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A new pseudo C_2-symmetric tertiary diamine for the enantioselective addition of MeLi to aromatic imines

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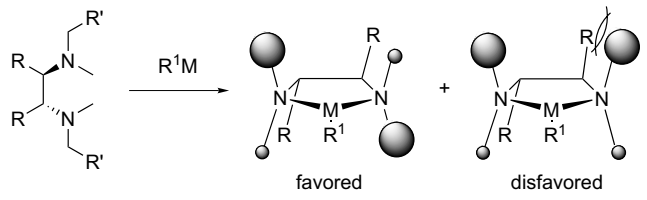
Abstract—A new tertiary pseudo C_2-symmetric 1,2-diamine derived from (1*S*,2*S*)-(+)-pseudoephedrine was synthesized and tested in the enantioselective addition of MeLi to aromatic imines. A comparative study with the analogous C_2-symmetric ligand successfully used previously in the same reaction showed comparable selectivity and better reactivity for this novel diamine.

1. Introduction

A large number of the 'privileged ligands'[1] used in asymmetric synthesis possess C_2-symmetry. The reason for choosing a C_2-symmetric ligand is to reduce the number of possible diastereoisomeric metal complexes, as well as the number of transition states. This consequence of C_2-symmetry can have a beneficial effect on stereocontrol, because the competing less selective pathways can be eliminated.

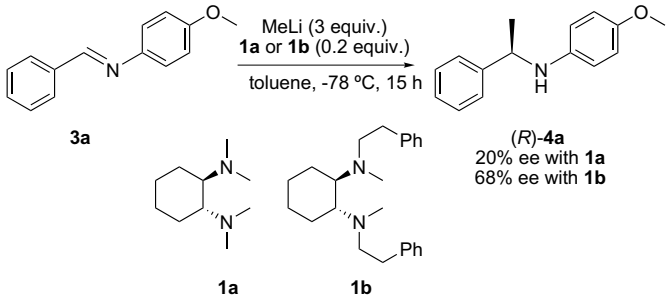
In our previous papers, we described conceptually new C_2-symmetric tertiary diamines in which nitrogen atoms could become stereogenic in the reactive species.[2] Upon complexation with a metal, it was expected that the diamine would adopt its most favored conformation in which the bulky substituent CH_2R' would be in a *trans* relationship with the R group of the chiral backbone. In this context, we could talk about chirality transfer from a chiral carbon backbone to a nitrogen atom, thus allowing space discrimination in a cyclic chelated intermediate (Scheme 1).



Scheme 1.

2. Results and discussion

This concept was validated during a study of the asymmetric addition of MeLi to *N*-*p*-methoxyphenyl imines promoted by C_2-symmetric tertiary diamines **1** based on the cyclohexane core. Whereas product **4a** was obtained in only 20% ee with *N*,*N*,*N*′,*N*′-tetramethylated diamine **1a**, 68% ee was achieved with diamine **1b** bearing two bulky phenethyl substituents on nitrogen (Scheme 2).[2]



Scheme 2.

Chirality transfer means that substitution on the nitrogen may govern the stereochemical pathway to a much greater extent than the chiral carbon backbone. It is reasonable to believe that the cyclohexane core could be changed to

