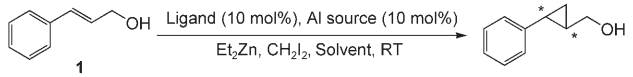
Although the mechanism of this reaction is unclear, the experimental results show that the introduction of the N-methyl group remarkably diminishes the enantioselectivity of



7 **8** **9** **10**

11 **12** **13**

Table 1: Asymmetric Simmons–Smith reactions of **1** with Al(salalen) complexes.[a]

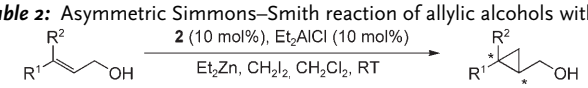


1

Entry	Ligand	Al source	Solvent	Yield [%][b]	*ee* [%][c]	Config.[d]
1	**2**	$(iBu)_2AlH$	CH_2Cl_2	>99	91	1*S*,2*S*
2	**3**	$(iBu)_2AlH$	CH_2Cl_2	>99	7	1*S*,2*S*
3	**4**	$(iBu)_2AlH$	CH_2Cl_2	>99	18	1*S*,2*S*
4	**5**	$(iBu)_2AlH$	CH_2Cl_2	81	8	1*R*,2*R*
5	**6**	$(iBu)_2AlH$	CH_2Cl_2	>99	14	1*S*,2*S*
6	**2**	Me_3Al	CH_2Cl_2	>99	91	1*S*,2*S*
7	**2**	Et_2AlOEt	CH_2Cl_2	>99	86	1*S*,2*S*
8	**2**	Et_2AlCl	CH_2Cl_2	>99	95	1*S*,2*S*
9[e]	**2**	Et_2AlCl	CH_2Cl_2	>99	95	1*S*,2*S*
10[e]	**2**	Et_2AlCl	$(Cl_2CH)_2$	>99	95	1*S*,2*S*
11[e,f]	**2**	Et_2AlCl	THF	61	<1	–
12[e,g,h]	**2**	Et_2AlCl	CH_2Cl_2	>99	93	1*S*, 2*S*

[a] All reactions were carried out with 2 equiv of Et_2Zn and 3 equiv of CH_2I_2 for 1 h unless otherwise noted. [b] Calculated from ^{1}H NMR (400 MHz) analysis by using 1-bromonaphthalene as an internal standard. [c] Determined by HPLC analysis by using a chiral stationary phase column (Daicel Chiracel OD—H; hexane/*i*PrOH = 9:1). [d] Determined by chiroptical comparison (references [9b]). [e] 2 equiv of Et_2Zn and 1.2 equiv of CH_2I_2 were used. [f] Run for 24 h. [g] Catalyst loading was 5 mol%. [h] Run for 3 h.

Table 2: Asymmetric Simmons–Smith reaction of allylic alcohols with **2**.



Entry	Substrate	*t* [h]	Yield [%][a]	*ee* [%][b]	Config.[c]
1	**7**	3	>99 (93)	94	1*S*,2*S*
2	**8**	1	>99 (94)	94	1*S*,2*S*
3	**9**	1	>99 (99)	58	1*R*,2*S*
4	**10**	3	>99 (95)	86	1*S*,2*S*
5	**11**	3	>99 (99)	90	n.d.[d]
6	**12**	3	>99 (98)	87	1*S*,2*S*
7	**13**	4	98	63	1*S*,2*S*
8[e]	**13**	10	>99 (92)	70	1*S*,2*S*

[a] Calculated from ^{1}H NMR (400 MHz) analysis by using 1-bromonaphthalene as an internal standard. The values in the parentheses show the yields of the isolated products. [b] Determined by HPLC analysis by using chiral stationary phase column. For details, see the Supporting Information. [c] Determined by chiroptical comparison. For details, see the Supporting Information. [d] Not determined. [e] Reaction was carried out at 0°C.

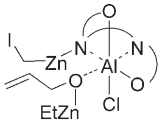


Figure 2. A plausible intermediate for Al-(salalen)-catalyzed Simmons–Smith reactions of allylic alcohols.

the reaction, and that the complex bearing a chloride ligand at the apical position is a better catalyst than the complex bearing an ethoxy ligand. This suggests that the bifunctional catalysis of the Al(salalen) complex is essential for obtaining high enantioselectivities (Figure 2).

