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Biphenol-based ligands for Cu-catalyzed asymmetric conjugate addition

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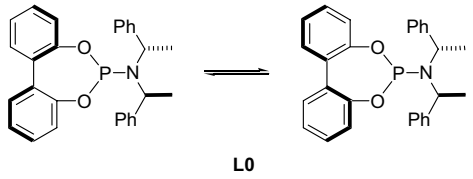
Abstract—The synthesis and characterization of seven new phosphoramidite ligands are described, as well as their use in copper-catalyzed 1,4-addition of diethylzinc to a wide range of substrates. Enantioselectivities of up to >99.5% are obtained.

1. Introduction

The conjugate addition reaction has seen an impressive amount of development over the past decade.[1] Among the whole variety of ligands used in this reaction, phosphorus-based ones are by far the most widely used chiral source.[1f] The combination of such ligands with the use of dialkylzinc reagents has made this enantioselective methodology extensive and successful.[2] Any kind of trivalent phosphorus ligands (phosphanes, phosphites, phosphoramidites, phosphonites) strongly accelerates the reaction.[3]

We have recently demonstrated that phosphoramidite ligands based on the atropoisomerically flexible biphenol unit (Scheme 1) are excellent ligands.[4] Thus, the induced atropoisomerism of ligand **L0** allows high enantioselectivity in the asymmetric conjugate addition of dialkyl zincs to a variety of Michael acceptors.



L0

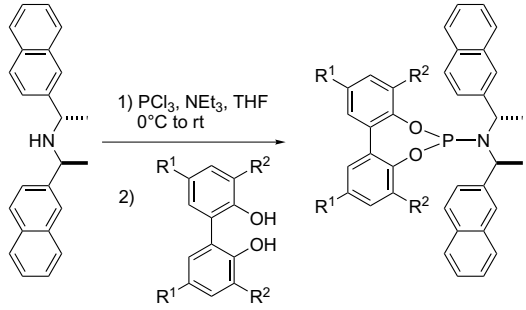
Scheme 1. Conformational atropoisomerism of **L0**.

The modularity of these phosphoramidite ligands allows for easy variation of the amino part as well as the biphenol part. We report herein the modification of the biphenol scaffold of **L0**, together with a new amine moiety and the consequence of the enantioselectivity on the transformation of each substrate, in the presence of these new ligands.

2. Results and discussion

Using a bis-(*S*)-(1-naphthalen-2-yl-ethyl)-amine derivative,[5] we modified the biphenol core by introducing

Table 1. Synthesis of phosphoramidite ligands **L1**–**7**



B1-7

Entry	Ligand	R^1	R^2	Yield[a] (%)
1	**L1**	H	H	50
2	**L2**	Me	Me	55
3	**L3**	Cl	Cl	37
4	**L4**	Me	OMe	27
5	**L5**	H	Allyl	26
6	**L6**	H	Methallyl	53
7	**L7**	Ph	Ph	44

[a] Determined after alumina chromatography.

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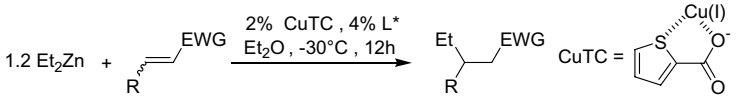
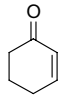
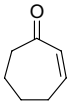
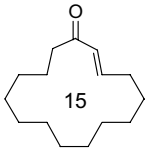
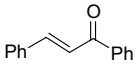
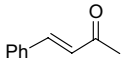
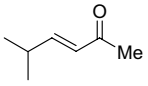
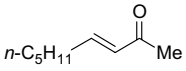
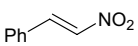
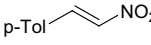
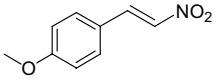
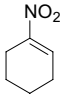
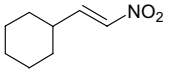
different functional groups at the *ortho*, *ortho'*-positions (R^2, Table 1). For some biphenols, it was easier to introduce an additional substitution at the R^1 position, although the latter does not play a significant role.[6] All ligands **L1**–**7** were synthesized by reaction of the chiral amine with PCl_3, followed by addition of the biphenol **B1**–**7**. They were isolated either as white powders or colorless oils in 26–55% yields.

