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α,α-Disubstituted Boron Enolates in the Asymmetric Synthesis of Quaternary Carbon Centers

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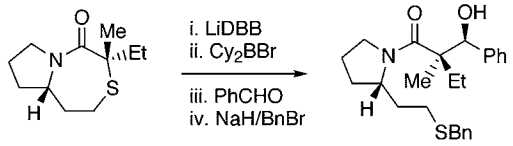
ABSTRACT



Reduction of α,α-disubstituted thioglycolate amides with lithium di-*tert*-butylbiphenylide affords α,α-disubstituted enolates with high *Z*/*E* selectivity. Transmetalation of the enolates with dicyclohexylboron bromide facilitates highly diastereoselective aldol reaction with aromatic and α,β-unsaturated aldehydes.

The aldol reaction is one of the most powerful tools in synthesis. Countless examples of asymmetric aldol reactions have been reported over the years, mostly focusing on reactions that produce either β-hydroxy carbonyls (e.g., acetate aldols) or α-alkyl-β-hydroxy carbonyls (e.g., propionate aldols). In the case of propionate aldols, control of syn/anti stereochemistry is a major concern. In many instances, high syn/anti control can result through the combination of a single enolate stereochemistry (i.e., *E*/*Z*) reacting within a chairlike (i.e., Zimmerman-Traxler) transition state. In sharp contrast to acetate and propionate aldols, there are no general aldol methods for the asymmetric synthesis of α,α-dialkyl-β-hydroxy carbonyls.[1] The reason for this is the general inaccessibility of acyclic α,α-disubstituted enolates of defined stereochemistry. Recently, we described a solution to this problem using a two-electron reduction of thioglycolate lactams.[2] In this communication, we describe the extension of this methodology to the formation of α,α-dialkyl-β-hydroxy amides with excellent control of absolute and relative stereochemistry.

The reduction of 5,7-bicyclic lactam **1a** with lithium di-*tert*-butylbiphenylide produces (*Z*)-enolate **2a** with 94:6 selectivity (Scheme 1). The stereoselectivity in this reaction arises from constraints in the bicyclic system that hold the sulfur rigidly on one face of the carbonyl plane such that upon two-electron reduction, the *E*/*Z* stereochemistry of the enolate is governed by the relative locations of the α-alkyl groups in the starting lactam. The (*Z*)-lithium enolates have subsequently been employed in highly stereoselective alkylations to form quaternary carbon stereocenters (e.g., **3**).[3]

Aldol condensation of lithium enolate **2a** with benzaldehyde at −78 °C in THF proceeded in good yield. The diastereoselectivity of the reaction could be determined by HPLC only after S-benzylation of the product. Not surprisingly, the lithium aldol proceeded with low syn/anti selectivity (52:48). In addition, the facial selectivity with respect to the approach of the aldehyde on the enolate diastereofaces was low for both the syn and anti products.[4] To improve the stereoselectivity, transmetalation of the lithium enolates with various metal halides was investigated (Table 1). Trans-

(1) For approaches to this problem using allylmetal species, see: (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898. (b) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488. For an alkylation approach, see: (c) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825, 2829.

(2) Manthorpe, J. M.; Gleason, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2091.

(3) Manthorpe, J. M.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2338.

(4) For purposes of convenience, the syn product is defined as the one with the larger group at the α-position and the hydroxyl group both forward when drawn in an extended format.

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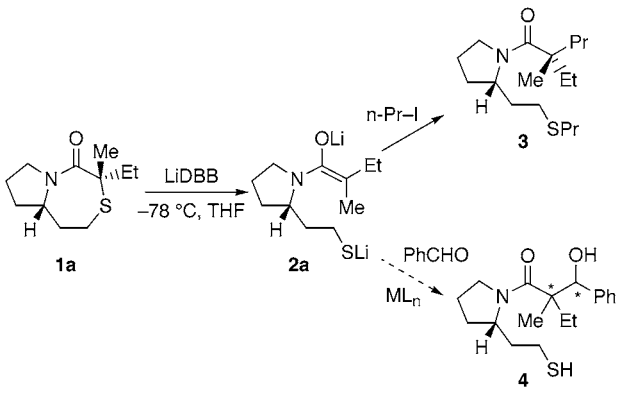
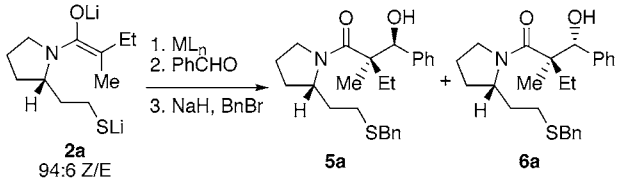
Scheme 1. Alkylation and Aldol Reactions to Form Quaternary Carbon Centers



metalation with Cp_2ZrCl_2 afforded a modest increase in syn/anti stereocontrol, while titanium and tin enolates afforded no significant improvement.

