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Synthesis of chiral ligands derived from the Betti base and their use in the enantioselective addition of diethylzinc to aromatic aldehydes

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Abstract—A novel procedure for selective direct *N*,*N*-alkylation of the chiral Betti base was developed, and a new family of chiral ligands, (*S*)-1-(α-cycloaminobenzyl)-2-naphthols, were prepared. The ligands with five- and six-membered cyclic amines showed highly efficient asymmetric induction in the addition of diethylzinc to aromatic aldehydes in 93–96% yields and 91–99% ee.

Chiral 1,2- and 1,3-amino-hydroxy compounds have proved to be a very efficient class of ligands in a variety of asymmetric syntheses catalyzed by metallic ions. Most have been derived from a few readily available natural products.[1] To increase the understanding of asymmetric reactions, the design and synthesis of chiral ligands from non-natural resources is essential research in the field of synthetic chemistry.[2] Therefore, chiral amino-phenols are gaining increasing importance.[3]

Racemic 1-(α-aminobenzyl)-2-naphthol (**1**, the Betti base) is available in bulk and was resolved into its enantiomers, (*S*)-**1** and (*R*)-**1**, early last century (Chart 1).[4] However, they were never employed as chiral ligands in asymmetric catalysis until Cardellicchio's work in 1998, in which the asymmetric addition of diethylzinc to benzaldehyde was achieved with ees as high as 99%.[3b,c] Similar to other reported amino-hydroxy ligands, tertiary amines gave better results than primary and secondary amines in most cases.[3c,f]

No suitable method exists for regioselective *N*-alkylation of Betti base **1**, its chiral *N*,*N*-dialkyl derivatives being prepared by resolving the corresponding racemic isomers[3b,c,5] or by condensation with chiral amines[3e–g] rather than directly from (*S*)-**1** or (*R*)-**1**. Herein, we would like to report a novel procedure for selective direct *N*-alkylation of (*S*)-**1**, by which a series of chiral cycloamine–phenol ligands **4a**–**c** were prepared. In the asymmetric addition of diethylzinc to aromatic aldehydes, these ligands showed highly efficient asymmetric induction to give the products in up to 96% yield and 99% ee.

All of our initial attempts using published procedures for selective direct *N*-alkylation of (*S*)-**1** failed. For example, pentanediol was obtained quantitatively from 1,5-pentanedial and $NaBH_4$–H_2SO_4,[3a] or a mixture of *O*-alkylated products was produced using 1,5-dihalopentane and a variety of bases.[6]

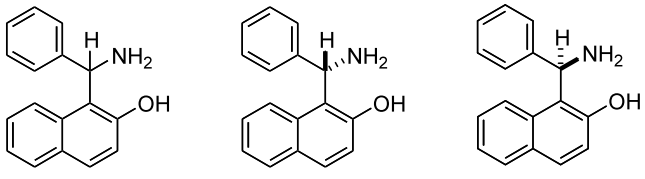
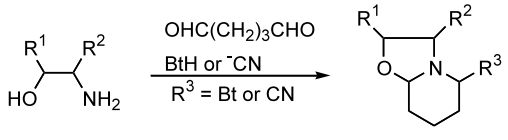


Chart 1.



Scheme 1.

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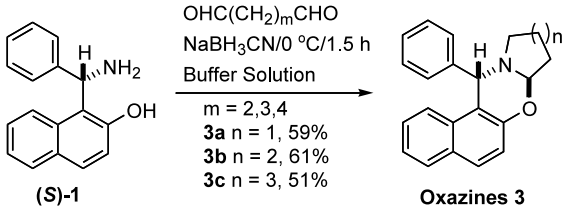
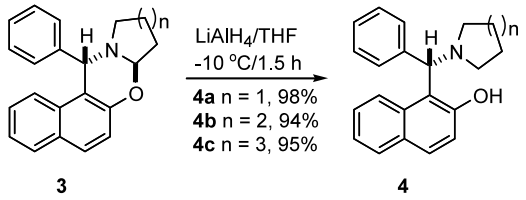


Scheme 2.



Scheme 3.

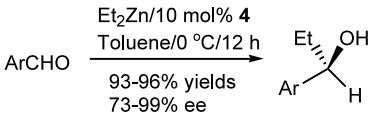
However, the *N*-cyclization of a 1,2-amino-alcohols with bis-aldehydes attracted our attention (Scheme 1). These procedures usually proceed in the presence of a nucleophilic agent, such as a benzotriazole[7] or ^{-}CN,[8] to yield substituted piperido[2,1-*b*]oxazolidine derivatives **2** (Scheme 1). The mechanism strongly suggests that an unsubstituted product could be obtained by using H^{-} as a nucleophilic species.