All the ligands were screened under previously reported new experimental conditions[7] with a variety of Michael acceptors, such as cyclic and acyclic enones and nitro-olefins (Table 2).

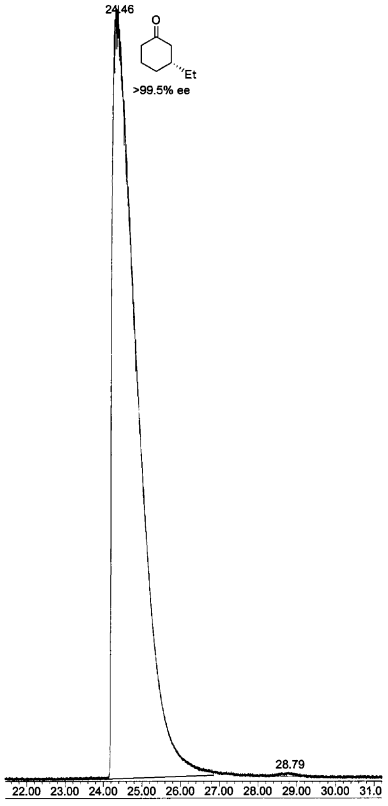
The replacement of the usual bis-(*S*)-(1-phen-2-yl-ethyl)-amine by the new amine bis-(*S*)-(1-naphthalen-2-yl-ethyl)-amine brings a larger steric requirement, which has some positive effects on the enantioselectivity. However, in some other cases, the steric hindrance causes negative effects. Associated with a simple biphenol unit (ligand **L1**) there was no notable improvement. Ligands **L2** and **L5** both have in common a small *ortho*-substituent on the biphenol part (Me for **L2** and allyl for **L5**). The results with cyclohexenone and cycloheptenone (representative of cyclic enones) were impressive; cyclohexenone afforded the highest reported ee (see Table 2 and Scheme 2). The results with other substrates were

Table 2. Enantioselective copper-catalyzed 1,4-addition of diethylzinc on various substrates



Entry	Substrate	Conversion%, ee%,[a] (absolute stereochemistry)						
		L1	**L2**	**L3**	**L4**	**L5**	**L6**	**L7**
1		>99, 89, (*R*)[b]	>99, **99.5**, (***R***)[c]	>99, 95, (*R*)	>99, 98, (*R*)	>99, **99.3**, (***R***)	>99, 98, (*R*)	94, 90, (*R*)[c]
2		>99, 95, (*R*)[b]	>99, **98**, (***R***)	98, 72, (*R*)	>99, **98**, (***R***)	>99, **98**, (***R***)	>99, 94, (*R*)	>99, 92, (*R*)[c]
3		>99, 47, (+)[b]	>99, 54, (+)	>99, 20, (−)	98, 34, (+)	98, 26, (+)	91, 17, (−)	>99, 10, (+)[c]
4		>99, 30, (*S*)[b]	>99, 39, (*S*)	>99, 9, (*S*)	>99, 40, (*S*)	90, 71, (*R*)	88, 71, (*R*)	>99, 47, (*S*)[c]
5		>99, 60, (*S*)[b]	99, **81**, (***S***)	24, 12, (*S*)	80, 60, (*S*)	—	33, 72, (*S*)	93, 50, (*S*)[c]
6		>99, 32, (*R*)[b]	>99, 41, (*R*)	40, 15, (*R*)	95, 7, (*R*)	>99, 80, (*R*)	99, **90**, (***R***)	—
7		97, 74, (*S*)[b]	>99, 74, (*S*)	>99, 63, (*S*)	95, 72, (*S*)	>99, 42, (*S*)	>99, 6, (*R*)	>99, 35, (*S*)[c]
8		—	>99, 72, (*R*)	>99, 40, (*S*)	>99, 59, (*S*)	>99, **86**, (***S***)	>99, 73, (*S*)	—
9		—	—	—	>99, 54, (*S*)	>99, **87**, (***S***)	>99, 74, (*S*)	—
10		—	—	—	>99, 70, (*S*)	>99, **90**, (***S***)	>99, 51, (*S*)	—
11		—	>99, **94**, (***S***)[c]	—	—	—	—	—
12		—	90, 80, (+)[c]	—	>99, **90**, (+)	95, 82, (+)	>99, 81, (+)	—

