Synthesis of C_2-symmetrical diamine based on (1R)-(+)-camphor and application to oxidative aryl coupling of naphthols

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Abstract—The new C_2-symmetrical 1,2-diamine {N,N'-bis[(1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1,2-ethanediamine}**3** has been synthesized from commercial (1R)-(+)-camphor **1** and scrutinized as ligand in the oxidative biaryl coupling of naphthol derivatives. Under the optimal conditions employing a Cu(I)-**3** triflate complex (10 mol%) in dichloroethane–MeCN and molecular sieves with air as the oxidant, aryl coupling of naphthol derivatives could be achieved in satisfactory yields (48–90% yield) and ees of up to 65%. The ester moiety at the 3-position of the substrate was found to be crucial for a satisfactory asymmetric induction in the present coupling reaction. © 2003 Elsevier Science Ltd. All rights reserved.

1,2-Diamines represent an important class of compounds employed as precursors in the synthesis of heterocyclic ring systems as well as chelating agents (e.g. polyazamacrocycles) in medicinal chemistry and radiopharmaceuticals.[1] Notably, their chiral non-racemic derivatives have been used as auxiliaries in the asymmetric synthesis of a large and varied number of arrays of compounds.[2] A particularly appealing and successful approach toward enantioselective C–C bond formation is via catalysis employing transition-metal complexes based on C_2-symmetrical diamines, some of them are now commercially available in both enantiomeric forms.[3] Despite the many existing chiral 1,2-diamines, the design of new and improved enantiomerically enriched ligands are still sought. Recent studies in our lab have focused on the development of new chiral auxiliaries for the asymmetric synthesis of phosphonic acid derivatives under mild and simple reaction conditions.[4] Herein, we report the preparation of a new C_2-diamine **3** based on commercially available (1R)-camphor **1** and its use as a chiral

bidentate ligand in a copper-catalyzed oxidative coupling of 2-naphthol derivatives. Thus, (1R)-(+)-camphor **1** (1.0 equiv.) and ethylenediamine (0.6 equiv.) were mixed in refluxing toluene with catalytic BF$_3$·Et$_2$O (1–5 mol%), followed by azeotropic removal of water (12 h) giving the diastereomerically pure (E,E)-bis(camphorylidene)ethylenediamine **2** in an almost quantitative yield[5] (Scheme 1). A variety of acid catalysts
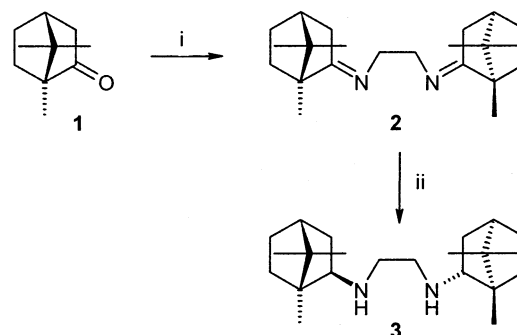
Scheme 1. *Reagents and conditions*: (i) ethylenediamine (0.50 equiv.), BF$_3$·Et$_2$O (1–5 mol%), PhMe, reflux (Dean–Stark), 12 h; (ii) NiCl$_2$ (2.1 equiv.), NaBH$_4$ (3.0 equiv.), MeOH, −40°C→rt, 12 h.

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(PTSA, $ZnCl_2$, $Yb(OTf)_3$, Amberlyst®-15) were also screened; however, none were superior to $BF_3 \cdot Et_2O$ in performance. Initial attempts to effect the subsequent reduction of **2** were unsuccessful. Many well-established methods failed to give a clean reaction including use of complex metal hydrides (i.e. $NaBH_4$, $NaBH_3CN$, $NaBH(OAc)_3$, $LiAlH_4$, $Zn(BH_4)_2$) in a range of solvents. Finally, reduction of **2** in the presence of nickel boride[6] [in situ generated from anhydrous $NiCl_2$ (2.1 equiv.) and $NaBH_4$ (3 equiv.)] in MeOH at $-40°C \rightarrow rt$ (12 h) resulted in a 94% yield of diamine **3** with 19:1 *exo,exo*-selectivity (by ^{1}H NMR).

