Chiral Lewis Acid-Hydroxylamine Hybrid Reagent for Enantioselective Michael Addition Reaction Directed Towards β-Amino Acids Synthesis

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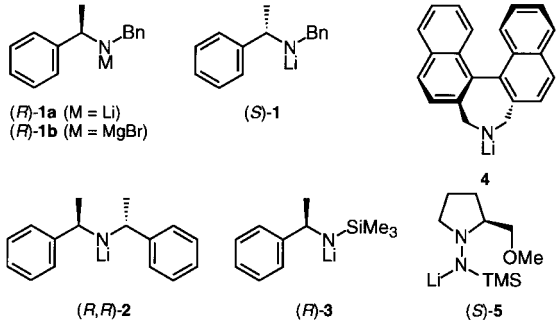
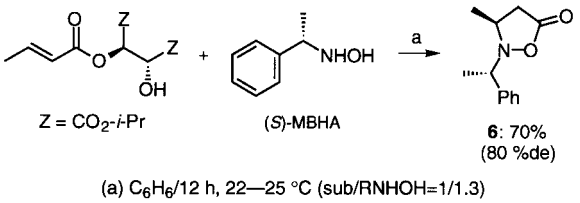
Abstract: We have succeeded in introducing a chiral auxiliary tethered by an appropriate metal into the hydroxy group of N-benzylhydroxylamine. The thus-obtained recyclable chiral reagent can act as an amine nucleophile to give chiral isoxazolidinones (up to 71% ee) as a β-amino acid synthon on the reaction with α,β-unsaturated carbonyl compounds.

Recent physiological interests in a type of oligopeptide in which β-amino acid units are incorporated as an important segment[1] have motivated synthetic organic chemists to develop methods for the synthesis of such amino acids in an optically pure form.[2] Among them Michael addition of chiral metal amides (**1**,[2a] **2**,[2b] **3**,[2c] **4**,[2d] **5**[2e]) to α,β-unsaturated esters seems to be straightforward and approved as a promising and efficient methods for chiral β-amino acid synthesis.

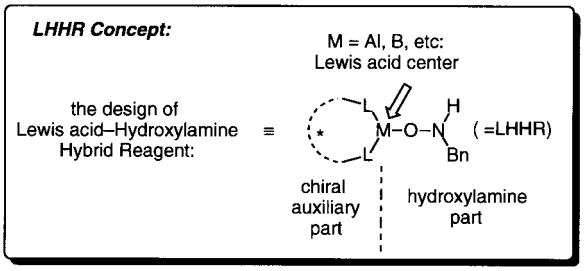


We have also been involved in this field and recently reported that Michael addition of chiral (N-α-methylbenzyl)hydroxylamine[3] [(*S*)-MBHA] to diisopropyl (*R*,*R*)-(O-crotonoyl)tartrate resulted in the formation of isoxazolidinone **6** in 70% yield with 80% de as a result of double stereo differentiation (Scheme 1).[4]

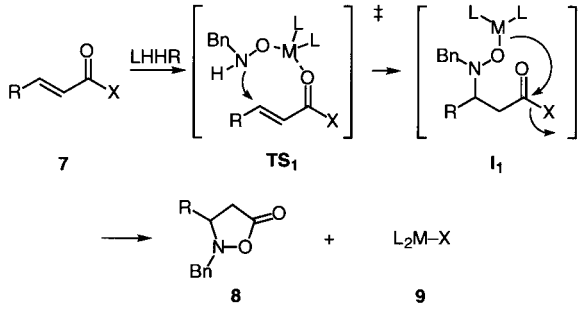


Scheme 1

However, there exists a common drawback in these asymmetric syntheses that the stereo centers of **1**—**4** or (*S*)-MBHA are to be destroyed when submitted to any deprotection protocol to generate free amines. Hence more economical chiral amine nucleophiles bearing removable and recyclable chiral auxiliaries are desirable.[5] This situation strongly motivated us to answer this problem and we were intrigued by the functionality of hydroxylamine again. If we can introduce the chiral auxiliary tethered by an appropriate metal into its hydroxyl group, the hydroxylamine can act as the chiral amine nucleophile as requested above. This idea is illustrated below and referred to as LHHR concept (Lewis acid-Hydroxylamine Hybrid Reagent) because the tethered atom (Al, B, etc.) can play the role of a Lewis acid as shown in Scheme 2. This communication describes the first example of such chiral hydroxylamine derivatives and reagent-controlled asymmetric synthesis of isoxazolidinones as a precursor for β-amino acids[6] via amino Michael addition processes.

