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Enantioselective reactions of α-methoxybenzyllithium generated by *t*-BuLi/chiral bis(oxazoline) complex with aldehydes

Katsuhiko Tomooka, Lan-Fang Wang, Nobuyuki Komine and Takeshi Nakai *

Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152-8552, Japan

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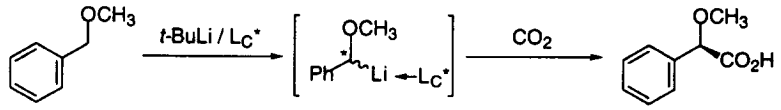
Abstract

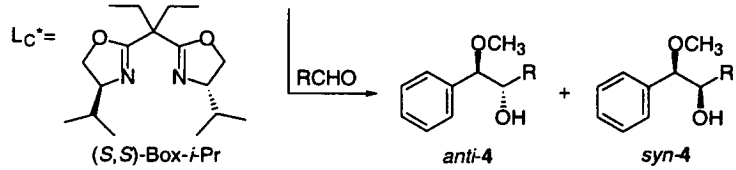
The title reaction is shown to afford the corresponding 1,2-diol monomethyl ethers in moderate-to-high levels of % *ee* (up to 98%) and % *de* (up to 90% *anti*), depending markedly on the aldehyde reactivity. The origin of the enantioselectivity is discussed in terms of a dynamic thermodynamic resolution mechanism. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: α-methoxybenzyllithium; enantioselection; 1,2-diol.

As part of a research program to develop the external chiral ligand-based enantioselective organolithium reactions,[1,2] we have reported in the preceding paper that the enantioselective carboxylation of α-methoxybenzyllithium species **2**, generated from ether **1** via the asymmetric lithiation with *t*-BuLi/chiral bis(oxazoline) (Lc^*) provides α-methoxyphenylacetic acid (**3**) in remarkably high enantioselectivity (Eq. 1).[3] To further enhance the synthetic utility of this chiral ligand-bound organolithium species **2** and gain insight into the asymmetric induction mechanism for this type of enantioselective S_E2 reactions, we have now investigated the enantioselective reaction of the chiral Li-species **2** with aldehydes which poses an additional problem of diastereoselectivity (Eq. 2). We report herein that the asymmetric reaction of chiral Li-species **2** with aldehydes proceeds under a dynamic thermodynamic resolution to afford the corresponding 1,2-diol monomethyl ether **4** in moderate-to-high levels of enantioselectivity and *anti*-diastereoselectivity, depending markedly on the structure of aldehydes used.



1 **2** (*R*)-**3**, >95% *ee* (1)



(*S*,*S*)-Box-*i*-Pr *anti*-**4** *syn*-**4** (2)

* Corresponding author. Fax: +81 35734 2885; e-mail: takeshi@o.cc.titech.ac.jp

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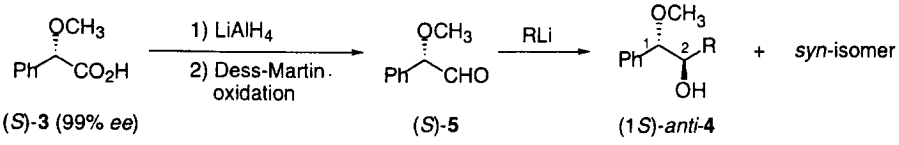
First, we carried out a series of reactions of Li-species **2**, generated from **1** with a *t*-BuLi/(*S,S*)-Box-*i*-Pr complex in the same manner as described in the preceding paper,[3] with aldehydes to give a stereoisomeric mixture of adduct **4**. The results thus obtained are summarized in Table 1. These results reveal that the reactions consistently afford the *anti*-isomer as the major diastereomer and the (1*R*)-isomer as the major enantiomer for either diastereomer. Of special note is that the relative stereochemistry of the products was determined by ^{1}H NMR comparison with those of an authentic *anti*-rich sample prepared from (*S*)-α-methoxyphenylacetic acid via the following sequence (Eq. 3) in which the reaction of aldehyde (*S*)-**5** with organolithium reagents is reasonably postulated to give (1*S*)-*anti*-**4** as the major diastereomer,[4,5] and the absolute configuration was assigned by ^{1}H NMR comparison of their MTPA esters with those of the authentic samples.[6] In fact, etherification of the major diastereomer **4a** (R=Ph) obtained in entry 1 with methyl iodide gave *meso*-1,2-dimethoxy-1,2-diphenylethane.[7]

Table 1
Reactions of chiral Li-species **2** with aldehydes[a]

