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# Chiral aminophosphine–oxazoline auxiliaries applied to copper-catalysed enantioselective 1,4-additions to enones

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**Abstract**—A series of chiral aminophosphine–oxazoline auxiliaries has been prepared and applied in the copper-catalysed 1,4-addition of diethylzinc to enones. The addition products are obtained quantitatively in up to 67% ee. The most efficient ligand of the series is based on L-indoline carboxylic acid and L-valinol.


The catalytic asymmetric conjugate addition to α,β-unsaturated systems is one of the most important organic synthetic methodologies allowing a stereoselective formation of C–C bonds.[1,2] Several chiral catalysts have been developed to promote such transformations.[2] Previously, the enantioselective conjugate addition of organometallic reagents (Grignard reagents, organolithium derivatives, and dialkylzinc species) has been assisted more or less efficiently by chiral copper[3] and nickel catalysts.[4]

The catalytic system introduced originally by Alexakis et al., which is composed of an organozinc reagent and a copper complex modified by a trivalent chiral phosphorus based auxiliary,[5] has undergone a noteworthy development. Actually, the various phosphorus based chiral auxiliaries designed afterwards for that catalytic reaction were based either on monodentate or on bidentate ligands. As such, Feringa and co-workers has introduced phosphoramidites as chiral ligands in copper-catalysed 1,4-additions of dialkylzinc reagents.[6] Additional phosphoramidites[7] and other monodentate phosphorus based auxiliaries have been designed based on TADDOL, binaphthol or tartrate and used with success.[7–9] Phosphorus based bidentate ligands have also been used, that is, diphosphite[10] and phosphite–oxazolines.[11] For the synthesis of new chiral auxiliaries, the use of the chiral pool as the source constitutes an interesting alternative. As such, Hoveyda and co-workers prepared phosphorus ligands based on peptides and applied them with success in the enantioselective copper-catalysed additions of alkylzinc to acyclic aliphatic enones.[12]

During our continuing search for new chiral auxiliaries based on the chiral pool,[13] we have prepared a new family of aminophosphine–oxazolines and reported on their successful use in asymmetric allylic alkylation.[14] Here, we report on the synthesis of new ligands of that family and on their use in copper-catalysed conjugate additions to enones.

The aminophosphine–oxazoline ligands **1a** and **1b** (Scheme 1) based on (*S*)-indoline carboxylic acid have been prepared following the synthesis reported previously for ligands **2a** and **2b** based on proline and **3a** and **3b** based on tetrahydroisoquinoline carboxylic acid.[14] Thus, the two new ligands have been synthesized following the route depicted in Scheme 2.[14] Commercial (*S*)-indoline carboxylic acid **4** was first converted into its methyl ester **5**. Then, the reaction of **5** with chlorodiphenylphosphine in the presence of triethylamine in THF provided the intermediate aminophosphine derivative, which was protected as a thiophosphine in the presence of sulfur in toluene. The aminothiophosphine **6** was isolated after work-up in 65% yield for the two steps. The acid **7** was obtained through hydrolysis of the ester **6**. Then, in separate experiments, a standard peptide coupling between **7** and both isomers of valinol provided the two diastereomeric aminothiophosphines **8a** and **8b**, quantitatively after work-up. The oxazolines **9a** and **9b** were obtained easily via cyclisation of the corresponding amidoalcohols **8a** and **8b** in the presence of *p*-tosylchloride under basic conditions and isolated in

