Carbometalation of Cyclopropene. Ligand-Induced Enantioselective Allylzincation

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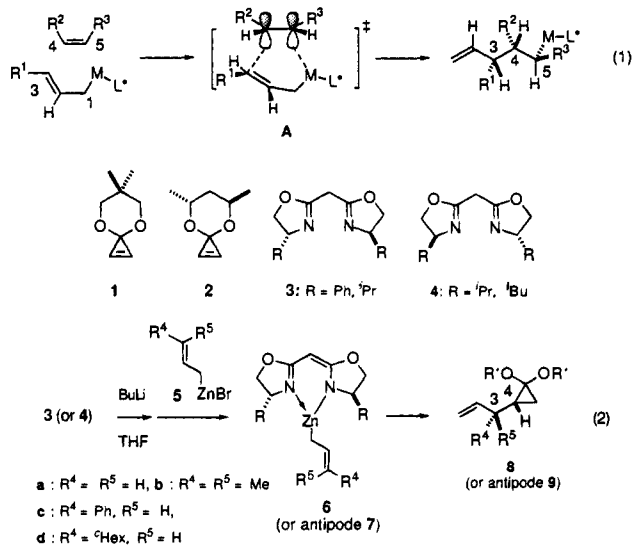
Unlike the addition of an allylic metal reagent to a carbonyl compound,[1] enantioselective allylmetalation of an isolated olefin has received little attention (eq 1).[2] The issue of product selectivity, which creates three chiral centers in a single step, is an intricate process and provides an intellectual challenge. We have previously pointed out the basic selectivity problems in this reaction[3] and solved a few of them, including the C(3)−C(4) relative stereochemistry (the mutual face selection) in a twist-chair transition state (TS) **A**.[4] In such a TS, the selectivity depends on the enantio- and regioselection for the π-lobes of the olefin rather than on simple enantioface selection.[5] In this communication, we report the first example of enantioselective allylmetalation of an olefin, made possible with the aid of the chiral bis(oxazoline) (BOX) ligands **3** and **4** (eq 2). We also found that theoretical analysis provides useful information on the nature of the ligand-induced stereocontrol.



As in our previous work,[6] we took the cyclopropenone acetals (CPAs) **1** and **2** as olefinic substrates. The usefulness of this probe stems from its ready availability,[7] synthetic applicability,[8] and, particularly, the symmetrical cis structure that eliminates the aforementioned regiochemical problem.[5] Although we examined, in vain, various chiral amino alcohols, used for carbonyl addition of *dimeric* zinc reagents,[9,10] we eventually found that the BOX ligands[11] **3** and **4** are highly effective (Table 1).

Table 1. Ligand-Induced Enantioselective Allylzincation of CPA[a]

run	CPA	allylZn (R =)	major product		yield[b] (%)	ds[c]	es[d]
1	1	**6a** (Ph)		**8a**	85	–	> 2:98
2	1	**7a** (*i*-Pr)		**9a**	89	–	> 99:1
3	1	**7b** (*i*-Pr)		**9b**	90	–	96.5:3.5
4	1	**7c** (*i*-Pr)		**9c**	86	73:27	78:22
5	1	**7d** (*i*-Pr)		**9d**	94	83:17	81:19
6	1	**7d** (*t*-Bu)		**9d**	58	81:19	98.5:1.5
7	2	**6a** (*i*-Pr)		**10a**	73	—	0.8:99.2
8	2	**7a** (*i*-Pr)		**10a**	76	—	49:51
9	2	**7c** (*i*-Pr)		**10b**	94	86:14	1:99
10	2	**7c** (*t*-Bu)		**11d**	70	80:20	54:46

[a] Acetal moieties X and Y are $-OCH_2C(CH_3)_2CH_2O-$ and $-OCH(CH_3)CH_2CH(CH_3)O-$, respectively. [b] Isolated yield based on CPA. [c] The C(3)−C(4) diastereoselectivity. [d] The enantioselectivity determined for the major C(3)−C(4) diastereomer; the ratio refers to C(4)−H down *vs* up.

The reaction procedure is simple. The BOX ligand (**3** (R = Ph), 1.38 mmol) derived from (*R*)-phenylglycine was lithiated (1.38 mmol of butyllithium at −78 to 0 °C in THF) and reacted with allylzinc bromide (**5a**, 1.25 mmol, from allyl bromide and activated zinc) at 0 °C to room temperature. The chiral reagent **6a** (R = Ph) was then reacted with CPA **1** (1.1 mmol) at room temperature for several hours. Quenching with NH_4Cl and silica gel purification afforded the product **8a** (4*R*) in 85% yield with 96% ee (Table 1, run 1) as well as a 2:1 crystalline complex of the BOX and Zn(II),[12] from which the BOX ligand (80% yield, 100% ee) was recovered (10 equiv of ethylenediamine dihydrochloride in dry CH_2Cl_2). The chiral allyl- and prenylzinc reagents **7a** (R = ^{i}Pr) and **7b** (R = ^{i}Pr) derived from (*S*)-valine gave the antipodes **9a** and **9b** with >98% and 93% ee,

(1) Review: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. See also: Shihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490. Marshall, J. A.; Tang, Y. *Synlett* **1992**, 653. Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.

