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Palladium-catalyzed asymmetric allylic alkylation using chiral glucosamine-based monophosphines

Mustapha Tollabi, Eric Framery, Catherine Goux-Henry and Denis Sinou*

Laboratoire de Synthèse Asymétrique, associé au CNRS, CPE Lyon, Université Claude Bernard Lyon 1, 43, boulevard du 11 novembre 1918, 69622 Villeurbanne Cedex, France

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Abstract—An easy access to a new chiral phosphine-amide derived from D-glucosamine is described. Palladium-catalyzed asymmetric allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate with various carbon and aminonucleophiles in the presence of this ligand has been successfully carried out, enantiomeric excesses of up to 97% being obtained.

1. Introduction

Palladium-catalyzed asymmetric allylic alkylation has recently become a very useful process for asymmetric carbon–carbon as well as carbon–heteroatom bond forming reactions.[1] In order to achieve high enantioselectivities in this catalytic reaction, a large variety of chiral ligands have been studied. For example, Trost's P–P ligand **1**[2] or Pfaltz's P–N ligand **2**[3] (Fig. 1) have been successfully employed in various allylic alkylations, giving enantioselectivities higher than 95%. The use of chiral monophophine ligands in this reaction however is less common.[4] Chiral phosphine-amide ligands **3** gave enantioselectivities up to 40, 12 and 78% ee, when R = H, CH_2Ph, and NR_2, respectively,[5] while ligands **4**[6] and **5**[7] gave enantioselectivities up to 90 and 78% ee in this palladium-catalyzed allylic alkylation. ^1H NMR studies as well as a X-ray crystallography of a (π-allyl)palladium complex unambiguously showed that these ligands acted as bidentate ligands and chelated the (π-allyl)Pd in the *P*,*O*-chelation mode in which a carboxamide oxygen act as the *O*-ligand. Moreover, if Trost's ligand **1** formed *P*,*P*-chelate complexes with palladium,[8] it was shown that the *P*,*O*-coordination between phosphine and the amide carbonyl was generated even in solution when the ratio of palladium to **1** was raised (i.e. ≥ 1).[9] As a result we became interested in chiral amidophosphine ligands derived from aminocarbohydrates.[10] Herein we report the palladium-catalyzed asymmetric allylic alkylation using chiral phosphine-amide ligands **6a**–**b** derived from D-glucosamine (Fig. 1).

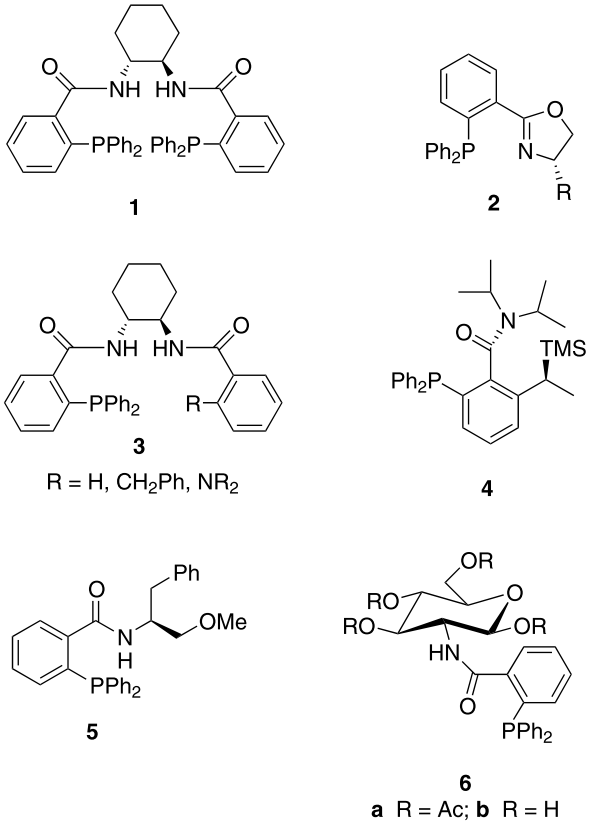

Figure 1.

