A FACILE SYNTHESIS OF THE ENANTIOPURE, NITROGEN-SUBSTITUTED 2,2′-DIAMINO-1,1′-BINAPHTHYLS AS POTENTIAL LIGANDS FOR CATALYTIC ASYMMETRIC REACTIONS

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Reductive alkylation of (*R*)-(+)-2,2′-diamino-1,1′-binaphthyl (**1**) with various ketones has been accomplished by means of $NaBH_4/H_2SO_4$ in THF at room temperature. Bisalkylation predominated with the sterically less demanding acetone (**1** → **3a**; 82%), whereas the bulky 2-adamantanone afforded mainly the monoalkylated product **4c** (71%). Both mono- and bisalkylated diamines (*R*)-**3** and (*R*)-**4** were reductively permethylated on reaction with CH_2O, $NaBH_4$, and H_2SO_4. The Pd(0)-catalyzed phenylation of (*R*)-(+)-**1** with PhBr afforded the *N*,*N*′-diphenyl derivative (*R*)-**7** (70%).

Key words: Biaryls; Binaphthyls; Axial chirality; Chiral ligands; Amine reductive alkylation; Amine arylation; Palladium catalysis.

The success of 2,2′-disubstituted 1,1′-binaphthyls as chiral ligands in asymmetric reactions is mainly due to the chiral environment into which they wrap the metal center[1]. In contrast to the wide use of BINOL (ref.[1]), BINAP (ref.[1]), MOP (ref.[2]), and NOBIN (refs[3,4]), the diamine[1] **1** has been much less popular[1] in spite of its straightforward, one-step synthesis from 2-naphthol and hydrazine and of its ready resolution into enantiomers[5]. We reasoned that introducing a bulky substituent at each amino group of the latter diamine **1** should restrict the conformational mobility and thereby create a more crowded chiral pocket. A metal catalyst, derived from these ligands, can therefore be expected to exhibit improved asymmetric induction and increased solubility in common organic solvents. Herein, we report on the synthesis of the *N*,*N*′-alkylated or phenylated diamines (derived from **1**) with the alkyl groups of different size.

We have recently shown that the NH_2 group of 2-hydroxy-2′-amino-1,1′-binaphthyl (NOBIN) can be readily dimethylated on treatment with 40% aqueous CH_2O and $NaBH_4/H_2SO_4$ (refs[6,7]). It was therefore desirable to explore the potential of this

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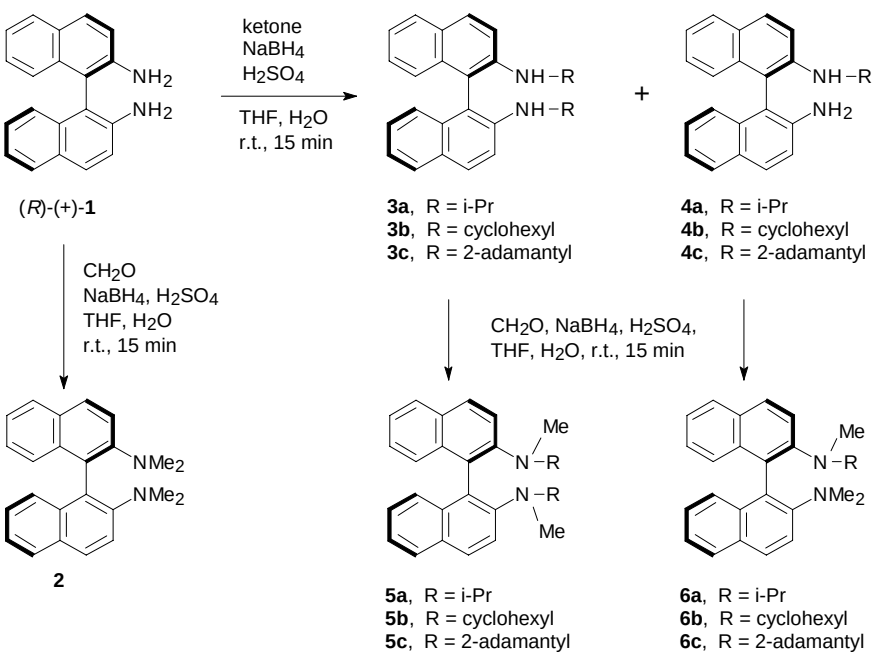
method, in particular, its feasibility with other carbonyl partners of increased bulk. To this end, the diamine (*R*)-(+)-**1** and formaldehyde, acetone, cyclohexanone, and 2-adamantanone were selected as model compounds.

