Diastereopure Preparation of α-Benzotriazolyl 1-Azacycloalka[2,1-*b*][1,3]-oxazines and their Application as Versatile Chiral Precursors

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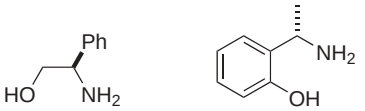
Abstract: A group of diastereopure α-benzotriazolyl 1-azacycloalka[2,1-*b*][1,3]oxazines were prepared from non-racemic Betti base and they were employed as the versatile precursors for the preparation of chiral ligands and chiral substituted azacyclics with significant advantages in the stereoselectivity.

Key words: Betti base, chiral [1,3]oxazines, chiral ligands, chiral substituted azacyclics

Although a number of chiral amino-hydroxy compounds have been used as excellent ligands in the metallic ion catalyzed asymmetric reactions,[1] only a few of them could be employed as chiral auxiliaries, such as 2-phenylglycinol (**1**)[2–4] and 2-(1-aminoethyl)phenol (**2**)[5] (Figure 1), thanks to their ability to dissociate the benzyl residues from the products under a variety of conditions.

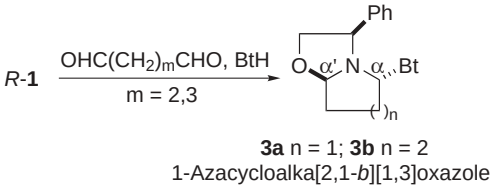


R-**1** *S*-**2**

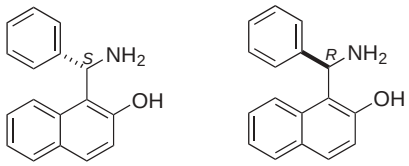
Figure 1

Recently, Katritzky reported an elegant method by using *R*-(–)-2-phenylglycinol (*R*-**1**) as an auxiliary to synthesize chiral substituted azacyclics as well as structurally related natural products.[3] As illustrated in Scheme 1, its key strategy is to construct α-benzotriazolyl 1-azacycloalka[2,1-*b*][1,3]oxazole (**3**) by a condensation between *R*-**1** and a dial in the presence of BtH (benzotriazole), followed by an alkylation at the newly formed chiral carbon (α- or α′-positions) separately. However, some limitations for this method have been observed. For example, **3b** cannot be obtained as a single diastereoisomer and its alkylation suffered from low yields and less stereoselectivity.

Betti base contains a 1,3-benzylamino-hydroxy skeleton and its enantiomers (*S*-**4** or *R*-**4**) (Figure 2) should be excellent chiral auxiliaries. To our surprise, none of them has been used for this purpose and even most of the reported chiral N-alkylated derivatives of Betti base did not derived from them.[6] This unusual phenomenon may result from the fact that Betti base normally is not stable and reversed Mannich reaction occurs spontaneously in the usage and storage.



Scheme 1



S-**4** *R*-**4**

Figure 2

In our recent work, non-racemic Betti base was used stably and conveniently as its salt of tartaric acid.[7] Herein, we report a diastereopure preparation of α-benzotriazolyl 1-azacycloalka[2,1-*b*][1,3]oxazines (**5a**–**c**) derived from *S*-**4**, as well as their application as a group of newly chiral precursors to the preparation of chiral ligands and chiral azacyclics.

Following Katritzky's procedure, a mixture of *S*-**4** [as a salt of L-(+)-tartaric acid], pentane-1,5-dial and BtH in CH_2Cl_2 was stirred at 0 °C for 5 hours. As expected, the diastereopure α-benzotriazolyl 1-piperido[2,1-*b*][1,3]-oxazine (**5b**) was obtained in 91% yield (Scheme 2). Its diastereopurity was confirmed by the benzyl proton as a singlet peak at δ = 5.28 ppm in the ^{1}H NMR spectroscopy and the two newly formed chiral carbons are *R*-configurations deduced from its single crystal X-ray diffraction analysis. Similarly, replacement of pentane-1,5-dial by butane-1,4-dial and hexane-1,6-dial, the five- and seven-membered azacyclic analogues **5a** and **5c** were obtained respectively in high yields (93% and 91%) and diastereoseletivities.

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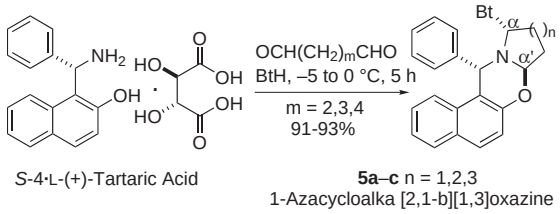
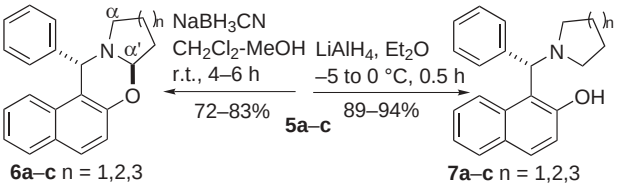


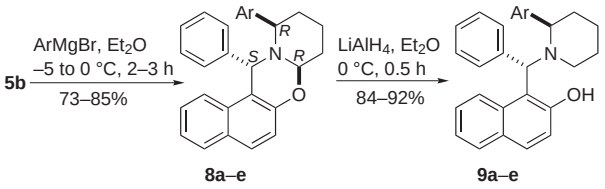
Scheme 2

The oxazines **5a**–**c** have completely different structures and stereochemistry compared to oxazoles **3a**,**b**. We observed that the C-O bond in α′-position of oxazine **5** is more stable than that of oxazole **3** probably because its oxygen atom comes from the phenol. Thus, a selective cleavage of C-Bt bond was achieved by treatment of **5a**–**c** with $NaBH_3CN$ in CH_2Cl_2–MeOH at room temperature for 4–6 hours and the corresponding **6a**–**c** were obtained in 72–83% yields (Scheme 3). However, both C-Bt and C-O bonds were cut clearly via $LiAlH_4$ within half hour at 0 °C to afford **7a**–**c** in high yields (89–94%), which have been proved to be excellent chiral ligands in the asymmetric addition of $ZnEt_2$ to aldehydes.[7] The improved procedures are particularly suitable for the bulky synthesis of **6a**–**c** and **7a**–**c**.



