Enantioselective carboxylation of α-methoxybenzyllithium generated via asymmetric lithiation with a *t*-BuLi/chiral bis(oxazoline) complex

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Abstract

Treatment of benzyl methyl ether with a *t*-BuLi/chiral bis(oxazoline) complex followed by carboxylation is shown to afford α-methoxy phenylacetic acid in high % *ee* (up to 95%). The asymmetric induction was proved to occur at the post-lithiation step. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: bis(oxazoline); lithiation; carboxylation; enantioselection.

In view of the eminent position of organolithium chemistry in synthetic organic chemistry, the development of enantioselective organolithium reactions is a significant challenge to organic chemists. In recent years much attention has been focused on the *external chiral ligand* (Lc*)-based asymmetric lithiation protocol, and impressive successes have been achieved mostly by using (−)-sparteine (A) as Lc*.[1] Recently, we have reported that the [2,3]-Wittig rearrangement of benzylic and propargylic ethers, when induced by asymmetric lithiation using as Lc* the chiral bis(oxazoline), (*S,S*)-Box-*i*-Pr (B), provides a significantly higher enantioselectivity than those observed when sparteine was used.[2] Encouraged by this success, we became intrigued by the enantioselective S_E2 reactions of α-alkoxybenzyllithiums generated via such asymmetric lithiation protocol. Herein we wish to report that the enantioselective α-carboxylation of benzyl methyl ether (1a) via asymmetric lithiation with *t*-BuLi/chiral bis(oxazoline) B affords α-methoxyphenylacetic acid (3a) in high enantiomeric purity (Eq. 1).[3]

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A   (*S,S*)-Box-*i*-Pr (**B**)   (1)

1a   **2a**   (*R*)-**3a**
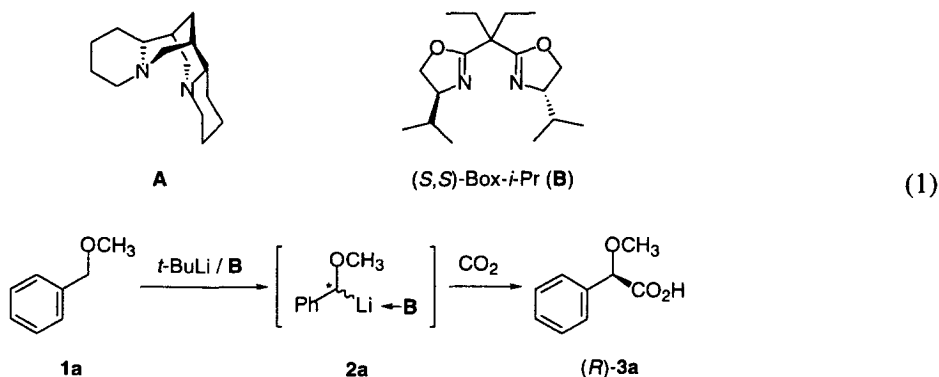
At the outset, we examined the asymmetric lithiation/carboxylation reactions of the two benzyl ethers **1a** and **1b** using different combinations of butyllithiums and Lc* (**A–D**)[4] (Eq. 2). The results thus obtained are summarized in Table 1.

1a, P=CH$_3$

1b, P=CH$_2$OCH$_3$

(2)