The reductive alkylation of (*R*)-(+)-**1** with formaldehyde and $NaBH_4/H_2SO_4$ in THF (Scheme 1) proved to occur readily at room temperature, affording the *N*,*N*,*N*′,*N*′-tetramethyl derivative[8,9] (*R*)-**2** (88%). By contrast, the reaction with acetone predominantly led to the product of bisalkylation, namely to the *N*,*N*′-diisopropyldiamine (*R*)-**3a** (82%), which was accompanied by a small amount of the monoalkylated product[9,10] (*R*)-**4a** (15%). Enhancing the steric demands of the ketone led to a gradual decrease of bis-alkylation in favor of mono-derivatization. Thus, the reaction with cyclohexanone furnished *ca* 2 : 1 mixture of the bis- and monoalkylated diamines (*R*)-**3b** (64%) and (*R*)-**4b** (28%), whereas 2-adamantanone gave mainly the monoalkylated product (*R*)-**4c** (71%); in the latter instance, the bis-derivative (*R*)-**3c** was formed in only 15% yield. Extending the reaction period, varying the temperature, and employing an excess of the ketone and/or $NaBH_4$ had little effect on the production of (*R*)-**3c**.

The bisalkylated diamines (*R*)-**3a**–(*R*)-**3c** were subsequently permethylated with CH_2O (aq.) under the same conditions ($NaBH_4$, H_2SO_4, THF; room temperature) to give (*R*)-**5a** (76%), (*R*)-**5b** (75%), and (*R*)-**5c** (59%), respectively. Similarly, the monoalkylated diamines (*R*)-**4a**–(*R*)-**4c** were converted into (*R*)-**6a** (65%), (*R*)-**6b** (68%), and

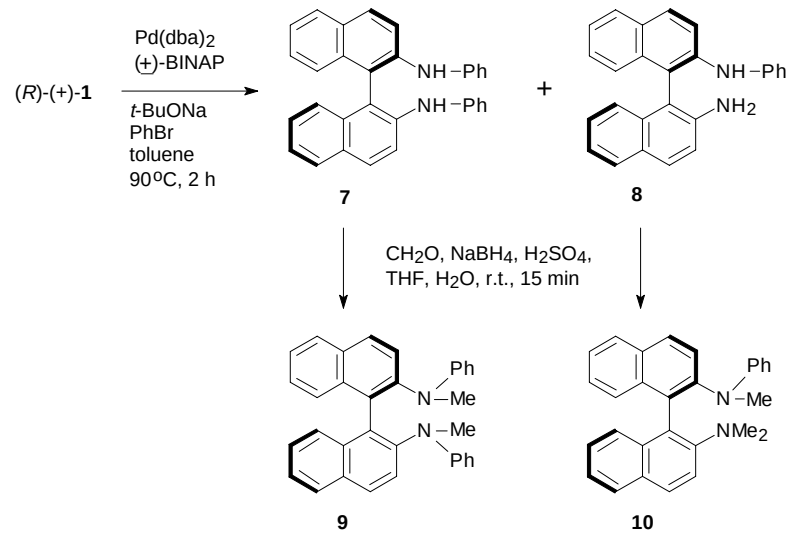


ketone = acetone, cyclohexanone, or 2-adamantanone

SCHEME 1

(*R*)-**6c** (64%), respectively, demonstrating that the second alkylation of the Ar–NHR group can only be attained with a sterically non-demanding aldehyde and not with a ketone.

N-Phenylation was accomplished by employing the recently developed Hartwig–Buchwald methodology[11]. Thus, the Pd(0)-catalyzed coupling of (*R*)-(+)-**1** with bromobenzene afforded mainly the *N*,*N*′-diphenyl derivative (*R*)-**7** (70%)[12,13] contaminated by the monophenylated product[13] (*R*)-**8** (18%) (Scheme 2). Standard reductive methylation (CH_2O, $NaBH_4$, H_2SO_4, THF; room temperature) of (*R*)-**7** gave the expected dimethylated diamine (*R*)-**9** (85%) and, similarly, (*R*)-**8** afforded the trimethylated derivative (*R*)-**10** (61%).



