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An insoluble polymer-bound phosphoramidite for the copper-catalysed enantioselective 1,4-addition of $ZnEt_2$ to 2-cyclohexenone

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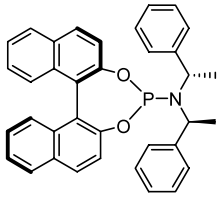
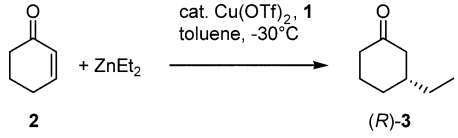
Abstract—The preparation of a chiral phosphoramidite ligand anchored to a Merrifield resin has been studied and its use in the copper-catalysed heterogeneous enantioselective conjugate addition of $ZnEt_2$ to 2-cyclohexenone investigated. The insoluble polymer bound ligand could be recovered quantitatively by filtration, affording e.e. values in the range 65–84% in the course of successive recycle runs.

Phosphoramidites embedding the 1,1′-binaphthalen-2,2′-diol unit (e.g. **1**) have recently emerged as a new, effective class of chiral phosphorus ligands for enantioselective catalysis,[1] allowing the attainment of high enantioselectivity levels not only in the copper-catalysed conjugate addition of organozinc reagents to α,β-enones (Scheme 1),[2] but also in other transition metal mediated asymmetric transformations.[3]



(*R*,*S*,*S*)-**1**

Despite the remarkable stability of these ligands, the phosphoramidite unit is not likely to tolerate the normal acidic work-up required by reactions involving organometallic reagents, making the recovery and reuse of the chiral auxiliary difficult. From this point of view, the development of insoluble polymer-supported phosphoramidites would be desirable, allowing the separation of the heterogeneised ligand by simple filtration under anhydrous conditions and ideally permitting its recycling.[4,5]



2 (*R*)-**3**

Scheme 1.

Indeed very recently Waldmann et al. reported the preparation of a small polystyrene-supported library of binaphthol-based phosphoramidite ligands containing a piperidine or bispidine-type amine unit, and their use in the asymmetric conjugate addition of $ZnEt_2$ to 2-cyclohexenone **2** to afford **3**.[6] While this approach allowed the combinatorial evaluation of the influence of the substitution pattern of the binaphthyl and amine moieties on the enantioselectivity, the e.e. values did not exceed 67% and the possibility of recycling the immobilised ligand was also not mentioned.[7] This communication prompted us to disclose our preliminary results on the covalent immobilisation of a phosphoramidite related to **1** onto a polystyrene resin and its use as a recyclable supported ligand for the heterogeneous enantioselective addition of $ZnEt_2$ to **2**.

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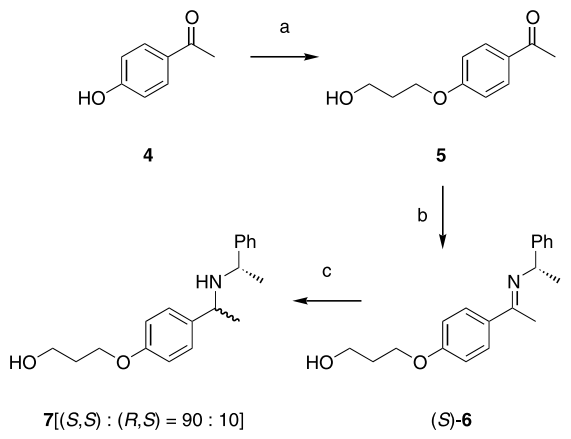
To introduce a linking point and a spacer group in the structure of the parent system **1**, 4-hydroxyacetophenone **4** was converted in the substituted bis-(1-phenylethyl)amine **7** via the route depicted in Scheme 2.

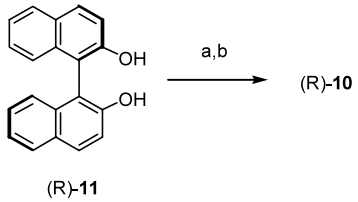


Scheme 2. *Reagents and conditions*: (a) $Br(CH_2)_3OH$, K_2CO_3, cat 18-c-6, acetone, reflux, 24 h (94%); (b) (*S*)-$PhCH(CH_3)NH_2$, cat. TsOH, MS 3A, toluene, reflux, 48 h; (c) H_2 (3 bar), 10% Pd/C, THF, 24 h (38% over two steps).

