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Design and synthesis of new bidentate phosphoramidite ligands for enantioselective copper-catalyzed conjugate addition of diethylzinc to enones

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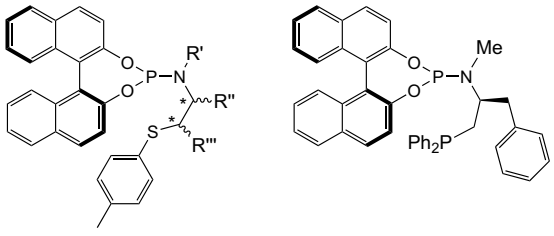
Abstract—Several thioaryl- and phosphino-phosphoramidite ligands have been synthesized from commercially available β-aminoalcohols. This new family of bidentate ligands are highly active in the enantioselective copper-catalyzed conjugate addition of diethylzinc to both cyclic and acyclic enones showing moderate to good enantiomeric excesses of up to 81%.

1. Introduction

The 1,4-conjugate addition of nucleophilic reagents to α,β-unsaturated compounds is one of the most powerful methods for the formation of carbon–carbon bonds in organic synthesis.[1] Most efforts have been realized through the development of copper[2] and rhodium[3] asymmetric conjugate addition of various alkylmetal (organozinc reagents,[4] organoaluminium reagents[5] and Grignard reagents)[6] and arylboronic acids[7] to cyclic and acyclic unsaturated carbonyls. Phosphoramidites have proved to be particularly efficient in a wide range of catalyzed reactions.[8] Although monodentate phosphoramidites are commonly used in Cu-catalyzed asymmetric conjugate addition of diorganozinc reagents,[9] only one example of bidentate phosphoramidites[10] has been reported for that reaction.[10d]

Herein, we report the design and the synthesis of new bidentate phosphoramidite ligands **1** and **2** derived from commercially available β-aminoalcohols (Fig. 1). These ligands have been evaluated in the enantioselective copper-catalyzed conjugate addition of diethylzinc to both cyclic and acyclic enones.



1 2

Figure 1. Easily available thioaryl- or phosphine-phosphoramidite **1** and **2**.

2. Results and discussion

Various phosphoramidite ligands, bearing a BINOL moiety along with various amine moieties, were synthesized to study the influence of steric hindrance and rigidity towards selectivity. Ligands **1a–f** were synthesized following the simple procedure described in Scheme 1. Mesylates **3a–c**[11] were treated with sodium thiocresolate to give thioethers **4a–c**. Then, reduction of the Boc group with $LiAlH_4$ gave methyl amines **5a–c**. Alternatively, **4b** was deprotected under classical conditions to afford amine **5d**, which was then converted under reductive amination conditions to **5d**.

Ligands **1a–f** were obtained from amines **5a–d** and BINOL following a classical procedure:[12] PCl_3 was reacted with amines **5a–d** in the presence of Et_3N at 75 °C. Then, at

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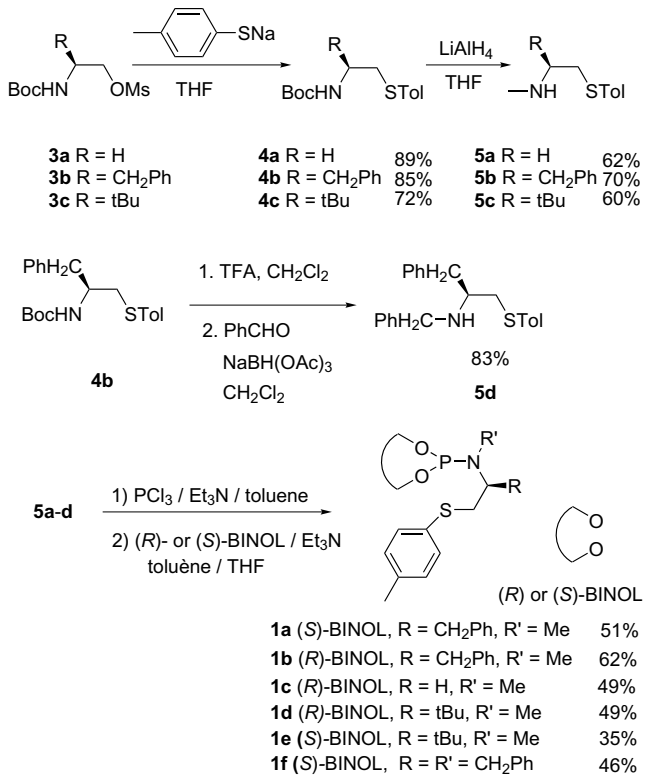
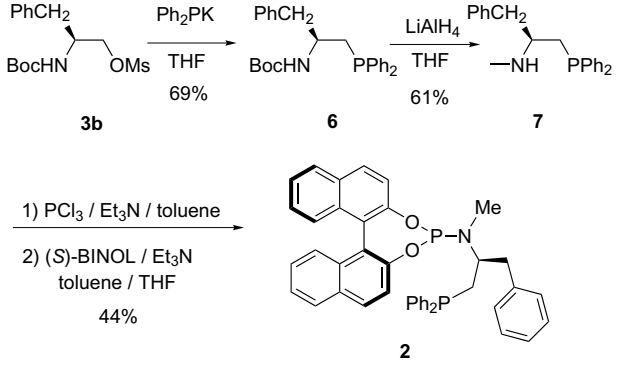
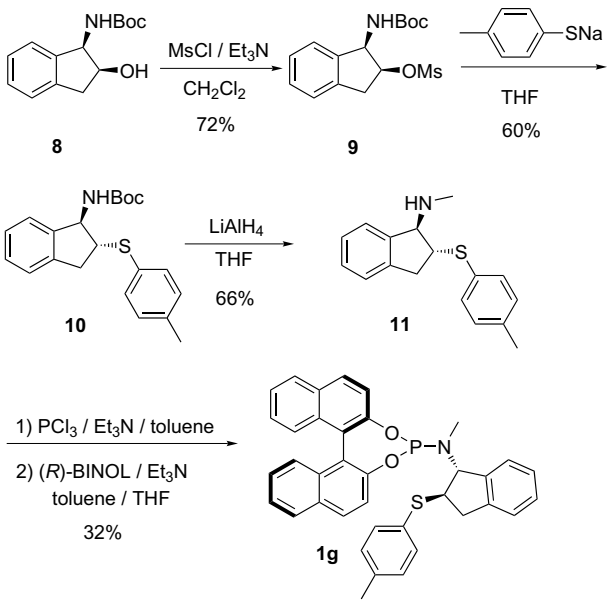


