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Asymmetric Construction of Quaternary Carbon Centers by Regio- and Enantiocontrolled Allylzincation†

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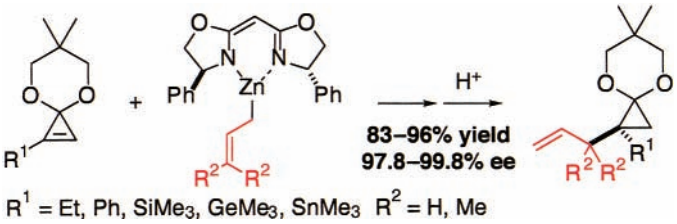
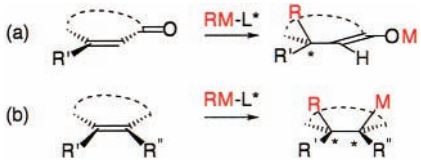
ABSTRACT



An allylic zinc reagent bearing a chiral bisoxazoline ligand adds to a substituted cyclopropenone acetal to produce an optically active cyclopropanone acetal possessing a quaternary chiral center in high yield with 97.8–99.8% ee. The steric effects of the bulky bisoxazoline ligand overwhelm the regioselectivity inherent to the electronic property of the olefinic acceptor. High pressure exerts favorable effects on the reaction rate without affecting the high enantio- or regioselectivity.

The enantioselective addition of an organometallic reagent to a trisubstituted sp^2 carbon atom of a substituted olefin is a prime candidate for a method for straightforward construction of a quaternary chiral carbon center.[1] Enantioselective conjugate addition of an organometallic reagent to a β,β-disubstituted α,β-unsaturated carbonyl compound, a seemingly ideal methodology, has thus far failed to serve such a purpose (Scheme 1, route a).[2] We report herein the first example of enantioselective construction of a quaternary chiral center through a ligand-controlled carbometalation reaction (Scheme 1, route b). A particularly noteworthy finding was that the regioselectivity of the carbometalation inherent to the nature of the olefinic acceptor can be entirely reversed by the use of a bulky chiral ligand in place of a halide ligand on the metal atom.

Scheme 1. 1,4-Addition and Carbometalation for Enantioselective Construction of a Quaternary Chiral Center[a]



[a] RM = organometallic reagent; L* = chiral ligand; R′ = alkyl, aryl, Me_3Si, Me_3Ge, Me_3Sn; R″ = H.

An allylic zinc reagent possessing an anionic bisoxazoline (BOX) ligand (**2**−**5**) can be prepared in situ as shown in Scheme 2 and undergoes various types of enantioselective additions,[3] among which the addition to nonsubstituted cyclopropenone acetal (CPA) **1a** served as a prototype for the present studies.[4] The product of the carbometalation

† This paper is dedicated to Prof. Jose Barluenga of Universidad de Oviedo on the occasion of his 60th birthday.

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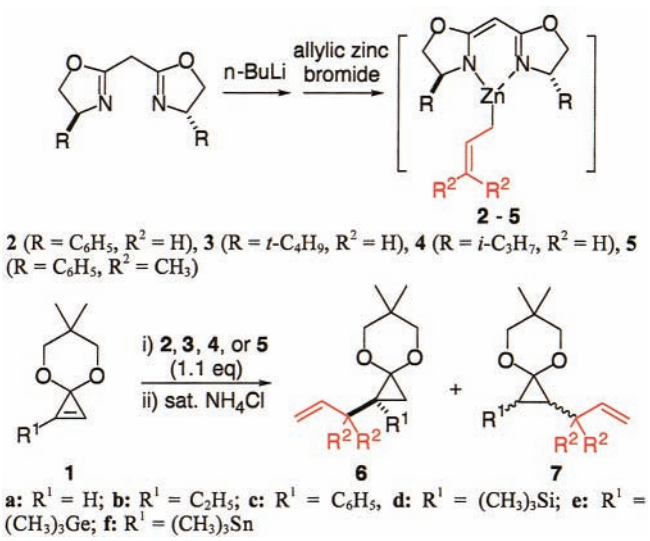
reaction is a cyclopropanone acetal (**6**) which serves as a useful synthon for organic synthesis.[4a,5] For this reaction to generate a quaternary carbon center, it needs first to react with a substituted cyclopropene[6] (**1b**−**f**) and then to react regioselectively to afford **6** rather than **7** (Scheme 2). To