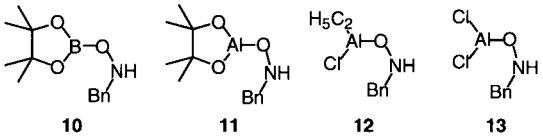


Scheme 2



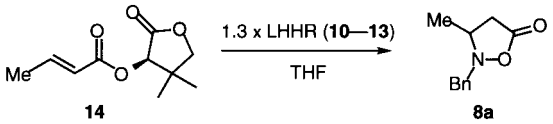
In the first place an achiral version of the LHHR (**10**—**13**) was prepared in a conventional manner as a clear solution in THF, which was directly used for the reaction with **14**.[7] For instance, **10** was prepared via two-step transformation involving the reaction of 2,3-dimethyl-2,3-butanediol (1 eq) with borane-THF complex (1 eq) (THF/0 °C, 30 min) and subsequent reaction with N-benzylhydroxylamine (BHA: 1 eq; 0 °C, 30 min). For NMR diagnosis the THF was removed under reduced pressure to give highly viscous gum, which was dissolved in $CDCl_3$: a cycle of evaporating the $CDCl_3$ and dissolving the residue in fresh $CDCl_3$ was followed three times to give the desired NMR sample. The structure of these LHHR was revealed on the basis of ^1H- and ^{13}C-NMR spectra of this sample.[8] It turned out that the LHHRs **10**—**13** exhibited 10 or more times as high reactivity as BHA itself when subjected to the reaction with **14** and the expected conjugated addition took place even at –78 — –50 °C to give the corresponding isoxazolidinones **8a** in high yield. The results pertinent to this reaction are summarized in Table 1.

Particularly interesting is that dialkoxy-*N*-benzylaminoxyborane (**10**) or aluminum (**11**) exhibited the highest reactivity as a Michael donor amine nucleophile among those examined because we can easily change these reagents into the corresponding chiral versions by replacing the dialkoxy moieties of **10** or **11** with those containing chiral centers or axes. Thus, chiral 2-boradioxolane- or 2-aluminadioxolane-type LHHRs



10 **11** **12** **13**

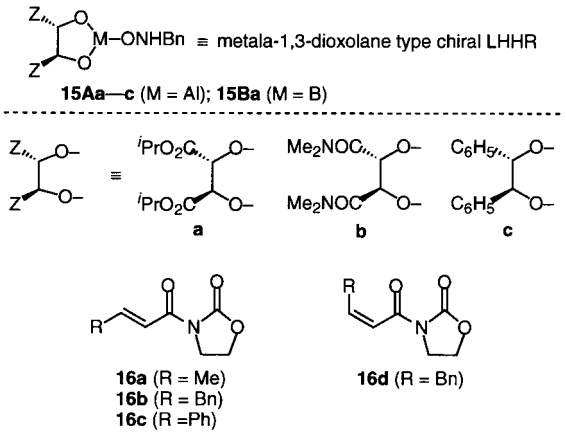
Table 1. Michael type addition of achiral LHHR (**10**—**13**) to α,β-unsaturated esters (**14**) in THF

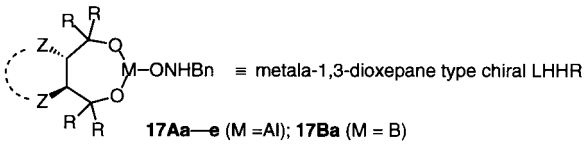


14 **8a**

Nu:	Temp/°C	Time/h	Yield/%
BHA	22	25	98
10	23	2	75
	–78 ~ –40	5	90
11	23	2	78
	–78 ~ –50	4	69
12	–64	2.5	82
13	–78 ~ 23	18	72