Scheme 1. Synthesis of ligands **1a**–**f**.

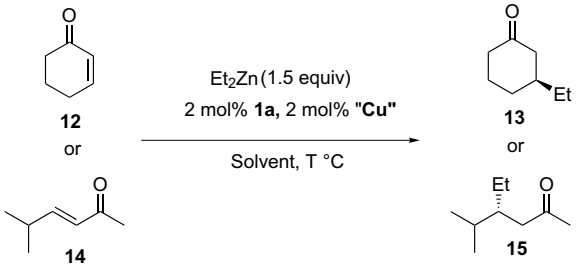


Scheme 2. Synthesis of ligand **2**.



Scheme 3. Synthesis of ligand **1g**.

Table 1. Optimization of the reaction conditions with ligand **1a**



Entry	Enone	Cu complex	Solvent	Temp (°C)	Time (h)	Conv.[a] (%)	ee[b] (%)
1	**12**	$Cu(OTf)_2$	Et_2O	rt	12	>99	56 (*S*)
2	**12**	CuTC	Et_2O	rt	3	>99	54 (*S*)
3	**12**	CuTC	Et_2O	0	3	>99	72 (*S*)
4	**12**	CuTC	Et_2O	−30	6	84	81 (*S*)
5	**12**	CuTC	Toluene	0	3	90	57 (*S*)
6	**14**	CuTC	Toluene	−30	8	69	32 (*R*)
7	**14**	CuTC	Toluene	0	3	90	57 (*R*)
8	**14**	CuTC	Et_2O	0	3	93	63 (*R*)

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis (Lipodex E).

−78 °C, a solution of BINOL and Et_3N was added. Phosphoramidites were isolated in moderate yields after chromatography. Ligand **2** was obtained from mesylate **3b** following a similar procedure, except that Ph_2PK was used instead of sodium thiocresolate (Scheme 2). Ligand **1g** was obtained from protected (1*R*,2*S*)-1-amino-2-indanol **8** following a similar route (Scheme 3). Both phosphoramidites were isolated in moderate yields after chromatography.

We then evaluated their potential in the enantioselective copper-conjugate addition of diethylzinc on 2-cyclohexenone **12** and 5-methyl-3-hexen-2-one **14** (Table 1). We began the study with the thiocresol-phophoramidite ligand **1a** derived from (*S*)-phenylalaninol and (*S*)-BINOL. When we used 2 mol% of copper(II) triflate ($Cu(OTf)_2$) as the pre-catalyst and 2 mol% of **1a**, addition of diethylzinc to 2-cyclohexenone **12** in diethylether at room temperature yielded (*R*)-adduct **13** in complete conversion after 12 h and 56% ee (entry 1).