SCHEME 2

Interestingly, the Hartwig–Buchwald method is sensitive to the ligand, in particular to its bite angle; BINAP and the ferrocenyl-derived diphosphine dppf are among the best[11]. Naturally, if a nonchiral target compound is to be synthesized, economical criteria would dictate that the inherently chiral BINAP be used in its racemic form[11]. This raises the question of whether or not application of the enantiomerically pure BINAP would, in the case of a racemic substrate, lead to any kinetic resolution. To address this issue, diamine (±)-**1** was treated under the Hartwig–Buchwald conditions (*vide supra*) in the presence of (*S*)-BINAP. Analysis of the reaction mixture at *ca* 25% conversion (60 °C, 1 h) by HPLC on a chiral column revealed a preferential formation of (*R*)-**7** in 17% e.e., demonstrating the feasibility of this approach[14]. Although the enantioselectivity could be in principle improved by fine-tuning of the ligand and the reaction conditions, this issue was not further pursued in view of the straightforward synthesis of the enanti-

omerically pure starting diamine (*R*)-(+)-**1**. On the other hand, successful kinetic resolution of this type may prove useful in the synthesis of other enantiopure compounds, where the classical resolution of the corresponding racemate is more difficult than in the present case.

In conclusion, we have demonstrated that a simple, high-yielding reductive alkylation of (*R*)-(+)-**1** can be accomplished with a ketone even as bulky as 2-adamantanone and $NaBH_4/H_2SO_4$ in THF at room temperature; $NaBH_4$ proved to be more efficient than $NaBH_3CN$. Related *N*-phenyl derivatives were obtained *via* the Pd(0)-catalyzed coupling of (*R*)-(+)-**1** with PhBr as the key step. All these transformations proceeded without loss of enantiomeric purity, as revealed by chiral HPLC. We are currently investigating the utilization of the resulting binaphthyls (*R*)-**2** – (*R*)-**10** and their analogues prepared from 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) in the same way, as chiral ligands in asymmetric catalysis.

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7. This method proved to be superior to the classical Eschweiler–Clarke reaction[6].
8. Tetramethylation of the diamine **1** with CH_2O/HCO_2H (heating overnight) has been described earlier: Benson S. C., Cai P., Colon M., Haiza M. A., Tokles M., Snyder J. K.: *J. Org. Chem.* **1988**, *53*, 5335.
9. All yields refer to “isolated” yields rather than “GC yields”. All new compounds gave satisfactory analytical data.
10. *Typical experiment for reductive alkylation of* **1**: A solution of the enantiomerically pure (*R*)-(+)-**1** (ref.[5]) (284 mg, 1 mmol) in THF (10 ml) and solid $NaBH_4$ (530 mg, 14 mmol) were added to a mixture of acetone (812 mg, 14 mmol) and 20% aqueous H_2SO_4 (2 ml) in THF (5 ml)

over a period of 15 min, while cooling with a water bath. The mixture was stirred for an additional 15 min and then poured into a 2% aqueous KOH (100 ml). The resulting suspension was extracted with AcOEt (3 × 20 ml) and the extract was dried with $MgSO_4$ and evaporated. The crude product was purified by flash chromatography on silica (20 g) with toluene to give (*R*)-(+)-**3a** (301 mg, 82%): m.p. 83–84 °C (toluene); $[\alpha]_D$ +89° (*c* 0.4, THF). IR spectrum, ν(NH): 3 398 cm^{-1}. ^1H NMR spectrum (300 MHz, δ-scale, *J* in Hz): 0.96 and 1.04 2 × d, 2 × 6 H, *J* = 6.3; 3.40 bs, 2 H; 3.73–3.86 m, 2 H; 6.91 dd, 2 H, *J* = 8.1, *J* = 0.9; 7.08–7.22 m, 4 H; 7.25 d, 2 H, *J* = 9.0; 7.75 dd, 2 H, *J* = 8.1, *J* = 0.9; 7.85 d, 2 H, *J* = 9.0. ^{13}C NMR spectrum: 23.20 (q), 44.49 (d), 112.38 (s), 114.95 (d), 121.76 (d), 123.99 (d), 126.46 (d), 127.54 (s), 127.88 (d), 129.42 (d), 134.03 (s), 144.04 (s). Mass spectrum, *m/z* (%): 368 ($M^{+\bullet}$, 100); HRMS (EI): 368.2260 ($C_{26}H_{28}N_2$ requires 368.2252). The more polar byproduct was identified as the monosubstituted diamine (*R*)-(+)-**4a** (50 mg, 15%): m.p. 158–161 °C (toluene); $[\alpha]_D$ +137° (*c* 0.2, THF). IR spectrum, ν(NH): 3 485 (NH_2, asym) and 3 393 (NH_2, sym) cm^{-1}. ^1H NMR spectrum (300 MHz, δ-scale, *J* in Hz): 0.98 and 1.05 2 × d, 2 × 3 H, *J* = 6.0; 3.42 bs, 1 H; 3.64 bs, 2 H; 3.75–3.83 m, 1 H; 6.96 d, 1 H, *J* = 7.5; 7.03 d, 1 H, *J* = 8.1; 7.20–7.23 m, 5 H; 7.27 d, 1 H, *J* = 9.0; 7.75–7.82 m, 3 H; 7.86 d, 1 H, *J* = 9.0. ^{13}C NMR spectrum: 23.18 (q), 23.33 (q), 44.77 (d), 112.31 (s), 112.85 (s), 115.26 (d), 118.20 (d), 121.90 (d), 122.34 (d), 123.81 (d), 124.10 (d), 126.62 (d), 126.67 (d), 127.65 (s), 128.02 (2 × d), 128.44 (s), 129.45 (2 × d), 133.71 (s), 133.92 (s), 142.88 (s), 144.01 (s). Mass spectrum, *m/z* (%): 326 ($M^{+\bullet}$, 75); HRMS (EI): 326.1777 ($C_{23}H_{22}N_2$ requires 326.1783).

