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Synthesis of optically active aldol derivatives through chirality transfer type 1,2-Wittig rearrangement of α-alkoxycarboxamides

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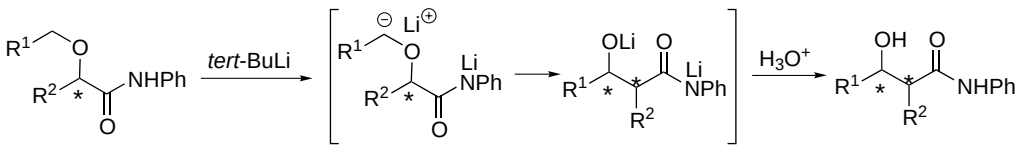
Abstract—Treatment of chiral α-benzyloxy- or α-propargyloxycarboxamide with *tert*-BuLi gave β-hydroxycarboxamides (aldol derivatives) in high optical purity through the formation of α-lithiated ethers and the subsquent 1,2-Wittig rearrangement.

Isomerization to metal alkoxide through the 1,2-alkyl migration of α-metalated ethers is well known as the 1,2-Wittig rearrangement.[1] A radical pair dissociation–recombination mechanism is widely accepted as the most reasonable mechanistic pathway of the 1,2-Wittig rearrangement.[1,2] Furthermore, with substrates having chiral centers at the migrating carbon (not metal-bearing carbanion center), it has been confirmed that the reaction proceeds with retention of the migrating carbon.[3] On the other hand, despite the many reports on such mechanistic and streochemical studies, 1,2-Wittig rearrangement of synthetically useful levels has not so far been reported except for a few examples.[4] In this paper, we report a 1,2-Wittig rearrangement with chiral α-alkoxycarboxamides which proceeds with a high level of retention at the migrating center to give optically active β-hydroxycarboxamides (aldol derivatives) (Scheme 1).

Aldol derivatives, β-hydroxy carbonyl compounds, are a useful synthetic intermediate for the preparation of various natural products. Accordingly, the development of asymmetric aldol reactions to get the optically active forms has been also investigated by many groups.[5] Asymmetric aldol reaction would be classified as a diastereoselective version using a chiral auxiliary and an enantioselective version using a chiral reagent or catalyst.[5c] We found a new synthetic method of optically active aldol derivatives through 1,2-Wittig rearrangement with chiral *N*-phenyl α-alkoxycarboxamides.

When (*R*)-*N*-phenyl *O*-benzylmandelamide **1a** derived from (*R*)-mandelic acid is treated with 3 equiv. of *tert*-BuLi at −78°C, deprotonation of benzyl hydrogen and subsequent 1,2-Wittig rearrangement of the resulting α-lithiated ether smoothly proceeds to give β-hydroxy-α,β-diphenyl propanamide **2a** in good yield (69%) with relatively high diastereoselectivity (*anti*-**2a**/*syn*-**2a** = 9.9) (Scheme 2).[6] The ee of the major diastereomer *anti*-**2a** was estimated to be 94% by HPLC analysis using a chiral column.[6] Thus, the present reaction was found to proceed with a high level of chirality transfer without racemization of **1a**. As the reaction substrate, the use of *N*-monosubstituted anilide derivative is essential; for example, in the reaction with the *O*-benzyl ether of mandelic acid, *iso*-pro-



Scheme 1.