Scheme 3

By using compound **5b** as a model, the arylation at its α-position was carried out by treatment it with ArMgBr to give a series of diastereopure compounds **8a**–**e** in good yields. Although the products are consistent with that of **3b**, the current procedure can be performed under very mild conditions (Scheme 4, Table 1) rather than at –78 °C for 12 hours.[3b] The arylated carbons were assigned as *R*-configurations deduced from the single crystal X-ray diffraction analysis of **8e**. Reductions of **8a**–**e** via $LiAlH_4$ yielded a group of highly hindered 1,3-amino-phenols **9a**–**e**, which could serve as potential chiral ligands in the catalytic asymmetric reactions.

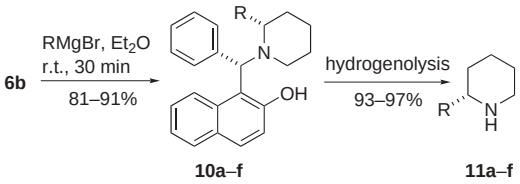


Scheme 4

In agreement with our expectation, the alkylation at the α′-position in **6b** with RMgBr yielded highly diastereopure **10a**–**f** in satisfactory yields (Scheme 5, Table 2). The configurations of the chiral carbons were assigned by the single crystal X-ray diffraction analysis of **10a**. Hydrogenolysis of **10a**–**f** afforded corresponding chiral 2-alkylpiperidines including the natural product *R*-(–)-coniine (**11c**). Since the similar compounds prepared by the alkylation of **3b** suffered seriously from the low yields and lower distereoselectivities,[3b] our procedure afforded a valuable alternative to the existed methods.

Table 1 Reductions of Compounds **8a**–**e** with $LiAlH_4$

8,**9**	Ar	Yield of **8** (%)	Yield of **9** (%)
a	C_6H_5	84	86
b	4-MeC_6H_4	77	85
c	4-ClC_6H_4	81	84
d	4-PhC_6H_4	73	83
e	1-Naphthyl	85	92



Scheme 5

Table 2 Hydrogenolysis of Compounds **10a**–**f**

10,**11**	R	Yield of **10** (%)	Yield of **11** (%)
a	Me	85	93
b	Et	81	94
c	*n*-Pr	81	94
d	*n*-$C_{12}H_{25}$	91	97
e	CH_2=$CHCH_2$	92	93 (**11c**)
f	Bn	86	96

In conclusion, a group of diastereopure α-benzotriazolyl 1-azacycloalka[2,1-*b*][1,3]oxazines **5a**–**c** were prepared from non-racemic Betti base and they were employed as versatile chiral precursors for the preparation of chiral ligands and chiral azacyclics with significant advantage in the stereoselectivity. This may result from the fact that an unique four-atom plane defined by C1 and C2 on the naphthalene as well as the attached carbon and oxygen occurs in **5a**–**c**, which keeps each molecule in a very rigid conformation.

Acknowledgment

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References

(1) For reviews, see: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (c) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757.

(2) (a) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383. (b) Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1997**, *62*, 6704. (c) Francois, D.; Poupon, E.; Lallemand, M.-C.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 3209. (d) Blanchet, J.; Bonin, M.; Nicouin, L.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 6423. (e) Poupon, E.; Luong, B.-X.; Chiaroni, A.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 7208. (f) Cutri, S.; Micouin, L.; Husson, H.-P.; Chiaroi, A. *J. Org. Chem.* **2003**, *68*, 2645.

(3) (a) Katritzky, A. R. *J. Heterocycl. Chem.* **1999**, *36*, 1501. (b) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699. (c) Kartritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979.

(4) (a) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814. (b) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36. (c) Munchof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 3189. (d) Munchof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084. (e) Munchof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7086. (f) Munchof, M. J.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607. (g) Kamata, K.; Agata, I.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 3113. (h) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413.

(5) (a) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron. Lett.* **1999**, *40*, 739. (b) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 465. (c) Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett.* **2001**, *3*, 193. (d) Ito, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469.

(6) (a) Cardelliccnio, C.; Ciccarella, G.; Naso, F.; Schingaro, E.; Scordari, F. *Tetrahedron: Asymmetry* **1998**, *9*, 3667. (b) Cardelliccnio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685. (c) Bernardinelli, G.; Fernandez, D.; Gosmini, R.; Meier, P.; Ripa, A.; Schupfer, P.; Treptow, B.; Kundig, E. P. *Chirality* **2000**, *12*, 529. (d) Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3361. (e) Liu, D.-X.; Zhang, L.-C.; Wang, Q.; Da, C. S.; Xin, Z.-Q.; Wang, R.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2001**, *3*, 2733. (f) Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759. (g) Wang, Y.; Li, X.; Ding, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1291. (h) Ji, J.; Qiu, L.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589.

(7) (a) Lu, J.; Xu, X.; Wang, C.; He, J.; Hu, Y.; Hu, H. *Tetrahedron Lett.* **2002**, *43*, 8367. (b) Lu, J.; Xu, X.; Wang, S.; Wang, C.; Hu, Y.; Hu, H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2900.