Boron enolates are well-known to afford some of the highest stereoselectivities in aldol condensations.[5] However, in most cases, boron enolates are formed through direct enolboration of carbonyl substrates. This generally limits boron enolate formation to more acidic species such as ketones, imides, and thioesters; simple amides are normally not substrates for enolboration.[6] Transmetalation of lithium enolates to boron has only been reported in a few isolated cases. However, yields and the syn/anti stereoselectivity of subsequent aldol reactions can be variable.[7,8] Transmetalation

Table 1. Transmetalation Effects on Aldol Stereoselectivity



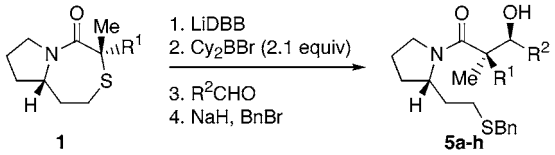
entry	additive	equiv	syn/anti (**5a**/**6a**)[a]	de (syn) (%)[a,b]	yield (%)
1	none		52:48	23	71
2	$TiCl_4$	1.1	45:55	20	nd
3	Cp_2ZrCl_2	2.0	71:29	52	nd
4	$SnCl_4$	1.05	46:54	48	nd
5	Bu_2BOTf	2.2	79:21	95	48
6	Bu_2BOTf	3.0	83:17	92	39
7	Cy_2BOTf	2.2	69:31	30	46
8	Cy_2BOTf	3.3	91:9	93	53
9	Bu_2BCl	2.1	75:25	81	63
10	Cy_2BCl	1.1	73:37	50	nd
11	Cy_2BCl	2.1	92: 8	96	31
12	Cy_2BBr	1.1	55:45	93	nd
13	**Cy_2BBr**	**2.1**	**91:9**	**94**	**80**

[a] Determined by HPLC using a Chiracel-OD column. [b] The minor diastereomer has the S-configuration at the quaternary center (structure not shown).

of lithium enolate **2a** with dibutylboron triflate (3.0 equiv) prior to condensation with benzaldehyde improved the syn/anti selectivity to 83:17 and also provided a significant increase in absolute stereocontrol. The syn/anti selectivity was further improved to 91:9 by switching from dibutylboron triflate to the more sterically demanding dicyclohexylboron triflate. The syn/anti selectivity in this reaction is very close to the *Z*/*E* ratio of the intermediate enolate (94:6 *Z*/*E*). However, the yield was only modest and the use of fewer equivalents of boron reagent resulted in reduced selectivity. A subsequent survey of dicyclohexylboron species showed that the bromide reagent afforded equivalent stereoselectivity but with improved and more reproducible yields. In addition, in the case of boron halides, only 2 equiv of reagent were necessary to achieve optimum stereoselectivity (vs 3 equiv for the corresponding triflates).

A survey with a series of aldehydes revealed that under the optimum reaction conditions (2.1 equiv of Cy_2BBr), high stereoselectivity and yields could be achieved with both aromatic and α,β-unsaturated aldehydes (Table 2). In the

Table 2. Aldol Reactions of α,α-Disubstituted Boron Enolates



entry	R^1	R^2	syn/anti[a]	de (syn) (%)[a,b]	yield (%)
1	Et	Ph−	91:9	94	80
2	Et	4-(MeO)Ph−	91:9	98	83
3	Et	4-BrPh−	93:7	99	81
4	Et	(*E*)-PhCH=CH−	91:9	99	63
5	Et	CH_2=C(Me)−	98:2	95	44
6	Et	(*E*)-MeCH=C(Me)−	91:9	91	95
7	allyl	Ph−	92:8	91	71
8	Bn	Ph−	91:9	99	91

[a] Determined by HPLC using a Chiracel-OD column. [b] The minor diastereomer has the S-configuration at the quaternary center (structure not shown).

latter case, higher yields are observed for β-substituted aldehydes. Some aldol products that have also undergone

(5) Crowden, C. J.; Patterson, I. *Org. React.* **1997**, *51*, 1.

(6) Although simple amides have not been reported to undergo enolboration, *N*-acyl isoxazolidines have been shown to be useful substrates. See: Abiko, A.; Liu, J.-F.; Wang, G.-Q.; Masamune, S. *Tetrahedron Lett.* **1997**, *38*, 3261.