[a] The best ee for each substrate is in bold.
[b] $Cu(OTf)_2$, toluene.
[c] $Cu(OAc)_2 \cdot H_2O$, Et_2O.



Scheme 2. Chromatogram of ethylcyclohexanone, using **L2**.

also among the best: 81% ee for benzalacetone (entry 5), 94% for nitrocyclohexene (entry 11) with **L2**; 86% ee for nitrostyrene (entry 8), 90% for *p*-methoxynitrostyrene (entry 10) with **L5**.

The presence of electron-withdrawing groups on the biphenol unit (ligand **L3**) had a detrimental effect, particularly with acyclic enones and nitro-olefins. The potential chelation with an *ortho*-methoxy group was considered with ligand **L4**. The enantioselectivities with the cyclic enones were excellent (both 98% ee), but much less pronounced with acyclic enones. Surprisingly, this ligand gave the best ee with cyclohexyl nitroethene: 90% (entry 12).

The *ortho*-methallyl group of ligand **L6** brings a slightly higher steric requirement than the allyl group of **L5**. This subtle difference was enough to improve the ee to 90% for methyl-hexenone (entry 6); however, in general, the enantioselectivities were lower. An even larger *ortho*-group, such as phenyl (ligand **L7**) clearly has a negative effect.

3. Conclusion

This series of new ligands shows that the steric requirements, either on the biphenol part, or on the amino part, of the phosphoramidite ligand has a strong influence with small groups (Me, allyl) having a favorable influence on a wide range of substrates. In contrast, larger groups (Ph) impede the coordination of the ligand with Cu, resulting in lower enantioselectivities. In summary, some of the new phosphoramidite ligands, based on the induced atropoisomerism of the biphenol unit, are the best ligands for cyclohexenone and many nitro-olefins, although no ligand showed general enantioselectivity on every substrate.

4. Experimental

4.1. General procedure for the ligand synthesis

To a stirred mixture of Et_3N (111 mmol) and PCl_3 (22.2 mmol) at 0 °C, a solution of bis-(*S*)-(1-naphthalen-2-yl-ethyl)-amine (22.2 mmol) in THF (10 mL) was added and the reaction mixture stirred for 3 h at room temperature. Biphenol (22.2 mmol) in a solution of THF (5 mL) was slowly added to the reaction mixture at 0 °C and then the suspension stirred at room temperature overnight. The suspension was diluted in toluene (8 mL) and filtered on neutral alumina and the solution then concentrated and purified by flash chromatography through neutral alumina using pure toluene as eluent, to give the pure ligand as either a white solid or a colorless oil.

4.2. (5,7-Dioxa-6-phospha-dibenzo[*a*,*c*]cyclohepten-6-yl)-bis-(*S*)-(1-naphthalen-2-yl-ethyl)-amine, L1

Yield 50%; white foam; $[\alpha]_D^{20} = -404.9$ (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.17 (m, 22H), 4.82–4.78 (m, 2H), 1.90 (d, 6H, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 151.8, 151.0, 140.4, 132.9, 132.4, 131.2, 130.0, 129.8, 129.2, 129.0, 128.2, 127.9, 127.3, 127.0, 126.1, 125.7, 125.6, 125.3, 124.7, 124.1, 122.5, 122.1, 52.8, 52.7, 22.1. ^{31}P NMR (203 MHz; $CDCl_3$) δ 146.3.