As expected on the basis of previous findings,[8] the hydrogenation step of the intermediate imine (*S*)-**6** afforded **7** as a 90:10 mixture of (*S*,*S*):(*R*,*S*) diastereomers (by ^{13}C NMR).[9] The configuration of the new sterogenic centre in the major and minor diastereomers of **7** was confirmed by comparing the relative chemical shift of the NMR resonances of CH and CH_3 groups, with those reported in the literature for analogous bis(1-phenylethyl)amines.[8,10] In spite of its incomplete stereochemical purity, **7** was suitable for the aims of this work (vide infra) and was therefore directly used in the subsequent steps.

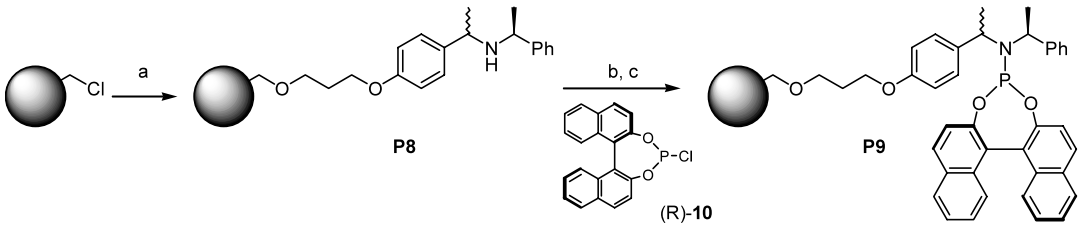
In order to eliminate the need of any further chromatographic purification, the preparation of the supported phosphoramidite was pursued by adopting a solid-phase synthesis strategy (Scheme 3). The anchoring of **7** to a Merrifield resin (2% cross-linking, 2.3 mmol/g of Cl) afforded the supported amine **P8** (1.5 mmol/g, by nitrogen elemental analysis), that was characterised by spectroscopic means.[11] The conversion of **P8** into the corresponding phosphoramidite **P9** was initially attempted following the published procedure for **1**.[12] Accordingly, the material was treated with *n*-BuLi to metallate the anchored amine and then added of a solution of chlorophosphite (*R*)-**10**, prepared by reacting (*R*)-1,1′-bi(2-naphthol) **11** and PCl_3, in the presence of Et_3N in toluene.[13]

Unfortunately, the persistent red colour of the polymer suggested a lack of reactivity under these conditions of the supported lithium amide, as confirmed by elemental analysis that indicated a low phosphorus incorporation. Speculating that an increase of the medium polarity would result in a faster phosphitylation, a THF solution of (*R*)-**10** was prepared by metallation of (*R*)-**11** with n-BuLi, followed by reaction with PCl_3 (Scheme 4).[14]



Scheme 4. *Reagents and conditions*: (a) 2 equiv. *n*-BuLi, THF, −40°C→rt, 2 h; (b) 1 equiv. PCl_3, THF, −90°C→rt, 2 h.

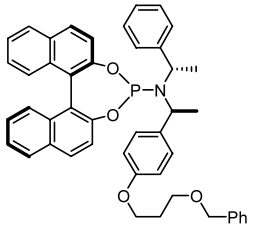
Indeed the addition of (*R*)-**10** in THF to metalated **P8** led to the fading of the lithium amide colour within few hours, indicating the smooth formation of the supported phosphoramidite. After repeated washings with THF to remove the soluble compounds (UV check), the material **P9** was dried in vacuo and characterised.[15] The elemental analysis of **P9** afforded a nitrogen and phosphorus content of 1.0 and 0.83 mmol/g, respectively, indicating a 83% conversion of the supported amine. Moreover, the gel-phase ^{31}P NMR of the $CDCl_3$ swollen resin showed a moderately broadened resonance at 144.2 ppm, a chemical shift value similar to those of related phosphoramidites (e.g. **1**, 145.3 ppm).[12] For comparative purposes, starting with the THF solution of (*R*)-**10** the model **12** of the supported ligand was also prepared.[16] As expected on the basis of the stereochemical composition of **7**, the presence of a minor phosphoramidite component was observed in the ^{31}P NMR spectrum of **12** in C_6D_6. Indeed two resonances were present at 147.1 (92%) and 147.3 ppm (8%), tentatively attributed to the (*R*,*S*,*S*) and (*R*,*R*,*S*) diastereomers of **12**.