Replacement of the precatalyst by a more soluble copper complex such as copper(I) thiophencarboxylate (CuTC)[9b,13] considerably accelerated the rate of the addition (3 h instead of 12 h) and increased the selectivity to 72% ee (entry 2). The choice of the solvent and the temperature appeared to be important (entries 2–5). The selectivity proved to be dependant on the solvent and the

substrate. For example, the best selectivity (81% ee) was observed at −30 °C with 2-cyclohexenone (entry 4), while in toluene the best result was obtained at 0 °C with enone **14**. In the furthest studies, the reactions were carried out at 0 °C, as the reaction was found to be sometimes very slow at −30 °C in the presence of some substrates (e.g., 12% conversion after 6 h with dimethylcyclohexenone, Table 3, entry 1). The best results were obtained in Et_2O as the solvent (see for instance entries 3 and 5).

Having identified these optimal reaction conditions, we screened various chiral ligands to determine the most efficient ones (Table 2). Firstly, because this bidentate ligand possessed two chiral moieties,[2a] we evaluated ligand **1b** derived from (*R*)-BINOL and (*S*)-phenylalaninol. 56% enantiomeric excess was obtained for the addition of diethylzinc to 2-cyclohexenone (entry 2) instead of 72% obtained with **1a** (entry 1). This clearly shows the mismatched effect occurring in ligand **1b**. Secondly, the absence of a stereogenic centre on the amine moiety of the phosphoramidite ligand led to a slight decrease in selectivity (65% ee, entry 3). Moreover, when a more bulky group such as a *tert*-butyl was introduced (**1e**, entry 5), lower activity (72% of conversion) and selectivity (56% ee) were observed. The substitution of the *N*-methyl group in ligand **1a** by a benzyl group (ligand **1f**, entry 6) did not allow to increase the selectivity (66% ee), but led to a dramatic loss of activity (only 54% of conversion after 4 h). In order to reduce the flexibility of the chiral chelating side chain at the amine moiety, we introduced the indane framework (ligand **1g**). Whereas ligands **1a** and **1g** were similar in activity, the selectivity observed with **1g** was much lower, reaching only 47% ee (entry 7). This had been confirmed by the use of ligand **16** possessing a thiomethylether aryl group as chelating side chain. No selectivity was observed in this case (entry 8). Finally, ligand **2**, to which the initial thioaryl chelating group has been replaced by a diphenylphosphine function, was evaluated. In this case, the activity remained similar but the selectivity decreased to 53% ee (entry 9). Concerning the addition of diethylzinc to the acyclic enone **14**, a rapid screening of the ligands showed that **1a** provided the best stereoselectivity (63% ee, entry 10) while the diphosphine analogue **2** yielded poor results both in activity and selectivity (entry 12).

Having established the best ligand for the conjugate addition, we then evaluated the activity of ligand **1c** towards other cyclic enones (Table 3). In the case of more hindered substrates, such as 4,4-dimethylcyclohexenone, a moderate conversion was obtained after 6 h at 0 °C with 78% ee (entry 1). Addition of Et_2Zn to 2-cycloheptenone (entry 2) was achieved over 6 h with 64% ee. We next screened several

Table 2. Enantioselective copper-catalyzed conjugate addition of diethylzinc to cyclic and acyclic enones with ligand **1a**

Entry	Enone	Ligand	Time (h)	Yield[a] (%)	ee (%)[b]
1	**12**	**1a**	3	>99	72 (*S*)
2	**12**	**1b**	4	96	56 (*R*)
3	**12**	**1c**	3	93	65 (*R*)
4	**12**	**1d**	2.5	>99	30 (*R*)
5	**12**	**1e**	6	72	56 (*S*)
6	**12**	**1f**	4	54	66 (*S*)
7	**12**	**1g**	3	>99	47 (*R*)
8	**12**	**16**	3	>99	0
9	**12**	**2**	3	97	53 (*S*)
10	**14**	**1a**	3	93	63 (*R*)
11	**14**	**1c**	5	80	33 (*S*)
12[c]	**14**	**2**	4	66	5 (*S*)

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis (Lipodex E).
[c] Reaction performed in toluene.

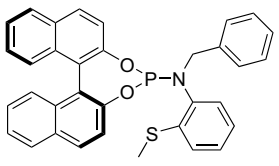


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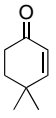
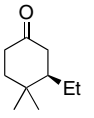
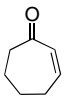
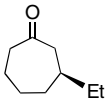
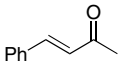
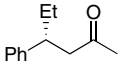
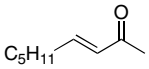
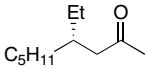
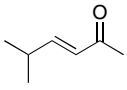
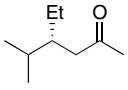
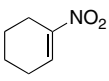
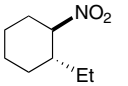
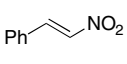
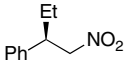
Table 3. Enantioselective copper-catalyzed conjugate addition of diethylzinc to cyclic and acyclic enones with ligand **1a**