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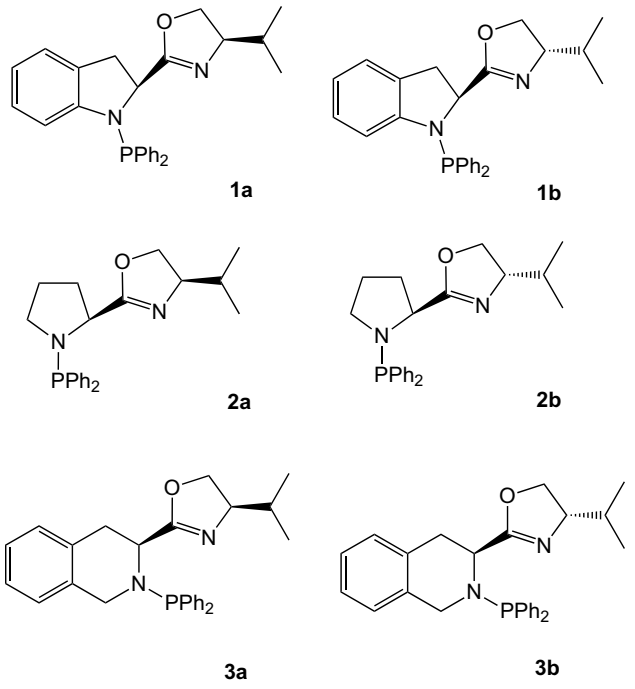
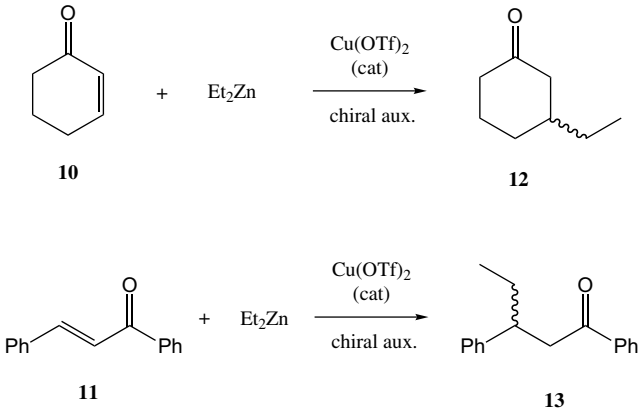


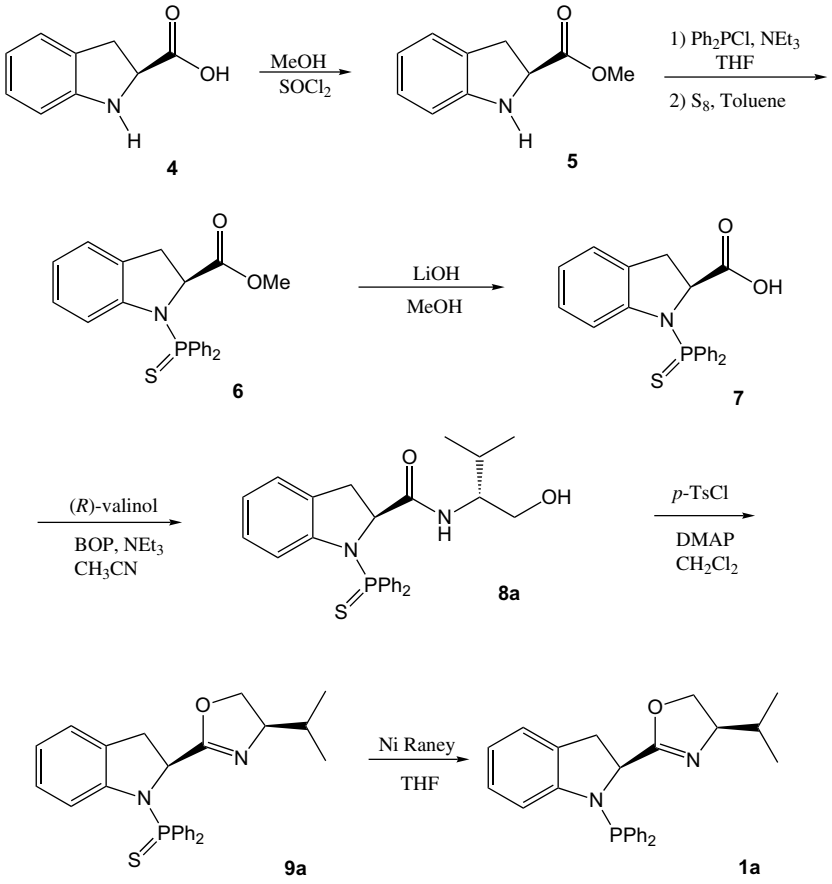

Scheme 1.

