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A parallel preparation of a bicyclic *N*-chiral amine library and its use for chiral catalyst screening

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Abstract—A parallel library of optically active bicyclic tertiary amines bearing *N*-chiral bridgehead nitrogen atoms was readily prepared by condensation of primary amines, cyclic amino acids and aldehydes. The enantiocontrolling ability of each of the library members was examined for the asymmetric alkylation of benzaldehyde with diethylzinc, and (3*R*,6*R*,7a*S*)-(2,3-diphenyl-6-hydroxy)hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one, which contains a β-amino alcohol unit, showed high enantioselectivity.

Functionally rich nitrogen heterocycles occupy a prominent position in organic chemistry as both useful synthetic reagents and molecules of biological interest. In particular, optically active bicyclic amines bearing chiral sp^3-nitrogen atoms at their bridgehead positions (e.g. the Cinchona alkaloid family) find widespread use as chiral reagents for a variety of organic transformations.[1] With a view to obtaining enantioselective reactions, we are particularly interested in a diversity-based approach[2] to *N*-chiral tertiary amines possessing enantiocontrolling abilities. Herein we report a simple construction of a library of *N*-chiral bicyclic tertiary amines **1** from primary amines (**2**), cyclic amino acids (**3**), and aldehydes (**4**) and its preliminary use for screening of chiral catalysts for the asymmetric alkylation of benzaldehyde with diethylzinc in which the β-amino alcohol unit is identified as a lead structure of enantioselective catalysts.[3]

A typical experiment for the preparation of the bicyclic amine analogues is shown in Scheme 1 in which aniline, hydroxyproline and benzaldehyde were used as starting components, and the trifluoroacetyl group as the protecting group. Thus, L-hydroxyproline (**3***{2}*) was treated with trifluoroacetic anhydride in chloroform at 0°C for 2 h and then concentrated. The resulting crude material was dissolved in toluene and PCl_5 was added to the solution at 0°C. After 90 min, aniline (**2***{2}*) and triethylamine were added to the solution at room temperature. The reaction mixture was stirred for 30 min and then washed with dil. HCl. After removal of the solvent, the desired **5***{2,2}* was isolated by short column filtration over silica gel in 87% yield.[4] The anilide **5***{2,2}* was treated with benzaldehyde in methanolic potassium carbonate at room temperature for 2 h during which deprotection of trifluoroacetamide and cyclization with benzaldehyde took place successively to give (3*R*,6*R*,7a*S*)-(2,3-diphenyl-6-hydroxy)hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**1***{2,2,7}*) in one pot.[5] The product **1***{2,2,7}* was extracted with AcOEt and purified by filtration through silica gel to give an 86% isolated yield of **1***{2,2,7}*.[6] According to this simple method which comprises two sets of one-pot reactions and chromatographic filtrations, the bicyclic amine library **1***{1–5,1–2,1–18}*, *{2,4–5,1}*, *{2,4–5,7–9}* was readily constructed.[7] Silyl ethers **1***{2,3,1–9}* were prepared from the corresponding **1***{2,2,1–9}* as additional library members.

Having successfully synthesized a range of bicyclic amines **1**, we examined the resulting *N*-chiral amines for the reaction of benzaldehyde with diethylzinc (Scheme 2).[8] The alkylation was carried out in toluene at −5°C under an argon atmosphere for 72 h in the presence of 5 mol% of **1** in parallel in individual reaction vessels to give 1-phenylpropanol (**6**). The chemical yield and enantiomeric purity of **6** were determined by GC analysis of the product mixture using a chiral stationary phase capillary column. Selected data obtained with **1***{1–5,2,1}*, *{2,1–5,1}*, and *{2,2,1–18}* are shown in graphs 1, 2, and 3, respectively (Fig. 1). As