* Corresponding author. Tel.: 33 (0)4 72448183; fax: 33 (0)4 78898914; e-mail: sinou@univ-lyon1.fr

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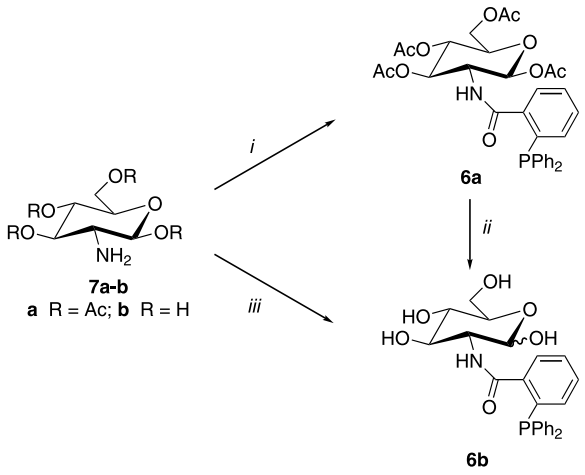
2. Results and discussion

Ligand **6a** was easily obtained from the reaction of 2-diphenylphosphinobenzoic acid with 2-amino-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **7a** in a mixture of CH_2Cl_2/THF in the presence of EDC (or 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide) and HOBT (or 1-hydroxybenzotriazole) in 74% yield. Deacetylation of **7a** with a catalytic amount of sodium methoxide in methanol gave the polyhydroxy phosphine **6a** in 80% yield, as a 87:13 mixture of the α- and β-anomers. This compound was also obtained directly by the condensation of D-glucosamine **7b** with 2-diphenylphosphinobenzoic acid in the presence of EDC, HOBT, and $NaHCO_3$ in a mixture of DMF/water as the solvent resulting in an 85% yield (Scheme 1).

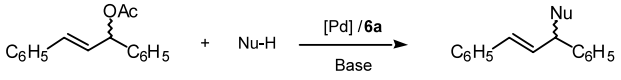


Scheme 1. *Reagents and conditions*: (i) 2-diphenylphosphinobenzoic acid, EDC, HOBT, CH_2Cl_2/THF, 5 h, 74%; (ii) CH_3ONa, CH_3OH, THF, 1 h, 80%; (iii) 2-diphenylphosphinobenzoic acid, EDC, HOBT, DMF, H_2O, 24 h, 85%.

We examined the chiral ligands **6a**–**b** in the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with various nucleophiles (Table 1). This reaction was first carried in the presence of 2 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4 mol% of chiral ligand, and dimethyl malonate (3 equiv.) acting as the nucleophile. We used in the first experiment NaH as the base and THF as the solvent; the conversion however was only 78% after 24 h, and the enantioselectivity very low (25% ee) (Table 1, entry 1). When a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 2 mol% LiOAc was used as the base instead of NaH in THF, the conversion was complete and the enantioselectivity in the alkylated product raised to 83% (Table 1, entry 2). Such a behavior has already been reported by Mino et al.[7]

The effect of the ratio **6a**/palladium on the enantioselectivity of this alkylation reaction was also investigated. Increasing the ratio of ligand **6a** to the palladium

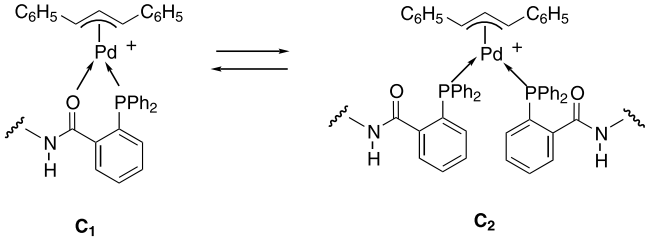
Table 1. Asymmetric allylic alkylation of racemic 1,3-diphenylprop-2-enyl acetate using various nucleophiles[a]