52–60% yields.[15] Finally, the aminophosphine residues were recovered from **9a** and **9b** through reduction with Ni-Raney in THF providing **1a** and **1b** in ca. 95% yield.




Scheme 3.

In order to investigate the influence of the chiral aminophosphine and oxazoline moieties, the ligands were next applied in copper-catalysed enantioselective additions to enones.[16] Two model substrates have been investigated, that is, the cyclic 2-cyclohexenone **10** and the acyclic chalcone **11** (Scheme 3). The results are summarised in Table 1. For our first attempts, we considered the reaction between **10** and $ZnEt_2$ in the presence of either $Cu(OTf)_2$-**1a** or $Cu(OTf)_2$-**1b** in toluene (entries 1 and 2). The precatalysts $Cu(OTf)_2$-**1a** and $Cu(OTf)_2$-**1b** were prepared ex situ through reaction of




Scheme 2.

**Table 1.** Cu catalysed conjugate addition of diethylzinc to enones[a]

| Entry | Enone | Ligand | Solvent | Temp. (°C) | Conv. (%)[b] | Ee (%) (config.)[c] |
|---|---|---|---|---|---|---|
| 1 | **10** | **1a** | Toluene | −20 | 100 | 47 (*S*) |
| 2 | | **1b** | Toluene | −20 | 100 | 62 (*S*) |
| 3 | | **2a** | Toluene | −20 | 100 | 35 (*S*) |
| 4 | | **2b** | Toluene | −20 | 100 | 63 (*S*) |
| 5 | | **3a** | Toluene | −20 | 100 | 34 (*S*) |
| 6 | | **3b** | Toluene | −20 | 100 | 29 (*S*) |
| 7 | | **1a** | Toluene/hexane[d] | −20 | 100 | 43 (*S*) |
| 8 | | **1a** | THF/hexane[d] | −20 | 99 | 24 (*S*) |
| 9[e] | | **1a** | Toluene/hexane | −20 | 88 | 27 (*S*) |
| 10 | | **1a** | Toluene | 20 | 100 | 41 (*S*) |
| 11 | | **1b** | Toluene | 20 | 100 | 32 (*S*) |
| 12 | | **2b** | Toluene | 20 | 100 | 37 (*S*) |
| 13 | | **3b** | Toluene | 20 | 100 | 37 (*S*) |
| 14[f] | | **2b** | Toluene | −20 | 100 | 67 (*S*) |
| 15[g] | | **2b** | Toluene | −20 | 100 | 61 (*S*) |
| 16 | **11** | **1b** | Toluene | −20 | 100 | 30 (*S*) |
| 17 | | **2b** | Toluene | −20 | 100 | 6 (*S*) |
| 18 | | **3b** | Toluene | −20 | 100 | 11 (*S*) |

[a] The catalytic reactions were carried out in the presence of a ligand/Cu initial ratio of 1.2 unless otherwise stated. Substrate/Cu: 100.
[b] The conversions were determined by $^1$H NMR on the crude reaction mixture through integration of allyl and ethyl groups.
[c] Enantiomeric excesses were determined by chiral GC analysis using a Lipodex E column. The configurations were determined by comparison with literature data.[18]
[d] The hexane corresponds to the amount introduced while adding $ZnEt_2$ 1.1 M in hexane to the precatalyst in solution in the mentioned solvent (actual mixture: 1/1).
[e] Using $Cu(MeCN)PF_6$ as catalyst.
[f] 0.5 mol% initial copper amount.
[g] 2.5% initial copper amount.

