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New homochiral phosphine ligands having a hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolone backbone: preparation and use for palladium-catalyzed asymmetric alkylation of cycloalkenyl carbonates

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Abstract—New chiral ligands having a pyrrolo[1,2-*c*]imidazolone backbone were prepared by condensation of anilides of homochiral cyclic amino acids with 2-(diphenylphosphino)benzaldehyde. Of these ligands, (3*R*,9a*S*)-(3-(2-diphenylphosphino)phenyl-2-phenyl)tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one was found to be effective for palladium-catalyzed asymmetric allylic alkylation of cycloalkenyl carbonates with dimethyl malonate to give the corresponding dimethyl cycloalkenylmalonates with e.e. of up to 89%.

1. Introduction

The development of new ligands for use in asymmetric catalysis continues to undergo very rapid growth. Organophosphorus compounds having a homochiral backbone are recognized as one of the most versatile and successful classes of ligands in transition metal-catalyzed asymmetric reactions. We have recently designed and prepared a library of bicyclic tertiary amines bearing an sp^3-bridgehead nitrogen with a view to using it for screening enantioselective amine reagents.[1] Highly functionalized bicyclic amines having a hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolone framework were identified through library-based screening as effective chiral amine agents. These results prompted us to prepare triarylphosphines having a pyrrolo[1,2-*c*]imidazolone skeleton as new basic chiral units for transition metal-catalyzed asymmetric reactions (Fig. 1).[2] Herein, we wish to report the development of (3*R*,9a*S*)-3-[2-(diphenylphosphino)phenyl] - 2 - phenyltetrahydro - 1*H*-imidazo[1,5-*a*]indole-1-one (β-**3**) as a new chiral ligand and its use for palladium-catalyzed asymmetric alkylation of cyclic allyl esters with dimethyl malonate where high stereoselectivity of up to 89% e.e. was achieved.

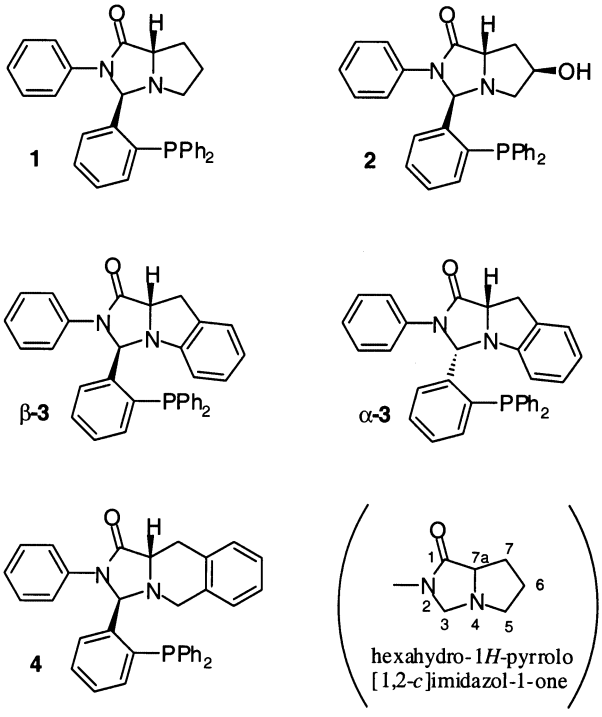

Figure 1. Homochiral phosphine ligands having a pyrroloimidazole backbone.

