Asymmetric Catalysis

DOI: 10.1002/anie.200702186

# SimplePhos Monodentate Ligands: Synthesis and Application in Copper-Catalyzed Reactions**

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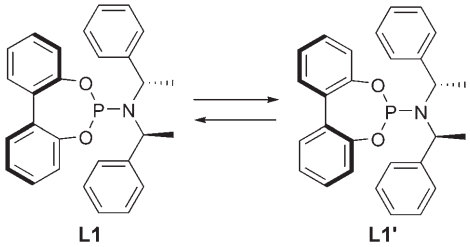
The design of chiral ligands is the key to attaining high asymmetric induction in transition-metal-catalyzed reactions. Subtle changes in the conformational, steric, and/or electronic properties of the chiral ligand can often lead to dramatic variation of the reactivity and enantioselectivity. As a result of strong substrate dependence in most cases, tunable and readily synthesized ligands are desirable to obtain high enantioselectivities.

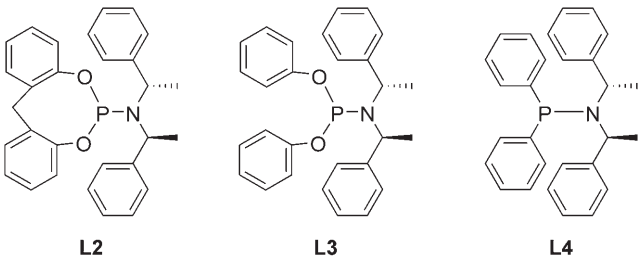
Nowadays, asymmetric copper-catalyzed conjugate addition and allylic substitution are well-developed methodologies for creating C–C bonds. Many efforts have been made in designing efficient systems and identifying new ligands to improve enantioselectivities.[1]

Among the most efficient ligands, those based on the atropoisomerism[2] of a binaphthol[3] or a biphenol[4] moiety play a prominent role. We have demonstrated that phosphoramidite ligands based on the atropoisomerically flexible biphenol unit are also excellent ligands (Scheme 1). Thus, the atropoisomerism of the biphenol part of the ligand induced by the amine moiety allows high enantioselectivity in the Cu-catalyzed enantioselective conjugate 1,4-addition of dialkyl zinc to a variety of Michael acceptors. In the course of our studies to find new types of efficient chiral ligands, we report herein the modification of the biphenol moiety of phosphoramidite ligands.




***Scheme 1.*** Conformational atropoisomerism of **L1**.

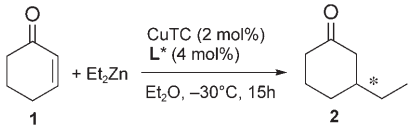
Keeping in mind that the induced helicity, promoted by the amine part, is the most important point, we sought to replace the biphenol unit by other aromatic groups that might adopt a helical conformation. Thus, we modified the biphenol core by ring expansion (**L2**), by opening the biphenol unit (**L3**), or by creating a phosphinamine-type ligand with two phenyl groups on the phosphorus atom (**L4**; Scheme 2). These




***Scheme 2.*** Newly synthesized ligands.

new ligands were tested for the addition of $Et_2Zn$ to 2-cyclohexenone (**1**) catalyzed by copper thiophene carboxylate (CuTC) to compare their efficiency (Table 1).

***Table 1:*** Addition of $Et_2Zn$ to 2-cyclohexenone (**1**) catalyzed by CuTC in the presence of various ligands **L***.




| Entry | Ligand | Conversion [%][a] | *ee* [%][b] |
|---|---|---|---|
| 1 | **L1** | >99 | 96 |
| 2 | **L2** | >99 | 35 |
| 3 | **L3** | >95 | 22 |
| 4 | **L4** | >99 | 71 |

[a] Determined by GC-MS. [b] Determined by chiral GC.

The ring expansion in **L2** or the opening of the biphenol unit in **L3** resulted in lower enantioselectivities, probably because the degree of flexibility allowed by these systems is too high. However, ligand **L4** afforded a significantly better

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[**] The authors thank the Swiss National Research Foundation (grant no. 200020-113332) for financial support, and BASF for a generous gift of chiral amines.