$Cu(OTf)_2$ with the corresponding auxiliary **1a** or **1b** (ligand to copper ratio: 1.2) in toluene at room temperature for 2 h. Then, after lowering the temperature to −20 °C, $ZnEt_2$ (in solution in toluene 1.1 M) was added to the homogeneous solution followed by the enone. In the presence of 1 mol% of an initial copper complex amount, the two reactions went to completion within, nonoptimised, 15 h and provided selectively the 1,4-addition product **12** in 47% and 62% ee, respectively (entries 1 and 2). It has to be noticed that the reaction went also to completion within 30 min at −20 °C. This experimental procedure was perfectly reproducible. While applying the same catalytic conditions for reactions carried out in the presence of the ligands **2a**, **2b**, **3a** and **3b**, total conversions are also obtained and the addition product **12** was isolated in 29–63% ee (entries 3–6). The two auxiliaries **1b** and **2b** exhibit identical selectivities (entries 2 and 4). Interestingly, the same enantiomer (*S*) of the product **12** is formed with the three pairs of diastereomeric chiral auxiliaries (**1a/1b**, **2a/2b**, **3a/3b**). For ligands **1a/1b** and **2a/2b** the (*S*,*R*) ligands are providing the highest ee's (entries 2 and 4), whereas the opposite is true for the pair **3a/3b** where the (*S*,*S*) ligand **3b** is leading to a higher ee value (entry 5). Thus, there is no obvious trend observed within this ligand series in correlation with the level and sense of asymmetric induction for the 1,4-addition reaction.

The addition was also carried out with $ZnEt_2$ in solution in hexane while the precatalyst was prepared either in toluene (entry 7) or in THF (entry 8). The presence of hexane is slightly detrimental to the enantioselectivity ($\Delta ee = -4\%$) when associated to toluene. The mixture THF/hexane led to a more significant decrease of the selectivity ($\Delta ee = -23\%$). This important decrease is attributed to the THF solvent used. Indeed, in our case, a noncoordinating solvent seems the most appropriate.[5,6,17]

When the copper(I) complex $[Cu(MeCN)]PF_6$ was employed to prepare the catalyst instead of $Cu(OTf)_2$, the reaction was slightly slower as a conversion of 88% was reached and the addition product **12** was obtained in only 27% ee (entry 9 vs 7) ($\Delta ee = -16\%$). Thus, copper(II) precatalysts are preferably used over copper(I) species, the former being also easier to handle.

On the other side, the reaction is quite sensitive to the temperature. Indeed, a reaction carried out at room temperature is leading to a slightly lower selectivity in the presence of ligand **1a** ($\Delta ee = -6\%$) (entry 10 vs 1) whereas a more significant decrease is observed with ligands **1b** ($\Delta ee = -30\%$) (entry 11 vs 2), and **2b** ($\Delta ee = -26\%$) (entry 12 vs 4). On the contrary, an opposite variation is observed with ligand **3b** ($\Delta ee = +9\%$) (entry 13 vs 6).

The overall conformational rigidity presented by the auxiliaries **1a/1b** and **2a/2b** due to the presence of the five-membered ring skeleton bearing the aminophosphine residue is probably very similar as close asymmetric inductions are achieved with the corresponding copper catalysts. The flexibility of the six-membered cycle of **3a** and **3b** prevents the preferential formation of a single well defined complex in solution and leads to several less selective conformations. Such a behaviour can explain the opposite impact on the selectivity observed with the diastereomeric auxiliaries **3a** and **3b**.

By lowering the initial concentration of the chiral catalyst to 0.5 mol%, the ee of the addition product **12** increased slightly to 67% ($\Delta ee = +4\%$) (entry 14 vs 4), whereas, an increase of the concentration to 2.5% led to a little drop of the ee was observed ($\Delta ee = -2\%$) (entry 15 vs 4). As mentioned by Feringa and co-workers, copper complexes at different concentrations may form different catalytic species leading to different selectivities.[6]

The results show that both the chiral oxazoline and the chiral aminophosphine units have an influence on the enantioselectivity of the process. The stereochemical outcome of the reaction seems however to be essentially related to the configuration of the aminophosphine residue as the chirality is imposed by the aminophosphine framework alone. Indeed, the absolute stereochemistry of the addition product is the same in all cases where homochiral aminophosphine skeletons have been used.