were prepared in a similar manner as that for achiral LHHRs employing well-known C_2-symmetric chiral diols such as diisopropyl tartrate, *N,N,N',N'*-tetramethyltartaramide, or trans-stilbenediol. The reactions of these chiral LHHRs with **14** or **16a** were, however, totally disappointing in terms of enantioselectivity: for instance the reaction of **15Ac** (1 eq) with **16a** (1 eq) (THF/22°C, 7 hr) gave **8a** in 58% yield and the enantioselectivity was 37% ee preferentially in (R)-configuration, which was the best result among them. Other chiral reagents of this class (**15Aa**,**b** and **15Bb**) downgraded the degree of % ee significantly (≤1% ee). Hence, we turned our attention to an aluminum- or boron-based dioxepane-type LHHR such as **17Aa—e**[9] or **17Ba** in the hope of significant improvement in the enantioselectivity because of the flexible nature of this type of LHHR as compared with the dioxolane-type LHHR (**15**). Much better results with regard to the enantioselectivity, though moderate (43—71% ee),[10] have been achieved when aluminum-based LHHRs such as **17Aa**, **17Ab**, or **17Ae** were reacted with **14** and **16**. These results are summarized in Table 2. On the other hand the boron reagent such as **17Ba** was far from satisfactory (<5% ee). This is also the case for other aluminum reagents such as **17Ac** and **17Ad** which led to very poor stereoselectivity (<5% ee).





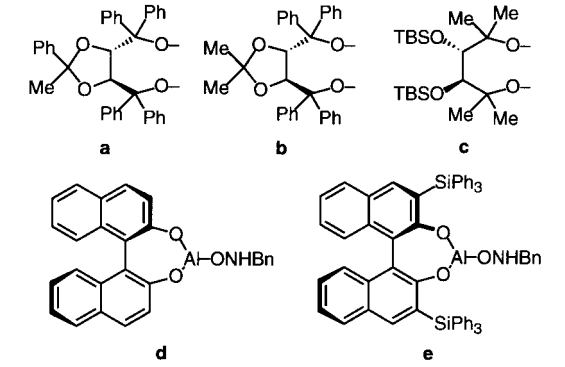
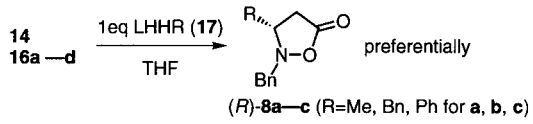


Table 2. Michael-type addition of chiral LHHR (**17**) to α,β-unsaturated ester (**14**) and imides (**16a**—**d**) in THF



Subst	LHHR	Temp/°C	Time/h	Yield/%[a]	ee%[b]
16a	**17Aa**	0 — 22	15	**8a** 71	63
	17Ab	0 — 22	15	**8a** 77	63
	17Ae	rt	21	**8a** 49	61
16b	**17Aa**	0 — 22	13	**8b** 59	71
16c	**17Aa**	0 — 22	20	**8c** trace	–
16d	**17Aa**	0 — 22	20	**8b** 40	43
14	**17Aa**	23	7	**8a** 71	43

a) Isolated yield by column chromatography; b) See ref. 10.

The potency of dioxepane-type chiral LHHR **17** probably stemmed from its conformationally more flexible nature than the dioxolane-type one **15**.[11] Since stereogenic centers or chiral axes of the diol ligands incorporated into **17** are located far from the nucleophilic nitrogen center, the two phenyl groups (**17a**,**b**) or substituted aromatic ring (**17e**) would play an important role in transmitting the chirality sphere to the reaction sphere. In addition, the conformationally flexible seven-membered rings in these LHHRs should be convenient to adjust transition state assembly as appropriate as possible. Also the degeneracy intrinsic to C_2-symmetry of these ligands is capable of minimizing diastereomeric turbulence leading to lower selectivity.[11] We are now making an effort to tune up this type of reagent-controlled asymmetric synthesis in terms of % ee by elaborating LHHR, which will be disclosed elsewhere.

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References and Notes

(1) For a recent review, see Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.

(2) (a) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *Synlett* **1993**, 461; (b) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2385; (c) Rico, C. J.; Dindmark, R. J.; Rogers, T. E.; Boby, P. R. *J. Org. Chem.* **1993**, *58*, 7948; (d) Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1992**, *57*, 2114; (e) Enders, D.; Wahl, F.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455; for enantio-selective synthesis of β-amino acids from β-amino-α,β-unsaturated esters based on catalytic hydrogenation with chiral metal complexes, see Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron*: *Asymmetry* **1991**, *2*, 543 and references cited therein.

