DOI: 10.1002/adsc.201200133

Palladium-Catalyzed Asymmetric 1,4-Addition of Diarylphosphines to Nitroalkenes for the Synthesis of Chiral P,N-Compounds

Jian-Jun Feng,[b] Miao Huang,[b] Zi-Qi Lin,[a] and Wei-Liang Duan[a,*]

[a] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China
Fax: (+86)-21-6416-6128; phone: (+86)-21-5492-5203; e-mail: wlduan@mail.sioc.ac.cn
[b] School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, People's Republic of China

Received: February 17, 2012; Revised: August 9, 2012; Published online: November 4, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200133.

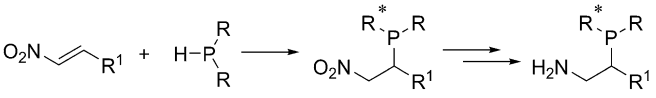
Abstract: A highly stereoselective asymmetric 1,4-addition of diarylphosphines to nitroalkenes catalyzed by a bis(phosphine) pincer-palladium complex has been developed for the synthesis of chiral P,N compounds with good to excellent enantioselectivities (up to 94% *ee*) under mild conditions.

Keywords: 1,4-addition; asymmetric hydrophosphination; diarylphosphines; nitroalkenes; pincer palladium catalysts

Introduction

Chiral phosphines play a very important role in asymmetric catalysis as ligands coordinated to transition metal catalysts or organocatalysts.[1] Phosphorus-Michael addition reactions are well known processes for the synthesis of phosphine compounds; however their use in the formation of enantiopure phosphines has been scarely explored.[2,3] Some examples of catalytic asymmetric nucleophilic phosphorus addition to electron-deficient alkenes with good to excellent enantioselectivities have been reported only very recently.[4]

Nitroalkenes are typical substrates in asymmetric 1,4-additon reactions.[5] They are frequently used to react with various nucleophiles, and their nitro group can be easily reduced to an amino moiety under mild conditions. The asymmetric nucleophilic phosphorus addition to nitroalkenes followed by a nitro group reduction step generates optically active P,N compounds (Scheme 1), which are valuable chiral ligands in metal-catalyzed asymmetric hydrogenation and enantioselective organocatalyzed reactions.[6,7] This process has been recently realized by Mechiolrre and his co-workers through the use of *Cinchona* alkaloids as catalysts for the reaction of diphenylphosphine with nitroalkenes, producing the 1,4-adduct with moderate enantioselectivity.[8] Tan and his co-workers also reported an asymmetric addition of diarylphosphine oxides as nucleophiles to nitroalkenes in the presence of a chiral biscyclic guanidine catalyst.[9] Typically, when bis(2-naphthyl)phosphine oxide is used, the product is isolated with 99% *ee*. However, the development of new catalytic protocols still remains attractive in term of the relatively narrow substrate scope (only for β-aryl nitroalkenes) and high catalyst loading (10–20 mol%) of the reported catalytic systems. Recently, we have developed a highly efficient bisphosphine (PCP) pincer-PdOAc catalyst for the enantioselective hydrophosphination of electron-deficient alkenes.[4d,k,m] To continue our interest in the synthesis of chiral phosphines, in the current report, a PCP pincer palladium-catalyzed asymmetric 1,4-addition of diarylphosphines to β-aryl and β-alkyl nitroalkenes with good to excellent enantioselectivty is described as an alternative method for the synthesis of chiral P,N compounds.

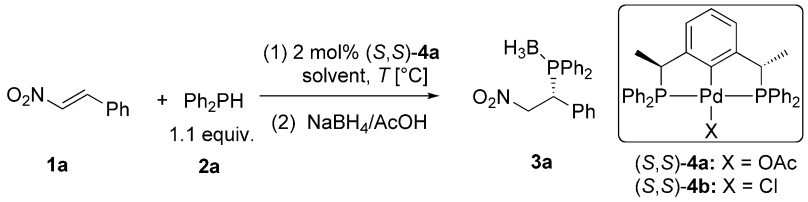


Scheme 1. Synthesis of chiral P,N compounds through asymmetric hydrophosphination of nitroalkenes.

Results and Discussion

The current experiment began with the reaction of *trans*-β-nitrostyrene with diphenylphosphine in the presence of 2 mol% of PCP pincer-PdOAc (*S*,*S*)-**4a**[4d,10,11] catalyst as the model reaction (Table 1),

Table 1. Palladium-catalyzed asymmetric addition of diphenylphosphine to *trans*-β-nitrostyrene **1a**.



