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# Design and solid-phase synthesis of chiral acyclic and cyclic diamine ligands

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**Abstract**—A model resin-bound oligoamide functionalized with a rationally designed non-interfering diamine spacer was reduced with borane–THF to provide the corresponding diamine derivative. The latter was transformed using an efficient orthogonal sequence of transformations into two acyclic chiral model diamines **19** and **22** and two cyclic diamine ligands **23** and **24**.


## 1. Introduction

Chiral oligoamine derivatives have been employed as bases, additives, ligands, and catalysts in a wide variety of useful synthetic transformations. In particular, a number of chiral 1,2-diamines of diverse structural types have been used in several asymmetric reactions.[1] Notable examples of such reactions include enantioselective enolization with lithiated diamine **1**,[2] the asymmetric desymmetrization of meso epoxides with lithiated **2**,[3] kinetic resolution by palladium-catalyzed aerobic oxidation of secondary alcohols with sparteine **3** as ligand,[4] the Noyori ruthenium-catalyzed transfer hydrogenation using ligands of type **4**,[5] the allylation of hydrazones using diamine ligand **5**,[6] and the organocatalytic aldol reaction employing **6** (Fig. 1).[7]

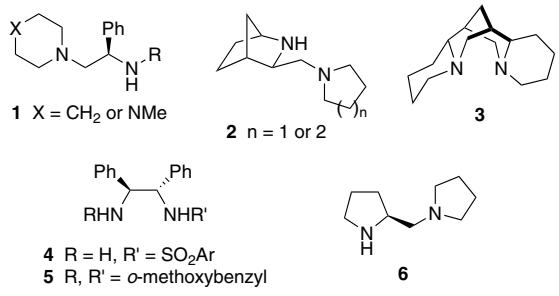


**Figure 1.** Examples of chiral diamines used in asymmetric synthesis.

Unfortunately, there does not appear to be a universal structural type of chiral diamine that can accommodate a wide scope of reactions and substrates. Consequently, there is great interest in the development of a general approach for quickly generating highly diverse chiral diamine derivatives that could be rapidly evaluated using parallel combinatorial chemistry techniques.[8] Ideally, such an approach would employ readily available chiral building blocks, and would be modular and flexible for accessing several different structural types (e.g., acyclic, cyclic, *N*-substitution). To this end, we believed that a solid-phase approach based on the reduction of chiral oligoamides and peptides derived from amino acids would be most advantageous. Our laboratory[9,10] and others[11] have optimized a solid-phase synthesis of polyamines based on the exhaustive reduction of polypeptides with diborane followed by an appropriate work-up (Fig. 2). Very importantly, the stereochemical integrity of the α-amino acid residues is preserved in this process. Herein, we report the solid-phase synthesis of

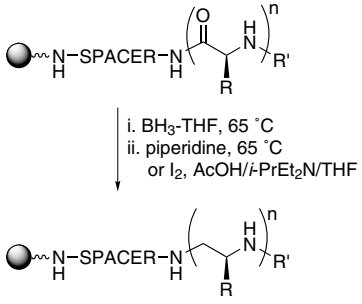


**Figure 2.** General solid-phase synthesis of polyamines from peptides.

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four model chiral diamine ligands, two acyclic ones and two cyclic derivatives.

## 2. Results and discussion

The harsh conditions for the solid-phase borane-promoted reduction of peptides were found to be compatible with only very few resin linkers.[9] Fortunately, trityl resin-linked amines are particularly reliable substrates, which can be cleaved easily with a mild acid at the end of the sequence. Application of this solid-phase strategy to the synthesis of diamine ligands however, requires post-cleavage removal or some modification of the anchoring amine so that it does not interfere with the desired reaction, and neither acts as a coordinating group in the desired metal complex. Our design of diamines **7** is centered on the use of a 4-aminomethyl piperidine linker, and involves post-cleavage neutralization of the piperidinyl anchor as a pivalic amide (Fig. 3).