C   **D**
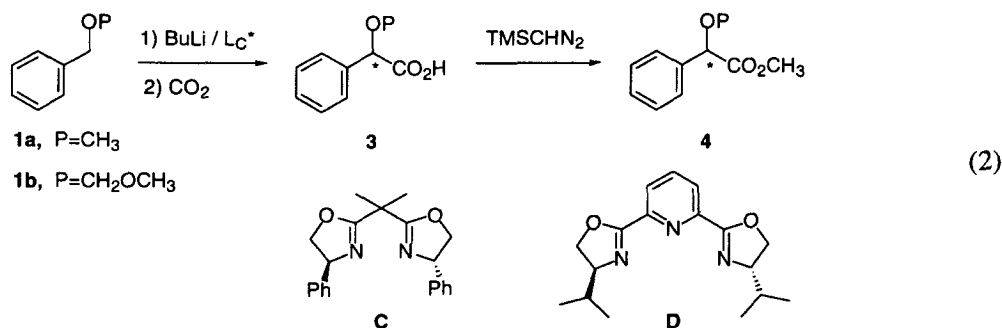
Among the conditions examined, the most favorable results were obtained when ether **1a** was used as substrate and the *t*-BuLi/ligand **B** complex was used as the lithiating agent (entries 7–9). Apparently, bis(oxazoline) **B** is superior to sparteine (**A**) as Lc*, and methyl ether **1a** is superior to methoxymethyl ether **1b** as substrate. Interestingly, the use of *s*-BuLi in place of *t*-BuLi provided a much lower % *ee* (entry 3 vs 7). Also notable is that the use of hexane as solvent is essential; other solvents such as ether and THF led to a much lower % *ee* (entries 10 and 11). Thus, the best procedure afforded (*R*)-α-methoxyphenylacetic acid (**3**)[5] in respectably high % *ee* and chemical yield. Rather surprisingly, an increased % *ee* was observed when the period of carboxylation was extended (entry 8). Most significantly, when the carboxylation was conducted after the Li-species initially generated at −78°C was cooled to −110°C, a remarkably enhanced % *ee* (95% *ee*) was obtained (entry 9).

The question immediately arises as to whether the enantioselectivity is determined at the lithiation or post-lithiation step. To answer the question, we carried out a similar reaction using the racemic α-deuterated ether **1a**-*d* under the same conditions (Eq. 3). The deuterium content of the product obtained in 73% yield was more than 96% and its enantiopurity was comparably high (74% *ee*). This observation strongly suggests that the initially formed **B**-bound Li-species **2a** are epimerized to each other and hence the enantio-determining step is the post-lithiation event. The next question is whether or not the enantioselectivity is governed by a dynamic kinetic resolution where the epimerization is much faster than the carboxylation. Thus, we examined the influence of the relative amount of CO$_2$ on the *ee* value. Interestingly enough, the % *ee* was found to decrease gradually with decreasing the amount of CO$_2$ added: 74% *ee* for >95% conversion with 4 equiv., 48% *ee* for 26% conv. with 0.5 equiv, and 45% *ee* for ca. 10% conv. with 0.1 equiv.[6] This trend, coupled with the enhancement of % *ee* observed in

Table 1
The enantioselective carboxylations[a]

Entry	Substrate	BuLi / L_C^*	Solvent	%Yield[b]	% ee[c] (Config.)[d]
1	1a	s-BuLi / A	hexane	34	0
2	1b			>95	10 (R)
3	1a	s-BuLi / B	hexane	60	58 (R)
4	1b			46	30 (R)
5	1a	s-BuLi / C	hexane	<5	17
6		s-BuLi / D	hexane	5	1
7	1a	t-BuLi / B	hexane	59	74 (R)
8[e]				81	82 (R)
9[f]				>95	95 (R)
10	1a	t-BuLi / B	THF	85	17 (S)
11	1a		ether	>95	1

[a] Unless otherwise noted, ether 1 was treated with a butyllithium (1.5 equiv.) pre-mixed with L_C^* (1.5 equiv.) in hexane at -78 °C for 1.0 h, then excess of CO_2 was added, and the resulting mixture was stirred at that temperature for 1.5 h to provide, after acidic workup, acid 3. [b] Refers to the yield of the methyl ester 4 obtained by treatment with $TMSCHN_2$. [c] Determined by GLC analysis of methyl ester 4 using CP-chiralsil-DEX CB as the chiral column (110 °C); t_R= 43.3 min (R) and 45.2 min (S) for 4a and 89.2 min (S) and 90.5 min (R) for 4b. [d] For the assignment, see ref. 5. [e] The carboxylation time was extended to 4 h. [f] CO_2 was added after the Li-species-containing mixture was cooled to -110 °C to make the mixture heterogeneous.

entry 8, argues definitely against the dynamic kinetic resolution mechanism. Instead, this conversion-dependence of % ee suggests that, while the two epimeric Li-species initially formed are equilibrated, but not on the time scale of carboxylation, the predominately existing (thermodynamically more stable) species forming (R)-3 could be trapped *more slowly* than the minor species forming (S)-3 and hence the ee value increases with increasing the degree of carboxylation.[7] Therefore, it appears likely that the enantioselectivity is governed mainly by the so-called 'dynamic thermodynamic resolution'[8] where the epimerization is slower than the carboxylation. This mechanism also explains the enhancement of % ee observed when the epimerization was frozen out by cooling the Li-species prior to carboxylation (entry 9).