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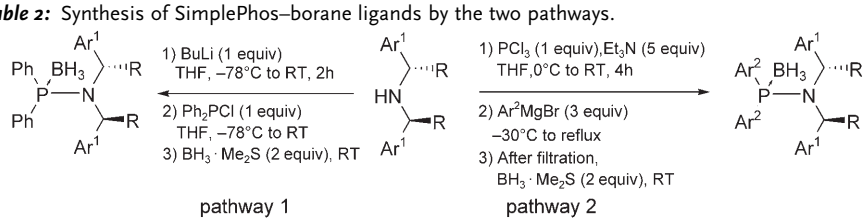
enantioselectivity of up to 71% *ee* (Table 1, entry 4). This interesting result introduced a novel class of chiral phosphorus ligands. Contrary to biphenol-based ligands, the chirality was induced by the helicity of the two aryl groups, which were also chirally flexible as tropos ligands (Scheme 3).

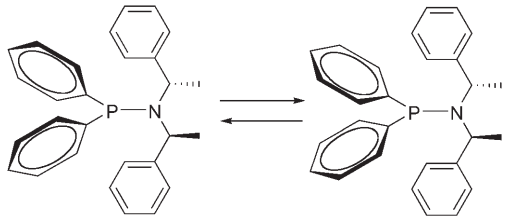
To our surprise, ligand **L4** has not been previously described. For convenience, we called the class for which **L4** is the first example SimplePhos. The potential modularity of this phosphinamine ligand is worth mentioning, and lies in the flexible variation of the amine moiety and separately the aryl groups on the phosphorus atom.

***Table 2:*** Synthesis of SimplePhos–borane ligands by the two pathways.



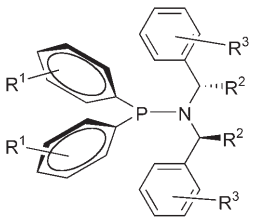

| Entry | Ligand | $Ar^1$ | $Ar^2$ | R | Yield [%][c] |
|---|---|---|---|---|---|
| 1 | **L4**[a] | Ph | Ph | Me | 68 |
| 2 | **L4**-$BH_3$ | Ph | Ph | Me | 82 |
| 3 | **L5**-$BH_3$ | Ph | Ph | Et | 84 |
| 4 | **L6**-$BH_3$ | *o*-OMe($C_6H_4$) | Ph | Me | 58 |
| 5 | **L7**-$BH_3$ | 2-naphthyl | Ph | Me | 41 |
| 6 | **L8**[b] | 1-naphthyl | Ph | Me | 78 |
| 7 | **L9**[b] | Ph | *p*-tolyl | Me | 94 |
| 8 | **L10**[b] | Ph | xylyl | Me | 67 |
| 9 | **L11**-$BH_3$ | Ph | *m*-$CF_3$($C_6H_4$) | Me | 25 |

[a] Synthesized without addition of borane complex. [b] Free ligand was obtained exclusively; protection with borane did not work. [c] Yield of isolated product.




***Scheme 3.*** Interconversion of helicity in **L4**.

The SimplePhos ligands can bear similar or different $R^1$ groups. The substituents on these aromatic rings can exert a steric influence when placed in the *ortho* or *meta* position.




They can also exert an electronic effect (for example, $CF_3$ or OMe) or a coordination effect (for example, *o*-OMe). On the amine part, $C_2$ symmetry is not a requirement. Again, steric as well as electronic or coordination effects can be brought about by variation of $R^2$ and $R^3$. Thus, the modularity of the SimplePhos family is remarkable.

SimplePhos ligands were prepared via two pathways, by starting from a chiral $C_2$-symmetric amine (Table 2). For the first synthesis, ligands **L4** to **L8** (Table 2, entries 2–6) were obtained by deprotonation of the chiral amine by BuLi followed by the addition of $Ph_2PCl$ (pathway 1). Ligand **L4** is stable towards oxidation in the solid state but slightly air-sensitive in solution. Although traces of oxide do not impede catalysis, we decided to protect our ligands with borane[5] to form phosphine–borane complexes, which are air-stable and readily purified by chromatography on alumina. Note, however, that hindered ligands, such as **L8**, **L9**, and **L10**, are perfectly stable and do not easily form the borane complexes.