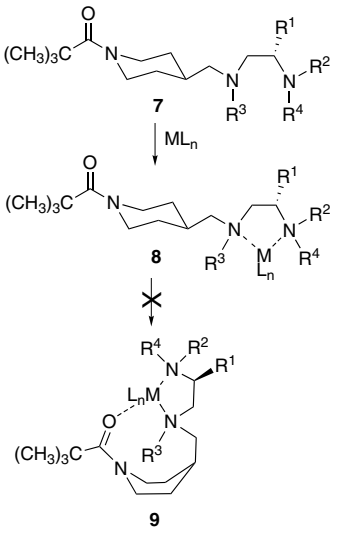
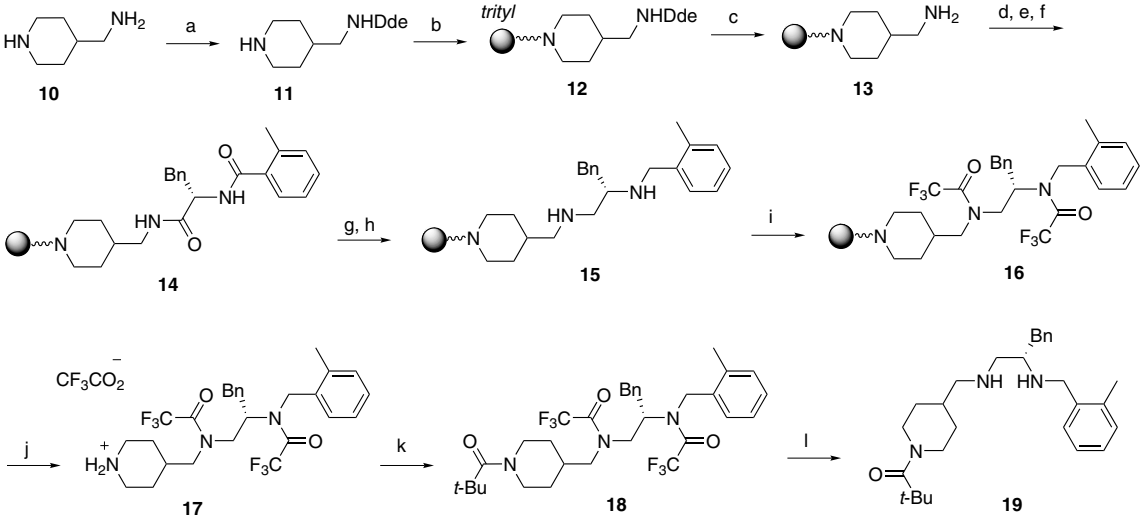


**Figure 3.** Design of chiral diamine ligands with a non-interfering spacer.

It was anticipated that a non-enolizable hindered tertiary amide would be tolerant to a wide range of reaction conditions, such as the use of strong bases and most oxidants and reductants. Furthermore, the piperidinyl spacer would make internal coordination of the amide carbonyl to a metal unfavorable. For this to happen, the piperidinyl ring would need to adopt a boatlike conformation, with a twisted amide and a pseudo-axial aminomethyl substituent. These unfavorable requirements make it rather improbable for the pivaloyl amide of putative complex **8** to interfere as an internal ligand and form the tricoordinate complex **9**.