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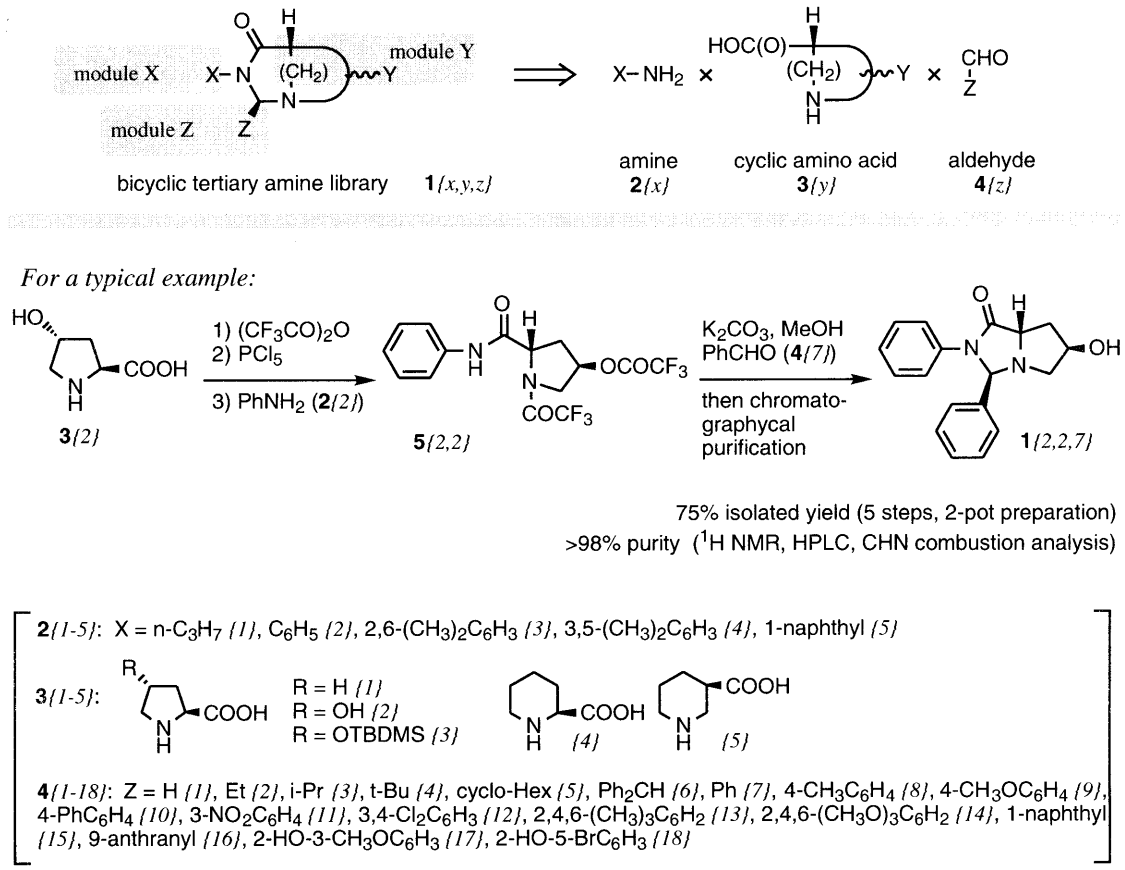
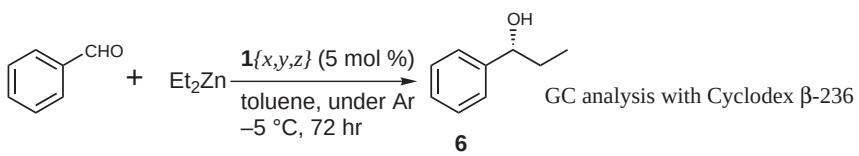


Scheme 1.