The major component possesses a 2-fold axis of symmetry (C_2) which is in agreement with the 11-line ^{13}C NMR spectrum. Notably, this mixture (as the dihydrochloride) could be readily enriched to diastereomeric purity by simple crystallization from EtOH affording excellent recovery (>95%) of **3**[7] while the minor *exo,endo*-diastereomer in the mother liquor was identified by ^{13}C NMR (i.e. 22 resonances by virtue of its C_1-symmetry).[8] In order to corroborate the absolute stereochemistry of the major diamime **3**, it was decided to perform a single-crystal X-ray diffraction analysis. Numerous attempts to obtain satisfactory crystals from the dihydrochloride proved to be unrewarding. However, the counterion switch to L-(+)-tartrate, followed by the slow

diffusion of Et_2O into a saturated solution of the crude material in EtOH, induced the formation of **3**·L-(+)-tartrate dihydrate as suitable crystals (Fig. 1).[9]

We targeted optically active diamine **3** (as its copper complex) as a catalyst for enantioselective oxidative aryl coupling due to the wealth of asymmetric transformations which utilize this kind of ligands.[10] The feasibility study with this reaction was initially carried out on 2-naphthol **4a** and it was apparent that the course of the reaction critically depended on the substrate structure. In order to optimize the reaction conditions, several combinations of Cu(I) or Cu(II) catalysts, solvents, ligand:copper ratios, metal loadings and additives were scrutinized. The best results in terms of the Cu source were obtained with in situ formed 1:1 diamine **3**:Cu(OTf) complex and this catalyst, initially tried at 15% molar amount, was subsequently decreased up to 10% without affecting the yield or rate. Changes in the diamine to copper stoichiometry (L:Cu 1:1 or 2:1) had little effect on the reaction course. The copper complexes of **3** obtained by interaction with either Cu(II) [$Cu(BF_4)_2 \cdot H_2O$, $Cu(OTf)_2$] or Cu(I) [CuI, CuCl, $Cu(MeCN)_4(BF_4)$] salts were catalytically active in the conversion of **4a** to **5a**, albeit to different extent (30–65% yield). Under the tried reaction conditions all of the active catalysts are Cu(II) species. When Cu(I) sources (e.g. CuX) were employed, the catalyst was reasonably the bis-μ-hydroxo dimeric complex [(**3**)Cu(OH)]$_2$X$_2$ which forms in the presence of air.[11] Dichloroethane–MeCN mixtures were found to be far superior than more polar and coordinating solvents such as MeCN, THF or MeOH alone. In addition, the reaction rate was effectively accelerated by the presence of molecular sieves.

Optimally, the oxidative coupling of **4a** was carried out under an open atmosphere using 10 mol% (−)-**3**, 10 mol% [$Cu(OTf)_2 \cdot C_6H_6$] complex and powdered oven-dried 4 Å MS in dichloroethane–MeCN (2:1, v/v) and was complete within 48 h (TLC) at 40°C to afford BINOL **5a** in 65% isolated yield. However, prior to chromatographic purification, analysis of the crude reaction mixture by chiral phase HPLC ($\lambda = 254$ nm, Chiralpack®AD column, 30% isopropanol in hexane, 1.0 mL/min) revealed that the reaction proceeded with low enantioselectivity (6% ee favouring R-absolute configuration) and all attempts to improve the selectivity proved unsuccessful. These conditions allowed for the synthesis of a range of 3,3′-disubstituted BINOL derivatives **5b–f** (45–90% yield, Table 1) and noteworthy were the enantioselectivities (65 and 61% ee, respectively, all favouring the R-absolute configuration) obtained starting from naphthols **4b–c** bearing an
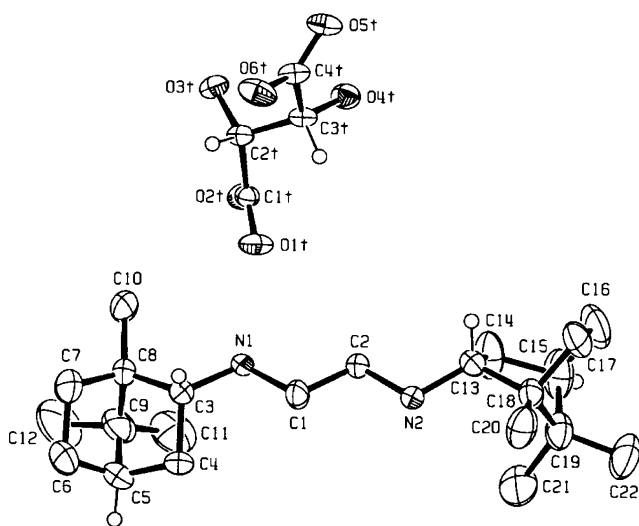