(3) Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1995**, 1171: the reaction of methyl crotonate with (*S*)-MBHA has been reported so far from two laboratories: see Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron*, **1984**, *40*, 4363 (43% de) and Baldwin, S. E.; Aubé, J. *Tetrahedron Lett.* **1987**, *28*, 179 (60% de). Asymmetric syntheses of β-amino acid precursors using *O*-benzylhydroxylamine as a nucleophile have recently been developed: Cardillo, G.; Casolari, S.; Gentilucci, L.; Tomasini, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1848 (substrate control); Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc*. **1998**, *120*, 6615 (chiral Lewis acid catalysis).

(4) For the double stereo differentiation, see Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(5) The compound [(*S*)-**5**] developed by Enders is the first example of a chiral amine nucleophile in which the chiral auxiliary moiety is removable and recyclable. For this purpose, however, two chemical events after the conjugate addition have to be done and the yields of β-amino acids are rather low (16—58%).

(6) Isoxazolidinone represents one of the *N*,*O*-protected form of β-amino acids.

(7) The alkoxy moiety of **14** comes from optically pure pantolactone in the hope of obtaining optically active product. However, the product turned out to be 5% ee at most.

(8) Prepared by mixing borane·THF complex or trimethylaluminum with 2,3-dimethylbutane-2,3-diol followed by the addition of BHA. With regard to the boron reagent **10**, for instance, a narrow-lined simple NMR spectrum was observed: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.17 (s, 12H, 4 × CH_3), 3.98 (s, 2H, CH_2-Ar), 7.08 (s, 1H, NH), 7.24 (s, 5H, Ar-H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 24.5, 64.4, 82.6, 127.7, 128.3, 129.4, 136.0. On the other hand, for the corresponding aluminum reagent **11** the proton-NMR exhibited highly broadened signals at methyl, benzyl methylene linked to the nitrogen, and NH and aromatic proton regions and the ^{13}C-NMR as well, suggesting the occurrence of random association and disproportionation.

(9) For chiral diols involved in these reagents, see Narasaka, K.; Iwasawa, I.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc*. **1989**, *111*, 5340 (for **a**), Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954 (for **b**), Jacques, J.; Fouquey, C. *Org. Syn*. **1988**, *67*, 1 and Truesdale, L. K. *ibid*. **1988**, *67*, 13 (for **d**), and Maruoka, K.; Itoh, T.; Shirasaka, H.; Yamamoto, H. *J. Am. Chem. Soc*. **1988**, *110*, 310 and Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, H.; Yamamoto, H. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 2975 (for **e**). The diol ligand **c** was prepared through the reaction of dimethyl (*R*,*R*)-*O*-bis-(*tert*-butyldimethylsilyl)tartrate with CH_3MgBr (> 4 eq): neither EtMgBr nor PhMgBr reacted with this tartrate under the same reaction conditions as those for the CH_3MgBr.

(10) The absolute configurations and % ee's for isoxazolidinones **8** listed in Table 2 were determined by chemical correlation and/or NMR spectroscopy of Mosher esters. In the event, **8** was led to 3-(*N*-acylated)aminobutanoate through a series of reactions involving hydrogenolysis of the N—O bond to β-amino acid, *N*-acylation with acid halides [benzoyl chloride, Mosher acid chloride, or $(Boc)_2O$], and final esterification of a carboxylic acid group with $TMSCHN_2$. Since the optical rotation values of methyl (3*S*)-3-(*N*-benzoyl)aminobutanoate (Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824) and (3*R*)-4-phenyl-3-(*N*-*tert*-butoxycarbonyl)aminobutanoic acid (Seki, M.; Matsumoto, K. *Tetrahedron Lett*. **1996**, *37*, 3165) are known, **8a** and **8b** were able to be correlated with these compounds. The absolute configuration of **8c**, however, was merely estimated on the analogy of the relationship between the absolute structure and sign of rotation of **8a** and **8b.** It turned out that the absolute configuration of **8b** obtained from **16d** of (*Z*)-geometry was the same as that obtained from the (*E*)-isomer **16b** with a preference for *R*-configuration.

(11) For this discussion, see Noyori, R., *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, 1994, pp 47–49.