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New Isoxazolidine-based Chiral Auxiliaries for Asymmetric Syntheses

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Abstract: New chiral auxiliaries based on the bicyclic-isoxazolidine skeleton, 3-oxa-2,7-diazabicylo[3,3,0]octane derivatives, were synthesized in 60~80% overall yields from amino acids. Asymmetric alkylation and boron aldol reaction using the auxiliaries proceeded with high selectivities. "Carboxylic amide" has been used for the asymmetric boron-mediated aldol reaction for the first time.
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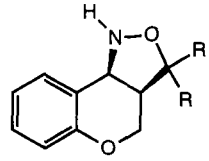
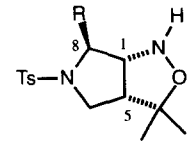
Recently we have shown that benzopyrano-isoxazolidines **1** serve as effective chiral auxiliaries in several asymmetric syntheses.[1] These auxiliaries have exhibited advantageous features compared to the conventional chiral auxiliaries, such as oxazolidinones or camphorsultam: 1) Acylation of the auxiliaries can be executed readily with the aid of acid chloride and amine or DCC condensation. 2) High reactivity of the "amide enolate" enabled direct elongation of the β-branched alcohols with a "reduced propionate" unit. 3) The reaction products were converted to the corresponding chiral alcohols, aldehydes and ketones with the recovery of the auxiliaries with a single operation. Further studies on the isoxazolidine-based chiral auxiliaries have led to the development of new chiral bicyclic-isoxazolidine auxiliaries, 3-oxa-2,7-diazabicyclo[3,3,0]octane derivatives **2**. Here we disclose the synthesis and applications of **2** to several asymmetric reactions.



1

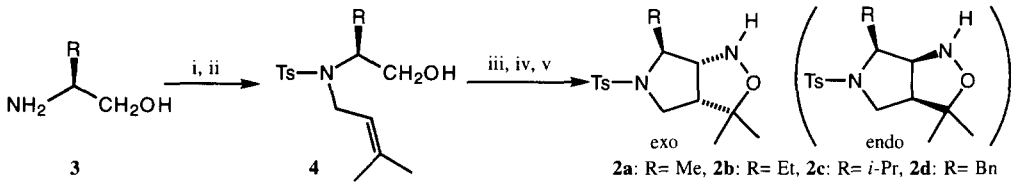


2

The framework of **2** was chosen on the basis of the characteristic feature exhibited by the bicyclo[3,3,0]octane structure. The enantiomerically pure reagents **2a~2d** were synthesized from the corresponding amino acids (Scheme 1). Thus, the chemoselective functionalization of the amino group of β-aminoalcohols[2] was achieved *via* consecutive tosylation (TsCl, Et_3N in CH_2Cl_2) and prenylation (prenyl chloride, Cs_2CO_3, in CH_3CN) in quantitative yields to give **4**. Oxidation of the alcohols to the labile aldehydes without racemization was best achieved with Swern oxidation. The aldehydes, without purification, were converted to the corresponding oxime as a mixture of isomers. The isoxazolidine skeleton was constructed by

the $ZnCl_2$ catalyzed [2+3] cycloaddition reaction,[3,4] the stereoselectivity being varied from exo:endo=5:1 for **2a** (R=Me) to exo:endo=20:1 for **2c** (R=*i*-Pr).[5] The major exo isomers were isolated by crystallization from a reaction mixture in 60~80 % overall yield from **4**.[6] The stereochemistry of the major bicyclic isoxazolidine was determined by the coupling constants of the C1-C5 and C1-C8 protons,[7] and finally established by x-ray analysis of an alkylation product. This synthesis does not require the purification of any synthetic intermediates, and is easily scaled up to several decagrams.

Scheme 1

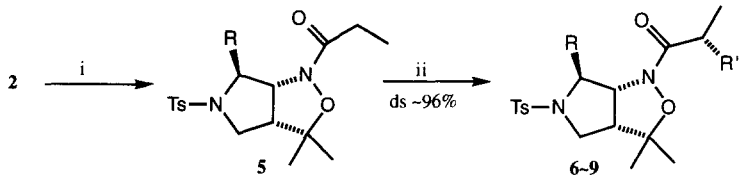


3 **4** **2a**: R= Me, **2b**: R= Et, **2c**: R= *i*-Pr, **2d**: R= Bn

i) TsCl, Et_3N, CH_2Cl_2; ii) prenyl chloride, Cs_2CO_3, CH_3CN, reflux; iii) Swern oxidation; iv) NH_2OH-HCl. $NaHCO_3$, aqEtOH; v) $ZnCl_2$ (cat), benzene, reflux