Scheme 2. Addition of Chiral Allylic Zinc Reagent to Substituted CPA



2 ($R = C_6H_5$, $R^2 = H$), **3** ($R = t\text{-}C_4H_9$, $R^2 = H$), **4** ($R = i\text{-}C_3H_7$, $R^2 = H$), **5** ($R = C_6H_5$, $R^2 = CH_3$)

a: $R^1 = H$; **b:** $R^1 = C_2H_5$; **c:** $R^1 = C_6H_5$, **d:** $R^1 = (CH_3)_3Si$; **e:** $R^1 = (CH_3)_3Ge$; **f:** $R^1 = (CH_3)_3Sn$

this end, we examined substituted CPA bearing various Group 14 R^1 subsituents (**1d**−**f**) for the addition of a chiral and achiral allylic zinc reagent.

The reaction of the 2-ethyl- or 2-phenyl-substituted CPA (**1b** or **1c**) was slow but 100% regioselective, favoring the formation of **6** regardless of the allylzinc reagent employed. It proceeded in such a manner that the carbon nucleophile added to the more substituted olefinic carbon to generate a more stable anionic product (Scheme 2 and Table 1). The regioselectivity conforms to the general rule proposed for substituted alkynes.[7]

Allylzincation reactions of 2-ethylcyclopropenone acetal **1b**[5] were examined first. Addition of allylzinc bromide proceeded sluggishly under ambient conditions (conditions A: 25 °C, atmospheric pressure) to afford the single regioisomer **6b** ($R^2 = H$) in 45% yield (entry 1). The chiral allylic zinc reagent **2** that bears a phenyl-substituted bis-oxazoline ligand also reacted sluggishly to give the same regioisomer, **6b** ($R^2 = H$), in moderate yield. When the R group on the chiral ligand was changed from phenyl to *tert*-butyl (**3**) and isopropyl (**4**), the reaction slowed and the enantioselectivity dropped (entries 3 and 4). Allylation of

Table 1. Enantioselective Allylzincation of Substituted CPA **1b** and **1c**

entry	olefin	allylic zinc[a]	conditions[b]	major product[c]	% yield[d]	% ee[e]
1	**1b**		A, 36 h	**6b** ($R^2 = H$)	45	—
2	**1b**	**2**	A, 200h	**6b** ($R^2 = H$)	64	>99
3	**1b**	**3**	A, 72 h	**6b** ($R^2 = H$)	<5	87[f]
4	**1b**	**4**	A, 72 h	**6b** ($R^2 = H$)	48	74[f]
5	**1c**	**2**	A, 70 h	**6c** ($R^2 = H$)	51	>99.6
6	**1b**	**5**	A, 72 h	**6b** ($R^2 = CH_3$)	19	>99.5[f]
7	**1b**	**2**	B, 12 h	**6b** ($R^2 = H$)	95	>98
8	**1c**	**2**	B, 12 h	**6c** ($R^2 = H$)	98	>98
9	**1b**	**5**	B, 12 h	**6b** ($R^2 = CH_3$)	93	>99.5[f]

[a] Slight excess (1.1−1.2 equiv) of allylic zinc reagent was used. [b] A: the reaction was carried out at 25 °C under atmospheric pressure. B: the reaction was carried out at 25 °C under high pressure (1 GPa). [c] The other regioisomers was not detected by GLC analysis. [d] Isolated yield. [e] Determined by GLC analysis of the product obtained by hydrogeation of the terminal olefinic bond unless otherwise noted. The peak due to the enantiomeric product could not be detected in the cases where a > mark is used, and the ee data refers to the detection limit under the analytical conditions employed. [f] Determined by ^1H NMR analysis after conversion to MTPA derivatives.

2-phenyl-substituted CPA **1c** with **2** gave exclusively the allylation product **6c** ($R^2 = H$) with >99.6% ee (entry 5).

