Ligand Control in the Stereoselective Allylzincation of Cyclopropenes

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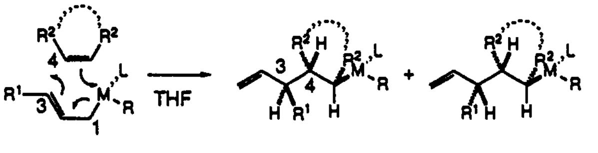
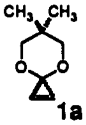
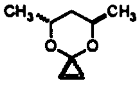
The addition of an allylic metal compound to an olefin has the potential to create three contiguous chiral centers in one operation (eq 1). However, in order for this reaction to become useful for the synthesis of diastereomerically and enantiomerically pure molecules, it must show high levels of (a) S_E2'-regioselectivity, (b) diastereoselectivity (ds) with regard to the new C_3–C_4 bond, and (c) face selectivity with respect to the acceptor olefin. However, little is known for these issues. We have investigated the allylzincation[1] of achiral[2] (**1a**) and C_2 chiral[3] cyclopropenes (**1b**) as a prototype reaction and found that, by employing covalent "dummy" (R) and coordinative (L) ligands as stereocontrolling elements, each of the three varieties of selectivity can be raised to the level of ~96–98.5%. Ab initio theoretical studies on a model reaction provided a working model for the selectivities.



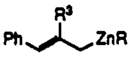
(1)



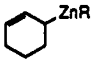
1a



1b



2: R^3 = H
3: R^3 = CH_3



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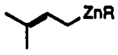

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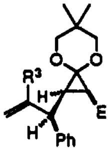
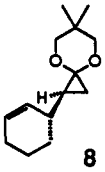


6: R^3 = H
7: R^3 = Me



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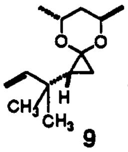

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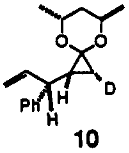

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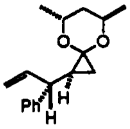

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For the reaction between **1a** and allylic zinc reagents,[4] we investigated the issue of C_3–C_4 diastereoselectivity—an issue rarely examined in the carbometalation of olefins. The reaction of **1a** with a zinc reagent (**2**, R = Br) prepared from *trans*-cinnamyl bromide and zinc metal in THF took place slowly at 0 °C to give the adduct **6** (E = H) with 64% ds (Table I, entry 1). Replacement of the bromide ligand with a bulky electron donor not only accelerated the addition but also improved selectivity. Thus, mixed reagents prepared by treatment of **2** (R = Br) with 1 equiv of either BuLi or 2,4,6-trimethylphenyllithium (mesityllithium) reacted with **1a** at -23 °C with 81–89% ds (entries 2 and 3). Addition of HMPA (2 equiv)[5] further improved the selectivity to 95–96% ds (entries 4–6). Use of CH_2Cl_2 in place of THF reversed the selectivity (entry 7).[6] In all cases, the allylic group was transferred selectively to the cyclopropene with virtually complete S_E2'-regioselectivity (>97%). The reaction of the β-methylcinnamylzinc reagent **3** bearing a *tert*-butyl dummy ligand also proceeded with 96% ds (entry 8). Cyclohexenylzinc bromide **4** (R = Br) in THF showed 92% ds by itself and 98.5% ds with a *tert*-butyl dummy ligand (entry 9).

Table I. Diastereoselective Allyzincation of **1**[a]

entry	1	sol-vent[b]	allyl-ZnR	R	selectivities (% ds) C₃–C₄[c]	chiral[d]	yield[e] (%)	major product[f]
1	**1a**	A	**2**	Br	64	*g*	81	**6** (E = H)
2	**1a**	A	**2**	*n*-Bu	81	*g*	87	**6** (E = H)
3	**1a**	A	**2**	mesityl	89	*g*	97	**6** (E = H)
4	**1a**	B	**2**	*n*-Bu	95	*g*	66	**6** (E = H)
5	**1a**	B	**2**	*t*-Bu	92	*g*	93	**6** (E = D)
6	**1a**	B	**2**	mesityl	96	*g*	70	**6** (E = H)
7	**1a**	C	**2**	Br	24	*g*	64	*h*
8	**1a**	B	**3**	*t*-Bu	96	*g*	79	**7**
9	**1a**	A	**4**	*t*-Bu	98.5	*g*	85	**8**
10	**1b**	A	**5**	Br	*g*	81	94	**9**
11	**1b**	A	**5**	*t*-Bu	*g*	97	98	**9**
12	**1b**	B	**5**	*t*-Bu	*g*	93	58	**9**
13	**1b**	B	**2**	mesityl	97	91	80	**10**
14	**1b**	C	**2**	Br	26	7	48	**11**

[a] The reactions were generally carried out at -23 °C (except for cases with R = Br and in entry 7, performed at 0 °C) and quenched with H_2O except in entries 5 and 13 (with D_2O). Excess (1.5–2 equiv) of titrated zinc reagents were used. [b] A = THF; B = THF with HMPA, two equiv to Zn(II); C = CH_2Cl_2. [c] Referring to the C_3–C_4 relative stereochemistry. [d] Referring to the selectivity relative to the chiral acetal group. [e] Based on pure isolated product. [f] Stereochemistry has been established for **6**, **9**, **10**, and **11**. [g] Not applicable. [h] The major product was the diasteromer of **6**.