can be seen from graphs, the N2 substituent (module X) is not a decisive diversity group, its relatively uniform reactivity and stereoselectivity being observed in each case using **1**{*1–5,2,1*} (graph 1). Although a comparable chemical yield was also obtained with **1**{*2,1–5,1*}, the enantiomeric purity of the product **6** was significantly affected by module Y (graph 2). Thus, **1**{*2,2,1*} having a hydroxy group at its C6 position showed good enantioselectivity to give 55% ee of (*R*)-**6**, while {*2,1,1*}, {*2,3,1*}, {*2,4,1*}, and {*2,5,1*}, which lack the hydroxy group, gave less than 5% ee of **6** irrespective of their bicyclic framework. Graph 3 lists the results of the asymmetric alkylation in the presence of (2-phenyl-6-hydroxy)pyrroloimidazolinones **1**{*2,2,1–18*} incorporating various aldehydes (module Z). The module Z was identified as an effective diversity site because the C3 substituents should lie in close proximity to the zinc atom coordinated with the bridgehead nitrogen. Thus, aromatic substituents at the C3 position (**1**{*2,2,7–12*}) afforded high enantioselectivities (around 70% ee), while sterically bulky substituents (**1**{*2,2,2–6*} and {*2,2,13–17*}) gave lower enantioselectivities. Of the library members {*2,2,1–18*}, the pyrroloimidazoline containing the phenyl group on its imidazoline ring (**1**{*2,2,7*}) turned out to be the best catalyst exhibiting the highest enantioselectivity where the enantiomeric purity of (*R*)-**6** was increased to 75% ee.

The catalyst **1**{*2,2,7*} identified from the library screens was re-synthesized independently and tested in the asymmetric alkylation. The result obtained is shown in Fig. 2, which also includes those obtained with **1**{*2,1,7*} and {*2,3,7*} for comparison. The alkylation of benzaldehyde with Et_2Zn (2 equiv.) in toluene at −5°C for 24 h under argon in the presence of 5 mol% of **1**{*2,2,7*} gave 77% ee of (*R*)-phenylpropanol ((*R*)-**6**) in 96% yield.[9] Little asymmetric induction was observed with **1**{*2,1,7*} or {*2,3,7*} again indicating that the C6 hydroxy group plays a crucial role in asymmetric induction. It has been well-documented that the β-amino alcohol unit is a crucial structure in bringing about high enantioselectivity in the present catalysis. The enantioselective catalyst **1**{*2,2,7*} contains a β-amino alcohol unit which demonstrates the effectiveness of a diversity-



Scheme 2.

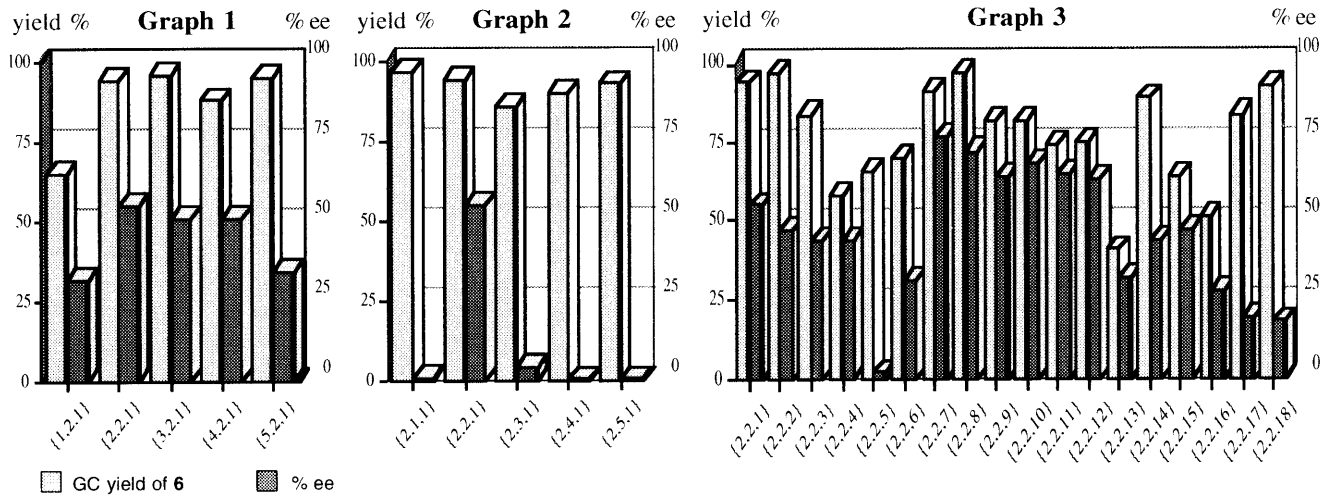


Figure 1. Chemical yields and enantiomeric purities of **6** obtained with **1**{*x*,*y*,*z*} (selected data).