Figure 1. X-Ray structure of **3**·L-(+)-tartrate dihydrate (ORTEP view with arbitrary numbering). The thermal ellipsoids are drawn at 50% probability. Water molecules and hydrogen atoms are omitted for clarity.
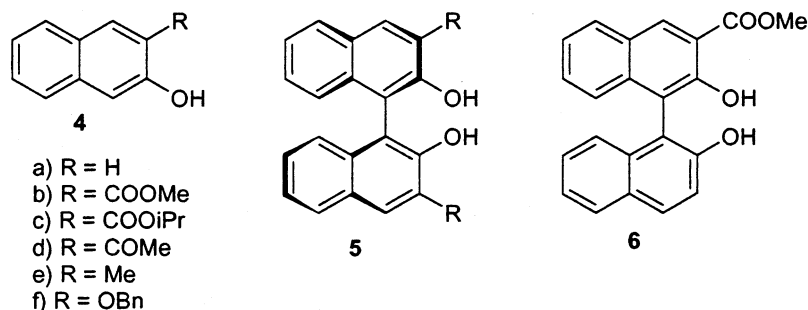

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a) R = H
b) R = COOMe
c) R = COOiPr
d) R = COMe
e) R = Me
f) R = OBn

5

6

Table 1. Enantioselective oxidative coupling of 2-naphthols catalyzed by (−)-**3**–Cu(OTf) complex

Naphthol(s)	Product	Chemical yield (%)[c]	Ee (%)[d]
4a[a]	**5a**	65	6
4b[a]	**5b**	90	65[e]
4c[a]	**5c**	83	61
4d[a]	**5d**	81	32
4e[a]	**5e**	63	9
4f[a]	**5f**	48	19
4a/4b[b]	**5g**	62	7

[a] Unless stated otherwise reactions were carried out as follows: 0.5 mmol **4a**–**f** (0.1 M), DCE–MeCN (2:1 v/v), 10 mol% (−)-**3**, 10 mol% [(CuOTf)$_2$·C$_6$H$_6$], 4 Å MS, air, 40°C, 5–48 h.

[b] 0.25 mmol **4a**/0.25 mmol **4b**.

[c] Isolated yield.

[d] Enantiomeric excess determined by HPLC (Chiralpak® AD). Absolute configuration was R for all cases.

[e] Upgraded to 95% by trituration in EtOAc

alkoxy carbonyl moiety at the 3-position. In addition, an attractive feature was that the crude BINOL **5b** tends to be highly crystalline and thus presented the opportunity for enantiomeric upgrading.[11] For example, the ee of **5b** increased from 65 to 95% after trituration in EtOAc and recovery from mother liquor (66% yield). Conversely, when this coupling reaction was applied to 2-naphthols **4d**–**f** with pendant ketone, alkyl or alkoxy moieties, respectively, the ees observed were once again disappointingly poor (<9% ee), thereby implying that the ester group was crucial for the an efficient asymmetric induction. This was in accordance with the observations independently made by Kočovský,[12] Nakajima[11] and Kozlowski[13] on the mechanism of copper-catalyzed asymmetric aerobic oxidation of naphthols and evaluation of the impact of structural changes upon enantioselectivity. Finally, upon subjecting a 1:1 mixture of **4a** and **4b** to the above reaction conditions, a similar reactivity/selectivity profile was observed, providing an optical yield of only 7% ee for the cross-coupling product **6** (62% yield).[12,14]

In summary, the preliminary results herein described highlight the potential of the new diamine **3** as a chiral ligand in coupling of 2-naphthols to BINOLs. Identifying the limitations of this catalyst, ongoing optimization studies will be aimed at improving the efficiency of this catalyst by tuning the substitution pattern around the N atoms in **3**. Bearing in mind the simple high-yielding synthesis of **3** and that both enantiomers of the starting material are equally accessible, diamine **3** should find its place in the growing arsenal of C_2-based catalysts that promote the asymmetric aerobic aryl coupling of naphthols.

