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Palladium-catalysed asymmetric allylic alkylation using new chiral phosphinite–nitrogen ligands derived from D-glucosamine

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Novel phosphinite–nitrogen chiral ligands synthesized from D-glucosamine furnish a high level of enantiomeric excess (up to 96% ee) in palladium-catalysed allylic alkylation.

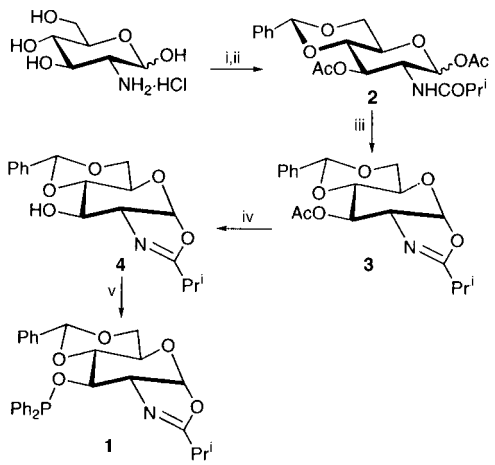
Palladium-catalysed allylic alkylation is known as a powerful synthetic tool for the construction of carbon–carbon bonds.[1] Enantioselective versions of the reaction have been explored and large enantiomeric excesses have been achieved using various C_2- and C_1-symmetric bidentate chiral ligands.[2] While they are excellent ligands, expensive chiral sources and tedious synthetic steps are sometimes needed for their synthesis. Recently carbohydrates have attracted a great deal of interest as a source of chiral ligands, because they exist widely in nature and have many chiral centres in their skeletons.[3,4] Now, we report the synthesis of novel phosphinite–nitrogen chiral ligands from commercial D-glucosamine hydrochloride (2-amino-2-deoxy-D-glucopyranoside hydrochloride), which have been less frequently used as chiral ligands,[4,5] and their application to the Pd-catalysed allylic alkylation.

First, we prepared compound **1** according to the procedures illustrated in Scheme 1. *N*-Acylation of D-glucosamine hydrochloride with $(Pr^iCO)_2O$ and NaOMe, and the protection of both 4,6- and 1,3-positions by benzylidene and acetyl groups gave D-glucopyranoside **2** in good yield. This compound could be readily converted into oxazoline derivative **3** using $SnCl_4$ without removing the benzylidene protecting group.[6] Deacetylation of the 3-position followed by treatment with Ph_2PCl and Et_3N gave phosphinite–nitrogen chiral ligand **1**. This ligand was easily oxidized by air in solution, but was relatively stable in the solid state.

Asymmetric allylic substitution of 1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and KOAc was carried out with the palladium complex generated *in situ* by mixing chiral ligand **1** and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$. The results are summarized in Table 1. In the presence of only 0.25 mol% Pd complex, the reaction proceeded very smoothly with high enantioselectivity. The best result was obtained when the reaction was carried out in toluene at 0 °C (entries 1–5).

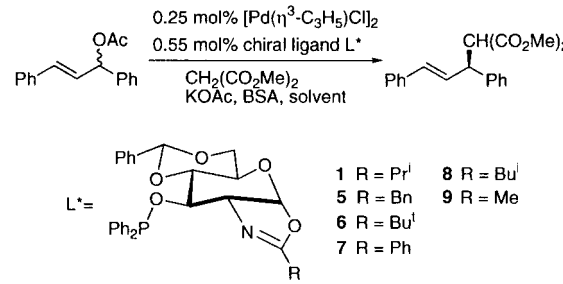
Next, we synthesized phosphinite–nitrogen ligands **5**–**9**† by the procedure described in Scheme 1 using anhydrides or acid chlorides such as BnCOCl, $(Bu^tCO)_2O$, PhCOCl, $(Bu^iCO)_2O$ and Ac_2O, and applied them to the palladium-catalysed asymmetric allylic alkylation under the previously determined optimum conditions (entries 6–10).‡ As can be seen in Table 1, a dramatic substituent effect on the enantiomeric excess was observed. The use of the ligand **5** (R = Bn) or **6** (R = Bu^t) (entries 6 and 7) gave lower enantioselectivities compared with the case of ligand **1**. On the contrary, the use of the ligand **7** (R = Ph) or **8** (R = Bu^i) increased the selectivity (entries 8 and 9). Furthermore, it was noted that the highest enantiomeric excess (96% ee) was achieved using ligand **9** (R = Me) (entry 10).