For the other strategy (pathway 2), the same methodology as for the synthesis of phosphoramidite ligands was used. After formation of the aminophosphine dichloride, prepared in situ from bis[(*S*)-1-phenylethyl]amine and a solution of $PCl_3/Et_3N$, three equivalents of aryl Grignard reagent (prepared in THF) were added to form the free ligand after one night under reflux. Ligands **L9** and **L10** (Table 2, entries 7 and 8) were not protected, because they crystallized spontaneously in pentane without oxidation. Ligand **L11** (Table 2, entry 9) could not be protected in situ and needed prior filtration on neutral alumina under an inert atmosphere.

Attempts to obtain suitable crystals for X-ray analysis of **L4** in various solvents (pentane, hexane, cyclohexane) were unsuccessful. However, crystallization of **L4**-$BH_3$ in hexane provided suitable white needles and the molecular structure is shown in Figure 1.

Although it is known that phosphine–borane complexes may be directly used in catalysis,[5] the results obtained with **L4**-$BH_3$ were clearly inferior to those with unprotected **L4**. Thus, these ligands need prior deprotection for copper-catalyzed reactions. The deprotection reaction, performed with ten equivalents of morpholine in $Et_2O$ at room temperature, afforded the free ligands with very high yields (Table 3).

All the newly synthesized ligands were screened in conjugate addition[1] (CuTC, 5 mol%; **L***, 10 mol%) and in allylic substitution.[6] Preliminary tests of the addition of $Et_2Zn$ to 2-cyclohexenone (**1**) are summarized in Table 4.

Among the variations on the amine part, ligand **L7** (2-naphthyl substituent) afforded the best result, with complete conversion and a very high *ee* value of up to 95% (Table 4,

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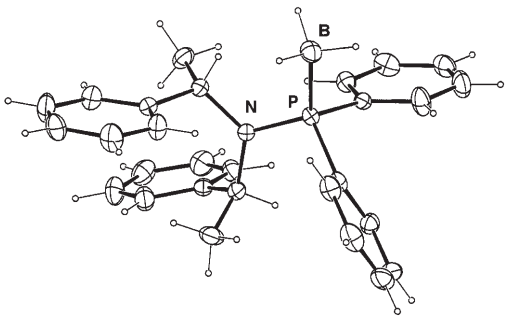
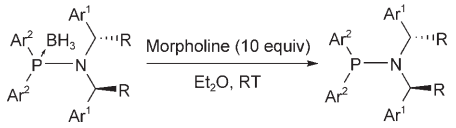



***Figure 1.*** ORTEP plot of the structure of ligand **L4**-$BH_3$.

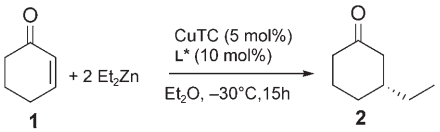
***Table 3:*** Deprotection of borane ligands by morpholine.




| Entry | Ligand | $Ar^1$ | $Ar^2$ | R | Yield [%][a] |
|---|---|---|---|---|---|
| 1 | **L5** | Ph | Ph | Et | 98 |
| 2 | **L6** | *o*-OMe($C_6H_4$) | Ph | Me | 93 |
| 3 | **L7** | 2-naphthyl | Ph | Me | 97 |
| 4 | **L11** | Ph | *m*-$CF_3$($C_6H_4$) | Me | 83 |

[a] Yield of isolated product.