Acknowledgements

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7. Selected data for **3**: $[\alpha]_D^{20}$ −107.7 (c 0.65, EtOH); ^{1}H NMR (CDCl$_3$+D$_2$O, 200 MHz): δ 2.70–2.49 (m, 6H), 1.75–1.40 (m, 8H), 1.18–1.07 (m, 6H), 1.01 (s, 6H), 0.87 (s, 6H), 0.81 (s, 6H); ^{13}C NMR (CDCl$_3$, 50.3 MHz): δ 66.4 (CH), 48.2 (C), 48.1 (CH$_2$), 46.5 (C), 45.1 (CH), 38.9 (CH$_2$), 36.8 (CH$_2$), 27.3 (CH$_2$), 20.5 (CH$_3$), 20.4 (CH$_3$), 12.1 (CH$_3$). MS (CI, CH$_4$): m/z (rel. int.) 333 ([MH$^+$], 100), 181 (15), 167 (47), 166 (43), 152 (30), 137 (32), 95 (34), 81 (35). Elem. anal.: C, 79.27; H, 12.30; N, 8.35. Calcd for C$_{22}$H$_{40}$N$_2$: C, 79.45; H, 12.12; N, 8.42. Selected data for **3**·2HCl: mp 123°C (EtOH); $[\alpha]_D^{20}$ −71.6 (c 1.05, EtOH); ^{1}H NMR (D$_2$O, 600 MHz): δ 3.56 (m, 2H), 3.39 (m, 2H), 3.21 (dd, 2H) (J_1 9.0 Hz, J_2 5.7 Hz), 1.97 (m, 2H), 1.89 t (2H) (J 4.2 Hz), 1.85 (dd, 2H) (J_1 13.5 Hz, J_2 9.0 Hz), 1.76 (m, 2H), 1.67 (dt, 2H) (J_1 13.5 Hz, J_2 4.2 Hz), 1.18 (m, 4H), 1.03 (s, 6H), 0.93 (s, 6H), 0.87 (s, 6H).

8. ^{13}C NMR (CDCl$_3$, 50.3 MHz): δ 66.6 (CH), 63.1 (CH), 53.1 (C), 48.9 (CH$_2$), 48.3 (CH$_2$), 46.5 (C), 45.1 (CH), 44.9 (CH), 39.1 (CH$_2$), 38.0 (CH$_2$), 36.8 (CH$_2$), 35.7 (C), 32.1 (C), 28.3 (CH$_2$), 27.3 (2×CH$_2$), 20.4 (2×CH$_3$), 19.7 (CH$_3$), 18.5 (CH$_3$), 14.1 (CH$_3$), 12.1 (CH$_2$).

9. Crystal data for compound **3** L-(+)-tartrate dihydrate: [(C$_{22}$H$_{42}$N$_2$)$^{2+}$(C$_4$H$_4$O$_6$)$^{2-}$·2H$_2$O], F_w = 518.68, monoclinic, space group P2$_1$, a = 10.7005(8), b = 9.3956(7), c = 14.7791(10) Å, β = 107.614(6)°, V = 1416.2(2) Å^3, Z = 2, D_{calcd} = 1.216 Mg m^{-3}, μ (Mo Kα) = 0.089 mm^{-1}; crystal dimensions 0.50×0.40×0.17 mm, Mo Kα radiation, λ = 0.71073 Å, graphite monocromator, Bruker P4 diffractometer. Data collection: θ/2θ scan mode, 2θ<55.00°;

6858 collected reflections, 3453 unique [2985 with $I_o > 2\sigma(I_o)$], merging $R = 0.0220$. The structure was solved by SIR-92[15] and refined by SHELXL-97[16] by full-matrix least-squares based on F_o^2, with weights $w = 1/[\sigma^2(F_o)^2 + (0.0443P)^2 + 0.0538P]$, where $P = (F_o^2 + 2F_c^2)/3$. Hydrogen atoms were refined isotropically with restraints on bond lenghts and atomic displacement parameters. The final consistence index were $R = 0.0410$ and $R_w = 0.0853$ (0.0338 and 0.0819, respectively, for observed reflections), goodness-of-fit = 1.011. The final map ranges were between −0.13 and 0.19 e Å^3. The absolute configuration was determined on the basis of that of tartrate anion (Fig. 1). The structure contains two water molecules, linked by strong hydrogen bonds to both cation and anion. Detailed crystallographic data were deposited as CCDC-185585 with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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