(2) 1,4-Addition of chiral allylic sulfoxides and phosphonyl compounds to enones: Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088. Hanessian, S.; Gomtsyan, A.; Payne, A.; Herve, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032.

(3) Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297.

(4) Kubota, K.; Nakamura, M.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5867.

(5) If R^2 and R^3 are the same (as in **1** and **2**), two olefinic faces are homotopic. In contrast, the two π-faces of a carbonyl compound are generally enantiotopic.

(6) Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428.

(7) Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, *48*, 2045.

(8) Review: Nakamura, E. *J. Synth. Org. Chem., Jpn.* **1994**, *52*, 935.

(9) Cf.: Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.

(10) For the importance of dimeric species in stereocontrol, see: (a) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016. (b) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Chem. Soc., Faraday Trans.* **1994**, 1789.

(11) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. Helmchen, G.; Krotz, A.; Ganz, K. T.; Hansen, D. *Synlett* **1991**, 257. Hall, J.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1.

(12) The structure, which features (distorted) tetrahedral coordination of the zinc atom, has been established by X-ray crystallography: unpublished results.

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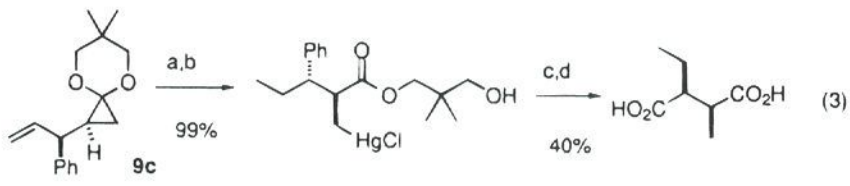
respectively (runs 2 and 3).[13] The chiral reagents were several times more reactive than the parent zinc bromide **5a**.

The issue of double stereodifferentiation was addressed for the C_2 chiral CPA **2**, which has preference for 4*R* chirality (<98% ds) for **5**.[4] When **2** was reacted with the *R*-selective reagent **6a** (R = ^{i}Pr) (run 7), the 4*R* selectivity was complete (>99:1), but with the *S*-selective reagents **7a** (R = ^{i}Pr), the intrinsic selectivities nearly canceled each other (run 8).

We then examined the reaction of trans-substituted reagents **7c** and **7d**. The sense of enantioselectivity was the same as found for **7a** and **7b**, and the mutual face selectivity was the same as for the achiral reagents **5c** and **5d**,[4] while both selectivities were uniformly moderate with the BOX ligand **3** (R = ^{i}Pr). Thus, the C(3)−C(4) diastereoselectivities for **7c** (R = ^{i}Pr) and **7d** (R = ^{i}Pr)[14] were 73:27 and 83:17, respectively, with ca. 60% ee. The use of a bulkier BOX ligand (R = ^{t}Bu) improved the latter to 97% ee (run 5 vs 6), whereas the C(3)−C(4) selectivity remained as 81:19. The C(3)−C(4) selectivity was also moderate with the chiral CPA **2** either for the matched (run 9) or mismatched pair (run 10).

The absolute stereochemistry and the relative stereochemistry of the major diastereomers were determined by correlation to known compounds as exemplified for **9c** in eq 3. This sequence also illustrates the rich synthetic possibility available for CPA in the creation of optically active compounds.



(3)

a: $KO_2CN{=}NCO_2K$, AcOH; b: $Hg(OAc)_2$, MeOH; sat. NaCl, 1N HCl; c: $NaBH_4$, NaOH; $LiAlH_4$; d: $NaIO_4/RuCl_3$

While an empirical stereochemical model[15] proved insufficient to explain the observed selectivities, we found that theoretical analysis provides valuable information on the role of the ligand in determining the enantio- and diastereoselectivities. With the MNDO Hamiltonian,[16,17] we found four diastereomeric TS for the reaction of **7a** (R = ^{i}Pr) with **1** lacking the acetal *gem*-dimethyl group; the lowest energy TS is shown in Figure 1. The acetal group is fitted into the "cleft" (curved lines) formed by the two isopropyl groups of the ligand. The second lowest energy TS (0.32 kcal/mol higher in energy) is due to the approach of the cyclopropene from the top side (heavy arrow, **C**) with the acetal orientation as indicated. The two alternative approaches (light arrows, **D** and **E**) are higher in energy (1.13 and 1.69 kcal/mol, respectively). These approaches are stereochemically degenerate: both **B** and **C** produce one enantiomer, and **D** and **E** another. The calculated energetics thus qualitatively reproduces the experimental selectivity.