***Table 4:*** Addition of $Et_2Zn$ to 2-cyclohexenone (**1**) catalyzed by CuTC in the presence of SimplePhos ligands.

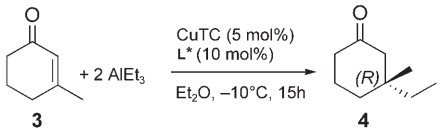



| Entry | Ligand | Conversion [%] | *ee* [%] |
|---|---|---|---|
| 1 | **L4** | 97 | 80 |
| 2 | **L5** | >99 | 81 |
| 3 | **L6** | >99 | 63 |
| 4 | **L7** | >99 | 95 |
| 5 | **L8** | >99 | 70 |
| 6 | **L9** | >99 | 67 |
| 7 | **L11** | >99 | 73 |
| 8 | **L11** | >99 | 90 |

entry 4). As we observed previously for biphenol-based phosphoramidite ligands, an increase of the steric bulk on the amine favors enantioselectivity. Furthermore, replacement of the two phenyl groups by bulkier electron-rich *p*-tolyl or xylyl groups (Table 4, entries 6 and 7) is less favorable than replacement by an electron-withdrawing group (*m*-$CF_3$-($C_6H_4$); Table 4, entry 8). This surprising electronic effect could not be observed with phosphoramidite ligands. Cycloheptenone gave similar results, the best ligand being **L7** (92% *ee*). Although these SimplePhos ligands do not induce the highest recorded *ee* values, they lie among the best 10% for this conjugate addition.

Another, more demanding copper-catalyzed conjugate addition was tested: the addition of $AlEt_3$ to trisubstituted cyclohexenones to induce the formation of stereogenic quaternary carbon centers (Table 5). The test substrate, 3-

***Table 5:*** Addition of $AlEt_3$ to 3-methylcyclohex-2-enone catalyzed by CuTC in the presence of various SimplePhos ligands.

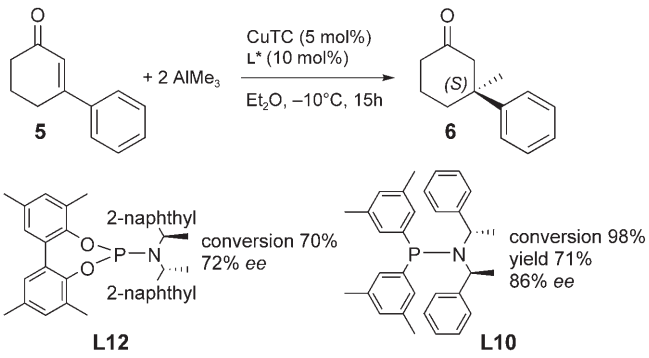



| Entry | Ligand | Conversion [%][a] | *ee* [%] |
|---|---|---|---|
| 1 | **L4** | 85 | 90 |
| 2 | **L5** | >99 (71) | 93 |
| 3 | **L6** | 98 (73) | 86 |
| 4 | **L7** | >99 | 93 |
| 5 | **L8** | 99 | 70 |
| 6 | **L9** | >99 (60) | 90 |
| 7 | **L10** | >99 (81) | 86 |
| 8 | **L11** | 82 | 80 |

[a] Yield of isolated product in parentheses.

methyl-2-cyclohexenone (**3**), gave at best 96% *ee* with a biphenol-based phosphoramidite ligand **L12** (see Scheme 4).[7] Conversely, two SimplePhos ligands, **L5** and, again, **L7**, had close *ee* values of 93% (Table 5, entries 2 and 4).

An even more demanding substrate was tested: 3-phenyl-2-cyclohexenone (**5**; Scheme 4). The addition of $Me_3Al$ gave 72% *ee* with the phosphoramidite ligand **L12**. Both the




***Scheme 4.*** Addition of $AlMe_3$ to 3-phenyl-2-cyclohexenone (**5**).

conversion and the enantioselectivity were better with the SimplePhos ligand **L10**. The addition of a methyl group has never been described with this substrate, and our SimplePhos ligand seemed to be very efficient for this catalytic system.

In the allylic substitution, tests were carried out on our latest substrate, 1,4-dibromobutene (**7**; Scheme 5).[8] Again, SimplePhos ligands compare favorably with the best phosphoramidite ligand (91% *ee*[8]).

