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# Effect of Ligand Structure on the Zinc-Catalyzed Henry Reaction. Asymmetric Syntheses of (–)-Denopamine and (–)-Arbutamine

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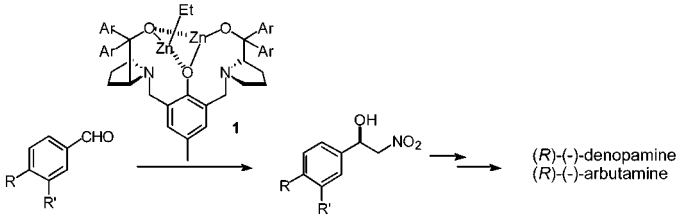
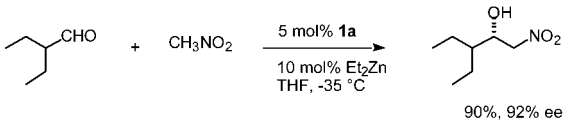
## ABSTRACT




**Syntheses of variously modified ligands for the dinuclear zinc catalysts for the asymmetric aldol and nitroaldol (Henry) reactions are reported. Catalytic enantioselective nitroaldol reactions promoted by these modified ligands led to efficient syntheses of the *β*-receptor agonists (–)-denopamine and (–)-arbutamine.**

The nitroaldol (Henry) reaction is an atom-economic approach to *β*-hydroxynitroalkanes, valuable synthetic intermediates.[1] The asymmetric version of this reaction through the use of heterobimetallic catalysis with lanthanide binol systems by the group of Shibasaki was not known until quite recently.[2] As part of our study of a new dinuclear zinc catalyst for the aldol reaction,[3] we demonstrated the utility of this new system for the nitroaldol reaction using our standard ligand **1a** as shown in eq 1.[4] To ascertain the structural features important for the chiral recognition, we systematically varied the ligand and report our results herein.




(1)

To test the effect of the p$K_a$ of the phenol on the reaction, ligands **1b**−**d** (Figure 1) were synthesized as shown in Scheme 1. The preparation of dibromides **4** was based upon literature precedents.[5] The reactivity of the dibromides **4** led to their immediate use in the substitution reaction. For the synthesis of **1a** the substitution was performed with triethylamine in methylene chloride using proline methyl ester followed by addition of ArMgBr, or potassium carbonate in DMF using diphenylprolinol **3a**.[6] For the remaining examples, potassium carbonate in DMF was employed. Methyl

(1) For recent reviews on nitroaldol reactions, see: (a) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1996; Vol. 2, p 321. (b) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915. (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; Chapter 3, p 30.

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(3) (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (c) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497.

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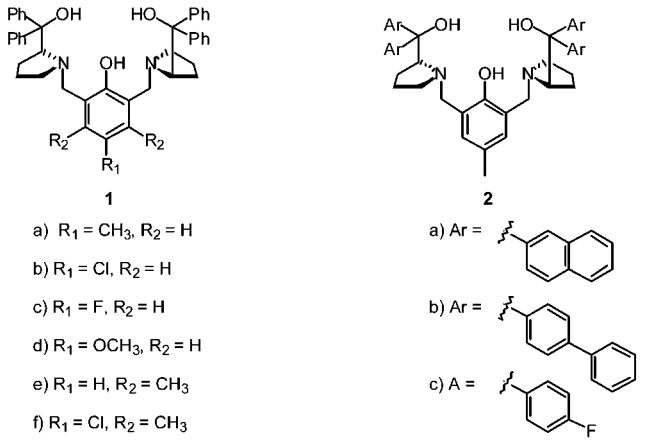
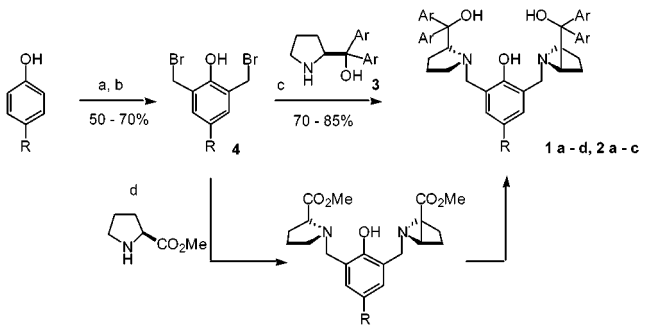



**Figure 1.**

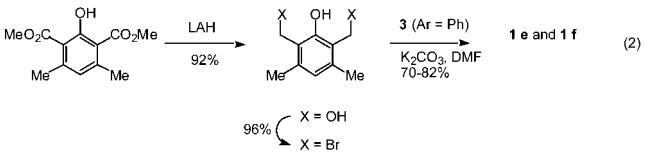
groups were placed at the meta positions of the aryl ring to influence the conformations of the proline with the anticipation that such buttressing effects would rigidify the chiral

**Scheme 1.** Synthesis of Ligands[a]




[a] (a) NaOH, HCHO, $H_2O$, rt; (b) HBr, HOAc, rt; (c) $K_2CO_3$, DMF, rt; (d) $(C_2H_5)_3N$, $CH_2Cl_2$, rt; (e) ArMgBr, THF, rt.