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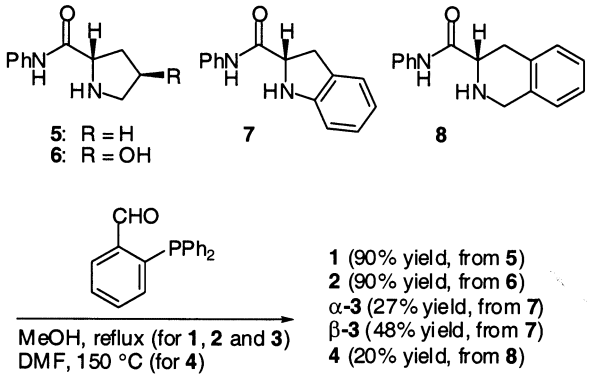
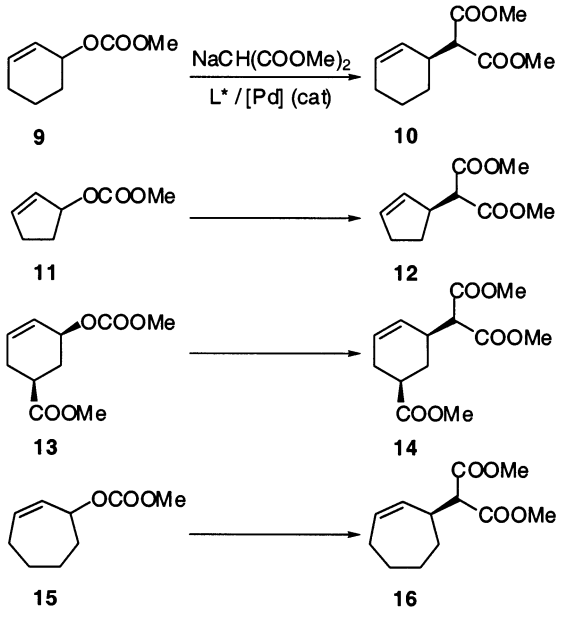
2. Results and discussion

The triarylphosphine ligands **1**, **2** and **3** having a homochiral pyrroloimidazolone backbone were prepared from the corresponding anilides **5**, **6** and **7**, respectively (Scheme 1). Thus, reaction of 2-(diphenylphosphino)benzaldehyde with anilides **5** and **6**, which were readily prepared from proline and *trans*-4-hydroxyproline,[3] in refluxing methanol gave (pyrroloimidazolone)phosphine **1** and its 6-hydroxyl derivative **2** both in 90% yield. The phosphine ligand **3** having an imidazoindole unit was obtained as a mixture of diastereomers α-**3** (27%) and β-**3** (48%) from the anilide of (*S*)-indoline-2-carboxylic acid **7** by a similar procedure. Condensation of the tetrahydroisoquinoline carboxamide **8** with 2-(diphenylphosphino)benzaldehyde in DMF at 150°C gave imidazoisoquinoline **4** in 20% yield.

The enantiocontrolling abilities of the chiral phosphine ligands **1**, **2**, α-**3**, β-**3** and **4** were examined for palladium-catalyzed asymmetric allylic alkylation of cyclic allyl esters (Scheme 2). Although the palladium-catalyzed asymmetric allylic alkylation of acyclic substrates is one of the most thoroughly investigated carbon–carbon bond forming reactions using a variety of chiral ligands, the corresponding substitution of cycloalkenyl esters is still a major challenge.[4] Reaction of the cyclohexenyl methyl carbonate **9** with the sodium salt of dimethyl malonate in THF was catalyzed by



Scheme 1.



Scheme 2.

chiral phosphine–palladium complexes to give the dimethyl (cyclohexen-2-yl)malonate **10**. The enantiomeric purity of the alkylated product **10** was determined by GC analysis using a chiral stationary phase capilliary column (Cyclodex CB). The results, summarized in Table 1 (entries 1–5), revealed that the most stereoselective ligand is (3*R*,9a*S*)-3-[(2-diphenylphosphino)phenyl]-2-phenyltetrahydro-1*H*-imidazo[1,5-*a*]-indole-1-one (β-**3**). Thus, the allylic alkylation of **9** with dimethyl malonate in the presence of 2.5 mol% of a palladium complex generated in situ by mixing the bis(μ-chloro)bis(η^3-allyl)dipalladium(II) ([PdCl(η^3-C_3H_5)]$_2$) and 1.5 equiv. (versus palladium) of the (imidazoindole)phosphine ligand β-**3** was carried out at 25°C for 3 h to give compound **10** with 82% e.e. (*S*) in 86% yield (Table 1, entry 4). Palladium complexes of the pyrroloimidazolones **1** or **2**, which lack fused benzene rings, were significantly less enantioselective to give **10** with 14 and 7% e.e., respectively (entries 1 and 2). A palladium complex coordinated with the imidazoindole ligand α-**3** showed slightly higher catalytic

Table 1. Asymmetric allylic alkylation of cycloalkenyl carbonates with dimethyl malonate[a]