Because of the importance of the asymmetric alkylation methodology, efforts still continue to explore reagents with both high reactivity and selectivity.[8] The asymmetric alkylation using **2** was found to be very efficient. Acylation of **2** was readily achieved with propionyl chloride and triethylamine in quantitative yield. The alkylation of **5** with various alkylating reagents, including cyclohexylmethyl triflate, proceeded with excellent selectivities (ds~96%) in high yields under the standard conditions (Scheme 2, Table 1).[1a,d] The stereochemistry of the newly formed stereogenic center was determined after conversion to the corresponding chiral alcohols (*vide infra*), and x-ray analysis of **6c**. Consequently, **ent-5b** (R=Et) and **5c** (R=*i*-Pr) could be selected as enantiomeric reagents.[9]

Scheme 2



2 **5** **6~9**

6: R'= CH_2=$CHCH_2$-
7: R'= $PhCH_2$-
8: R'= *c*-$HexCH_2$-
9: R'= *n*-Hex-

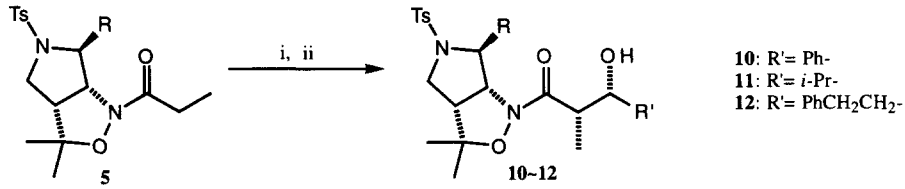
i) EtCOCl, Et_3N, CH_2Cl_2, ~100%; ii) R'-X, KHMDS

Table 1. Asymmetric Alkylation of the Isoxazolidine Reagent **5**

Entry	Reagent (**5**)	R'-X	Product (yield %)	mp (°C)	$[\alpha]_D$ (conc, in $CHCl_3$)
1	**5c**	allyl bromide	**6c** (91)	127~128	188.3 (1.54)
2	**5c**	benzyl bromide	**7c** (95)	125~126	124.3 (1.75)
3	**5c**	*c*-$HexCH_2OTf$	**8c** (94)	99~100	152.8 (1.17)
4	**5c**	*n*-HexOTf	**9c** (92)	66~68	162.7 (1.19)
5	**ent-5b**	benzyl bromide	**ent-7b** (97)	153~154	-170.1 (1.19)
6	**ent-5b**	*c*-$HexCH_2OTf$	**ent-8b** (90)	155~156	-195.8 (1.04)
7	**ent-5b**	*n*-HexOTf	**ent-9b** (91)	104~105	-207.3 (1.09)

Recently, the boron aldol methodology has been expanded to carboxylic esters and amides,[10] and a practical solution to the *anti*-selective asymmetric aldol reaction has been devised using a chiral carboxylic ester.[11] The boron-mediated aldol reaction of "amide" **5** was found to proceed in high yields with excellent *syn*-selectivities (Scheme 3, Table 2). Thus, treatment of **5** with 1.5 equiv of dicyclopentylboron triflate (or dicyclohexylboron triflate in some cases, see Table 2) and 1.7 equiv of triethylamine at -78 ℃ for 2 h, followed by the reaction with aldehydes (-78 ℃ 1 h, 0 ℃ 1 h) afforded the corresponding *syn*-aldol products in high yields (>90%), only less than 2% of the corresponding *anti*-isomers being detected in the reaction mixture. The diastereofacial selectivity of the *syn*-isomer was >96:4 and the major product was assigned to be **10** (or **11**, **12**) (*vide infra*). To our best knowledge, this is the first example of the boron-mediated asymmetric aldol reaction of "carboxylic amide".[10]

Scheme 3



i) $R"_2BOTf$, Et_3N, CH_2Cl_2, -78°C, 2 h; ii) R'CHO, -78°C 1 h, 0°C 1 h.

Table 2. Asymmetric Boron-Mediated Aldol Reaction of the Isoxazolidine Reagent **5**

Reagent (**5**)	R"	Aldehyde	Product (yield)	ds (syn)	mp (°C)	$[\alpha]_D$ (conc, in $CHCl_3$)
5c	*c*-Pen	PhCHO	**10c** (90 %)	>99: 1	70~72	156.0 (1.00)
5c	*c*-Hex	*i*-PrCHO	**11c** (92)	99: 1	175~176	143.6 (1.02)
5c	*c*-Pen	$PhCH_2CH_2CHO$	**12c** (90)	>99: 1	118~119	137.8 (0.96)
ent-5b	*c*-Hex	PhCHO	**ent-10b** (92)	>98: 2	60~62	-138.7 (1.30)
ent-5b	*c*-Hex	*i*-PrCHO	**ent-11b** (93)	96: 4	121~123	-140.7 (1.17)
ent-5b	*c*-Hex	$PhCH_2CH_2CHO$	**ent-12b** (90)	97: 3	90~91.5	-190.6 (1.07)