Entry[a]	Temp. [°C]	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1	r.t.	THF	2	41	83
2	r.t.	CH_2Cl_2	2	64	73
3	r.t.	CH_3CN	2	55	64
4	r.t.	*t*-BuOH	2	50	54
5	r.t.	*t*-AmOH	2	59	60
6	r.t.	toluene	2	63	87
7[d]	r.t.	toluene	2	68	39
8	0	toluene	5	72	89
9	−10	toluene	5	80	91
10	−20	toluene	5	69	91
11	−30	toluene	5	70	91
12	−40	toluene	5	64	91

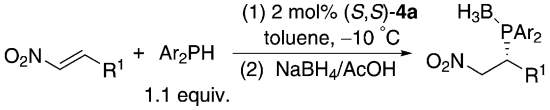
[a] The reaction was quenched with 2.5 equiv. $NaBH_4$/3.0 equiv. AcOH.
[b] Isolated yields.
[c] Determined by HPLC with hexane/2-propanol.
[d] 2 mol% of (*S*,*S*)-**4b** was used as the catalyst.

Given the oxygen sensitivity of the phosphine group of the 1,4-adduct, $NaBH_4$ and HOAc were added at the work-up step to obtain a borane-phosphine complex. The reaction proceeded well in various solvents at room temperature (entries 1–5). Toluene is the optimal solvent, producing the adduct **3a** with 87% *ee* (entry 6). The use of PCP PdCl complex (*S*,*S*)-**4b** only afforded the product with 39% *ee* and 68% yield (entry 7), which indicates the important role of acetate anion on the palladium atom of **4a**. Temperature screening results show that −10 °C reaction temperature afforded the adduct with the best yield and *ee* (80% yield and 91% *ee*; entry 9).

Under the optimized conditions with (*S*,*S*)-**4a** as the catalyst, various nitroalkenes were reacted with diarylphosphines; the results are shown in Table 2. The substrates bearing the electron-donating or electron-withdrawing groups on the aryl moiety all reacted with diphenylphosphine with high enantioselectivities and yields (70–90% yield, 87–91% *ee*; entries 1–7). Moreover, alkyl-substituted substrates under the current system also afforded adducts with good stereoselectivities (72–73% yield, 85–91% *ee*; entries 8 and 9). For the nucleophilic component, phosphines bearing electron-donating or electron-withdrawing groups reacted smoothly with **1a**, affording the phosphination products with high yields and enantioselectivities (80% yield, 76–91% ee; entries 10 and 11).

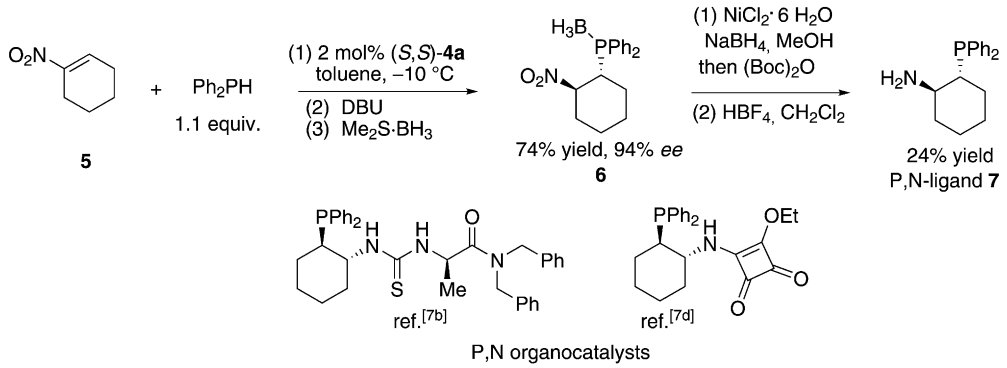
The reaction of α,β-disubstituted nitroalkene substrates such as 1-nitrocyclohexene (Scheme 2) was also examined, given the capacity of the 1,4-adduct to be converted into a *trans* P,N bidentate phosphine

Table 2. Palladium-catalyzed asymmetric addition of diarylphosphines to nitroalkenes.