Entry	Nu–H	Base	Solvent	*T* (°C)	Conversion (%)[b] (yield%[c])	E.e. (%)[d] (config.)[e]
1	$CH_2(CO_2Me)_2$	NaH	THF	25	78	25 (*R*)
2	$CH_2(CO_2Me)_2$	BSA–LiOAc	THF	25	100 (98)	83 (*R*)
3[f]	$CH_2(CO_2Me)_2$	BSA–LiOAc	THF	25	100	62 (*R*)
4	$CH_2(CO_2Me)_2$	BSA–LiOAc	CH_2Cl_2	25	100 (99)	53 (*R*)
5	$CH_2(CO_2Me)_2$	BSA–LiOAc	Et_2O	25	100 (94)	62 (*R*)
6	$CH_2(CO_2Me)_2$	BSA–LiOAc	Toluene	25	100 (97)	54 (*S*)
7	$CH_2(CO_2Me)_2$	BSA–LiOAc	DMF	25	30	84 (*S*)
8	$CH_2(CO_2Me)_2$	K_2CO_3	THF/H_2O (1:1)	25	35	95 (*R*)
9	$MeCH(CO_2Me)_2$	BSA–LiOAc	THF	25	0	–
10	$MeCH(CO_2Me)_2$	BSA–LiOAc	THF	50	100 (94)	88 (*S*)
11	$AcNHCH(CO_2Me)_2$	BSA–LiOAc	THF	25	0	–
12	$AcNHCH(CO_2Me)_2$	BSA–LiOAc	THF	50	100 (86)	97 (*S*)
13	$CH_2(COCH_3)_2$	BSA–LiOAc	THF	25	0	–
14	Benzylamine	BSA–LiOAc	THF	25	100 (70)	93 (*S*)
15	Benzylamine	None	THF	25	18	64 (*S*)
16	(2-Naphthylmethyl)amine	BSA–LiOAc	THF	25	100 (58)	93 (*S*)[g]
17	Morpholine	BSA–LiOAc	THF	25	100 (92)	81 (*S*)[h]

[a] [Substrate]:[nucleophile]:[BSA]:[LiOAc]:[Pd]:[**6a**] = 25:75:75:1:1:1.
[b] Determined by GC analysis.
[c] Isolated pure product.
[d] Determined by HPLC analysis (column Chiralpak AD 0.46×25 cm).
[e] Determined by comparison with an authentic sample.
[f] [**6a**]:[Pd] = 2.
[g] $[\alpha]_D^{25} = +13.0$ (*c* 2.5, $CHCl_3$).
[h] $[\alpha]_D^{25} = +7.7$ (*c* 0.7, $CHCl_3$).

precursor to 2 (Table 1, entry 3) led to a quantitative transformation, but the enantioselectivity of the reaction decreased to 62% ee. This decrease in enantioselectivity with an increasing ratio of ligand/Pd can be explained by the different modes of chelation.[6–9] According to previous work, *P*,*O*-chelation mode has been shown to occur in the case of phosphine–amide ligands; this chelation is even in competition with *P*,*P*-chelation in the case of bisphosphine–amide ligands. In our case, we assumed an equilibrium between the two complexes $\mathbf{C_1}$ and $\mathbf{C_2}$ in this allylic alkylation reaction. The complex $\mathbf{C_1}$, where the ligand **6a** is a bidentate ligand, will give higher enantioselectivity, due to the rigidity of the complex. On the other hand, in the complex $\mathbf{C_2}$, with two ligands **6a** acting as a monodentate ligand, there is more freedom in the complex and so the enantioselectivity will be lower (Scheme 2).



Scheme 2.