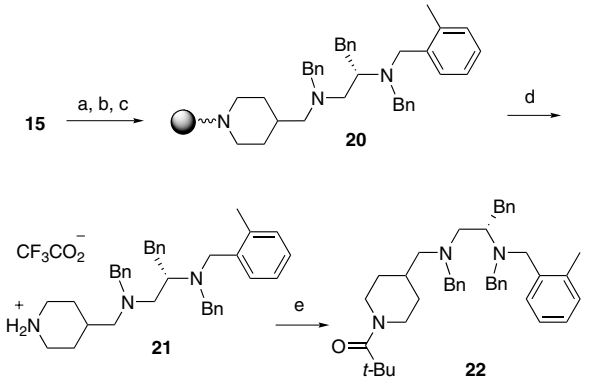
The preparation of the requisite piperidinyl diamine linker and its attachment to chlorotrityl polystyrene are exemplified with the preparation of acyclic secondary diamine **19** (Scheme 1). Thus, the selective monoprotection of **10** as bis-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene) ethyl] (Dde) derivative[12] **11** is followed by attachment of the latter to chlorotrityl resin. Removal of the protecting group using dilute methanolic hydrazine afforded primary amine **13**. Amino acid coupling using Fmoc-Phe-OH, followed by Fmoc removal and coupling with *ortho*-toluic acid provided common diamide precursor **14**. Reduction using the borane-promoted protocol afforded diamine **15**. At this stage, temporary protection of the thus formed amines as trifluoroacetamides is required in order to allow orthogonal derivatization of the anchoring secondary amine. Thus, treatment of **16** with TFA/$CH_2Cl_2$ afforded cleaved amine **17**. Its acylation as a pivaloyl amide followed by selective basic hydrolysis of the trifluoro-



**Scheme 1.** Reaction conditions: (a) 4-(aminomethyl)piperidine (1 equiv), Dde-OH (1.05 equiv), THF, rt, 1 h; (b) trityl chloride resin (1 equiv), 4-(Dde-aminomethyl) piperidine (4 equiv), DIPEA (4 equiv), DCM, rt, 3 h; (c) 2% $NH_2NH_2$/DMF, rt, 30 min; (d) HBTU, HOBt, DIPEA, Fmoc-L-phenylalanine; (e) 20% piperidine/DMF; (f) HBTU, HOBt, DIPEA, *o*-toluic acid; (g) $BH_3$/THF, 65 °C, 2 days; (h) piperidine, 65 °C, 16 h; (i) $(CF_3CO)_2O$ (10 equiv), pyridine (10 equiv), rt, 3 h; (j) 5% TFA/DCM, 30 min; (k) (*t*-BuCO)$_2$O (3 equiv), $Et_3N$ (3 equiv), THF, rt, 6 h; (l) 7% $K_2CO_3$ in MeOH/$H_2O$ (v/v 5:2), rt, 24 h.

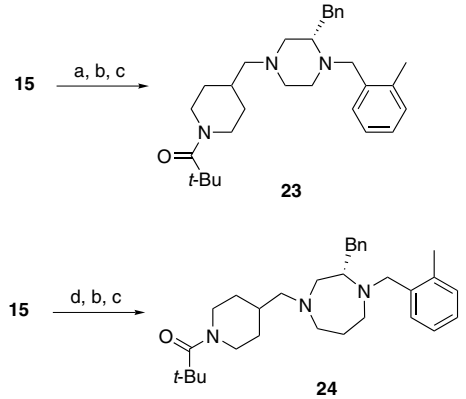
acetamide groups led to the crude diamine ligand **19**, which was purified by acid–base extractions or flash chromatography ($MeOH/CH_2Cl_2$). Acyclic secondary diamine **19** was obtained in >95% purity (HPLC–UV–ESMS) and 70% overall yield from chlorotrityl resin.[13]

Access to acyclic tertiary diamines from the common precursor **15** was best accomplished by the acylation of the two secondary amines followed by borane reduction, as opposed to a direct alkylation approach using alkyl halides. Thus, double benzoylation and reduction of **15** to give **20** were followed by resin cleavage and pivaloylation to afford tertiary diamine ligand **22** (Scheme 2). This product was obtained in 35% overall yield from chlorotrityl resin after flash-chromatography purification (>95% purity by HPLC–UV–ESMS).[13]




**Scheme 2.** Reaction conditions: (a) benzoyl chloride (10 equiv), DIPEA (10 equiv), THF, rt, 16 h; (b) 1 M $BH_3$–THF (20 equiv), THF, 65 °C, 3 days; (c) piperidine, 65 °C, 16 h; (d) 5% TFA/DCM, 30 min; (e) $(t\text{-BuCO})_2O$ (3 equiv), $Et_3N$ (3 equiv), THF, rt, 6 h.