Entry	Aldehyde	%Yield	*anti* / *syn*[b]	% *ee*[c] (*anti*)	% *ee*[c] (*syn*)
1	PhCHO	>95	82:18	71(1*R*, 2*S*)[d]	42 (1*R*, 2*R*)[d]
2[e]		>95	88:12	90	60
3	*n*-C_8H_{17}CHO	77	71:29	61	47
4	*c*-C_6H_{11}CHO	68	58:42	78	61
5	(*E*)-PhCH=CHCHO	17[f]	64:34	37	15
6	PhC≡CCHO	>95	90:10	>98(1*R*, 2*S*)[d]	84 (1*R*, 2*R*)[d]
7	*t*-$BuPh_2SiC$≡CCHO	>95	91: 9	>98(1*R*, 2*S*)[d]	86 (1*R*, 2*R*)[d]

[a] Ether **1** was treated with a pre-mixed *t*-BuLi (1.5 equiv.)/(*S,S*)-Box-*i*-Pr (1.5 equiv.) in hexane at -78 °C for 1.0 h; then an aldehyde was added and the resulting mixture was stirred at that temperature for 1.5 h to afford, after acidic workup, an isomeric mixture of **4**. [b] Determined by ^{1}H NMR analysis (cf. ref. 4). The *anti* configuration of the major product was assigned by ^{1}H NMR comparison with the *anti*-rich authentic sample or their similarities (ref. 5). [c] Determined by ^{1}H NMR assay of the MTPA ester. [d] Refers to the configuration of the major enantiomer which was assigned by ^{1}H NMR comparison of the MTPA ester with that of the authentic (1*S*)-isomer (ref. 6). [e] Benzaldehyde was added after cooling the resulting mixture containing the lithium species to -110 °C. [f] The reason for the poor yield is unclear.



(*S*)-**3** (99% *ee*) (*S*)-**5** (1*S*)-*anti*-**4** (3)

Inspection of the data in Table 1 reveals that these reactions consistently afford the (1*R*)-*anti*-**4** as a major product, the stereoselectivity depending markedly upon the aldehyde structures. Most significantly, the reactions with acetylenic aldehydes provide remarkably high % *ee*, together with relatively high *anti*-selectivity (entries 6 and 7). Thus, the present reaction provides a novel way for asymmetric synthesis of α-(α-methoxybenzyl) progargylic alcohols **4** (R=acetylenic groups), a potentially useful class of chiral molecules. Furthermore, similar reactions using *p*-methoxybenzyl methyl ether as substrate were found to provide somewhat lower levels of % *ee* and *anti*-selectivity: 74% *anti* and 59% *ee* (*anti*) for PhCHO and 69% *anti* and 81% *ee* (*anti*) for PhC≡CCHO.[8]

Next, our attention was turned to the mechanistic aspects of the present enantioselective reaction. Since the epimeric Li-species initially formed, (*R*)- and (*S*)-**2**, have been proved to epimerize,[3] the enantio-determining step is the post-lithiation event. The question is whether or not the enantioselectivity is determined by a similar mechanism to that proposed for the previously-developed carboxylation. To answer the question, we first carried out substoichiometric experiments on the reactions with benzaldehyde and phenylpropynal (Table 2). These outcomes reveal that both the % *ee* and % *de* decrease

Table 2
Substoichiometric experiments

	PhCHO				PhC≡CCHO			
Equiv. of RCHO	4.0	1.0	0.5	0.1	4.0	1.0	0.5	0.1
% Yield[a]	>95	35	21	4.3	94	34	26	3
% *anti*	82	80	73	69	90	89	88	83
% *ee* (*anti*)	71	74	56	36	>98	97	95	87
% *ee* (*syn*)	42	37	24	18	84	47	56	24

[a] Based on substrate **1**.

gradually with decreasing the amount of the aldehyde reacted in both cases, while the degree of decrease is significantly smaller in the reaction with the propynal. These trends strongly suggest that the present reaction also proceeds via the 'dynamic thermodynamic resolution mechanism'[9] where the epimerization is slower than the reaction with an aldehyde. Thus, the selective formation of (1*R*)-*anti*-**4** and the conversion-dependence of % *ee* and % *de* are explained as a result that the predominantly existing (thermodynamically more stable) Li-species (*S*)-**2**, though less reactive than the minor one (*R*)-**2**, reacts with an aldehyde in a highly retentive fashion and in higher *anti*-selectivity. The extremely high % *ee* observed with the propynals might be rationalized by assuming that the ability of such highly reactive aldehydes to discriminate between (*R*)- and (*S*)-**2** is greater than those of other aldehydes, although the exact reason for that is not clear. To gain further evidence for this mechanism, we made a 'double resolution' experiment where the Li-species **2** was reacted first with 0.5 equiv. of PhC≡CCHO, then with 0.5 equiv. of PhCHO. Interestingly, we found that the enantio-purity of the benzaldehyde adduct thus obtained was significantly improved up to 73% *ee* for *anti*-**4a** and 52% *ee* for *syn*-**4a**, compared with 56% *ee* and 24% *ee*, respectively, observed in the reaction with benzaldehyde only using 1.0 equiv. each of *t*-BuLi and (*S*,*S*)-Box-*i*-Pr.[10] This result suggests that the minor species (*R*)-**2** might be largely consumed by the propynal and hence benzaldehyde could react selectively with the remaining species (*R*)-**1**, thus leading to an enhanced % *ee*.