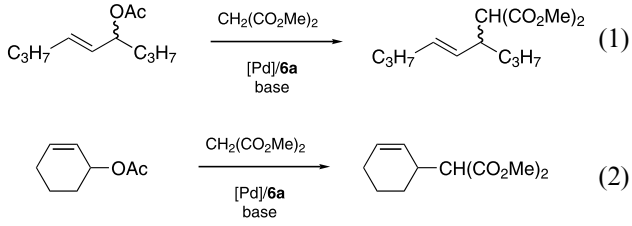
We were unable to determine the formation of the 'PdL_2' or 'PdL' complex by NMR whatever the conditions used. However, we prepared two complexes by mixing $PdCl_2$(COD) with 1 and 2 equiv. of ligand **6a**, respectively. The complexes thus obtained as amorphous powders were subjected to ES-MS. The complex obtained by mixing 1 equivalent of Pd complex and 2 equiv. of ligand **6a** showed effectively the most important signal at 1410.9 m/z corresponding to $[Pd(\mathbf{6a})_2Cl]^+$, and a very small signal at 775.9 m/z corresponding to $[Pd(\mathbf{6a})Cl]^+$. On the other hand, the solid obtained by mixing 1 equiv. of $PdCl_2$(COD) and 1 equiv. of **6a** showed the most important m/z at 775.9, characteristic of $[Pd(\mathbf{6a})Cl]^+$, and a smaller signal at 1410.9 m/z for $[Pd(\mathbf{6a})_2Cl]^+$. This is in agreement with a *P*,*O*-chelation mode. Since an equilibrium occurs between the two complexes $\mathbf{C_1}$ and $\mathbf{C_2}$ in solution, an excess of ligand **6a** will shift this equilibrium towards the $\mathbf{C_2}$ complex and so the enantioselectivity will be lower.

When the reaction was carried out in CH_2Cl_2, diethyl ether, or toluene, the conversion was complete, but the enantioselectivity was lower: 53, 62, and 54% ee, respectively (Table 1, entries 4-6). Using DMF as the solvent gave the alkylated product with 84% ee, but the conversion was also very low (30%) (Table 1, entry 7). The reaction was also performed in a 1/1 mixture of THF and water in the presence of K_2CO_3 as the base though the conversion after 24 h is only 35%, the enantioselectivity was as high as 95% (Table 1, entry 8). This last alkylation reaction prompted us to use ligand **6b** in the alkylation reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in water/THF. Unfortunately, whatever the conditions used (room temperature, 50°C, K_2CO_3, BSA, or DBU, as the base), no formation of the alkylated product was observed.

We then used other *C*-nucleophiles under the above-mentioned conditions in THF as the solvent. If dimethyl methylmalonate and dimethyl acetamidomalonate gave no reaction at 25°C, alkylation occurred quantitatively at 50°C with very high enantioselectivity: 88 and 97% ee, respectively (Table 1, entries 9–12). Acetylacetone though gave no reaction even at 50°C (Table 1, entry 12).

We also used amines as nucleophiles: Benzylamine, (2-naphthylmethyl)amine and morpholine gave the expected allylic amines at room temperature with high enantioselectivity: 93, 93 and 81% ee, respectively (Table 1, entries 14, 16, and 17). When the reaction was performed without adding BSA–LiOAc, in the case of benzylamine as the nucleophile (Table 1, entry 15), the enantioselectivity decreased to 64% ee with the conversion being very low (18%). Other nucleophiles were also used in this coupling reaction, such as potassium phthalimide, sodium toluene sulfinate, phenol; however, whatever the conditions used, no coupling product was obtained.

The reaction of dimethyl malonate was also carried out with two other allylic acetates, namely (*E*)-1-propylhex-2-en-1-yl acetate and cyclohexenyl acetate, in the presence of 2 mol% $[Pd(\eta_3\text{-}C_3H_5)Cl]_2$ associated with ligand **6a** in THF, with BSA-LiOAc being used as the base. Enantioselectivity of up to 58 and 14% was obtained, respectively (Eqs. (1) and (2)).



3. Conclusion

A chiral phosphine-amide ligand derived from D-glucosamine was easily obtained and used in the palladium-catalyzed asymmetric allylic alkylation with enantioselectivity of up to 97%, which is one of the highest values obtained in this reaction with a monophosphine. This new class of carbohydrate-derived ligands can very easily be modified. Work is currently in progress in order to determine the influence of the carbohydrate framework in this reaction, as well as in other asymmetric-catalyzed reaction.