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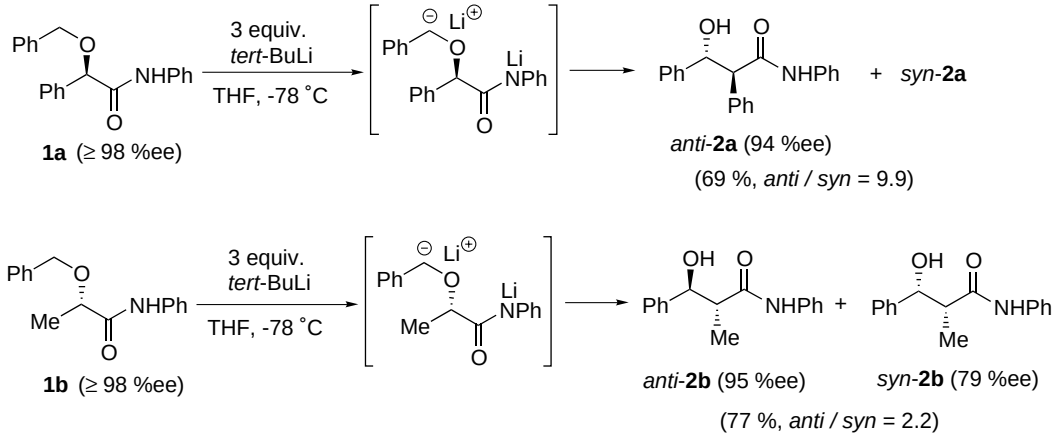
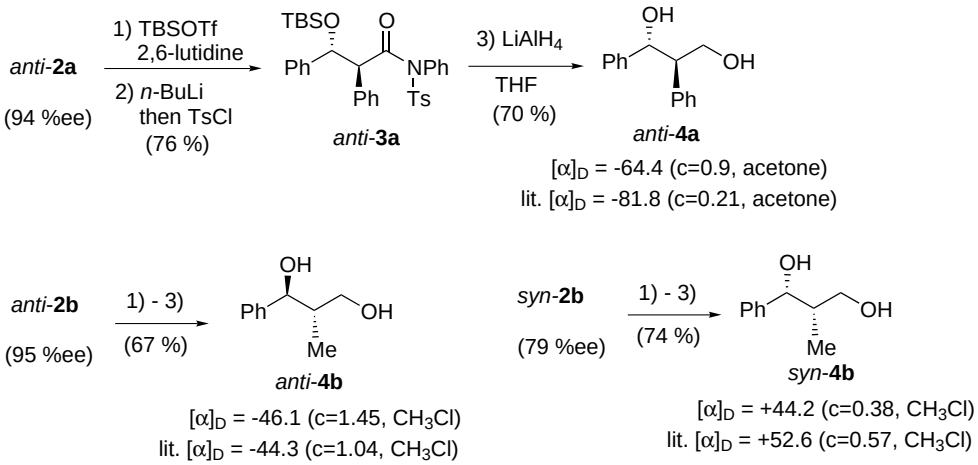


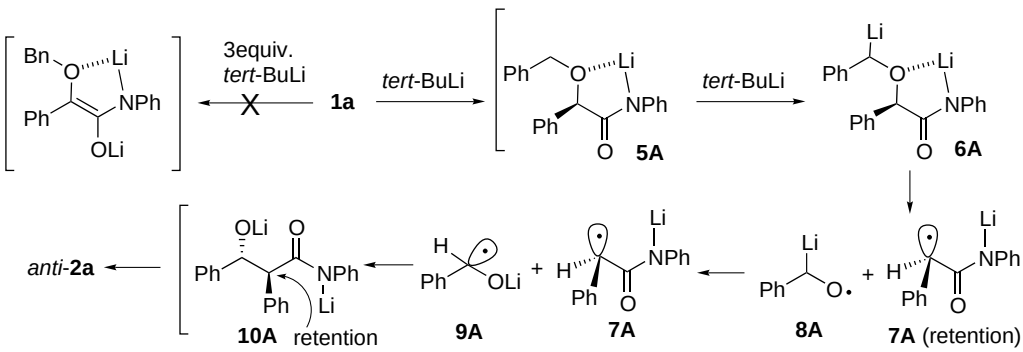
Scheme 2.

pyl mandelate or *N*,*N*-diethyl mandelamide, recovery of the starting material or formation of a complex mixture resulted without the formation of the 1,2-Wittig product. Although a decrease in diastereoselectivity was observed (*anti*-**2b**/*syn*-**2b** = 2.2), under the same conditions, 1,2-Wittig rearrangement of (*S*)-*N*-phenyl *O*-benzyllactamide **1b** derived from (*S*)-lactic acid also proceeded to give the product **2b** in good yield (77%) (Scheme 2). Similar to mandelamide **1a**, the ee of major diastereomer *anti*-**2b** was found to be 95% which indicates a high level of chirality transfer, while for minor diastereomer *syn*-**2b**, a decrease in the ee was observed (79% ee).[7] These reactions would be equivalent to an asymmetric aldol reaction of phenylacetic acid and propionic acid derivatives with benzaldehyde.

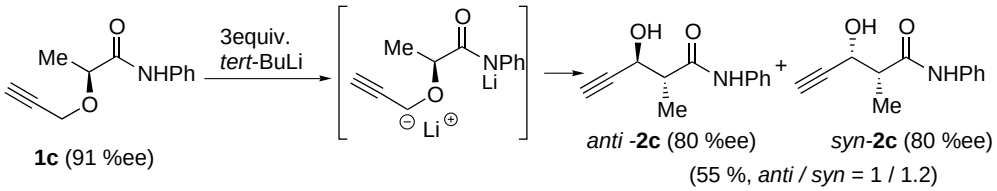
The relative and absolute stereochemistries of the products **2a** and **2b** were determined after conversion to known diols **4a**[8] and **4b**[9] in accordance with Scheme 3. On the basis of the results of Scheme 2 and Scheme 3, the stereochemical course of the present reaction may be rationalized as Scheme 4. The high ee and absolute