For trans-substituted reagents (i.e., the blackened hydrogen replaced by a substituent), the degeneracy is lifted. The C(4)-

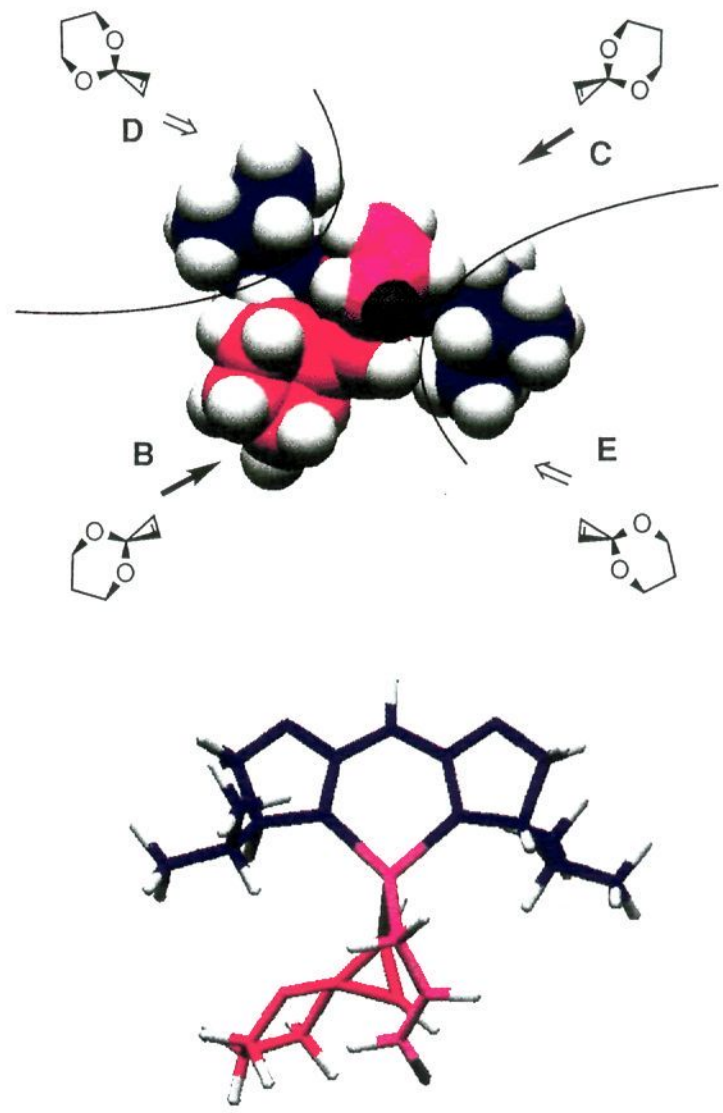


Figure 1. The lowest-energy MNDO TS of the allylzincation: CPA in red; allylzinc moiety in purple; BOX in blue; the hydrogen atom to be substituted (see text) in black. The tube structure is a top view of the TS.

enantiomeric pair, **B** and **C**, now gives two diastereomers. It is clear from the experiments that the BOX ligand cannot effectively differentiate these two paths, which is supported by the very small calculated **B**/**C** energy difference of 0.32 kcal/mol (vide supra). This is due to the flexibility of a twist-chair six-centered TS (**A**), as has been found for simpler models by ab initio calculations.[4,10b,18] In summary, the BOX ligand recognizes the global chirality of the TS with its asymmetric cleft, but cannot control effectively the local conformation of the TS inside this cleft.[19] The issue of global vs local controls is likely to be widespread among ligand-controlled stereoselective reactions.

Supplementary Material Available: Experimental data for Table 1 and structure determination (22 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) The S_E2' selectivity was complete in all cases.
(14) The products were correlated to those from the cinnamylzinc reagent.
(15) Cf.: Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.
(16) The MNDO calculations qualitatively reproduced the ab initio results in ref 4.
(17) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.
(18) The MNDO calculations qualitatively reproduced the experimental trend for **7c** (R = ^{i}Pr).
(19) The situation would be different in carbonyl additions including the aldol reaction, where the chair-type six-membered TS has its own stereocontrol.