Syn-addition of the organozinc reagent coupled with electrophilic trapping of the resultant intermediate cyclopropylzinc reagent (e.g., **7**, E = ZnR) with retention of C–Zn stereochemistry creates yet another center on the cyclopropane ring.[2,3] For example, quenching the reaction of cyclopropene **1a** and the β-methylcinnamylzinc reagent **3** (R = *t*-Bu) with D_2O and I_2 proceeded stereospecifically to give **7** (91% yield, E = D; 67%, E = I).[7] The synthetic utility of the cyclopropyl metal intermediate has already been demonstrated[2,3] in the context of homoenolate chemistry.[8]

We next investigated allylzincation of the chiral cyclopropene **1b**, wherein chirality transmission may occur through the spiro linkage.[3] Addition of **5** (R = Br) in THF at -23 °C took place with 81% ds to give **9** (entry 10), and the diastereoselectivity in this case was improved to 97% by the use of a *tert*-butyl dummy ligand (entry 11). The addition of HMPA was found to slightly lower the selectivity (entry 12).

Finally, we examined the reaction of the chiral acetal **1b** with the cinnamylzinc reagent **2** for the combined diastereoselectivities with respect to the C_3–C_4 bond and the chirality transmission. The best selectivity (97% and 91% ds, respectively, entry 13) was achieved with the mesityl/HMPA combination at -23 °C, and quenching with D_2O afforded **10** as a single major product (90% out of *16 possible isomers*).[9] Interestingly, the use of CH_2Cl_2

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[1] Cf.: Lehmkuhl, H. In *Organometallics in Organic Synthesis*; de Meijere, A., tom Dieck, H., Eds.; Springer: Berlin, 1988; p 185. Stoll, A. T.; Negishi, E.-i. *Tetrahedron Lett.* **1985**, *26*, 5671.

[2] Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297. See also: Nakamura, E.; Kubota, K.; Isaka, M. *J. Org. Chem.* **1992**, *57*, 5809.

[3] Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428.

[4] Highly reactive allyllithium and magnesium reagents showed poor selectivity.

[5] DMF, pyridine, TMEDA, and Ph_3P did not improve the selectivity as much as HMPA.

[6] This suggests the intervention of metal–acetal oxygen chelation in this solvent.

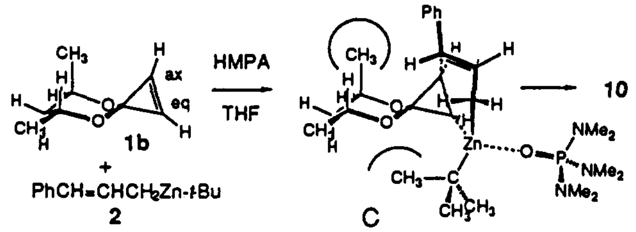
[7] Typical procedure: to a solution of **2** (R = Br, 7.5 mmol) in THF (15.0 mL) was added *t*-BuLi in pentane (7.5 mmol) at -70 °C. HMPA (11.3 mmol) and **1a** (4.0 mmol) in THF (5.5 mL) were added to the solution at -23 °C, and after 5 h, D_2O was added. Silica gel chromatography afforded **6** (E = D) as a colorless oil (1.20 g, 93%). Stereospecific deuterium incorporation was ascertained by ^1H NMR.

[8] Nakamura, E. *Synlett.* **1991**, 539.

[9] Two isomers may arise each from the regio- and diastereoselectivities, chirality transmission, and the stereoselectivity of the *cis*-addition/trapping.