(±)-1a-d   t-BuLi / B CO_2 (R)-3a-d, 74% ee   (3)
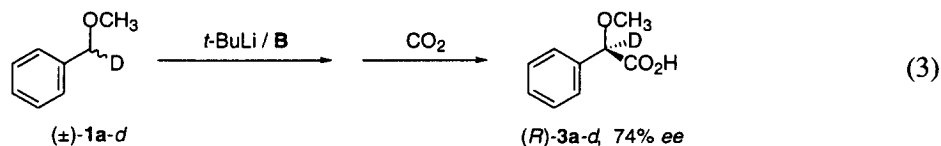
In summary, we have demonstrated that the enantioselective carboxylation of benzyl methyl ether via asymmetric lithiation using the t-BuLi/chiral bis(oxazoline) **B** complex affords α-methoxyphenylacetic acid in high enantiomeric excess. Further application of the external chiral ligand-based asymmeric lithiation protocol to other S_E2 reactions is in progress.

Acknowledgements

References

1. Reviews: (a) Beak, P.; Basu, A.; Gallageher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2283–2316.
2. Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 5513–5516.
3. Hoppe has reported that the asymmetric lithiation of benzyl *N,N*-diisopropylcarbamate with *s*-BuLi/(−)-sparteine in hexane followed by carboxylation provides the acid in 82% *ee* (unpublished work described in Ref. 1b). In our hands, however, such high % *ee* could not be reproduced (only 22% *ee* was observed) apparently due to the complication arising from crystallization of the lithium species as Hoppe has pointed out (Ref. 2b).
4. Ligand **A** was prepared by the reported method: Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. C.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884–4892. Ligands **B** and **C** were of commercial origin.
5. ^{1}H NMR (CDCl$_3$): **4a**, δ 7.52–7.35 (m, 5H), 4.78 (s, 1H), 3.72 (s, 3H), 3.41 (s, 3H); **4b**, δ 7.52–7.30, 5.18 (s, 1H), 4.75 (d, J=6.9 Hz, 1H), 4.69 (d, J=6.9 Hz,1H), 3.72 (s, 3H), 3.38 (s, 3H). The (*R*)-configuration of **4a** (95% *ee*) was assigned by the sign of optical rotation: [α]$_D$ −80.8 (*c* 0.56, acetone); lit. [α]$_D$ +88.7 (*c* 1.07, acetone) for (*S*)-**4a** (100% *ee*): Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126–3133. In a similar way, the (*R*)-configuration of **4b** (30% *ee*) was assigned: [α]$_D$ −36.9 (*c* 1.13, CHCl$_3$); lit. for (*S*)-(+)-**4b**: Barrett, A. G. M.; Rys, D. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1009–1017.
6. In these experiments (*R*)-**3a** was consistently formed as the major enantiomer (GLC assay).
7. At present, the question cannot definitely be answered which Li-species, (*R*)- or (*S*)-**2a**, forms (*R*)-**3a**, because the steric course (retention vs inversion) of the subsequent carboxylation is ambiguous (Ref. 1b). However, we believe that the present carboxylation proceeds with retention of configuration in view of the fact that the opposite sense of enantioselection has been observed in a similar enantioselective [2,3]-Wittig rearrangement of allyloxy benzyl ether which should proceed in a completely invertive fashion (Ref. 2). Moreover, the same sense of enantioselection was observed also in the reactions of Li-species **2a** with aldehydes (*Tetrahedron Lett.* **1999**, *40*, 6813) which is more likely to proceed with retention of configuration. Thus, the predominately existing Li-species might be (*S*)-configurated which produces (*R*)-**3a** as a major enantiomer.
8. For the definition and its general schematic energy profile, see Ref. 1a.