space. The parent phenol was prepared from the known diester[7] as shown in eq 2. Since our model envisions that

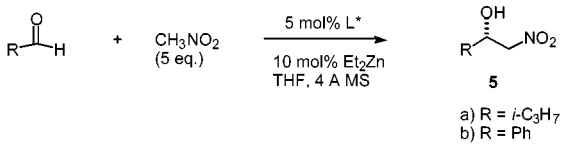



(2)

the aryl groups of the diarylcarbinol help define the chiral space, varying the size of the aryl rings as in **2a,b** should vary the steric demands of the chiral space. This series of ligands was synthesized by the route depicted in Scheme 1. Finally, the effect of the p$K_a$ of the tertiary hydroxyl group was also probed by synthesizing ligand **2c** as outlined in Scheme 1.

(7) (a) Bertz, S. H. *Synthesis* **1980**, 708. (b) Fahrni, C. J.; Pfaltz, A. *Helv. Chim. Acta* **1998**, *81*, 491.

Initial efforts focused upon the reactions using ligands that retained the diphenylcarbinol moiety and varied the phenol unit, i.e., ligands **1a**−**f**. The nitroaldol reaction of an aliphatic and an aromatic aldehyde was pursued as shown in eq 3




(3)

and Table 1. The results indicate that varying the substitution on the phenol ring had little effect on ee except for *p*-methoxy (**1d**) where a dramatic decrease occurred in both cases

**Table 1.** Nitroaldol Reaction with Ligands **1a**−**f**[a]

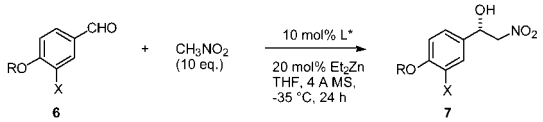
| entry | ligand | product | $T$ (°C) | % isolated yield | % ee[b] |
|---|---|---|---|---|---|
| 1 | **1a** | **5a** | −25 | 52 | 86 |
| 2 | **1a** | **5a** | −60 | 58 | 88 |
| 3 | **1b** | **5a** | −25 | 52 | 84 |
| 4 | **1c** | **5a** | −25 | 44 | 88 |
| 5 | **1d** | **5a** | −25 | 45 | 37 |
| 6 | **1e** | **5a** | −35 | 36 | 77 |
| 7 | **1f** | **5a** | −25 | 44 | 78 |
| 8 | **1a** | **5b** | −25 | 75 | 87 |
| 9 | **1a** | **5b** | −35 | 85 | 91 |
| 10 | **1b** | **5b** | −25 | 61 | 88 |
| 11 | **1c** | **5b** | −25 | 43 | 93 |
| 12 | **1d** | **5b** | −25 | 27 | 22 |
| 13 | **1e** | **5b** | −35 | 30 | 89 |
| 14 | **1f** | **5b** | −25 | 52 | 82 |

[a] All reactions were performed on 1 mmol scale using 5 mol % catalyst, 5 equiv of $CH_3NO_2$, at 0.33 M in THF at the indicated temperature for 16 h unless noted otherwise. [b] Determined by chiral HPLC; see Supporting Information for details.

(entries 5 and 12). Placing fluorine in the para position, on the other hand, gave a slight increase in ee (entries 4 and 11). A greater temperature dependence was observed with the aromatic aldehyde (entry 8 vs 9) compared with the aliphatic aldehyde (entry 1 vs 2).

Since the reactions were run for a fixed time, the isolated yields are more reflective of the rate of the reaction. Interestingly, reactions employing the "parent" ligand **1a** appear to be the fastest.

The impact of the diaryl carbinol moiety of the ligands was examined in the context of the aromatic aldehyde **6a**−**c** (eq 4). Surprisingly, the effects of variation of the aryl groups are modest. The biphenyl ligand **2b** gave small but real increases in ee compared to the "parent" (Table 2, entries 1




(4)

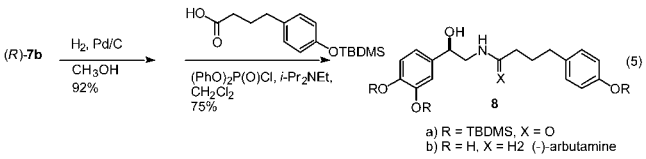
**Table 2.** Nitroaldol Reactions with Ligands **1a**−**c** and **2a**−**c**[a]

| entry | ligand | product | % isolated yield | ee (%)[a] |
|---|---|---|---|---|
| 1 | **1a** | **7a** | 59 | 87 |
| 2 | **1c** | **7a** | 40 | 87 |
| 3 | **2a** | **7a** | 72 | 84 |
| 4 | **2b** | **7a** | 88 | 90 |
| 5 | **2c** | **7a** | 64 | 84 |
| 6 | **1a** | **7b** | 65 | 83 |
| 7 | **2a** | **7b** | 89 | 89 |
| 8 | **2b** | **7b** | 88 | 85 |
| 9 | **1a** | **7c** | 69 | 78 |
| 10 | **1c** | **7c** | 40 | 87 |
| 11 | **2a** | **7c** | 68 | 85 |
| 12 | **2b** | **7c** | 47 | 86 |
| 13 | **2c** | **7c** | 50 | 85 |

