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Chiral Dienolate Chemistry in Remote Asymmetric Induction: The Asymmetric Aldol / Oxy-Cope Strategy for Asymmetric Synthesis of γ,δ-Dichiral α,β-Unsaturated Acid Derivatives

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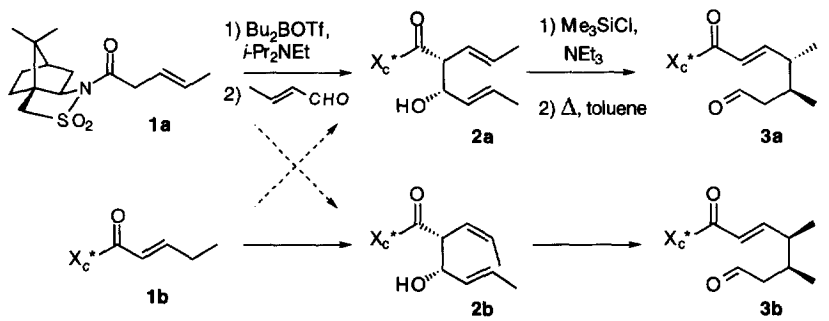
Abstract: *The asymmetric aldol reaction of the boron dienolate derived from chiral α,β- or β,γ-unsaturated imide followed by the siloxy-Cope rearrangement is shown to provide the γ,δ-anti- or -syn -α,β-unsaturated imide as the main product.*

The creation of a chiral center remote from the chiral auxiliary is a challenging problem in organic synthesis. In the preceding communication,[1] we described a general, efficient solution to this problem which relies upon the combination in tandem of the asymmetric induction via the allylation of chiral lithium dienolates with the asymmetric transmission via the Cope rearrangement to afford the γ-chiral α,β-unsaturated acid derivatives in high enantiomeric purities. As an extension of this strategy, we wish to report another asymmetric induction / transmission sequence which involves the asymmetric aldol reaction of a chiral dienolate derived from imides **1a** and **1b** followed by the oxy-Cope rearrangement of the aldol adducts, eventually providing the γ,δ-*anti*- (**3a**) or -*syn*-α,β-unsaturated imide (**3b**) in a highly stereocontrolled fashion (Scheme 1).[2,3] The key to the success is the combined use of the chiral boron dienolate in the asymmetric aldol process and the siloxy-Cope variant as the asymmetric transmission process.

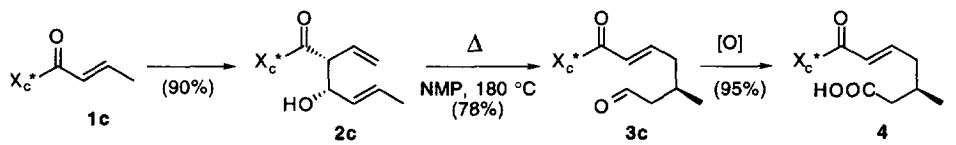
Scheme 1



At first, the aldol reaction of the lithium dienolate of **1a**[4] with crotonaldehyde was found to give a mixture of the aldol diastereomers in the ratio of 28:40:32.[5] In contrast, the use of the boron dienolate[6] afforded the (*E, E, syn*)-aldol (**2a**)[7] with a 99% "stereopurity"[5,8] in 90% yield. A similar reaction of **1b**[4] gave the (*Z, E, syn*)-isomer (**2b**) with a slightly lower stereopurity (*Z*, 84.5%) in 70% yield. Unfortunately, the oxy-Cope rearrangements (*N*-methyl-2-pyrrolidone,[9] 180 ℃) of **2a** and **2b** resulted in very low yields of **3a** (44%) and **3b** (27%) due to the considerable retro-aldol reaction that occurred. However, the siloxy-Cope variant[10] (toluene, 210 ℃, 15 min) of **2a** followed by hydrolysis (aq. HCl, THF) was found to afford 98% yield of the *anti*-isomer (**3a**)[7] with 99% stereopurity. This means that the siloxy-Cope rearrangement proceeds with almost complete asymmetric transmission through the usual chair-like transition states. A

similar rearrangement of **2b** afforded 98% yield of the *syn* isomer (**3b**)[7] with 83% stereopurity. Overall, the asymmetric aldol / siloxy-Cope sequence outlined here permits ready access to γ,δ-dichiral α,β-unsaturated acid derivatives in enantio- and diastereo-enriched forms, which are otherwise difficult to obtain.