Entry	Allyl ester	Ligand	Product	Yield (%)[b]	E.e.%[c] (config.)[d]
1	**9**	**1**	**10**	84	14 (*S*)
2	**9**	**2**	**10**	84	7 (*S*)
3[b]	**9**	α-**3**	**10**	100	47 (*S*)
4	**9**	β-**3**	**10**	86	82 (*S*)
5	**9**	**4**	**10**	100	46 (*S*)
6[b]	**11**	β-**3**	**12**	86	82 (*S*)
7	**13**	β-**3**	**14**	100	88 (*S*)
8	**15**	β-**3**	**16**	100	89 (*S*)

[a] All reactions were carried out in THF in the presence of 2.5 mol% Pd of Pd–L* complex generated in situ. A ratio of allyl ester/NaCH(COOMe)$_2$/Pd/L* = 1.0/2.0/0.025/0.038.
[b] Isolated yield.
[c] Determined by GC analysis using chiral stationary capillary column (Cyclodex CB).
[d] Determined by comparing the specific rotation with the literature value (Ref. 4e (Supporting Information)).

performance than its diastereomeric isomer β-**3** to give a quantitative yield of the alkylation product **10** within 1 h of reaction time, whereas the enantiomeric purity of **10** was much lower (entry 3). The allylic alkylation with (imidazoisoquinoline)phosphine ligand **4** also showed low enantioselectivity to give **10** with 46% e.e. (entry 5).

To explore the generality of this enantioselective reaction, we carried out the alkylation of the cycloalkenyl carbonates **11**, **13** and **15** under otherwise similar conditions. The cyclopentenyl carbonate **11** underwent alkylation with dimethyl malonate to give an 86% yield of **12** with 82% e.e. (entry 6). The alkylation of the racemic *cis*-5-carbomethoxy-2-cyclohexenyl methyl carbonate **13** gave 88% e.e. of **14** in a quantitative yield as a single diastereoisomer having the *cis*-configuration, demonstrating that the allylic alkylation proceeded through the generally accepted double inversion pathway (entry 7).[5] The highest enantioselectivity was observed in the reaction of the cycloheptenyl carbonate **15** to give a quantitative yield of **16** with 89% enantioselectivity (entry 8).

3. Conclusion

In summary, we have developed new homochiral phosphine ligands having a pyrrolo[1,2-*c*]imidazolone backbone, of which (3*R*,9a*S*)-3-[(2-diphenylphosphino)phenyl]-2-phenyltetrahydro-1*H*-imidazo[1,5-*a*]-indole-1-one was found to exhibit high enantioselectivity ranging from 82 to 89% e.e. in a palladium-catalyzed allylic alkylation of cycloalkenyl substrates.

4. Experimental

4.1. General

All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5 (Merck, Sicapent). NMR spectra were recorded on a Jeol JNM-AL400 spectrometer (400 MHz for ^{1}H NMR), or Jeol JNM LA500 spectrometer (500 MHz for ^{1}H and 202 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR, and to an external 85% H_3PO_4 standard for ^{31}P NMR. ^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ at 25°C. GC analysis was performed on Hewlett Packard HP 6890 and HP 4890 series with a chiral stationary phase capillary column, Cyclodex CB (50 m). Optical rotations were measured on a Jasco DIP-370 polarimeter.

4.2. (3*R*,7a*S*)-3-[2-(Diphenylphosphino)phenyl]-2-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one, 1

To a solution of (*S*)-2-anilinocarbonyl-1-trifluoroacetylpyrrolidine[3] (286 mg, 1.0 mmol) in methanol (3 mL) was added anhydrous K_2CO_3 (276 mg, 2.0 mmol) and the reaction mixture was stirred at room temperature for 1 h. To this mixture was added 2-(diphenylphosphino)benzaldehyde (580 mg, 2.0 mmol) and the reaction mixture was heated at 80°C in a sealed tube for 3 h. After being cooled to room temperature, the reaction mixture was extracted with chloroform, dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was chromatographed on silica gel (eluent: ethyl acetate/hexane = 1/3) to give **1** as a white solid (416 mg, 90%): $[\alpha]_D^{19} = +44$ (*c* 1.4, chloroform); EI MS (*m*/*z*): 462 (M^+); ^{1}H NMR (chloroform-*d*): δ 1.42–1.56 (m, 1H), 1.65–1.76 (m, 1H), 1.97–2.15 (m, 2H), 2.63–2.70 (m, 1H), 3.09–3.14 (m, 1H), 3.92 (dd, *J* = 4.4, 9.0 Hz, 1H), 6.53 (d, *J* = 6.1, 1H), 6.99–7.07 (m, 2H), 7.14–7.39 (m, 15H), 7.44 (d, *J* = 8.1 Hz, 2H); ^{31}P{^{1}H} NMR (chloroform-*d*): δ −18.0 (s). Anal calcd for $C_{30}H_{27}N_2OP$: C, 77.90; H, 5.88; N, 6.06. Found: C, 77.73; H, 5.98; N, 5.93%.