Next, two model cyclic diamines, **23** and **24**, were targeted from the common resin-bound precursor **15** (Scheme 3). Chiral piperazinyl diamine **23** was synthesized by the slow addition of ethane 1,2-ditriflate to resin **15** in the presence of Hunig's base. Analysis of the cleaved product by HPLC–ESMS confirmed that no cross-linked derivatives, nor any other side-products, were formed. Then, cleavage of the product from the resin and pivaloylation of the anchoring amine as described above provided cyclic diamine ligand **23** in 32% overall yield (flash-chromatography, >95% purity by HPLC–UV–ESMS).[13] The seven-membered cyclic diamine **24** was synthesized using the same approach with propane 1,3-ditriflate as reagent (22% yield from chlorotrityl resin, flash-chromatography purification, >95% purity by HPLC–UV–ESMS).[13]




**Scheme 3.** Reaction conditions: (a) $TfOCH_2CH_2OTf$ (5 equiv), DIPEA (8 equiv), DCM, 0 °C, 5 h, then rt, 10 h; (b) 5% TFA/DCM, 30 min; (c) $(t\text{-BuCO})_2O$ (3 equiv), $Et_3N$ (3 equiv), THF, rt, 6 h; (d) $TfO(CH_2)_3OTf$ (5 equiv), DIPEA (8 equiv), DCM, 0 °C, 5 h, then rt, 10 h.

## 3. Conclusion

Herein, we have reported the design and successful evaluation of a solid-phase synthetic route for the preparation of diverse structural types of chiral diamine ligands. Key to this approach is the use of a non-interfering spacer, and an efficient orthogonal amine protection scheme. The wide scope of α-amino acids compatible with the borane-promoted peptide reduction protocol has already been demonstrated.[9] Thus, the use of functionalized α-aminoacids, coupled with the different structural types of diamines accessible using the approach shown herein, could greatly facilitate the synthesis of parallel libraries of chiral diamine ligands. These diamines could be rapidly screened in a wide variety of asymmetric reactions. Work in this direction is in progress.

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13. Characterization of model diamine ligands. Compound **19**: TLC: $R_f = 0.42$ ($CH_2Cl_2$–MeOH = 8:1). IR ($CH_2Cl_2$ cast film): 1626, 2920, 3024, 3311 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$ (ppm): 0.95–1.05 (m, 2H), 1.25 (s, 9H), 1.58–1.70 (m, 3H), 2.25 (s, 3H), 2.27 (dd, $J = 6.5$, 11.8 Hz, 1H), 2.31 (dd, $J = 6.6$, 11.8 Hz, 1H), 2.46 (dd, $J = 7.9$, 12.0 Hz, 1H), 2.58 (dd, $J = 3.9$, 12.0 Hz, 1H), 2.65 (dd, $J = 9.4$, 15.7 Hz, 1H), 2.77 (app. t, $J = 11.7$ Hz, 2H), 2.88–2.95 (m, 2H), 3.68 (d, $J = 12.9$ Hz, 1H), 3.79 (d, $J = 12.9$ Hz, 1H), 4.32 (br s, 1H), 4.35 (br s, 1H), 7.10–7.14