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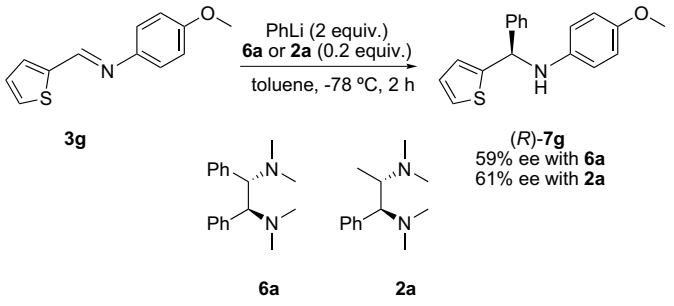
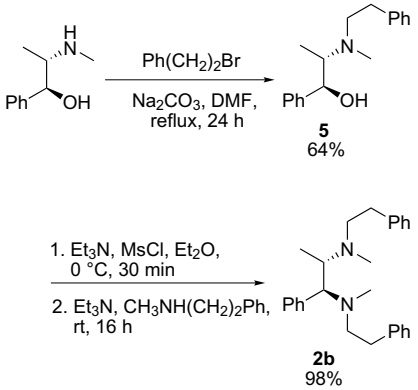
another chiral carbon backbone without significant loss of selectivity. This prompted us to design a new pseudo C_2-symmetric diamine **2b** based on the pseudoephedrine core. In previous work dealing with the addition of phenyllithium to the same kind of imines, it had been shown that pseudo C_2-symmetric ligand **2a** derived from (1*S*,2*S*)-(+)-pseudoephedrine gave the same results as C_2-symmetric **6a** derived from (1*S*,2*S*)-diphenyldiaminoethane (Scheme 3).[3] This represents an interesting feature given that pseudoephedrine derivatives could be easily prepared as described below. As an analogue of diamine **1b** bearing the same substituents on nitrogen atoms, it was expected that **2b** would afford the same level of enantioselectivity in the addition of MeLi to *N*-*p*-methoxyphenyl imines.



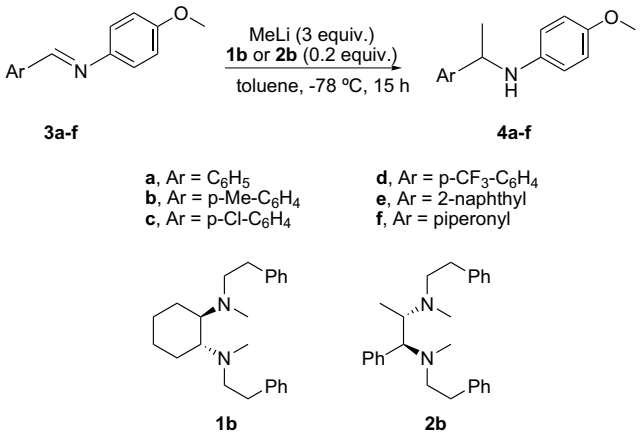
Scheme 3.

Diamine **2b** was synthesized in two steps starting from (1*S*,2*S*)-(+)-pseudoephedrine following literature procedures (Scheme 4). At first, N-alkylation[4] was carried out using anhydrous sodium carbonate and phenethyl bromide in refluxing DMF, affording amino alcohol **5** in 64% yield.[5] Subsequent mesylation followed by ring-opening of the aziridinium ion[6] with commercially available *N*-methyl phenethylamine cleanly afforded diamine **2b** with an overall retention of configuration in 98% yield.[7] Compound **2b** displays, in the ^{1}H NMR spectrum, a vicinal coupling constant of 10.1 Hz for the benzylic proton, which is characteristic of the pseudoephedrine relative stereochemistry.



Scheme 4.

Diamine **2b** was then tested in the enantioselective addition of MeLi to various *N*-*p*-methoxyphenyl imines (Scheme 5).[8] The same reaction conditions as previously reported[2] were applied for purposes of comparison with diamine **1b** (Table 1). It should be noted that substoichiometric amounts (20 mol %) of **2b** were used.



Scheme 5.

Table 1. Enantioselective addition of MeLi to imines **3a–f** promoted by diamines **1b** or **2b**

Entry	Product	Diamine	Yield (%)[a]	ee (%)[b,c]
1	**4a**	**1b**	100 (98)	68 (*R*)
2	**4a**	**2b**	85 (78)	60 (*S*)
3	**4b**	**1b**	50	74 (*R*)
4	**4b**	**2b**	63 (52)	69 (*S*)
5	**4c**	**1b**	66 (57)	68 (*R*)
6	**4c**	**2b**	71 (61)	58 (*S*)
7	**4d**	**1b**	55 (35)	58 (*R*)
8	**4d**	**2b**	100 (80)	58 (*S*)
9[d]	**4e**	**1b**	50 (42)	68 (*R*)
10[d]	**4e**	**2b**	17	55 (*S*)
11[e]	**4f**	**1b**	100 (88)	48 (*R*)
12[e]	**4f**	**2b**	100 (91)	30 (*S*)