4.3. Bis-(*S*)-(1-naphthalen-2-yl-ethyl)-(2,4,8,10-tetramethyl-5,7-dioxa-6-phospha-dibenzo[*a*,*c*]cyclohepten-6-yl)-amine, L2

Yield 55%; white foam; $[\alpha]_D^{20} = -435.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H, $J = 6.8$ Hz), 7.52–7.02 (m, 16H), 4.89 (m, 2H), 2.55 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H), 2.11 (s, 3H), 1.85 (d, 6H, $J = 4.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 141.2, 133.8, 133.3, 133.1, 132.7, 131.4, 130.6, 130.5, 129.7, 128.6, 128.2, 127.7, 127.6, 127.2, 126.6, 126.0, 125.8, 53.1, 53.0, 21.2, 17.8, 16.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 142.0.

4.4. Bis-(*S*)-(1-naphthalen-2-yl-ethyl)-(2,4,8,10-tetrachloro-5,7-dioxa-6-phospha-dibenzo[*a*,*c*]cyclohepten-6-yl)-amine, L3

Yield 37%; white foam; $[\alpha]_D^{20} = -417.0$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.66–7.40 (m, 18H), 4.90

(m, 2H), 1.93 (d, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 146.9, 145.8, 139.7, 132.8, 132.4, 130.2, 130.0, 128.2, 127.9, 127.8, 127.7,127.4, 127.3, 126.3, 125.9, 125.7, 125.6, 125.4, 124.8, 55.2, 53.3, 24.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 148.1.

4.5. (4,8-Dimethoxy-2,10-dimethyl-5,7-dioxa-6-phospha-dibenzo[*a*,*c*]cyclohepten-6-yl)-bis-(*S*)-(1-naphthalen-2-yl-ethyl)-amine, L4

Yield 27%; white foam; $[\alpha]_D^{20} = -408.7$ (c 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.19 (m, 14H), 6.92 (d, 1H, $J = 1.2$ Hz), 6.89 (d, 1H, $J = 1.0$ Hz), 6.81 (d, 1H, $J = 1.8$ Hz), 6.74 (d, 1H, $J = 1.8$ Hz), 4.87–4.79 (m, 2H), 3.97 (s, 3H), 3.66 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 1.90 (d, 6H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 151.3, 140.9, 133.8, 133.1, 133.0, 132.3, 131.8, 130.7, 129.1, 128.3, 127.9, 127.3, 127.2, 127.0, 126.1, 125.4, 125.3, 122.0, 121.8, 113.0, 112.4, 56.2, 55.7, 53.1, 52.9, 21.5, 21.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 146.1.

4.6. (4,8-Diallyl-5,7-dioxa-6-phosphadibenzo[*a*,*c*]cyclo-hepten-6-yl)-bis-(*S*)-(1-naphthalen-2-yl-ethyl)-amine, L5