In conclusion, we were able to show that the Al(salalen) complex, an Al Lewis acid/N Lewis base bifunctional catalyst, is a potent catalyst for the asymmetric Simmons–Smith reaction. Although good substrates are limited to *trans*-disubstituted allylic alcohols, the reaction proceeds with high enantioselectivities and in quantitative yields at room temperature. The present study provides a new approach to the development of catalytic asymmetric Simmons–Smith reactions.

Experimental Section

Typical example of an asymmetric Simmons–Smith reaction with **2**: A solution of Et_2AlCl (0.92 M, 54 μL, 0.05 mmol) in hexanes at 0 °C under a nitrogen atmosphere was added to a solution of salalen ligand **2** (41.5 mg, 0.05 mmol) in anhydrous dichloromethane (5 mL). The reaction mixture was warmed to room temperature and stirred for 30 min. Then **1** (64 μL, 0.5 mmol), a solution of Et_2Zn (1.0 M, 1.0 mL, 1.0 mmol) in hexanes, and CH_2I_2 (48 μL, 0.6 mmol) were successively added to the reaction mixture, which was then stirred for 1 h at room temperature. The mixture was quenched with an aqueous NaOH solution (2 N) and the organic layer was separated. The aqueous layer was extracted with dichloromethane, and then the organic layers were combined and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/diethyl ether = 2:1) to give the desired cyclopropylalcohol (71.0 mg, 96%) as a colorless oil. The enantiomeric excess of the product was determined to be 95% by HPLC analysis with a Daicel Chiralcel OD-H column (hexane/*i*PrOH = 9:1).

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[1] a) W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589–8627; b) J. Pietruszka, *Chem. Rev.* **2003**, *103*, 1051–1070; c) H. Asao, H. Sakauchi, S. Kuwahara, H. Kiyota, *Tetrahedron: Asymmetry* **2007**, *18*, 537–541.

[2] For recent reviews, see: a) A. B. Charette, A. Beauchemin, *Org. React.* **2001**, *58*, 1–415; b) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050; c) T. Katsuki in *Comprehensive Coordination Chemistry II*, *Vol. 9* (Ed.: J. McCleverty), Elsevier Science, Oxford, **2003**, pp. 207–264; d) A. Pfaltz in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 157–170.

[3] For recent examples of *trans*-selective reactions, see: a) A. V. Malkov, D. Pernazza, M. Bell, M. Bella, A. Massa, F. Teply, P. Meghani, P. Kocovsky, *J. Org. Chem.* **2003**, *68*, 4727–4742; b) Y. Chen, J. V. Ruppel, X. P. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 12074–12075; for recent examples of *cis*-selective reactions, see: c) C. Bonaccorsi, A. Mezzetti, *Organometallics* **2005**, *24*, 4953–4960; d) S. Kanchiku, H. Suematsu, K. Matsumoto, T. Uchida, T. Katsuki, *Angew. Chem.* **2007**, *119*, 3963–3965; *Angew. Chem. Int. Ed.* **2007**, *46*, 3889–3891.

[4] a) Y. Ukaji, M. Nishimura, T. Fujisawa, *Chem. Lett.* **1992**, 61–64; b) S. E. Denmark, J. P. Edwards, *Synlett* **1992**, 229–230; c) Y. Ukaji, K. Sada, K. Inomata, *Chem. Lett.* **1993**, 1227–1230.

[5] For the seminal studies on asymmetric Simmons–Smith reactions, see: a) S. Sawada, J. Oda, Y. Inouye, *J. Org. Chem.* **1968**, *33*, 2141–2143; b) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.* **1968**, *9*, 3495–3498.

[6] a) A. B. Charette, H. Juteau, *J. Am. Chem. Soc.* **1994**, *116*, 2651–2652; b) A. B. Charette, H. Juteau, H. Lebel, C. Molinaro, *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952.

[7] a) H. Kitajima, Y. Aoki, K. Ito, T. Katsuki, *Chem. Lett.* **1995**, 1113–1114; b) H. Kitajima, K. Ito, Y. Aoki, T. Katsuki, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207–217.