(m, 3H), 7.17–7.22 (m, 4H), 7.25–7.30 (m, 2H). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ (ppm): 19.1 ($CH_3$), 28.8 ($CH_3$), 31.80 ($CH_2$), 31.82 ($CH_2$), 37.4 (CH), 39.8 (C), 40.3 ($CH_2$), 46.5 ($CH_2$), 46.6 ($CH_2$), 50.0 ($CH_2$), 53.9 ($CH_2$), 56.1 ($CH_2$), 59.2 (CH), 126.9 (CH), 127.4 (CH), 128.4 (CH), 130.31 (CH), 130.33 (CH), 131.4 (CH), 137.6 (C), 139.1 (C), 140.5 (C), 178.3 (CO). LC–MS: Zorbax SB-C8 reverse-phase column (4.6 × 50 mm, 3.5 μm), solvent: $CH_3CN$ (0.1% TFA)/water (0.1% TFA) 5:95–85:15 over 5 min then held for 7 min, flow rate: 0.5 mL/min, 25 °C, UV-DAD (210 and 254 nm) and ESMS. $R_t$ = 9.669 min, % purity >99%. *m/z* $(M+1)^+$ = 436.3. HR-MS for $C_{28}H_{42}N_3O$: *m/z* $(M+H)^+$ calcd 436.3328 found 436.3323. $[\alpha]_D^{25} = +17.3$ (*c* 0.070, $CHCl_3$).

Compound **22**: TLC: $R_f$ = 0.37 (hexanes–EtOAc = 2:1). IR ($CH_2Cl_2$ cast film): 1627, 2849, 2925, 3025 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ (ppm): 0.72 (ddd, *J* = 3.4, 12.2, 12.2 Hz, 1H), 0.89 (ddd, *J* = 3.4, 12.2, 12.2 Hz, 1H), 1.29 (s, 9H), 1.48–1.58 (m, 1H), 1.63 (d, *J* = 12.2 Hz, 1H), 1.72 (d, *J* = 12.3 Hz, 1H), 2.10 (s, 3H), 2.10 (dd, *J* = 5.0, 12.8 Hz, 1H), 2.16 (dd, *J* = 5.7, 12.8 Hz, 1H), 2.49 (dd, *J* = 8.2, 12.6 Hz, 1H), 2.61–2.71 (m, 2H), 2.75 (dd, *J* = 4.1, 12.7 Hz, 1H), 2.77 (dd, *J* = 8.7, 13.9 Hz, 1H), 2.92 (dd, *J* = 5.5, 13.9 Hz, 1H), 3.07 (m, 1H), 3.35 (d,*J* = 13.6 Hz, 1H), 3.62 (d, *J* = 13.8 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 3.65 (s, 2H), 3.73 (d, *J* = 13.7 Hz, 1H), 4.19 (br d, *J* = 12.0 Hz, 1H), 4.28 (br d, *J* = 12.8 Hz, 1H), 7.02–7.32 (m, 19H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ (ppm): 19.3 ($CH_3$), 28.4 ($CH_3$), 30.8 ($CH_2$), 31.0 ($CH_2$), 34.5 (CH), 35.9 ($CH_2$), 38.7 (C), 45.0 ($CH_2$), 45.2 ($CH_2$), 51.1 ($CH_2$), 54.0 ($CH_2$), 55.4 ($CH_2$), 58.3 (CH), 60.5 ($CH_2$), 61.1 ($CH_2$), 125.6 (CH), 125.8 (CH), 126.6 (CH), 126.8 (CH), 126.9 (CH), 128.0 (CH), 128.1 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.6 (CH), 130.1 (CH), 136.8 (C), 137.3 (C), 139.7 (C), 139.9 (C), 141.1 (C), 176.0 (CO). LC–MS: see diamine **19** for conditions, $R_t$ = 13.155 min, % purity >95%. *m/z* $(M+1)^+$ = 616.4. HR-MS for $C_{42}H_{54}N_3O$ *m/z* $(M+H)^+$ calcd 616.4261, found 616.4265. $[\alpha]_D^{25} = -47.3$ (*c* 0.012, $CHCl_3$).