An asymmetrically substituted allylic nucleophile such as prenyl zinc reagent **5** contains two sites of potential reactivity. To our pleasant surprise, this reagent reacted with 2-ethyl-CPA **1b** to afford the most sterically congested product **6** ($R^1 = C_2H_5$, $R^2 = CH_3$). The reaction was slow but took place with 100% regioselectivity with respect to both the allylic (S_E') and the olefinic groups. In addition, the enantioselection was complete (>99.5% ee, entry 6). The S_E' reactivity of the allylic zinc reagent suggests the participation of a σ-allylic metal species in the reaction as predicted by theoretical calculations.[8]

We found that high pressure (conditions B in Table 1)[9] accelerates the allylzincation reaction and significantly improves the product yield without affecting the high enantioselectivity.[10] Under a pressure of 10 kbar (1 GPa), the reactions of **2** with **1b** and **1c** were complete within 12 h at 25 °C and quantitatively afforded **6b** ($R^1 = C_2H_5$, $R^2 =$ H and $R^1 = C_6H_5$, $R^2 = H$) in >98% ee (entries 7 and 8). Even the reaction of **1b** with prenyl reagent **5** took place smoothly to give the congested product **6b** ($R^2 = CH_3$) in 93% yield with >99.5% ee (entry 9). The high pressure did not significantly affect the enantioselectivity and regioselectivity. This observation, along with the *syn*-addition mode,[11] supports the concerted nature of the allylzincation of olefins.[8]

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Effects of silyl substitution of the olefin in olefin carbometalation were investigated some time ago[12] as well as in recent years.[13] It has been shown that a Group 14 metal substituent, a stannyl substitutent in particular,[14] not only accelerates the carbometalation but controls the regioselectivity so that the reaction generates a *gem*-dimetallic product (e.g., the compound corresponding to **7** rather than **6**). Thus, the addition of allylzinc reagents to the silyl, germyl, and stannyl CPAs (**1d**−**f**) proceeded far faster than that to the carbon-subsituted CPAs (**1b** and **1c**). For instance, the addition of allylzinc bromide to the Group 14 metal derivatives was complete in an hour at 0 °C at ambient pressure and afforded the product with 80:20−95:5 selectivity favoring the formation of **7**[15] (Table 2, entries 1−3). Note that

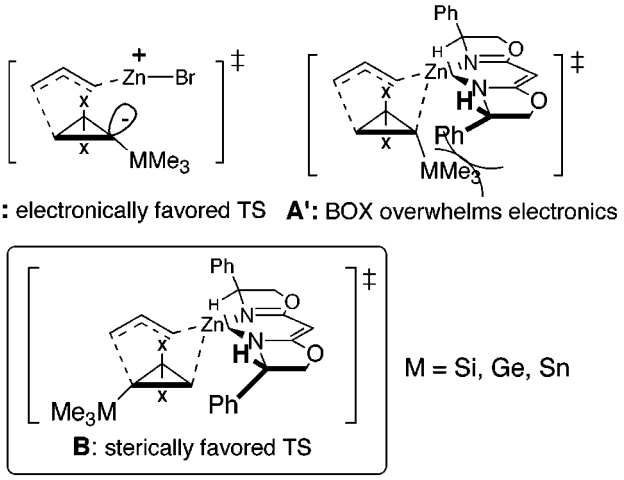
Table 2. Regio- and Enantioselective Allylzincation of Substituted CPA (**1d**−**f**)

entry	olefin	allyl zinc	major product	ratio (6:7)[a]	% yield[b]	% ee[c]
1	**1d**	ZnBr	**7d** (R_2 = H)	20:80	97	–
2	**1e**	ZnBr	**7e** (R_2 = H)	15:85	94	–
3	**1f**	ZnBr	**7f** (R_2 = H)	5:95	94	–
4	**1d**	**2**	**6d** (R_2 = H)	98:2	83	97.8
5	**1e**	**2**	**6e** (R_2 = H)	98:2	96	99.6
6	**1f**	**2**	**6f** (R_2 = H)	94:6	83	99.8

[a] Determined by ^{1}H NMR. [b] Combined yield of regioisomers obtained by isolation. [c] Determined by ^{1}H NMR and HPLC analysis after conversion to MTPA derivatives.

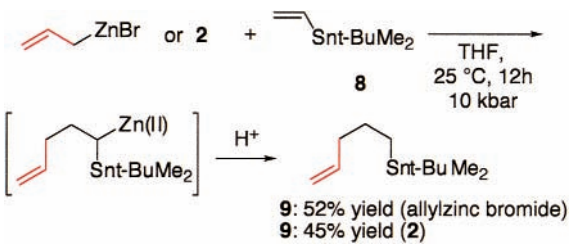
allylzinc bromide addition to 2-ethyl-CPA **1b** was incomplete even after 36 h at 25 °C (Table 1, entry 1). The observed regioselectivity has been ascribed to the predominant electrostatic interaction between the Lewis acidic zinc atom and the developing negative charge on the carbon connected to the metal substituent (**A** in Scheme 3).[7]