[a] Determined by ^{1}H NMR spectroscopy of the crude. Yields in parenthesis refer to yields after column chromatography.
[b] Determined by SFC Columns Chiracel OD-H for **4a** and **4f**, Chiralpak AS-H for **4b**, **4c**, and **4e**, Chiralpak AD for **4d**.
[c] The absolute configuration of **4a** was determined on the basis of previous work. For other products, the configurations were assigned by consideration of the stereochemical pathway and of the systematic inversion of configuration occurring using **1b** or **2b**.
[d] Reaction carried out for 35 h at −78 °C.
[e] Reaction carried out for 15 h at −30 °C.

Initially, in almost all cases, better conversions were obtained with diamine **2b**. In particular, imine **3d** was totally converted to product **4d** using ligand **2b**, whereas only half conversion was reached using **1b** (entry 8 vs 7). However, for imines **3a** and **3e** bearing a non-substituted aromatic part, diamine **2b** was found to be less reactive than **1b** (entries 2 vs 1 and 10 vs 9). Systematic inversion of configuration was obtained for all products, as expected with the inversion of configuration at the chiral backbone of the diamine. In terms of selectivity, ee's induced by diamine **2b**, ranging from 30% to 69%, were comparable, although slightly lower, to those induced by diamine **1b**, ranging from 48% to 74%. This could be due to a less efficient chirality transfer in **2b** than in **1b**. These two diamines

induced the best selectivity with imine **3b** prepared from *p*-tolualdehyde (entries 3 and 4). An interesting point is that **4a** was obtained in 60% ee with **2b** (Table 1, entry 2) and in 20% ee with **1a** (Scheme 2), confirming that the substitution on the nitrogen may govern the stereochemical pathway to a much greater extent than the chiral carbon backbone.

3. Conclusion

In summary, novel chiral pseudo C_2-symmetric 1,2-diamine **2b** was easily synthesized in two steps starting from commercially available (1*S*,2*S*)-(+)-pseudoephedrine. It was tested as a ligand for the enantioselective addition of MeLi to aromatic imines **3a**–**f**. In comparison with the analogous C_2-symmetric cyclohexane diamine based **1b**, lower enantioselectivities and generally better conversions of products **4a**–**f** were obtained. This study shows the potential of pseudo C_2-symmetric diamines based on the pseudoephedrine core and describes a procedure that could be applied to the preparation of various other diamines possessing different substituents on nitrogen atoms.