Entry	Substrate	Product	Time (h)	Conv.[a] (%)	ee[b] (%)
1			6 6[c]	60 12	78 80
2			6	96	64
3			1	>99	17
4			1	96	52
5			3.5	93	63
6			6	82	16
7			4	>99	6

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis (Lipodex E).
[c] Reaction performed at −30 °C.

other Michael acceptors with acyclic enones and nitroalkenes.[14] These substrates, which are known to be problematic, were tested under identical conditions at 0 °C. Whereas the high reactivity of the catalytic system was found to be good for all substrates, we have been disappointed in the moderate stereoselectivity of the addition. 63% ee was observed in the best case with acyclic enones (entry 5). Moreover, lower enantioselectivities were observed for the nitroalkene family, with which no value over 16% ee was obtained (entries 6 and 7). These last results clearly show the scope of use of this bidentate phosphoramidite family in the copper-catalyzed conjugate addition.

3. Conclusion

In conclusion, a new family of chiral bidentate phosphoramidite ligands was designed and synthesized easily in a five-step procedure. High reactivities and good enantioselectivities were obtained in the copper-conjugate addition of diethylzinc to cyclic and acyclic enones using the thioaryl-phosphoramidite ligand **1c** (up to 81% ee). A study in the use of ligands **1c** and **2** in asymmetric hydrogenation is currently under progress and will be reported in due course.

Acknowledgements

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References

1. (a) Perlmutter, P. *Conjugate Addition Reaction in Organic Synthesis*. In *Tetrahedron Organic Chemistry Series, No. 9*; Pergamon Press: Oxford, 1992; (b) Yamamoto, Y. *Methods Org. Chem.* **1995**, *4*, 2041–2057.
2. (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236; (b) Krause, N.; Hoffman-Röder, A. *Synthesis* **2001**, 171–196; (c) Ferringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353.
3. Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844.
4. For recent examples, see: (a) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779; (b) Krauss, I. J.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3201; (c) Clavier, H.; Coutable, L.; Guillemin, J. C.; Mauduit, M. *Tetrahedron: Asymmetry* **2005**, *16*, 921–924.
5. For examples, see: (a) Diégez, S. M.; Deeremberg, O.; Claver, C.; Van Leeuwen, P. W. N. M.; Kramer, P. *Tetrahedron: Asymmetry* **2000**, *11*, 3161–3166; (b) Fraser, P. K.; Woodward, S. *Chem. Eur. J.* **2003**, *9*, 776–783; (c) D'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378.
6. For examples, see: (a) Lopez, F.; Harutyunyan, S. R.; Meetsma, A.; Minaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2752–2756; (b) Lee, K.-S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184; (c) Martin, D.; Kehrli, S.; D'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417.
7. Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580.
8. See for instance: (a) Zhang, A.; Rajanbabu, T. V. *J. Am. Chem. Soc.* **2006**, *128*, 5620–5621; (b) Bernsmann, H.; van der Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; de Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943–951; (c) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192–17193; (d) Jensen, J. F.; Svendsen, B. Y.; la Cour, T. V.; Pedersen, H. L.; Johannsen, M. *J. Am. Chem. Soc.* **2002**, *124*, 4558–4559, and references cited therein.
9. See for instance: (a) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701; (b) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263.
10. (a) Huang, J. D.; Hu, X. P.; Duan, Z. C.; Zeng, Q.-H.; Yu, S. B.; Deng, J.; Wang, D. Y.; Zheng, Z. *Org. Lett.* **2006**, *8*, 4367–4370; (b) Zeng, Q. H.; Hu, X. P.; Duan, Z. C.; Liang, X. M.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 1233–1238; (c) Hu, X. P.; Zheng, Z. *Org. Lett.* **2005**, *7*, 419–422; (d) Mandoli, A.; Arnold, L. A.; de Vries, A. H. M.; Salvadori, P.; Feringa, B. L. *Tetrahedron: Asymmetry* **2001**, *12*, 1929–1937; (e) Francio, G.; Faraone, F.; Leitner, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1428–1430.
11. (a) Rosenquist, A.; Thorstensson, F.; Johansson, P. O.; Kvarnstroem, I.; Ayesa, S.; Classon, B.; Rakos, L.; Samuelsson, B. PCT Int. Appl. WO073216, 2005; (b) Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 3759–3766; (c) Shirude, P. S.; Kumar, V. A.; Ganesh, K. N. *Tetrahedron* **2004**, *60*, 9485–9491.
12. (a) De Vries, A. H. M.; Meetsma, A.; Ferringa, B. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374–2376; (b) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *1*, 79–80.
13. Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91–93.
14. (a) Duncan, A. P.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4117; (b) Polet, D.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 1529; (c) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829.