4.3. (3*R*,7a*S*)-3-[2-(Diphenylphosphino)phenyl]-6-hydroxy-2-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one, 2

The same procedure as employed for the preparation of **1** was followed with (2*S*,4*R*)-2-anilinocarbonyl-4-hydroxy-1-trifluoroacetylpyrrolidine[3] (302 mg, 1.0 mmol). The resulting crude product was chromatographed on silica gel (eluent: ethyl acetate/hexane = 2/1) to give **2** as a white solid (430 mg, 90%): $[\alpha]_D^{19} = +9$ (*c* 1.6, chloroform); EI MS (*m*/*z*): 478 (M^+); ^{1}H NMR (chloroform-*d*): δ 1.94–2.00 (m, 1H), 2.32–2.38 (m, 1H), 2.67 (dd, *J* = 3.6, 10 Hz, 1H), 3.13 (d, *J* = 10 Hz, 1H), 3.82 (dd, *J* = 4.5, 9.6 Hz, 1H), 4.10 (br s, 1H), 6.58 (d, *J* = 5.9 Hz, 1H), 7.05–7.13 (m, 2H), 7.19–7.38 (m, 15H), 7.57 (d, *J* = 7.8 Hz, 2H); ^{31}P{^{1}H} NMR (chloroform-*d*): δ −18.4 (s). Anal calcd for $C_{30}H_{27}N_2O_2P$: C, 75.30; H, 5.69; N, 5.85. Found: C, 75.24; H, 5.82; N, 5.62%.

4.4. (3*S*,9a*S*)-3-[2-(Diphenylphosphino)phenyl]-2-phenyltetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one, α-3 and (3*R*,9a*S*)-3-[2-(diphenylphosphino)phenyl]-2-phenyltetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one, β-3

The same procedure as employed for the preparation of **1** was followed with (*S*)-2-anilinocarbonylindoline **7**[6] (338 mg, 1.0 mmol). The resulting crude product was chromatographed on silica gel (eluent: acetone/hexane = 1/2) to give β-**3** (245 mg, 48%) and α-**3** (138 mg, 27%) as white solids: α-**3**: $[\alpha]_D^{25} = +135$ (*c* 1.0, chloroform); EI MS (*m*/*z*): 510 (M^+); ^{1}H NMR (chloroform-*d*): δ 3.38 (dd, *J* = 11.0, 16.5 Hz, 1H), 3.69 (dd, *J* = 4.2, 16.5 Hz, 1H), 4.72 (dd, *J* = 4.2, 11.0 Hz, 1H), 5.23 (d, *J* = 8.1 Hz, 1H), 6.56–7.64 (m, 23H); ^{31}P{^{1}H} NMR (chloroform-*d*): δ −20.0 (s). Anal calcd for $C_{34}H_{27}N_2OP$: C, 80.00; H, 5.33; N, 5.49. Found: C, 80.04; H, 5.48; N, 5.26%. β-**3**: $[\alpha]_D^{19} = +127$ (*c* 0.7, chloroform); EI MS (*m*/*z*): 510 (M^+); ^{1}H NMR (chloroform-*d*): δ 3.12 (dd, *J* = 10, 16 Hz, 1H), 3.54 (d, *J* = 16 Hz, 1H), 4.39 (dd, *J* = 1.6, 10 Hz, 1H), 6.90–7.63 (m, 24H); ^{31}P{^{1}H} NMR (chloroform-*d*): δ −20.0 (s).