A last example shows the efficiency of SimplePhos ligands in allylic substitution (Table 6). We have previously reported, in collaboration with Micouin,[9] the reaction of trialkyl aluminum reagents on bicyclic hydrazines. In this reaction, we demonstrated that phosphoramidite ligands were cleaved by these reagents in noncoordinating solvents, such as toluene or dichloromethane. The use of SimplePhos ligands could avoid this problem. Indeed, not only were SimplePhos ligands

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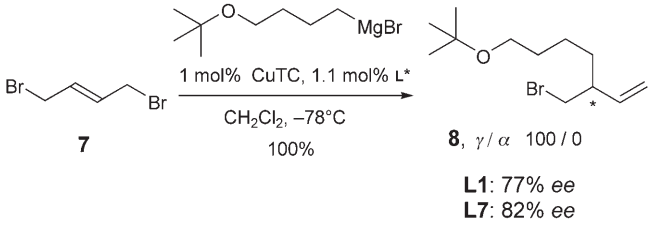
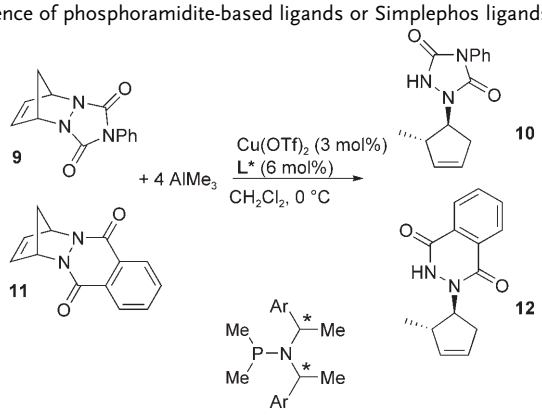



***Scheme 5.*** Enantioselective CuTC-catalyzed allylic alkylation of 1,4-dibromo-2-butene (**7**) with a Grignard reagent.

***Table 6:*** Desymmetrization of polycyclic hydrazines with $AlMe_3$ in the presence of phosphoramidite-based ligands or Simplephos ligands.




| Entry | Substrate | Ligand | Yield [%] | *ee* [%] |
|---|---|---|---|---|
| 1 | **9** | **L13** | 86 | 67 (−) |
| 2 | **9** | **L14** | 85 | 85 (+) |
| 3 | **9** | **L4** | 78 | 90 (−) |
| 4 | **9** | **L7** | 81 | 94 (−) |
| 5 | **9** | **L10** | 85 | 88 (−) |
| 6 | **11** | **L13** | 94 | 79 (−) |
| 7 | **11** | **L4** | 90 | 89 (−) |
| 8 | **11** | **L7** | 85 | 86 (−) |
| 9 | **11** | **L10** | 12 | 78 (−) |

untouched, but also they afforded significantly higher enantioselectivities (compare entries 1, 2, and 6 with entries 4 and 7 of Table 6).

In conclusion, we have described a novel class of chiral monodentate phosphorus ligands, termed SimplePhos. This family of chiral ligands is highly modular, versatile, and easy to synthesize. Preliminary tests in copper-catalyzed reactions showed that they are equal to or better than phosphoramidite ligands. Other applications in asymmetric synthesis are in progress and will be reported in due course.

## *Experimental Section*

Synthesis of ligand **L4**-$BH_3$: BuLi (1.25 M solution in hexane, 1 equiv) was added dropwise to a stirred solution of bis[(*S*)-1-phenylethyl]-amine (1 equiv) in THF at −70 °C under an inert atmosphere. The reaction mixture was stirred at −70 °C for 10 min, then allowed to warm to room temperature. After stirring for 2 h, the mixture was cooled to −70 °C and a solution of $Ph_2PCl$ (1 equiv) in THF was slowly added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Then, a solution of borane–dimethylsulfide complex (2 equiv) was added at room temperature and the reaction mixture was stirred overnight. After evaporation of the solvent under vacuum, the desired ligand was purified by flash chromatography on neutral alumina with toluene as solvent.

Received: May 17, 2007
Published online: August 14, 2007

**Keywords:** asymmetric catalysis · conjugate addition · copper · enones · P ligands

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