Yield 26%; colorless oil; $[\alpha]_D^{20} = -347.0$ (c 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.69 (d, 2H, $J = 7.4$ Hz), 7.56–7.16 (m, 18H), 6.09 (ddt, 1H, $J = 16.9$, 10.1, 6.6 Hz), 5.76 (ddt, 1H, $J = 16.9$, 10.1, 6.5 Hz), 5.23 (dq, 1H, $J = 16.9$, 1.7 Hz), 5.17 (dd, 1H, $J = 10.0$, 1.8 Hz), 4.87 (m, 2H), 4.84 (dq, 1H, $J = 10.1$, 1.3 Hz), 4.70 (dq, 1H, $J = 17.0$, 1.6 Hz), 3.94 (dd, 1H, $J = 15.2$, 6.5 Hz), 3.61 (dd, 1H, $J = 15.3$, 6.9 Hz), 3.15 (d, 2H, $J = 6.5$ Hz), 1.87 (d, 6H, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$), δ 149.6, 149.5, 148.8 (d), 136.6, 136.4, 133.0, 132.7, 132.4, 131.9, 131.8 (d), 130.7 (d), 129.7, 129.6, 129.1, 128.6, 128.5, 128.2, 127.9 (d), 127.4, 127.3, 126.9, 126.3 (d), 125.7, 125.6, 125.3, 124.4, 123.9, 116.2, 115.7, 52.8, 52.7, 35.5, 34.4; ^{31}P NMR (203 MHz, $CDCl_3$) δ 144.3.

4.7. [4,8-Bis-(2-methyl-allyl)-5,7-dioxa-6-phospha-di-benzo[*a*,*c*]cyclohepten-6-yl]-bis-(*S*)-(1-naphthalen-2-yl-ethyl)-amine, L6

Yield 53%; colorless oil; $[\alpha]_D^{20} = -249.1$ (c 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.71 (d, 2H, $J = 7.7$ Hz), 7.52–7.17 (m, 18H), 4.90 (s, 1H), 4.86 (s, 2H), 4.82 (s, 1H), 4.68 (s, 1H), 4.35 (s, 1H), 4.02 (d, 1H, $J = 14.5$ Hz), 3.49 (d, 1H, $J = 14.7$ Hz), 3.16 (d of AB system, 1H, $J = 16.7$ Hz), 3.12 (d of AB system, 1H, $J = 17.4$ Hz), 1.89–1.82 (m, 9H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 149.9, 149.8, 149.0 (d), 144.7, 144.2, 132.9, 132.4, 132.1 (d), 131.9 (d), 131.4, 130.7, 130.6, 130.6, 130.2, 130.1, 129.0, 128.6, 128.5, 128.2, 127.3 (d), 126.2, 125.5, 124.2, 123.6, 111.9, 111.6, 52.6, 52.5, 50.7, 39.4, 37.9, 22.9, 22.8, 22.6; ^{31}P NMR (203 MHz, $CDCl_3$) δ 144.0.

4.8. Bis-(*S*)-(1-naphthalen-2-yl-ethyl)-(2,4,8,10-tetraphen-yl-5,7-dioxa-6-phospha-dibenzo[*a*,*c*]cyclohepten-6-yl)-amine, L7

Yield 44%; white foam; $[\alpha]_D^{20} = -263.0$ (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.82–7.23 (m, 38H), 4.30 (m, 2H), 1.11 (d, 6H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 147.6, 143.1, 140.3, 138.3, 137.6, 132.7, 128.9, 128.8, 128.2 (d), 128.1, 127.9, 127.8, 127.7, 127.6, 127.1 (d), 127.0, 126.9, 125.9, 125.4, 124.8, 55.2, 24.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 145.7.

4.9. General procedure for the asymmetric conjugate addition

To a solution of copper thiophenecarboxylate (CuTC) (0.008 mmol) in Et_2O (1 mL) at room temperature under nitrogen, was added the ligand (0.0166 mmol) and 1 mL of Et_2O. The solution was stirred at 25 °C for 30 min and then cooled to −30 °C. Et_2Zn (1 mL, 0.5 mmol 15% in hexane) was added dropwise so that the temperature did not rise over −30 °C. The solution was stirred for 5 min, and the Michael acceptor (0.415 mmol) then added dropwise, either neat or in solution in 0.5 mL of toluene. The reaction mixture was stirred at −30 °C for 12 h before being quenched by 2 M, HCl/Et_2O (aq satd NH_4Cl in the case of nitroalkene compounds). The enantiomeric excesses were determined by chiral GC or SFC.[6]

Acknowledgements

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