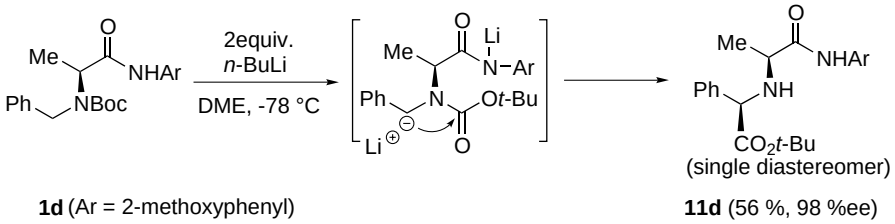
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

configurations of **2a** and **2b** indicate that the reaction proceeds with a high level of retention at the inherent chiral center (the migrating center). That is, the formation of dianionic lithium enolate by deprotonation of α-hydrogen and racemization of a radical intermediate such as **7A** should hardly occur. As far as we know, since no example of 1,2-Wittig rearrangement involving the formation of a carbonyl α-radical fragment has so far been reported, the high level of the chirality transfer in such reaction system should be noteworthy.

1,2-Wittig rearrangement using an α-alkoxy carboxamide derivative can be applied to not only *O*-benzyl ether derivatives **1a** and **1b** but also *O*-propargyl ether derivative **1c** (Scheme 5). Under the similar conditions, the reaction of (*S*)-*O*-propargyllactamide **1c** (91% ee) gave the product *anti*-**2c** and *syn*-**2c** in 55% yield, while decrease in the diasteroselectivity and the level of chirality transfer was observed in comparison with *O*-benzyl derivatives **1a** and **1b** (*anti*-**2c**/*syn*-**2c** = 1/1.2, *syn*-**2c** and *anti*-**2c**: 80% ee).[7,10]

An aza-version of 1,2-Wittig rearrangement with *N*-Boc *N*-benzyl alanine derivative **1d** was further investigated. However, in this case, migration of the Boc group to the resulting *N*-benzyl carbanion takes place, leading to the isolation of **11d** as a single stereoisomer without the formation of an aza-Wittig product (aza-aldol derivative) (Scheme 6).[10]

In conclusion, we have succeeded in the development of 1,2-Wittig rearrangement with chiral α-alkoxycarboxamides which proceeds with a high level of chirality transfer to give optically active β-hydroxycarboxamides (aldol derivatives). The present reaction should provide new methodology for the synthesis of optically active aldol derivatives from inexpensive chiral α-hydroxy acids.

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6. General procedure of 1,2-Wittig rearrangement. Under Ar atmosphere, to a solution of **1a** (159 mg, 0.5 mmol) in THF (3 ml) was added pentane solution of *tert*-BuLi (1.47 M, 1.02 ml, 1.5 mmol) at −78°C. After being stirred for 1 h at −78°C, the reaction mixture was poured into 2% HCl

and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography ($CHCl_3$) gave a mixture of *anti*-**2a** and *syn*-**2a** (110 mg, 69%). The ratio of *syn*-**2a** and *anti*-**2a** was determined by 300 MHz ^{1}H NMR. Further purification of the mixture by MPLC ($CHCl_3$) gave *anti*-**2a** (less polar) and *syn*-**2a** (more polar). The ee of *anti*-**2a** was determined on the basis of HPLC analysis using CHIRALPAK AS column [25 cm×0.46 cm; solvent, 10% *i*-PrOH in hexane; flow rate; 0.8 ml/min; major-enantiomer, $t_R=9.2$ min, minor-enantiomer, $t_R=11.8$ min]. *anti*-**2a**: colorless solid; mp 218–220°C; $[\alpha]_D=-66.9$ ($c=0.60$, acetone); ^{1}H NMR (DMSO-d_6): δ 10.14 (1H, brs), 7.65 (1H, d, $J=8.0$ Hz), 6.98–7.32 (14H, m), 5.67 (1H, d, $J=4.4$ Hz), 5.17 (1H, dd, $J=4.4$, 10.3 Hz), 3.91 (1H, d, $J=10.3$ Hz). ^{13}C NMR ($CDCl_3$): δ 171.0, 143.5, 139.6, 137.4, 128.9, 128.1, 127.8, 127.2, 127.1, 126.9, 123.3, 119.1, 75.1, 61.1.

7. The ee was determined on the basis of Mosher's analysis.
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10. The stereochemistries of *syn*-**2c** and **11d** were determined on the basis of X-ray analysis.