4. Experimental

4.1. General

Solvents were purified by standard methods and dried if necessary. All commercial available reagents were used as received. All reactions were monitored by TLC (TLC plates GF_{254} Merck); detection was effected by UV absorbance. Air and moisture sensitive reactions were performed under the usual inert atmosphere techniques. Reactions involving organometallic catalysis were carried out in a Schlenk tube under an inert atmosphere. Column chromatography was performed on silica gel 60 (230-240 mesh, Merck). Optical rotations were recorded using a Perkin–Elmer 241 polarimeter. NMR spectra were recorded with a Bruker AMX 300 spectrometer and referenced as following: ^1H (300 MHz), internal $SiMe_4$ at δ 0.00 ppm, ^{13}C (75 MHz), internal $CDCl_3$ at δ 77.23 ppm, and ^{31}P (121 MHz), external 85% H_3PO_4 at δ 0.00 ppm. Conversion was determined by GC using a Quadrex OV1 column (30 m×0.25 mm), and enantiomeric excess was determined by HPLC with a Chiralpak^{AD} column (25 cm×4.6 mm) using different ratios of hexane-*i*-propanol as the eluent.

4.2. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-{[2-(diphenylphosphino)benzoyl]amino}-β-D-glucopyranose, 6a

1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose **4a** (688 mg, 1.98 mmol), 2-diphenylphosphinobenzoic acid (551 mg, 1.8 mmol), EDC (414 mg, 2.16 mmol), and HOBT (291 mg, 2.16 mmol) were dissolved in a mixture of CH_2Cl_2 (10 mL) and THF (20 mL) in a Schlenk tube under argon. After being stirred for 5 h at rt, the solvents were evaporated. The residue was washed with 5% NaOH (10 mL), and 0.5 M HCl (5 mL), then dried under vacuum to give 847 mg of phosphine **1a** (yield 74%). Mp 148–150°C; R_f=0.58 (petroleum ether/ethyl acetate 3:2); $[\alpha]_D^{20}$=+36.3 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.03 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.77 (m, 1H, H-5), 4.13 (dd, *J*= 12.4, 2.1 Hz, 1H, H-6), 4.26 (dd, *J*=12.4, 4.2 Hz, 1H, H-6), 4.52 (ddd, *J*=9.8, 9.5, 8.8 Hz, 1H, H-2), 5.07 (dd, *J*=9.2, 8.8 Hz, 1H, H-4), 5.15 (dd, *J*=9.8, 8.8 Hz, 1H, H-3), 5.68 (d, *J*=8.8 Hz, 1H, H-1), 5.99 (d, *J*=9.5 Hz, 1H, NH), 6.95–7.55 (m, 14H, $H_{arom.}$); ^{13}C NMR ($CDCl_3$): δ 20.9, 21.0, 21.3, 21.4, 53.2, 61.7, 67.9, 72.4, 72.9, 92.6, 128.7, 128.8, 128.9, 129.2, 130.6, 131.8, 132.1, 132.5, 133.3, 133.4, 133.7, 133.8, 133.9, 135.1, 137.2, 137.4, 141.4, 141.7, 168.9, 169.3, 169.9, 170.8, 171.4; ^{31}P NMR ($CDCl_3$): δ −10.3. Mass $[MH]^+$ $C_{33}H_{35}O_{10}NP$ calcd 636.1998, found 636.1986.