[8] a) H. Takahashi, M. Yoshioka, M. Ohno, S. Kobayashi, *Tetrahedron Lett.* **1992**, *33*, 2575–2578; b) N. Imai, H. Takahashi, S. Kobayashi, *Chem. Lett.* **1994**, 177–180; c) N. Imai, K. Sakamoto, H. Takahashi, S. Kobayashi, *Tetrahedron Lett.* **1994**, *35*, 7045–7048; d) H. Takahashi, M. Yoshioka, M. Shibasaki, M. Ohno, N. Imai, S. Kobayashi, *Tetrahedron* **1995**, *51*, 12013–12026; e) N. Imai, K. Sakamoto, M. Maeda, K. Kouge, K. Yoshizane, J. Nokami, *Tetrahedron Lett.* **1997**, *38*, 1423–1426; f) N. Imai, T. Nomura, S. Yamamoto, Y. Ninomiya, J. Nokami, *Tetrahedron: Asymmetry* **2002**, *13*, 2433–2438.

[9] a) A. B. Charette, C. Brochu, *J. Am. Chem. Soc.* **1995**, *117*, 11367–11368; b) A. B. Charette, C. Molinaro, C. Brochu, *J. Am. Chem. Soc.* **2001**, *123*, 12168–12175.

[10] For highly selective asymmetric Simmons–Smith reactions of various enol ethers and ethers of allylic alcohols, see: a) J. Long, Y. Yuan, Y. Shi, *J. Am. Chem. Soc.* **2003**, *125*, 13632–13633; b) J. Long, H. Du, K. Li, Y. Shi, *Tetrahedron Lett.* **2005**, *46*, 2737–2740; c) M.-C. Lacasse, C. Poulard, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 12440–12441; d) H. Du, J. Long, Y. Shi, *Org. Lett.* **2006**, *8*, 2827–2829; e) A. Voituriez, A. B. Charette, *Adv. Synth. Catal.* **2006**, *348*, 2363–2370.

[11] Other catalytic asymmetric Simmons–Smith reactions: a) S. E. Denmark, B. L. Christenson, D. M. Coe, S. P. O'Connor, *Tetrahedron Lett.* **1995**, *36*, 2215–2218; b) S. E. Denmark, B. L. Christenson, S. P. O'Connor, *Tetrahedron Lett.* **1995**, *36*, 2219–2222; c) S. E. Denmark, S. P. O'Connor, *J. Org. Chem.* **1997**, *62*, 584–594; d) S. E. Denmark, S. P. O'Connor, *J. Org. Chem.* **1997**, *62*, 3390–3401; e) J. Balsells, P. J. Walsh, *J. Org. Chem.* **2000**, *65*, 5005–5008; related systems for selective synthesis of cyclopropanes: f) V. K. Aggarwal, G. Y. Fang, G. Meek, *Org. Lett.* **2003**, *5*, 4417–4420; g) H. Y. Kim, A. E. Lurain, P. G. -García, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 13138–13139.

[12] For reviews on bifunctional catalysts, see: a) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1311; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236–1256; b) H. Gröger, *Chem. Eur. J.* **2001**, *7*, 5246–5251; c) G. J. Rowlands, *Tetrahedron* **2001**, *57*, 1865–1882; d) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989–1999; e) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491–1508.

[13] Although the allyloxy group is not a part of the dioxaborolane, it has been proposed that the oxygen atom of the coordinated allylic oxide serves as a Lewis base synergetically with the amide carbonyl group.[6]

[14] a) K. Matsumoto, B. Saito, T. Katsuki, *Chem. Commun.* **2007**, 3619–3627; b) B. Saito, H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2007**, *129*, 1978–1986; c) A. Berkessel, M. Brandenburg, E. Leitterstorf, J. Frey, J. Lex, M. Schäfer, *Adv. Synth. Catal.* **2007**, *349*, 2385–2391.

[15] A metal-bound amine is not a base, but the pK_a value of the amine proton is small. Under the conditions with diethylzinc, it should be deprotonated and the resultant amide should serve as a base.
[16] We recently found that Al(salalen) complexes showed unique catalysis for asymmetric oxidation of sulfides: a) T. Yamaguchi, K. Matsumoto, B. Saito, T. Katsuki, *Angew. Chem.* **2007**, *119*, 4813 – 4815; *Angew. Chem. Int. Ed.* **2007**, *46*, 4729 – 4731; b) K. Matsumoto, T. Yamaguchi, J. Fujisaki, B. Saito, T. Katsuki, *Chem. Asian J.* **2008**, *3*, 351 – 358..
[17] Kobayashi et al. have reported that Al– and Zn– disulfonamide complexes show similar asymmetric Simmons–Smith catalysis.[8b] Analogous intermediates generated by aggregation such as shown in Figure 1a have been proposed to participate in these reactions.
[18] Salalen ligands used in this study were prepared according to the reported procedures (references [14b,16b]).