We found that the unsubstituted piperido[2,1-*b*]oxazine derivative **3b** could be obtained in 61% yield when (*S*)-**1** was treated with 1,5-pentanedial in the presence of $NaBH_3CN$ in a buffer solution (aqueous EtOH solution of Na_2HPO_4–KH_2PO_4). Similarly, **3a** (59%) and **3c** (51%) were obtained smoothly by using 1,4-butanedial and 1,6-hexanedial, respectively (Scheme 2).

As shown in Scheme 3, when compound **3b** was treated with $LiAlH_4$, the C–O bond was cleaved selectively to yield the desired cycloamine–phenol **4b**. Although room temperature benefits the reaction time (30 min), it decreases the optical purity of the product. Thus, **3b** was converted into **4b** in 94% yield without any loss of enantiomeric excess at −10°C in 1.5 h. Similarly, **3a** and **3c** gave the corresponding cleavage products, **4a** and **4c** in excellent yields.

The asymmetric addition of $ZnEt_2$ to benzaldehyde was tested in toluene with 10 mol% of the chiral ligands **4a**–**c** to give the products in 93–96% yields and 73–99% ee (Scheme 4). As shown in Table 1, the size of the cyclic amine in ligands **4a**–**c** plays an important role in the asymmetric induction.

In summary, a novel procedure for selective direct *N*,*N*-alkylation of the chiral Betti base was developed and a new family of chiral ligands (*S*)-1-(α-cycloaminobenzyl)-2-naphthols were prepared. Their asymmetric induction was tested primarily in the addition of diethylzinc to aromatic aldehydes to give the products in up to 96% yield and 99% ee. Further applications of these ligands in asymmetric catalysis are being investigated.



Scheme 4.

Table 1. Enantioselective addition of $ZnEt_2$ to aromatic aldehydes catalyzed by ligands **4a**–**c**

Entry	Ar	Ligand	Y (%)[a]	% ee[b]
1	C_6H_5–	**4b**	95	98 (*R*)
2	4-$CH_3C_6H_4$–	**4b**	95	98 (*R*)
3	4-$CH_3OC_6H_4$–	**4b**	96	95 (*R*)
4	2-ClC_6H_4–	**4b**	95	91 (*R*)
5	4-FC_6H_4–	**4b**	96	98 (*R*)
6	4-$CF_3C_6H_4$–	**4b**	94	97 (*R*)
7	C_6H_5–	**4a**	93	99 (*R*)
8	C_6H_5–	**4c**	93	73 (*R*)

[a] Isolated yields.
[b] Determined by chiral GC (10% permethylated β-CD).

Acknowledgements

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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.
2. For selected recent reports, see: (a) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970; (b) Bolm, C.; Muniz-Fernandez, K.; Seger, A.; Raabe, G.; Gunther, K. *J. Org. Chem.* **1998**, *63*, 7860; (c) Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969; (d) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108; (e) Nugent, W. A. *Org. Lett.* **2002**, *4*, 2133.
3. (a) Vyskocil, S.; Jaracz, S.; Smrcina, M.; Sticha, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7727; (b) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Schingaro, E.; Scordari, F. *Tetrahedron: Asymmetry* **1998**, *9*, 3667; (c) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685; (d) Bernardinelli, G.; Fernandez, D.; Gosmini, R.; Meier, P.; Ripa, A.; Schupfer, P.; Treptow, B.; Kundig, E. P. *Chirality* **2000**, *12*, 529; (e) Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3361; (f) 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; (g) Cimarelli, C.; Mazzaanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759.

4. (a) Betti, M. *Gazz. Chim. Ital.* **1906**, *36 II*, 392; (b) Betti, M. *Org. Synth.* **1941**, *Coll. Vol. I*, 381.
5. Brode, W. R.; Littman, J. B. *J. Am. Chem. Soc.* **1930**, *52*, 5056.
6. (a) Juanes, O.; Rodriguez-Ubis, J. C.; Brunet, E.; Pennemann, H.; Kossenjans, M.; Martens, J. *Eur. J. Org. Chem.* **1999**, 3323; (b) Reddy, K. S.; Sola, L.; Moyana, A.; Pericas, M. A.; Riera, A. *Synthesis* **2000**, 165.
7. Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979.
8. Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.