In summary, we have shown that the enantioselective reaction of the chiral Li-species **2**, generated from benzyl methyl ether with a *t*-BuLi/(*S*,*S*)-Box-*i*-Pr complex, with aldehydes proceeds under dynamic thermodynamic resolution to afford the 1,2-diol monomethyl ether **4** in high enantio- and diastereoselectivity. Further application of the present asymmetric lithiation protocol to other S_E2 reactions is underway.

Acknowledgements

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2. For our previous works in this area: Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 5513–5516; Tomooka, K.; Komine, N.; Sasaki, T.; Shimizu, H.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 9715–9718.
3. Tomooka, K.; Wang, L.-F.; Komine, N.; Nakai, T. *Tetrahedron Lett.* **1999**, *40*, 6809.
4. The two methine protons and the methoxy protons in ^{1}H NMR ($CDCl_3$): *anti*-**4a** (R=Ph), δ 4.89 (d, J=5.7 Hz, 1H), 4.34 (d, 1H), and 3.23 (s, 3H); *syn*-**4a**, 4.65 (d, J=8.1 Hz, 1H), 4.12 (d, 1H), and 3.30 (s, 3H); *anti*-**4b** (R=*n*-C_8H_{17}), 4.11 (d, J=4.8 Hz, 1H), 3.76 (m, 1H), and 3.27 (s, 3H); *syn*-**4b**, 3.89 (d, J=8.1 Hz, 1H), 3.65 (m, 1H), 3.22 (s, 3H); *anti*-**4c** (R=*c*-C_6H_{11}), 4.16 (d, J=6.3 Hz, 1H), 3.58 (m, 1H), and 3.22 (s, 3H); *syn*-**4c**, 4.11 (d, J=7.5 Hz, 1H), 3.47 (m, 1H), 3.22 (s, 3H); *anti*-**4e** (R=Ph-C≡C), 4.73 (m, 1H), 4.45 (d, J=4.2 Hz, 1H), 3.38 (s, 3H); *syn*-**4e**, 4.67 (d, J=7.5 Hz, 1H), 4.31 (d, 1H), 3.34 (s, 3H); *anti*-**4f** (TBDPS-C≡C), 4.69 (m, 1H), 4.47 (d, J=9.9 Hz, 1H), 3.41 (s, 3H); *syn*-**4f**, 4.63 (d, J=7.8 Hz, 1H), 4.47 (d, 1H), 3.29 (s, 3H).
5. The reaction of (*S*)-**5** with the organolithium reagent gave an epimeric mixture of (1*S*)-**4**: *anti*:*syn*=57:43 for **4a** (R=Ph), 77:33 for **4e** (R=Ph-C≡C), and 79:21 for **4f** (R=TBDPS-C≡C).
6. The four stereoisomers of the MTPA esters were distinguishable by four sets of doublets due to the two methines: for **4a** (R=Ph), e.g., δ 6.48/4.40 (1*R*,2*S*), 6.31/4.34 (1*S*,2*R*), 6.43/4.28 (1*R*,2*R*), and 6.50/4.23 (1*S*,2*S*).
7. The ^{1}H NMR ($CDCl_3$) of *meso*-1,2-dimethoxy-1,2-diphenylethane: δ 7.32–7.24 (m, 6H), 7.21–7.14 (m, 4H), 4.31 (s, 2H), 3.16 (s, 6H).
8. ^{1}H NMR ($CDCl_3$): benzaldehyde adduct, δ 7.64–6.85 (m, 9H), 4.85 (d, J=5.6 Hz, 1H), 4.28 (d, 1H), 3.78 (s, 3H), 3.19 (s, 3H) for the *anti* isomer; δ 7.64–6.85 (m, 9H), 4.63 (d, J=8.6 Hz, 1H), 4.06 (d, 1H), 3.75 (s, 3H), 3.27 (s, 3H) for the *syn* isomer; phenylpropynal adduct, δ 7.45–6.86 (m, 9H), 4.62 (m, 1H), 4.33 (d, J=4.2 Hz, 1H), 3.75 (s, 3H), 3.29 (s, 3H), 2.53 (br. s, 1H) for the *anti* isomer; δ 7.45–6.86 (m, 9H), 4.54 (d, J=7.7 Hz, 1H), 4.18 (d, 1H), 3.75 (s, 3H), 3.25 (s, 3H), 2.95 (br. s, 1H).
9. The definition and its general schematic energy profile, see Ref. 1a.
10. The propynal adduct **4e** concurrently obtained in this experiment was of 94% *ee* (*anti*) and 57% *ee* (*syn*), which are significantly lower than those observed in the reaction with the propynal only (entry 6, Table 1).