Scheme 3. *Reagents and conditions*: (a) **7**, NaH, DMF, 36 h, then MeOH, 60°C, 2 h; (b) 1.5 equiv. *n*-BuLi, THF, −50°C, 40 min, then filtration; (c) 3.1 equiv. **10**, THF, −50°C→rt, 6 days.

By using **12** and $Cu(OTf)_2$, an initial homogeneous catalysis run in the conjugate addition of $ZnEt_2$ to 2-cyclohexenone **2** (Scheme 1) afforded within 5 min (*R*)-3-ethylcyclohexanone **3** in high yield and e.e. (Table 1, entry 1). These results, comparable to those obtained with (*R*,*S*,*S*)-**1** (95 yield, >98% e.e.),[1] clearly demonstrate that neither the phenyl ring substituent nor the presence of the minor diastereomeric component in **12** seriously affect the catalytic and stereochemical effectiveness of the parent phosphoramidite ligand.

Additionally, to test the stability of the catalytic system fresh **2** and $ZnEt_2$ were repeatedly added over 24 h to the mixture containing **12** and the copper salt, each time observing practically unchanged activity and selectivity (Table 1, entries 2–4).



12 [(*R*,*S*,*S*) : (*R*,*R*,*S*) = 92 : 8]

Having established the effectiveness of the modified phosphoramidite unit, we moved next to investigate the use of the supported ligand as a heterogeneous catalyst precursor.

The reaction in the presence of **P9** and $Cu(OTf)_2$ turned out to be slower than with **12**, requiring 2 h to reach a complete conversion. Nonetheless, under these conditions the 1,4-addition product (*R*)-**3** was obtained with high chemoselectivity, a substantial enantioselectivity degree and the same absolute configuration afforded by the soluble ligands (*R*,*S*,*S*)-**1** and **12** (Table 1, entry 5). It seems therefore that similar active species are present both in solution and on the polymer support, despite the fact that the catalytic cycle for the conjugate addition reaction with monodentate phosphoramidites is believed to involve a ligand:metal = 2:1 complex.[17] This is probably a consequence of the flexibility of gel-type polymeric matrix and the presence of the propylene spacer group in **P9**, that allow the attainment of the correct complexation geometry.

In view of the demonstrated stability of the copper-phosphoramidite complex (vide supra), an attempt to re-use the whole catalytic system was made at this point. For this purpose the polymer material was filtered under an inert atmosphere, washed with toluene, dried and suspended again in toluene. Unfortunately the subsequent addition of the substrate **2** and the organozinc reagent to the recovered catalyst resulted in a reduced conversion (<30% after 2 h), most likely because of the leaching of copper species. For this reason further recycles were carried out, adding each time the initial $Cu(OTf)_2$ amount (Table 1, entries 6–8). Adopting this procedure the original catalytic activity could be effectively restored, although somewhat at the expenses of chemoselectivity. Moreover, in the course of the recycles the e.e. values underwent an initial increase (84%) followed by a progressive reduction, possibly because of variable metal leaching, leading to different copper to supported ligand ratios during the consecutive runs.

In conclusion, a solid-phase synthesis approach for the anchoring of the ligand **1** onto a Merrifield resin has been developed, characterising the material **P9** by spectroscopic means. The use of **P9** in the copper-catalysed conjugate addition of $ZnEt_2$ to 2-cyclohexenone **2** afforded the product **3** in 65–84% e.e. in the course of successive recycles, a demonstration that the high effectiveness of the soluble ligand **1** could be largely preserved after immobilisation, providing the best enantioselectivity values reported to date with supported phosphoramidites.

Table 1. Asymmetric conjugate addition of $ZnEt_2$ to **2** with soluble and supported phosphoramidite ligands (Scheme 1)[a]

Run	Ligand	Time (min)	Conversion (%)[b]	Chemoselectivity (%)[c]	E.e. (%)[d]
1	**12**	5	94	>98	95 (*R*)
2	**12**[e]	5	>99	>98	96 (*R*)
3	**12**[e]	5	96	>98	97 (*R*)
4	**12**[e]	5	99	>98	97 (*R*)
5	**P9**	120	>99	>98	74 (*R*)
6	**P9**[f]	120	>99	94	84 (*R*)
7	**P9**[f]	120	95	89	66 (*R*)
8	**P9**[f]	120	>99	87	65 (*R*)

[a] Conditions: 2.5 mol% $Cu(OTf)_2$, 5 mol% **12** or 6 mol% **P9**, 1 mmol **2** (containing *p*-cymene internal standard), 1.5 equiv. $ZnEt_2$ (1.1 M in toluene), toluene (5 ml), –30°C.