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12. The IR, NMR, and mass spectra of this product were identical to those of an authentic sample of (±)-**6** prepared by the oxidative coupling of *N*-phenyl-2-aminonaphthalene[3c].
13. *Pd-catalyzed phenylation of* **1**: Bis(dibenzylideneacetone)palladium (0.1 mmol, 58 mg, 5 mole %), (±)-BINAP (0.15 mmol, 98 mg), sodium *tert*-butoxide (1.152 g, 12 mmol), diamine (*R*)-(+)-**1** (284 mg, 1 mmol), and bromobenzene (1.57 g, 1.046 ml, 10 mmol) were placed in a Schlenk tube under argon and suspended in dry toluene (5 ml). The tube was heated at 90 °C while stirring for 2 h. The mixture was then cooled and the crude product purified by flash chromatography on silica gel (50 g) with toluene as eluent to give (*R*)-(+)-**7** (304 mg, 70%) as an amorphous solid: $[\alpha]_D$ +63.4° (*c* 0.4, THF). IR spectrum, ν(NH): 3 402 cm^{-1}. ^1H NMR spectrum (250 MHz, δ-scale, *J* in Hz): 5.47 bs, 2 H; 6.79–6.89 m, 6 H; 7.05–7.24 m, 10 H; 7.59 d, 2 H, *J* = 9.1; 7.73–7.81 m, 4 H. ^{13}C NMR spectrum: 116.38 (s), 117.83 (d), 119.94 (2 × d), 122.13 (d), 123.43 (d), 124.42 (d), 127.01 (d), 128.19 (d), 129.20 (2 × d), 129.36 (d), 129.41 (s), 133.96 (s), 140.37 (s), 142.49 (s). Mass spectrum, *m/z* (%): 436 ($M^{+\bullet}$, 100); HRMS (EI): 436.1941 ($C_{32}H_{24}N_2$ requires 436.1939). The more polar byproduct was identified as the monosubstituted diamine (*R*)-(+)-**8** (65 mg, 18%): m.p. 240–241 °C (toluene), $[\alpha]_D$ +131° (*c* 0.4, THF). IR spectrum, ν(NH): 3 487 (NH_2, asym) and 3 397 (NH_2, sym) cm^{-1}. ^1H NMR spectrum (250 MHz, δ-scale, *J* in Hz): 3.69 bs, 2 H; 5.60 bs, 1 H; 6.83–6.91 m, 1 H; 6.98–7.02 m, 2 H; 7.07–7.32 m, 9 H; 7.68 d, 1 H, *J* = 9.1; 7.76–7.88 m, 4 H. ^{13}C NMR spectrum: 112.03 (s), 116.82 (s), 117.86 (d), 118.27 (d), 119.80 (2 × d), 121.95 (d), 122.53 (d), 123.33 (d), 123.85 (d), 124.52 (d), 126.85 (d), 126.99 (d), 128.13 (d), 128.17 (d), 128.44 (s), 129.09 (d), 129.20 (2 × d), 129.44 (s), 129.75 (d), 133.74 (s), 133.93 (s), 140.19 (s), 142.77 (s), 142.82 (s). Mass spectrum, *m/z* (%): 360 ($M^{+\bullet}$, 100); HRMS (EI): 360.1627 ($C_{26}H_{20}N_2$ requires 360.1626).
14. The enantiomeric excess was determined using chromatography on Daicel Chiralpak AD (elution: hexane–ethanol 20 : 1, flow rate 1 ml/min, UV detection at 256 nm, t_S = 4.3 min, t_R = 5.5 min). After prolonged reaction times, the results were as follows: *ca* 50% conversion of (±)-**1** (60 °C, 2 h) gave 10% e.e., *ca* 75% conversion (60 °C, 3 h) furnished 5% e.e., whereas *ca* 100% conversion (60 °C, 4 h) inevitably led to the racemic product.