4.3. 2-Deoxy-2-{[2-(diphenylphosphino)benzoyl]amino}-D-glucopyranose, 6b

A solution of 2-diphenylphosphinobenzoic acid (173.7 mg, 0.5 mmol), EDC (112 mg, 0.6 mmol), and HOBT (81 mg, 0.6 mmol) in DMF (4 mL) was stirred in a Schlenk tube under argon at 0°C for 1 h. A solution of D-glucosamine hydrochloride (215 mg, 1.0 mmol) in DMF (2 mL) was added, followed by the addition of a solution of $NaHCO_3$ (200 mg, 2.4 mmol) in H_2O (2 mL). After being stirred for 24 h at rt, the solvents were evaporated under reduced pressure to give a solid that was purified by flash-chromatography on silica gel using $CHCl_3$/EtOH 3:1 as the eluent to give 198 mg of phosphine **6b** (yield 80%). Mp 60–63°C; R_f=0.64 ($CHCl_3/C_2H_5OH$ 3:1); $[\alpha]_D^{20}$=+25.2 (*c* 1, THF); ^1H NMR (C_5D_5): δ 5.46 (ddd, *J*=9.4, 5.7, 2.1 Hz, 0.13H, H-5β), 5.64 (dd, *J*=9.4, 8.7 Hz, 0.13H, H-4β), 5.76 (dd, *J*=9.6, 8.9 Hz, 0.87H, H-4α), 5.81 (dd, *J*=11.7, 5.7 Hz, 0.87H, H-6α), 5.97 (dd, *J*=11.7, 2.3 Hz, 0.87H, H-6α), 6.20–6.32 (m, 1.74H, H-3α, H-5α), 6.43 (ddd, *J*=10.7, 8.5, 3.4 Hz, 0.87H, H-2α), 6.79 (bs, 4H, OH), 6.99 (d, *J*=8.3 Hz, 0.13H, H-1β), 7.40 (d, *J*=3.4 Hz, 0.87H, H-1α), 8.70–8.79 (m, 10H, $H_{arom.}$), 8.84–8.95 (m, 3H, $H_{arom.}$), 9.46–9.52 (m, 1H, $H_{arom.}$), 10.65 (d, *J*=8.5, 0.87H, NH), 11.13 (d, *J*= 8.3, 0.13H, NH); ^{31}P NMR (C_5D_5N): δ −7.1. Mass $[MH]^+$ $C_{25}H_{26}O_6NP$ calcd 468.1576, found 468.1574.

4.4. Saponification of compound 6a

To the acetylated phosphine **6a** (300 mg, 0.47 mmol) dissolved in THF (10 mL) under argon was slowly added a solution of Na (20 mg, 0.87 mmol) in CH_3OH (5 mL). After being stirred for 1 h at rt, the solvent was evaporated to give a yellow solid that was purified by flash-chromatography on silica gel using CH_2Cl_2/CH_3CO_2Et 90:10 as the eluent to give 187 mg of phosphine **6b** (yield=85%).

4.5. Standard alkylation reaction

In a Schlenk tube, $[Pd(C_3H_5)Cl]_2$ (8.8 mg, 24 μmol) and the ligand (48 μmol) were dissolved in the solvent (1 mL). After stirring the mixture for 1 h at the desired temperature, a solution of the racemic acetate **14** (302 mg, 1.2 mmol) in solvent (1 mL) was added. After 30 min, this solution was transferred to a Schlenk tube containing the nucleophile (3.6 mmol), *N*,*O*-bis-(trimethylsilyl)acetamid (732 mg, 3.6 mmol), and LiOAc (2.5 mg, 24 μmol) in 2 mL of solvent. The reaction mixture was stirred at the desired temperature for 24 h. The conversion was determined by GC analysis. The mixture was then diluted with diethyl ether (15 mL), and water (5 mL). The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue that was purified by chromatography (petroleum ether/ethyl acetate 10:1). The enantiomeric excess was determined by HPLC analysis (column Chirapalk AD 0.46×25 cm).

Acknowledgements

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References

1. (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422; (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Tokyo, 1999; Vol. 2, p. 833; (c) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1–14; (d) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203–214; (e) Williams, J. M. J. *Synlett* **1996**, 705–710.
2. Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343.
3. Von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566–568.
4. Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195–202.
5. (a) Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817–5820; (b) Kim, Y. K.; Lee, S. J.; Ahn, K. H. *J. Org. Chem.* **2000**, *65*, 7807–7813.
6. Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033–7040.
7. Mino, T.; Kashihara, K.; Yamashita, M. *Tetrahedron: Asymmetry* **2001**, *12*, 287–291.
8. Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817–5820.
9. (a) Butts, C. P.; Crosby, J.; Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun.* **1999**, 1707–1708; (b) Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Commun.* **1999**, 2447–2448.
10. Parisot, S.; Kolodziuk, R.; Goux-Henry, C.; Iourtchenko, A.; Sinou, D. *Tetrahedron Lett.* **2002**, *43*, 7397–7400.