Entry[a]	R^1	Ar	Yield [%][b]	*ee* [%][c,d]
1	Ph	Ph	80	91
2	*p*-$MeOC_6H_4$	Ph	70	90
3	*m*-$MeOC_6H_4$	Ph	71	90
4	*p*-BrC_6H_4	Ph	81	87
5	*m*-BrC_6H_4	Ph	85	85
6	2-naphthyl	Ph	92	90
7	2-furyl	Ph	90	86
8	cyclohexyl	Ph	73	85
9	*i*-propyl	Ph	72	91
10	Ph	*p*-$MeOC_6H_4$	80	76
11	Ph	*p*-ClC_6H_4	80	91

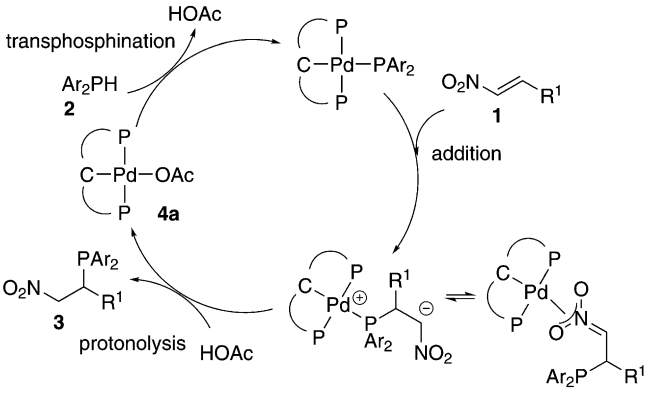
[a] The reaction was quenched with 2.5 equiv. $NaBH_4$/3.0 equiv. AcOH.
[b] Isolated yields.
[c] Determined by HPLC with hexane/2-propanol.
[d] The absolute configurations of products were determined to be *R* by comparison of the specific optical rotation of the adduct (entry 1) with the value reported in literature; see the Supporting Information for details.



Scheme 2. Palladium-catalyzed asymmetric addition of diphenylphosphine to 1-nitrocyclohexene.

amine ligand, which had been synthesized through the optical resolution of its racemate with enantiopure tartaric acid.[12] The reaction of diphenylphosphine with 1-nitrocyclohexene under the current conditions proceeded smoothly to give *cis* and *trans* isomers with a ratio of 3:2. The *cis*-adduct can be converted *in situ* to the more thermodynamically stable *trans*-isomer in the presence of DBU as the base. After quenching with a boron reagent, the *trans*-product, borane-phosphine complex **6**, was isolated with 94% *ee* in 74% yield. Finally, the product **6** was converted to the highly useful P,N compound **7** in two steps, which has been utilized as the chiral pool for the synthesis of various phosphine amine organocatalysts.[7]

A possible catalytic cycle of this reaction is shown in Scheme 3.[4d] First pincer-PdOAc **4a** reacts with diarylphosphine to generate a palladium phosphido complex. Then, the nucleophilic attack of the diarylphosphido group on palladium to the double bond of nitroalkenes, affords a zwitterionic Pd-phosphine complex with pendant anion,[3f,g] which may exist in equilibrium with the neutral nitro-palladium intermediate. Finally, the protonolysis of the formed Pd species with the acetic acid in the system furnishes the phosphine product along with regeneration of the catalyst.



Scheme 3. The catalytic cycle in the palladium-catalyzed asymmetric addition of diarylphosphines to nitroalkenes.

Conclusions

In summary, we have developed a PCP pincer Pd-catalyzed highly stereoselective addition of diarylphosphines to nitroalkenes, producing phosphination products with good to excellent enantioselectivities and yields. The application of the current method for the synthesis of a useful chiral P,N compound has also been demonstrated.

Experimental Section

General Remarks

All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen or in a glove box under nitrogen. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian instrument (400 MHz, 100 MHz and 162 MHz, respectively). ^{1}H and ^{13}C NMR chemical shifts are reported *vs.* tetramethylsilane signal or residual protio solvent signals. Toluene and THF were distilled over sodium benzophenone ketyl under nitrogen. Dichloromethane was distilled over CaH_2 under nitrogen. See the Supporting Information for a general procedure and data for the 1,4-adducts.