(7) Haubenrieich, T.; Hünig, S.; Schulz, H.-J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 398. Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **1995**, *60*, 7006. Vicario, J. L.; Badia, D.; Dominguez, E.; Rodriguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754. For a recent example of transmetalation from a sodium enolate, see: Lang, F.; Zewge, D.; Song, Z. J.; Biba, M.; Dormer, P.; Tschaen, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2003**, *44*, 5285. For transmetalation from copper, see: Lipshutz, B. H.; Papa, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4580.

(8) α,α-Disubstituted boron enolates prepared by treatment of silyl enol ethers with dibutylboron triflate have been reported to give high diastereoselectivity in aldol condensations. See: Yamago, S.; Machii, D.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2098.

conjugate addition of the thiolate to a second equivalent of electrophile are observed in the addition to enals. However, under the S-benzylation conditions, these revert through a β-elimination process to give the desired final products. Although the reaction does not proceed with aliphatic aldehydes, the α,β-unsaturated aldehydes can provide access to these substrates through hydrogenation. Examination also showed that the reaction extends to enolates beyond the simple ethyl/methyl substitution pattern (entries 7 and 8).[9]

The syn/anti stereochemistry of the condensation products was initially determined by cleavage of the amide using lithium amidoborohydride[10,11] and formation of an acetonide from the resulting diol followed by NOE studies. Subsequently, an X-ray crystal structure was obtained of product **5a** (Figure 1). This confirmed the assignment of the major

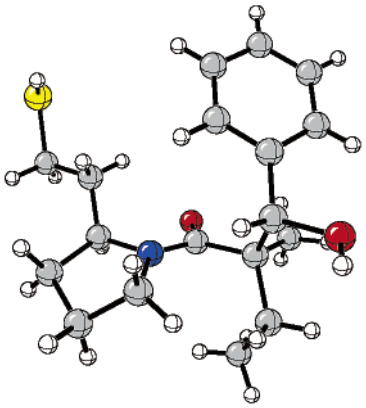


Figure 1. X-ray crystal structure of **5a**.

stereoisomer as the syn isomer and also showed that the absolute stereochemistry at the aldol was that depicted in structure **5a**. Although an acyclic transition state cannot be ruled out,[12] the syn stereochemistry is consistent with a chairlike transition state. In considering possible transition-state assemblies, we note that there is evidence for loss of conjugation of the nitrogen lone pair with the π-system in amide enolates.[13] Furthermore, a twisted geometry would minimize potential A^{1,3} strain between the nitrogen substituents and the groups at the α-positions on the enolate. If one considers envelope conformations of the pyrrolidine ring, two possible transition-state assemblies, shown in Figure 1, can be considered. In both of these structures, the enolate is held in a pseudoequatorial position to minimize steric interactions of the enolate with the pyrrolidine ring. Transition state **7a** is favored over **7b**, as the latter would have significant syn pentane interactions between the enolate oxygen and the pseudoaxial thioethylene chain.

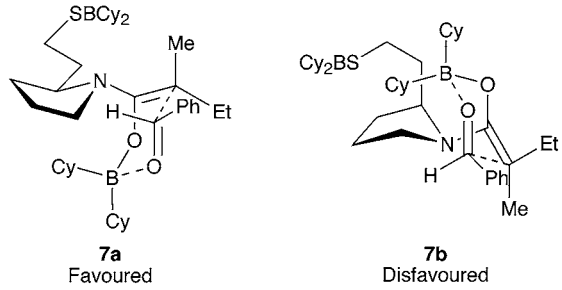


Figure 2. Potential transition state assemblies.

In conclusion, we have developed a diastereoselective method for the formation of quaternary carbon centers via an aldol process. The stereoselectivity of the reaction is controlled by a relatively rare lithium to boron transmetalation and provides excellent syn stereoselectivity as well as high diastereofacial selectivity.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, and X-ray crystallographic data for structure **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The corresponding anti aldol products could not be produced with high selectivity. Similar low selectivity was observed in the alkylations of (*E*)-enolates using this auxiliary system (ref 3).

(10) (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J.; *Tetrahedron Lett.* **1996**, *37*, 3623. (b) Myers, A. G.; Yang, B. H.; Chen. H.; Kopecky, D. J. *Synlett* **1997**, *5*, 457.

(11) Due to complications from retro-aldol processes, this reduction only works on the free (unbenzylated) thiols. These intermediates are easily isolated directly from the aldol reaction mixture.

(12) The pendant thioethylene chain presumably complexes to 1 equiv of the boron reagent, thus creating the possibility of an internal Lewis acid-directed aldol. For examples of external Lewis acids in boron aldols, see: (a) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173. (b) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747.

(13) (a) Kim, Y.-J.; Streitwieser, A.; Chow, A.; Fraenkel, G. *Org. Lett.* **1999**, *1*, 2069. (b) Pugh, J. K.; Streitwieser, A. *J. Org. Chem.* **2001**, *66*, 1334.