4.5. (3*R*,10a*S*)-3-[2-(Diphenylphosphino)phenyl]-2-phenytetrahydro-1*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1-one, 4

(*S*)-3-Anilinocarbonylisoquinoline **8**[7] (100 mg, 0.4 mmol) and 2-(diphenylphosphino)benzaldehyde (232 mg, 0.8 mmol) were dissolved in DMF (5 mL). The reaction mixture was heated to 150°C in a sealed tube for 12 h. After cooling to room temperature, the reaction mixture was extracted with chloroform and dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was chromatographed on silica gel (eluent: acetone/hexane = 1/5) to give **4** as a white solid (42 mg, 20%): $[\alpha]_D^{25} = +6$ (*c* 0.5, chloroform); EI MS (*m*/*z*): 524 (M^+); ^1H NMR (chloroform-*d*): δ 3.06 (dd, $J = 6.6$, 15.4 Hz, 1H), 3.14 (dd, $J = 6.6$, 15.4 Hz, 1H), 3.50 (d, $J = 14.9$ Hz, 1H), 3.67 (d, $J = 14.9$ Hz, 1H), 4.17 (br s, 1H), 6.66 (d, $J = 7.6$ Hz, 1H), 6.80 (d, $J = 7.3$ Hz, 1H), 7.00–7.41 (m, 22H); $^{31}P\{^1H\}$ NMR (chloroform-*d*): δ −20.0 (s).

4.6. Catalytic asymmetric alkylation of cycloalkenyl carbonates with dimethyl malonate

A typical procedure was given for the reaction of **9** with dimethyl malonate (Table 1, entry 4). To a suspension of NaH in THF (1 mL) was added a solution of dimethyl malonate (105.7 mg, 0.8 mmol) at 0°C. To a solution of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (1.8 mg, 0.005 mmol), ligand β-**3** (7.7 mg, 0.015 mmol) and cyclic allyl substrate **9** (68 mg, 0.4 mmol) in THF (2 mL) was added a THF solution of sodium salt of malonate and the reaction mixture was stirred at 25°C for 3 h. The reaction mixture was quenched with a small portion of saturated NH_4Cl solution, and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (eluent: *n*-hexane/ethyl acetate 5/1) to give **10** as a colorless oil (86.8 mg, 96%).

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References

1. (a) Uozumi, Y.; Mizutani, K.; Nagai, S.-I. *Tetrahedron Lett*. **2001**, *42*, 407; (b) Uozumi, Y.; Yasoshima, K.; Miyachi, T.; Nagai, S.-I. *Tetrahedron Lett*. **2001**, *42*, 411.
2. We have reported the immobilization of this class of chiral ligands on an amphiphilic polymer resin and their use for asymmetric catalysis in water, where up to 98% e.e. of asymmetric allylic alkylation of cycloalkenyl esters was achieved. See: Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc*. **2001**, *123*, 2919.
3. Mori, M.; Uozumi, Y.; Kimura, M.; Ban, Y. *Tetrahedron* **1986**, *42*, 3793.
4. For examples of palladium-catalyzed asymmetric allylic alkylation of cycloalkenyl substrates, see: (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc*. **1994**, *116*, 4089; (b) Knühl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem. Commun*. **1995**, 1845; (c) Nishimata, T.; Mori, M. *J. Org. Chem*. **1998**, *63*, 7586; (d) Kudis, S.; Helmchen, G. *Angew. Chem. Int. Ed*. **1998**, *37*, 3047; (e) Gilbertson, S.; Xie, D. *Angew. Chem. Int. Ed*. **1999**, *38*, 2750; (f) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc*. **2000**, *122*, 7905; (g) Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem*. **2000**, *65*, 4227; (h) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem*. **2001**, *66*, 206; (i) Hamada, Y.; Sakaguchi, K.; Hara, O. *Tetrahedron Lett*. **2001**, *42*, 1297; (j) Xiao, L.; Weissensteiner, W.; Mereiter, K.; Widhalm, M. *J. Org. Chem*. **2002**, *67*, 2206. Also see Ref. 3.
5. Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett*. **1986**, *27*, 191.
6. Roloff, A.; Gschwend, H. W. Eur. Pat. Appl., 1986.
7. Weir, E. C.; Niopas, I.; Samil, G. A. *Chem. Chrom*. **1989**, *18*, 3.