Under similar catalytic conditions, the conjugate addition of diethyl zinc to chalcone **11** provided the addition product **13** with overall lower selectivities, up to 30% ee in the presence of **1b** (entries 16–18). This feature is frequently observed while comparing the selectivities of the addition to this two substrates **10** and **11**.

In summary, we have described the easy preparation of new aminophosphine–oxazolines and their use in copper-catalysed conjugate additions to enones. The selectivities induced by these new chiral auxiliaries are in line with the behaviour of other bidentate auxiliaries containing a phosphine. The potential of the reported auxiliaries in other asymmetric transformations is under investigation in our laboratory.

## Acknowledgements

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15. **9a**: RMN $^1$H (300 MHz, $CDCl_3$): $\delta$ 0.76 (d, $J = 6.8$ Hz, 3H, $CH_3$); 0.87 (d, $J = 6.8$ Hz, 3H, $CH_3$); 1.55 (sext, $J = 6.8$ Hz, 1H, $CH(CH_3)_2$); 3.08 ($d_{app}$, $J = 16.2$ Hz, 1H, CHH′); 3.57 (dd, 1H, $J = 16.0$ and 10.4 Hz, CHH′); 3.67 (dd, $J = 17.0$ and 8.8 Hz, 1H, N–CH); 3.77 ($t_{app}$, 1H, $J = 8.5$ Hz, CHH′–O); 4.06 (dd, $J = 9.8$ and 8.4 Hz, 1H, CHH′–O); 4.89 (m, 1H, CH); 6.38 (d, $J = 7.5$ Hz, 1H, $H_{arom}$); 6.85 (m, 1H, $H_{arom}$); 7.15 (m, 1H, $H_{arom}$); 7.32 (m, 1H, $H_{arom}$); 7.45–7.54 (m, 6H, $H_{arom}$); 7.80–7.97 (m,

4H, $H_{arom}$). RMN $^{31}P$ (121.5 MHz, $CDCl_3$): $\delta$ 60.4 (s). RMN $^{13}C$ (50 MHz, $CDCl_3$): $\delta$ 18.5 (s, $CH_3$); 19.2 (s, $CH_3$); 32.7 (s, $CH(CH_3)_2$); 35.0 (d, $J = 4.9$ Hz, $CH_2$); 58.3 (d, $J = 3.9$ Hz, CH–N); 70.9 (s, $CH_2$–O); 72.3 (d, $J = 2.0$ Hz, CH); 114.8 (d, $J = 2.5$ Hz, $C_{arom}$); 121.7–132.8 (m, $C_{arom}$); 144.9 (d, $J = 3.7$ Hz, $C_{arom}$); 166.6 (d, $J = 2.5$ Hz, C=O.). Anal. Calcd for $C_{26}H_{27}N_2OPS$: C, 69.95; H, 6.01; N, 6.27. Found: C, 69.69; H, 6.20; N, 6.48. **1a**: RMN $^{31}P$ (121.5 MHz, $CDCl_3$): $\delta$ 43.1 (s).

16. Under nitrogen atmosphere, **1a** (13.2 mg, 0.034 mmol, 1.2 mol%) was dissolved in dry degassed toluene (2 mL). The solution was added to $Cu(OTf)_2$ (10 mg, 0.027 mmol, 1 mol%) and the resulting solution was stirred at room temperature for at least 2 h. The solution was transferred via canula to a Schlenk tube cooled to −20 °C containing $Et_2Zn$ (3.8 mL 1.1 M in toluene). The enone **10** (0.26 mL, 2.7 mmol) was added. The reaction mixture was stirred at −20 °C for 15 h and then quenched with a saturated solution of $NaHCO_3$. The organic phase was separated, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography gave 3-ethylcyclohexanone **12** in quantitative yield. The enantiomeric excess was determined by chiral GC using Lipodex E (carrier: $H_2$ 60 kPa; oven temperature: 90 °C; $t_R(R)$: 8.3 min; $t_R(S)$: 8.9 min).
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