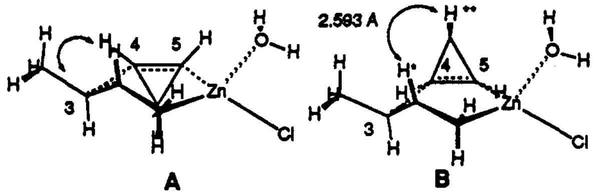
0002-7863/93/1515-5867$04.00/0

Scheme I



as solvent (entry 14) *reversed both selectivities* to afford the isomer **11** as a major product (76% of the total).[6]

Since little information is available for the transition structure (TS) of allylmetalation of olefins, we have carried out an ab initio examination (HF/6-31G*//HF/3-21G-ECP)[10] of the S_E2'-selective addition of (*E*)-$RCH{=}CHCH_2ZnCl(H_2O)$ (R = H and CH_3) to cyclopropene.[11] Two isomeric TSs **A** and **B** that are responsible for the C_3–C_4 diastereoselectivity were obtained (only R = CH_3 is shown, see supplementary material for details of the TSs). The calculated energy difference (0.369 kcal/mol) at this level of approximation of solution reactions should be viewed as negligible, yet some important characteristics were noted. First, only the half-chair TSs are available for the reaction (cf. the aldol[12] and related[13] reactions, where both chair and boat TSs are available).[14] Second, because of this arrangement, there occurs torsional strain for the forming C_3–C_4 bond in **A** (indicated by an arrow) which may slightly destabilize this TS. In the TS **B**, on the other hand, the short distance (2.593 Å) between the two asterisked hydrogens suggests that **B** would be significantly destabilized if H** were replaced by an alkoxy group as in our actual substrates **1**. Third, the TSs obtained for the reaction of cyclopropene with $CH_2{=}CHCH_2ZnCl$ (i.e., lacking coordinated H_2O; see supplementary material) are very similar to **A** and **B**, suggesting that the coordination environment around the zinc atom may not drastically change the essential structural and energetic features of the six-centered TSs. Finally, the "secondary strain effect" makes the cyclopropene moiety of the TSs rather product-like,[15] suggesting that the stereoselectivity of the present reaction may be conveniently predicted through product analysis.[16]



A (0.369 kcal/mol) **B** (0.0 kcal/mol)

(HF/6-31G*//HF/3-21G energies)

Out of four diastereomeric pathways possible for the allylmetalation of **1b** (cf. Scheme I, the ax and eq carbons as well as two diastereotopic olefinic faces are available for the attack by the allylic zinc reagent),[17] the MO observations suggest that the TS **C** (derived from **A**) is the most plausible working model of the reaction of **2** (e.g., R = *t*-Bu; L = HMPA). In this product-like TS, the zinc moiety bearing bulky ligands becomes attached to the less hindered equatorial olefinic carbon from the face opposite to the axial acetal methyl group.[16,18] Since the six-centered TS itself is quite insensitive to the ligand effects (vide supra), it is likely that the bulky ligands improve the C_3–C_4 diastereoselectivity by steric interactions with the acetal moiety.

We have shown that the stereoselectivities of allylzincation can be controlled by a suitable choice of ligands. This information now sets the stage for exploration of ligand-induced asymmetric carbometalation reactions.

Acknowledgment. Financial support of the Ministry of Education Science and Culture, Japan is gratefully acknowledged. M.N. thanks JSPS for a predoctoral fellowship.

Supplementary Material Available: Experimental procedures and characterization data; listing of physical properties of new compounds; stereochemical assignments; and optimized geometries based on the MO calculations (36 pages). Ordering information is given on any current masthead page.

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(10) Frisch, J. M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. *GAUSSIAN 90*; Gaussian, Inc.: Pittsburgh, PA, 1990. Structures were optimized without any symmetry assumption and characterized by harmonic vibrational frequency calculations. For the zinc atom, the innershell electrons were replaced by effective core potential (ECP), and the remaining electrons were described by basis functions of double-ζ quality: Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270, 284. Goddard, W. A., III; Kahn, L. R. *J. Chem. Phys.* **1972**, *56*, 2685. Melius, C. F.; Goddard, W. A., III *Phys. Rev. A* **1974**, *10*, 1528.

(11) Full theoretical discussions of allylmetalation reactions will be published elsewhere.

(12) Gennari, C.; Todeschini, R.; Beretta, M. G.; Farini, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 612. Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481.

(13) Allylboration reaction: Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236.

(14) This may be due to two electronic constraints: conjugation between the C=C and Zn–C bonds in the allylic zinc reagent and the spatial location of the C_3, C_4, C_5, and Zn atoms lying nearly on the same plane. The latter is due to the importance of π and π^* orbitals in carbometalation of olefins as opposed to *n* and π^* in carbonyl additions: see ref 15b.

(15) (a) See supplementary material for structures. (b) For discussions on the effects of a Lewis acidic metal (e.g., Cu(I) in carbometalation reactions, see: Nakamura, E.; Nakamura, M.; Miyachi, Y.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 99.

(16) Among four products of the reaction (for crotylzinc with R = *t*-Bu, L = Me_2O), the product via **C** was indeed found to be of the lowest energy by the MO analysis using MNDO Hamiltonian (see supplementary material).

(17) Note that the C_2 symmetry of **1b** reduces the number of the actual isolable isomers to only two.

(18) This model also accounts for the selectivity reported in ref 3.