[a] All reactions were performed on a 1 mmol scale using 10 mol % catalyst, 10 equiv $CH_3NO_2$ at 0.33 M in THF at −35 °C for 24 h. [b] Determined by chiral hplc; see Supporting Information for details.

vs 4, 6 vs 8, and 9 vs 12). Thus, this ligand was adopted as the standard. Similarly, the naphthyl ligand **2a** gave a more enhanced selectivity for **7b** (Table 2, entry 6 vs 7).

The important physiological roles that arylethanol amines play has led to many analogues being developed for coronary diseases. The asymmetric nitroaldol addition provides ready access to such compounds. For example, (−)-arbutamine[8] (**8b**), a mixed $\beta_1$-$\beta_2$ adrenoreceptor agonist useful as an exercise stimulating agent (ESA), is readily available asymmetrically via an asymmetric nitroaldol reaction. The absolute configuration of these types of targets requires use of *R*,*R*-ligands. Thus (*R*)-**7b** was reduced and acylated to form amide **8a** as shown in eq 5 in analogy to the work of Shibasaki[8e]

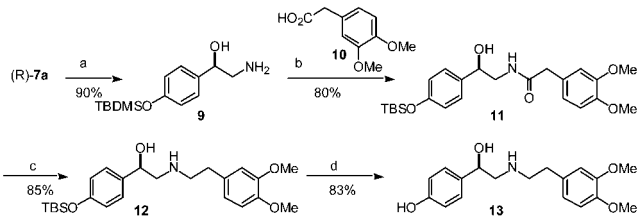



except that diphenyl chlorophosphate was employed for the coupling step. Reduction (92% yield) and global desilylation (90% yield) as described completed the synthesis of (−)-arbutamine (**8b**), $[\alpha]_D$ −17.3 (*c* 1.03, $C_2H_5OH$), mp 54−58 °C [lit.[8e] $[\alpha]_D$ −18.5 (*c* 1.6, $C_2H_5OH$), mp 55−58 °C].

(8) (a) Tuttle R. R.; Brown, C. E. Eur. Pat. Appl. 329,464; *Chem Abstr*. **1991**, *114*, 602. (b) Tuttle R. R.; Brown, C. E. U.S. Patent 5,395,970, 1989, 1995 (both to Gensia); *Chem. Abstr*. **1996,** *124*, 331421. (c) Young, M.; Pan, W.; Wiesner, D.; Bullough, G.; Balow, G.; Potter, S.; Metzner, K.; Mullane, K. *Drug Dev. Res*. **1994**, *32*, 19. (d) Hammond, H. K.; Mckirnan, M. D. *J. Am. Coll. Cardiol*. **1994**, *23*, 475. (e) For previous asymmetric synthesis, see: Takaoka, E.; Yoshikawa, N.; Yamada, Y. M. A.; Sasai, H.; Shibasaki, M. *Heterocycles* **1997**, *46*, 157.

(−)-Denopamine[9] (**13**), a selective $\beta_1$-adrenoceptor agonist that is clinically effective in congestive cardiomyopathy, is available from (*R*)-**7a** as shown in Scheme 2. As above,

**Scheme 2.** Asymmetric Synthesis of (−)-Denopamine[a]




[a] (a) $H_2$, 10% Pd/C, ethanol, rt; (b) *t*-$C_4H_9COCl$, $(C_2H_5)_3N$, THF, −78 to 0 °C to **10** then add **9**, $(C_2H_5)_3N$, −78 to 0 °C; (c) LAH, $Et_2O$, 40 °C; (d) HCl, KF, MeOH, rt.

catalytic hydrogenation formed the amine **9**, which was coupled to the arylacetic acid **10** via the mixed anhydride method to form amide **11.** Reduction to amino alcohol **12** followed by the deprotection completed the synthesis of (−)-denopamine, $[\alpha]_D$ −28.1 (*c* 1.2, $CH_3OH$), mp 162−163 °C [lit.[9f] $[\alpha]_D$ −27.5 (*c* 0.95, $CH_3OH$), mp 163−164 °C]. Starting from commercially available 4-hydroxybenzaldehyde, this five-step synthesis proceeded in 43% overall yield.

This approach for the asymmetric aldol and nitroaldol reaction benefits from the ease of modifying the chiral space as shown herein. The biphenyl-type ligand **2b** provides some enhancement and has been adopted as our standard for the nitroaldol with aryl aldehydes. This finding is in accord with the notion that the conformation of the diarylcarbinol moiety creates the chiral space responsible for enantiodiscrimination in these dinuclear zinc complexes.

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**Supporting Information Available:** Experimental procedures and spectroscopic characterization (IR, $^1H$, $^{13}C$ NMR, HRMS) of all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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