[b] Determine by GLC, using *p*-cymene internal standard.

[c] Selectivity of formation of 1,4-addition product **3**, determined by GLC using *p*-cymene internal standard.

[d] Determined by GLC (Astec G-TA, 110°C). Configuration of the major enantiomer in parentheses.

[e] **2** and $ZnEt_2$ added to the reaction mixture from the previous run.

[f] Supported ligand from the previous run.

Acknowledgements

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9. **Data for compound 7** [(*S*,*S*):(*R*,*S*) = 90:10]. $R_f = 0.13$ (SiO_2, Et_2O). $[\alpha]_D^{30} = -176$ (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) 7.14–7.32 (m, 5H), 7.11 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 4.12 (t, $J = 5.9$ Hz, 2H), 3.85 (t, $J = 5.9$ Hz, 2H), 3.39–3.52 (m, 2H), 2.04 (quint, $J = 5.9$ Hz, 2H), 1.92 (br s, 2H), 1.20–1.30 (m, 6H). Resonances assigned to the minor (*R*,*S*) diastereomer were present at 3.68–3.80 and 1.30–1.38 ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) 158.42, 130.43, 128.62, 128.4, 127.89, 127.77, 127.23, 114.52, 65.29, 59.50, 55.59, 55.38, 31.94, 22.94. Resonances assigned to the minor (*R*,*S*) diastereomer were present at 55.06, 54.53 and 21.84 ppm.
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11. **Data for material P8**. C, 84.73%; H, 8.15%; N, 2.24%. IR (KBr, cm^{-1}) 3439, 2914, 1676, 1607, 1508, 1448, 1235, 1171, 754. ^{13}C NMR (gel-phase, $CDCl_3$, 50 MHz, aliphatic region) 72.8, 66.7, 64.9, 54.9, 54.3, 45.0–40.0 (polystyrene backbone), 29.8, 25.0.
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14. **Data for 10**. ^{31}P NMR (THF) δ 176.2.
15. **Data for material P9**. C, 78.98%; H, 6.86%; N, 1.38%; P, 2.55%. ^{13}C NMR (gel-phase, $CDCl_3$, 50 MHz, aliphatic region) 66.6, 65.1, 52.2, 45.0–40.0 (polystyrene backbone), 30.0, 22.2. ^{31}P NMR (gel-phase, $CDCl_3$, 120 MHz) 144.2.
16. **Data for 12** [(*R*,*S*,*S*):(*R*,*R*,*S*) = 92:8]. $R_f = 0.29$ (SiO_2, *n*-hexane: $CH_2Cl_2 = 1{:}1$). $[\alpha]_D^{30} = -321$ (*c* 0.47, CH_2Cl_2). ^1H NMR (C_6D_6, 300 MHz) 6.66–7.68 (m, 26H), 4.50–4.60 (m, 2H), 4.23 (s, 2H), 3.75 (t, $J = 6.0$ Hz, 2H), 3.34 (t, $J = 6.0$ Hz, 2H), 1.82 (quint, $J = 6.0$ Hz, 2H), 1.54–1.59 (m, 6H). ^{13}C NMR (C_6D_6, 75 MHz) 158.38, 150.85, 150.76, 150.31, 143.47, 139.21, 135.28, 133.41, 133.31, 133.28, 131.88, 130.93, 130.73, 129.75, 129.58, 129.55, 128.63, 128.50, 128.44, 128.31, 128.08, 127.99, 127.67, 127.59, 127.50, 126.92, 126.46, 126.37, 124.96, 124.75, 122.93, 122.75, 114.11, 72.98, 66.89, 64.86, 52.54, 52.38, 52.16, 51.99, 30.10, 22.06. ^{31}P NMR (C_6D_6, 120 MHz) 147.1 (92%), 147.3 ppm (8%).
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