We suppose that nucleophilic attack occurs predominantly at the allyl terminus *trans* to the Pd–P bond in the π-allylpalladium complex.[8] Since the (*S*)-product was obtained as the major enantiomer, the reaction probably proceeds through *endo* intermediate **A** rather than *exo* intermediate **B**, as shown in



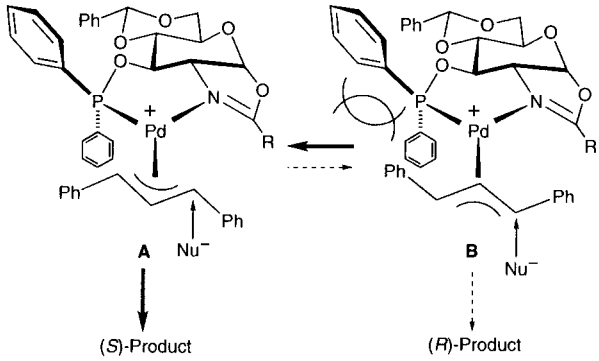
Scheme 1 *Reagents and conditions*: i, $(Pr^iCO)_2O$, MeONa, MeOH, room temp., 24 h, 82%; ii, PhCHO, $ZnCl_2$, room temp., 5 h, then Ac_2O, pyridine, room temp., 24 h, 43% (2 steps); iii, $SnCl_4$, CH_2Cl_2, room temp., 1 h, 52%; iv, K_2CO_3, MeOH, room temp., 1 h, 73%; v, Ph_2PCl, Et_3N–THF (1 : 1), cat. DMAP, room temp., 15 min, 46%.

Table 1 Palladium-catalysed asymmetric allylic alkylation with chiral ligands **1** and **5**–**9**[a]



Entry	L*	Solvent	*T*/°C	*t*/h	Ee (%)[b]
1	**1**	CH_2Cl_2	room temp.	1	85 (*S*)
2	**1**	THF	room temp.	0.5	86 (*S*)
3	**1**	toluene	room temp.	1	88 (*S*)
4	**1**	toluene	60	0.5	84 (*S*)
5	**1**	toluene	0	6	90 (*S*)
6	**5**	toluene	0	18	78 (*S*)
7	**6**	toluene	0	6	83 (*S*)
8	**7**	toluene	0	6	94 (*S*)
9	**8**	toluene	0	6	95 (*S*)
10	**9**	toluene	0	6	96 (*S*)

[a] The reaction was carried out under Ar using 1,3-diphenyl-3-acetoxyprop-1-ene (1.0 mmol), dimethyl malonate (3.0 mmol), BSA (3.0 mmol), KOAc (0.05 mmol), solvent (2.0 ml), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.25 mol%) and L* (0.55 mol%). Product was isolated in quantitative yield. [b] Measured by HPLC; the absolute configuration was determined by optical rotation (ref. 7).



Scheme 2

Scheme 2. In the transition state, the steric repulsion in **A** between the phenyl group on phosphorous and the substrate appears smaller than that in **B**.

In summary, we have demonstrated that the novel chiral ligands **1** and **5**–**9** are very efficient ligands for asymmetric allylic alkylation, using only 0.25 mol% Pd complex to provide a high enantioselectivity (up to 96% ee). These ligands can be prepared in six steps using commercial D-glucosamine hydrochloride as an inexpensive natural chiral source. They are a new type of P–N ligands using only the chirality of D-glucosamine, which is communicated to the coordination sphere built with both phosphorous and nitrogen. To the best of our knowledge, this is the first example of the application of phosphinite–nitrogen chiral ligands[9] to asymmetric allylic alkylation. Application of these ligands to other asymmetric reactions is now in progress.

Notes and references

† *Selected data* for **9**; δ_H 2.05 (d, *J* 1.1, 3H), 3.61–3.69 (m, 2H), 3.76 (t, *J* 8.5, 1H), 4.23–4.32 (m, 2H), 4.36 (dd, *J* 3.3, 8.5, 1H), 5.35 (s, 1H), 5.98 (d, *J* 7.4, 1H), 7.23–7.53 (m, 15H); δ_C 14.3, 62.9, 68.6, 69.4 (d, *J* 5.2), 79.6 (d, *J* 3.6), 82.3 (d, *J* 20.2), 101.2, 102.2, 126.0–136.9 (16 C), 141.9 (d, *J* 21.3), 142.2 (d, *J* 16.4), 165.0; δ_P 114.5; $[\alpha]_D^{20}$ −75.7 (*c* 0.25, $CHCl_3$).

‡ Procedure for the Pd-catalysed enantioselective allylic alkylation: To a stirring solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.91 mg, 2.5×10^{-3} mmol) in toluene was added ligand **9** (2.62 mg, 5.5×10^{-3} mmol) under Ar atmosphere. After 30 min, racemic 1,3-diphenyl-3-acetoxyprop-1-ene (0.25 g, 1.0 mmol) was added and the solution was stirred for 30 min. *N*,*O*-Bis(trimethylsilyl)acetamide (0.74 ml, 3.0 mmol), dimethyl malonate (0.35 ml, 3.0 mmol) and KOAc (4.8 mg, 0.05 mmol) were then added at 0 °C and the solution was stirred at this temperature. After the reaction was completed (6 h), the solvent was evaporated *in vacuo* and column chromatography on silica gel (hexane–EtOAc 5 : 1) of the residue yielded the pure product. The enantiomeric excess was determined to be 96% ee by HPLC (Daicel Chiralcel AD column, 1.0 ml min^{-1}, hexane–Pr^iOH 95 : 5).

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