Scheme 3. Regiochemistry of Allylzincation of CPAs Bearing a Group 14 Metal Substituent



To our surprise, however, this intrinsic regioselectivity can be completely reversed, favoring **6** with 94:6−98:2 selectivity (entries 4−6), when the BOX-bearing allylzinc reagent **2** reacted with **1d**−**f**. The enantioselectivity of the addition of **2** to **1d**−**f** was excellent (97.8−99.8% ee), and the sense of the selectivity was the same as that described in Table 1. The observed regio- and enantioselectivities combined with the transition structure (TS) obtained for the parent CPA (**1a**) by the ab intio calculation[8] indicate that the reaction took place through TS **B** shown in Scheme 3. Because of the presence of both the acetal and the Me_3M moiety, the electronically favored TS **A′** is precluded by the steric effect of the bulky BOX ligand.

To examine further the origin of the reversal of the regioselectivity, we studied the reactions of allylzinc bromide and **2** with the simple vinylstannane **8**. In contrast to the CPA cases, both reactions occurred in a manner dictated by the electronic property of the vinylstannane and afforded the same product **9** after hydrolysis. The results indicate that suitable steric factors will overwhelm the electronics of the reaction.



In summary, we have demonstrated that an allylic zinc reagent bearing a chiral BOX ligand adds to a substituted

(9) The zinc reagent **2** (R = C_6H_5) was prepared first. Thus, to a solution of phenyl-substituted (*R*,*R*)-BOX (818 mg, 2.67 mmol) and 2,2′-bipyridyl (ca. 1 mg) in dry THF (4.0 mL) was added a 1.49 M hexane solution of BuLi (1.8 mL, 2.68 mmol) at 0 °C, and the mixture was stirred further for 20 min at 25 °C. To the mixture was added a 1.58 M THF solution of allylzinc bromide (1.58 mL, 2.43 mmol) at 0 °C. After stirring for 20 min at 25 °C, a solution of CPA **1c** (480 mg, 2.20 mmol) in dry THF (2.67 mL) was added at 0 °C. The reaction mixture (8.0 mL) was transferred into a Teflon vessel under nitrogen, kept under high pressure (1 GPa) for 24 h at 25 °C, and then quenched with saturated NH_4Cl (20 mL). Purification with silica gel chromatography afforded the allylation product (*R*)-**6c** (R^2 = H) (424 mg, 93% yield): IR (neat) 3073, 2956, 2856, 1639, 1602, 1498, 1471, 1446, 1351, 1292, 1157, 1132, 1070, 1043, 910, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 1.07 (d, J = 5.9 Hz, 1 H), 1.07 (s, 3 H), 1.37 (dd, J = 1.5, 5.9 Hz, 1 H), 2.34 (dd with shoulders, J = 7.3, 14.7 Hz, 1 H), 2.76 (ddd, J = 1.5, 6.4, 14.7 Hz, 1 H), 3.30 (d, J = 11.0 Hz, 1 H), 3.35 (dd, J = 0.97, 11.0 Hz, 1 H), 3.60 (distorted dd, J = 0.97, 10.7 Hz, 1 H), 3.62 (distorted d, J = 10.7 Hz, 1 H), 4.86−4.94 (m, 2 H), 5.61−5.73 (m, 1 H) 7.15−7.22 (m, 1 H) 7.27−7.31 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.1, 22.7, 30.6, 37.4, 38.6, 75.5, 76.4, 92.0, 116.3, 126.2, 127.9 (2 C), 129.2 (2 C), 135.4, 139.4; $[\alpha]^{20}_D$ = 1.02 (c = 3.9, benzene). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.59. Found: C, 79.07; H, 8.83. The *R*-configuration of this product was determined through an eight-step conversion to (*R*)-2-methyl-2-phenylbutanoic acid.

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cyclopropanone acetal to generate new organometallic species bearing a quaternary carbon center with extremely high enantioselectivity. We have shown that high-pressure conditions accelerate the carbometalation reaction without affecting the high enantioselectivity. Interestingly, the regioselectivity of carbometalation can be controlled by the steric effects of the ligand on the metal atom.

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Supporting Information Available: Experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The configuration of the compounds **7d**−**f** was determined to be trans by ^{1}H NMR coupling analysis and is in accord with the *syn*-addition mode of the carbometalation (ref 5).