Compound **23**: TLC: $R_f$ = 0.30 (hexanes–EtOAc = 4:1). IR ($CH_2Cl_2$ cast film): 1628, 2924, 3023 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ (ppm): 1.02–1.11 (m, 2H), 1.28 (s, 9H), 1.58–1.69 (m, 1H), 1.76 (d, *J* = 13.0 Hz, 1H), 1.82 (d, *J* = 13.0 Hz, 1H), 2.02 (dd, *J* = 7.0, 12.2 Hz, 1H), 2.09 (dd, *J* = 7.5, 12.2 Hz, 1H), 2.14–2.26 (m, 2H), 2.26–2.33 (m, 1H), 2.38 (s, 3H), 2.33–2.48 (m, 2H), 2.68–2.82 (m, 4H), 2.83–2.92 (br t, 1H), 3.06 (d, *J* = 11.7 Hz, 1H), 3.50 (d, *J* = 12.0 Hz, 1H), 3.94 (d, *J* = 12.5 Hz, 1H), 4.39 (br s, 2H), 7.10–7.35 (m, 9H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ (ppm): 19.3 ($CH_3$), 28.5 ($CH_3$), 31.1 ($CH_2$), 31.3 ($CH_2$), 33.8 (CH), 38.7 (C), 45.28 ($CH_2$), 45.36 ($CH_2$), 45.39 ($CH_2$), 53.7 ($CH_2$), 56.7 ($CH_2$), 60.3 (CH), 64.5 ($CH_2$), 125.5 (CH), 125.8 (CH), 126.9 (CH), 128.3 (CH), 129.2 (CH), 129.6 (CH), 130.3 (C), 137.1 (C), 137.5 (C), 140.5 (C), 176.1 (CO). LC–MS: see diamine **19** for conditions, $R_t$ = 13.780 min, % purity >98%. *m/z* $(M+1)^+$ = 462.3. HR-MS for $C_{30}H_{43}N_3O$: *m/z* $(M+H)^+$ calcd 462.3479, found 462.3476. $[\alpha]_D^{25} = +49.5$ (*c* 0.012, $CHCl_3$).

Compound **24**: TLC: $R_f$ = 0.24 (hexanes–EtOAc = 1:1). IR ($CH_2Cl_2$ cast film): 1628, 2924, 3023, 3059 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 0.98–1.10 (m, 2H), 1.29 (s, 9H), 1.44–1.54 (m, 1H), 1.55–1.65 (m, 1H), 1.69 (d, *J* = 13.1 Hz, 1H), 1.75–1.90 (m, 2H), 2.20 (dd, *J* = 8.1, 12.4 Hz, 1H), 2.26 (dd, *J* = 6.4, 12.4 Hz, 1H), 2.31 (s, 3H), 2.45 (dd, *J* = 7.2, 13.8 Hz, 1H), 2.52–2.78 (m, 7H), 2.85 (dd, *J* = 5.3, 13.4 Hz, 1H), 2.90–3.04 (m, 2H), 3.78 (d, *J* = 12.2 Hz, 1H), 3.86 (d, *J* = 12.2 Hz, 1H), 4.36 (br s, 1H), 4.39 (br s, 1H), 7.06–7.34 (m, 9H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ (ppm): 19.2 ($CH_3$), 28.5 ($CH_3$), 27.0 ($CH_2$), 31.10 ($CH_2$), 31.14 ($CH_2$), 35.2 (CH), 38.6 ($CH_2$), 38.7 (C), 45.3 ($CH_2$), 45.4 ($CH_2$), 48.8 ($CH_2$), 55.9 ($CH_2$), 56.6 ($CH_2$), 58.5 ($CH_2$), 64.5 (CH), 65.1 ($CH_2$), 125.4 (CH), 125.7 (CH), 126.7 (CH), 128.1 (CH), 129.2 (CH), 129.5 (CH), 130.2 (CH), 137.2 (C), 138.2 (C), 140.8 (C), 176.1 (CO). LC–MS: see diamine **19** for conditions, $R_t$ = 9.170 min, % purity >98%, *m/z* $(M+H)^+$ = 476.4. HR-MS for $C_{31}H_{45}N_3O$: *m/z* $(M+H)^+$ calcd 476.3635, found: 476.3635. $[\alpha]_D^{25} = -21.1$ (*c* 0.013, $CHCl_3$).