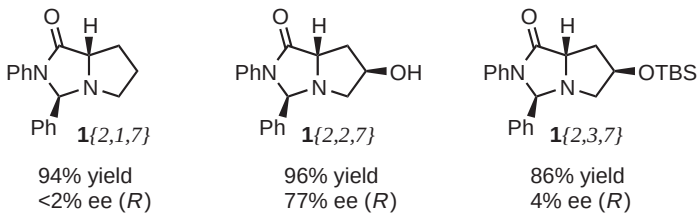


Figure 2.

based approach in identifying a lead structure for a given asymmetric transformation.

Acknowledgements

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References

1. For recent reviews, see: (a) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp. 389–411. (b) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; John Wiley: New York, 1994; pp. 323–345.
2. For reviews on combinatorial approaches to chiral catalysts: (a) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2494–2532. (b) Jandeleit, B.; Turner, H. W.; Uno, T.; van Beek, J. A. M.; Weinberg, W. H. *Cattech* **1998**, *2*, 101–123. (c) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; pp. 1389–1402.
3. For reviews: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–885. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69. (c) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999, pp. 911–922.
4. Mori, M.; Uozumi, Y.; Kimura, M.; Ban, Y. *Tetrahedron* **1986**, *42*, 3793–3806.
5. Preparation of pyrrolo[1,2-*c*]imidazolones so far reported: Cardinaux, F.; Brenner, M. *Helv. Chim. Acta* **1973**, *56*, 339–347. Also, see: Preston, P. N. *Condensed Imidazoles, 5-5 Ring Systems In Heterocyclic Compounds*; John Wiley: New York, **1986**; Vol. 46, pp. 4–77.
6. (*3R,6R,7aS*) - 2,3 - Diphenyl - 6 - hydroxy - hexahydro - 1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**1**{*2,2,7*}). 74% yield (from hydroxyproline); mp 193–196°C; $[\alpha]_D^{25}$ −4.7 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3370 (OH), 1685 (C=O); ^1H NMR ($CDCl_3$) δ: 1.56 (br, 1H, OH), 2.23 (dd, $J = 9.5$, 14.6 Hz, 1H, 7-CH), 2.54 (dt, $J = 4.9$, 14.4 Hz, 1H, 7-CH_2), 2.96 (dd, $J = 4.1$, 10.2 Hz, 1H, 5-CH), 3.45 (d, $J = 10.0$ Hz, 1H, 5-CH), 4.14 (q, $J = 4.6$ Hz, 1H, 7a-CH), 4.46 (m, 1H, 6-CH), 5.69 (s, 1H, 3-CH), 7.12 (d, $J = 7.6$ Hz, 1H, Ar), 7.26-7.47 (m, 7H, Ar), 7.49 (d, $J = 10.0$ Hz, 1H, Ar). Anal. calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.41; H, 6.13; N, 9.62.

7. The chemical structures and purities of all members of the parallel library **1** listed in Fig. 1 were fully analyzed (^{1}H NMR, HPLC, CHN analysis, optical rotation value).
8. Combinatorial approaches to enantioselective catalysts for alkylation of ArCHO with Et_2Zn: (a) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712–7713. (b) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 497–501.
9. (*R*)-**6** (77% ee) $[\alpha]_D^{25}+37.9$ (*c* 2.00, $CHCl_3$). Lit. for *S*-isomer (98% ee); $[\alpha]_D$ −47.6 (*c* 6.11, $CHCl_3$), see: Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.