Acknowledgement

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References

1. Yoon, P. Y.; Jacobsen, E. N. *Science* **2003**, *299*, 1691–1693.
2. (a) Kizirian, J.-C.; Caille, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 8893–8895; (b) Kizirian, J.-C.; Cabello, N.; Pinchard, L.; Caille, J.-C.; Alexakis, A. *Tetrahedron* **2005**, *61*, 8939–8946.
3. (a) Cabello, N.; Kizirian, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 4639–4642; (b) Cabello, N.; Kizirian, J.-C.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J.-C. *Eur. J. Org. Chem.* **2005**, 4835–4842.
4. Mealy, M. J.; Bailey, W. F.; Bech, S. M.; Luderer, M. R. WO Patent 082565, 2004.
5. (1*S*,2*S*)-(+)-2-(Methyl(phenethyl)amino)-1-phenylpropan-1-ol **5** was prepared according to the procedure described in Ref. 4: A suspension of (1*S*,2*S*)-(+)-pseudoephedrine (1.62 g, 9.80 mmol), anhydrous Na_2CO_3 (2.07 g, 19.5 mmol), and phenethyl bromide (1.66 mL, 12.2 mmol) in DMF (33 mL) was heated at reflux for 24 h. After cooling to room temperature, the mixture was filtered, and the filtrate partitioned between Et_2O and water. The layers were separated and the aqueous one extracted thoroughly with Et_2O. The combined organic layers were washed twice with water, once with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by distillation in a Kugelrohr apparatus (bp = 160 °C/0.3 mm Hg) to give **5** (1.69 g, 64%) as a yellow oil; $[\alpha]_D^{25} = +65.3$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.84 (d, $J = 6.6$ Hz, 3H), 2.44 (s, 3H), 2.65–3.00 (m, 5H), 4.29 (d, $J = 9.6$ Hz, 1H), 4.89 (br s, 1H), 7.28–7.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 7.3, 34.7, 36.0, 55.1, 65.7, 74.6, 126.1, 127.2, 127.5, 128.0, 128.3, 128.5, 139.8, 141.9; IR (neat): 3028, 2967, 1495, 1453, 1132, 1044, 750, 700 cm^{-1}; MS (EI), *m*/*z* (%): 268 (M−1), 178 (10), 163 (19), 162 (100), 148 (41), 106 (11), 105 (90), 91 (12), 84 (22), 77 (23), 58 (16); HRMS (ESI) calcd for $C_{18}H_{23}NO$ $[M+H]^+$ 270.1900, found 270.1855.
6. (a) Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663–1671; (b) O'Brien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304–307.
7. (1*S*,2*S*)-(+)-*N*,*N*′-Dimethyl-*N*,*N*′-diphenethyl-1-phenylpropane-1,2-diamine **2b** was prepared according to the procedure described in Ref. 6b: MsCl (0.20 mL, 2.58 mmol) was added dropwise to a stirred solution of amino alcohol **5** (584 mg, 2.17 mmol) and NEt_3 (0.50 mL, 3.60 mmol) in dry Et_2O (12 mL) at 0 °C under Ar. After 30 min, NEt_3 (0.60 mL, 4.30 mmol) was added and the mixture allowed to warm to room temperature. Then, commercially available *N*-methylphenethylamine (5.0 g, 37.0 mmol) was added and the mixture stirred vigorously overnight at room temperature. The layers were separated and the aqueous one extracted with Et_2O. The combined organic layers were washed with aqueous 5% $NaHCO_3$, water, dried over Na_2SO_4, and concentrated. The crude product was purified in a Kugelrohr apparatus by distillation of *N*-methylphenethylamine in excess to afford **2b** (836 mg, 99%) as a yellow oil; $[\alpha]_D^{25} = +19.1$ (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.63 (d, $J = 6.6$ Hz, 3H), 2.11 (s, 3H), 2.27 (s, 3H), 2.40–2.85 (m, 8H), 3.08–3.25 (m, 1H), 3.38 (d, $J = 10.1$ Hz, 1H), 6.80–6.98 (m, 2H), 7.00–7.25 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 11.1, 29.7, 34.6, 36.3, 37.4, 56.3, 56.5, 57.3, 70.9, 125.8, 127.8, 128.2, 128.3, 128.8, 129.2, 141.0; IR (neat): 3026, 2931, 1495, 1453, 1124, 1031, 748, 699 cm^{-1}; MS (EI), *m*/*z* (%): 388 (M+2, 8), 252 (10), 224 (67), 162 (100), 146 (12), 134 (15), 118 (16), 105 (85), 91 (59), 77 (23); HRMS calcd for $C_{27}H_{34}N_2$ 386.5723, found 386.2722.
8. Enantioselective addition of MeLi to aromatic imines **3a**–**f**. Typical procedure. MeLi (low halide, 0.90 mL as a 1.6 M solution in Et_2O) was added at −78 °C to a stirred solution of imine (0.48 mmol) and diamine (0.096 mmol) in dry toluene (8 mL). The mixture was stirred at −78 °C for 15 h unless otherwise indicated in Table 1. It was then quenched at low temperature with MeOH and then at room temperature with water. The organic layer was separated and the aqueous one was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated. ^{1}H NMR spectrum of this crude was analyzed to determine the conversion of the reaction. Finally, purification by silica gel column chromatography gave pure amines **4a**–**f** already fully characterized in Ref. 2b.