As a matter of course, the present methodology is applicable to the asymmetric synthesis of δ-chiral α,β-unsaturated acid derivatives as have recently been illustrated by Black and co-workers using a different chiral auxiliary.[3] Depicted below is our own example where the aldol reaction of **1c** with crotonaldehyde gave **2c**[7] as an essentially single stereoisomer, and its oxy-Cope rearrangement proceeded smoothly in *N*-methyl-2-pyrrolidone (180 ℃, 15 min) to afford, after Jones oxidation, acid **4**[7] in 94% de.[5]



1c **2c** **3c** **4**

In summary, we have demonstrated that the asymmetric aldol reaction of the chiral boron dienolate of **1** followed by the siloxy-Cope rearrangement effects the net remote asymmetric induction, thereby allowing the stereocontrolled preparation of the γ,δ-dichiral α,β-unsaturated acid derivatives (**3a-b**). Synthetic application of the present method is underway in our laboratories.

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References and Notes

1. Tomooka, K.; Nagasawa, A.; Wei, S.-Y.; Nakai, T., the preceding paper.
2. This work was presented at the International Chemical Congress of Pacific Basin Societies, Honolulu, 1995, ORG100.
3. Quite recently, a related work has been reported by the Merck Frosst group: Black, W. C.; Giroux, A.; Greidanus, G. *Tetrahedron Lett.* **1996**, *37*, 4471-4474. In their work, the aldol reactions of the boron dienolate derived from the crotonyl imide containing Evans' chiral auxiliary with various α,β-enals followed by the siloxy-Cope rearrangement have been shown to give the δ-chiral α,β-unsaturated imides in a high stereoselectivity. Note that in these cases the aldol adducts have no geometric problem.
4. Imides **1a** and **1b** were prepared from (*E*)-2-and (*E*)-3-pentenoyl chloride, respectively, via reaction with (2*R*)-bornane-10,2-sultam according to the reported procedure: Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767-2772.
5. The geometric and diastereomeric purity were determined by HPLC (ODS, CH_3CN/H_2O) and ^1H NMR analysis (*cf.* ref 7).
6. Review: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969-2004.
7. All the compounds were characterized by ^1H- and ^{13}C-NMR, and IR. Data for selected products are as follows. **2a**: ^1H NMR ($CDCl_3$) δ 3.73 (dd, *J*=8.5, 4.9 Hz, 1H, NCOC*H*), 4.42 (dd, *J*=6.4, 4.9 Hz, 1H, HOC*H*), 5.36-5.62 (m, 2H, vinyl), 5.63-5.90 (m, 2H, vinyl). ^{13}C NMR ($CDCl_3$) δ 123.46, 128.76, 129.91, 132.34 (vinyl), 172.94 (N*C*O). **2c**: ^1H NMR ($CDCl_3$) δ 3.81 (dd, *J*=8.5, 4.2 Hz, 1H, NCOC*H*), 4.48 (dd, *J*=6.9, 4.2 Hz, 1H, HOC*H*), 5.29-5.44 (m, 2H, vinyl), 5.44-5.58 (m, 1H, vinyl), 5.69-6.01 (m, 2H, vinyl). ^{13}C NMR ($CDCl_3$) δ 121.03, 128.93, 129.77, 131.05 (vinyl), 172.60 (N*C*O). **3a**: ^1H NMR ($CDCl_3$) δ 6.46 (dd, *J*=15.1, 1.1 Hz, 1H, COC*H*=CH), 6.85 (dd, *J*=15.1, 8.4 Hz, 1H, CH=C*H*CH_2), 9.66 (s, 1H, C*H*O). **3b**: ^1H NMR ($CDCl_3$) δ 6.46 (dd, *J*=15.2, 1.2 Hz, 1H, COC*H*=CH), 6.90 (dd, *J*=15.2, 8.1 Hz, 1H, CH=C*H*CH_2), 9.68 (s, 1H, C*H*O). **4**: ^1H NMR ($CDCl_3$) δ 6.50 (d, *J*=15.0 Hz, 1H, COC*H*=CH), 6.95 (dt, *J*=15.0, 7.2 Hz, 1H, CH=C*H*CH_2). ^{13}C NMR ($CDCl_3$) δ 163.9 (N*C*O), 178.0 (HOO*C*).
8. The " stereopurity" refers to the percentage of the major stereoisomer among all possible isomers.
9. Fujita, Y.; Onishi, T.; Nishida, T. *J. Chem. Soc., Chem. Commun.* **1978**, 972-973.
10. Thies, R. W.; Wills, M. T.; Chin, A. W.; Schick, L. E.; Walton, E. S. *J. Am. Chem. Soc.* **1973**, *95*, 5281-5285.

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