One of the most important features of the isoxazolidine auxiliaries is one-step transformation of the reaction products to the chiral alcohols, aldehydes or ketones. For the reduction to alcohols, $LiBH_4$ with 3 equiv of MeOH in THF (rt, 14 h) was found to be superior to the other reaction conditions.[12] The chiral alcohols were obtained in high yields (80~90%) without loss of the stereochemical integrity, concomitantly the auxiliary being recovered over 90% yields. The absolute stereochemistry of the alcohols were determined by the comparison of the optical rotation value with those of the authentic specimens. The conversion to the chiral aldehydes and ketones were achieved with $LiEt_3BH$ (in THF, rt, 2 h)[12] or alkyl lithium (MeLi in ether, 0°C, 2 h), respectively, in 85~95% yields.[13]

In summary, we have developed new chiral auxiliaries based on the bicyclic-isoxazolidine skeleton. They could be accessible more easily than the previously reported benzopyrano-isoxazolidine auxiliaries and showed excellent selectivities for the boron-mediated asymmetric *syn*-selective aldol reaction. Further studies on other asymmetric reactions using the isoxazolidine auxiliaries are in progress.[14]

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4. Attempted Bu_2SnO catalyzed nitrone formation with 5-hydroxypentanal oxime afforded the unexpected ene-products. Abiko, A. *Chemistry Letters*, **1995**, 357.
5. For preparative purpose, the oxime was used as a mixture of isomers. The major isomer of the oxime cyclized with high selectivity (~20:1), but the minor isomer less selectively (~5:1). The selectivities for the cyclization to **2b** and **2d** were exo:endo=10:1.
6. **Typical procedure of the synthesis of 2.**
   Synthesis of **2c**: A mixture of N-tosylvalinol (53 g), 1-chloro-3-methyl-2-butene (29 ml) and Cs_2CO_3 (75 g) in acetonitrile (500 ml) was heated under reflux for 2 h. After being cooled to room temperature, the salt was filtered and washed with CH_2Cl_2. Concentration of the filtrate and washings afforded **4c** (70 g, ~100%), which was used for the next reaction without purification. To a stirred solution of DMSO (30 ml) in CH_2Cl_2 (800 ml) was added oxalyl chloride (25 ml) at -78 °C. After 10 min, a solution of **4c** (70 g) in CH_2Cl_2 (300 ml) was added dropwise, followed by Et_3N (85 ml), then the whole mixture was warmed to 0°C. Usual aqueous work up afforded crude aldehyde, which was used for the next reaction immediately. To a solution of the aldehyde in 50% aqueous EtOH (600 ml) was added $NaHCO_3$ (70 g) and hydroxylamine hydrochloride (35 g). The mixture was stirred at room temperature for 16 h and concentrated. Extractive work up with CH_2Cl_2 afforded the corresponding oxime as a mixture of isomers, which was directly used for the cyclization reaction. A solution of crude oxime and $ZnCl_2$ (3 g) in benzene (600 ml) was heated under reflux for 6 h. The cooled reaction mixture was washed with 5 % ammonia water, H_2O and saturated brine, successively. Crude bicyclic-isoxazolidine was crystallized from ethyl acetate and hexane to give **2c** (53 g, 76%). More **2c** (5 g, 7%) and the corresponding endo isomer (2.5 g) could be isolated by chromatography.
   Selected physical and chiroptical properties of 2: 2a (R=Me) mp. 121-122°C, $[\alpha]_D$ -73.6 (c 2.18, $CHCl_3$); **ent-2b** (R=Et) mp. 74-75°C, $[\alpha]_D$ 53.7 (c 0.98, $CHCl_3$); **2c** (R=*i*-Pr) mp. 128.5-130°C, $[\alpha]_D$ -46.2 (c 1.03, $CHCl_3$); **2d** (R=Bn) mp. 88-89°C, $[\alpha]_D$-17.4 (c 0.90, $CHCl_3$).
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9. **Ent-5b** (R=Et) mp. 60-62°C, $[\alpha]_D$ -169.9 (c 1.10, $CHCl_3$); **5c** (R=*i*-Pr) mp. 109.5-111°C, $[\alpha]_D$ 177.6 (c 1.01, $CHCl_3$).
10. Abiko, A.; Liu, J.-F.; Masamune, S. *J. Org. Chem.* **1996**, *61*, 2590.
11. Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* in press.
12. The corresponding tertiary amines were formed <5%.
13. For the aldol products (**10~12**), β-hydroxy group was protected as methoxymethyl ether before reaction.
14. As preliminary experiments Horner-Emmons reaction with 4-*tert*-butylcyclohexanone (see ref 1c) and Lewis acid mediated Diels-Alder reaction of the acrylate derivative with cyclopentadiene were found to proceed with high selectivities.

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