Typical Procedure for the Palladium-Catalyzed 1,4-Addition Reaction of Diphenylphosphine to Nitroalkenes

Diphenylphosphine (41.0 mg, 0.22 mmol) was added to a solution of (*S*,*S*)-**4a** (2.7 mg, 4 μmol Pd) in toluene (2.0 mL) and the resulting solution was stirred for 4 min at −10 °C (realized with a refrigerated bath circulator). After addition of *trans*-β-nitrostyrene (29.8 mg, 0.20 mmol), the solution was stirred for 2–24 h at −10 °C, then concentrated under vacumm until 0.5 mL toluene was left. $NaBH_4$ (18.9 mg, 0.50 mmol), HOAc (36.0 mg, 0.60 mmol) in THF (0.3 mL)

wereadded and the resulting mixture was stirred for 1 h. After addition of 2 mL saturated NaCl aqueous solution and extraction with dichloromethane, the organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography with CH_2Cl_2/hexane = 1/1 to afford the product as a white solid (CAS 931411-28-8)[8]. The *ee* was determined on a Daicel ChiralPak AD-H column with hexane/2-propanol = 80/20, flow = 1.0 mL min^{-1}: retention times: 5.6 min [(*R*)-enantiomer], 6.6 min [(*S*)-enantiomer]; 91% *ee*; $[\alpha]_D^{20}$: −222 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 8.01–7.96 (m, 2H), 7.60–7.51 (m, 3H), 7.36–7.32 (m, 3H), 7.24–7.18 (m, 2H), 7.17–7.12 (m, 5H), 5.19–5.11 (m, 1H), 4.70–4.62 (m, 2H), 1.10 (br, 3H); ^{13}C NMR ($CDCl_3$): δ = 132.6 (d, $J_{C,P}$ = 8.1 Hz), 132.5 (d, $J_{C,P}$ = 9.6 Hz), 132.3 (d, $J_{C,P}$ = 2.2 Hz), 131.6 (d, $J_{C,P}$ = 2.2 Hz), 131.3 (d, $J_{C,P}$ = 1.5 Hz), 129.4 (d, $J_{C,P}$ = 9.6 Hz), 129.3 (d, $J_{C,P}$ = 4.5 Hz), 128.4 (d, $J_{C,P}$ = 11.9 Hz), 128.33, 128.30 (d, $J_{C,P}$ = 3.7 Hz), 125.74 (d, $J_{C,P}$ = 51.1 Hz), 125.72 (d, $J_{C,P}$ = 55.8 Hz), 75.5 (d, $J_{C,P}$ = 14.2 Hz), 41.5 (d, $J_{C,P}$ = 30.5 Hz); ^{31}P{1H} NMR ($CDCl_3$): δ = 21.6 (m). MS (ESI): m/z = 348 [$(M-H)^+$].

Acknowledgements

We thank the NSFC (20902099, 21172238), National Basic Research Program of China (973 Program 2010CB833300), and SIOC for financial support.

References

[1] *Phosphorus Ligands in Asymmetric Catalysis: Synthesis and Applications*, Vols. 1—3, (Ed.: A. Börner), Wiley-VCH, Weinheim, **2008**.

[2] For a review of 1,4-addition reactions of phosphorus nucleophiles to electron-deficient olefins, see: D. Enders, A. Saint-Dizier, M.-I. Lannou, A. Lenzen, *Eur. J. Org. Chem.* **2006**, 29.

[3] For reviews on catalytic asymmetric synthesis of chiral phosphanes, see: a) D. S. Glueck, *Chem. Eur. J.* **2008**, *14*, 7108; b) D. S. Glueck, *Synlett* **2007**, 2627; c) J. S. Harvey, V. Gouverneur, *Chem. Commun.* **2010**, 7477; d) D. Zhao, R. Wang, *Chem. Soc. Rev.* **2012**, *41*, 2095. For leading examples, see: e) I. Kovacik, D. K. Wicht, N. S. Grewal, D. S. Glueck, C. D. Incarvito, I. A. Guzei, A. L. Rheingold, *Organometallics* **2000**, *19*, 950; f) C. Scriban, I. Kovacik, D. S. Glueck, *Organometallics* **2005**, *24*, 4871; g) C. Scriban, D. S. Glueck, L. N. Zakharov, W. S. Kassel, A. G. DiPasquale, J. A. Golen, A. L. Rheingold, *Organometallics* **2006**, *25*, 5757; h) A. D. Sadow, I. Haller, L. Fadini, A. Togni, *J. Am. Chem. Soc.* **2004**, *126*, 14704; i) A. D. Sadow, A. Togni, *J. Am. Chem. Soc.* **2005**, *127*, 17012; j) P. Butti, R. Rochat, A. D. Sadow, A. Togni, *Angew. Chem.* **2008**, *120*, 4956; *Angew. Chem. Int. Ed.* **2008**, *47*, 4878; k) J. R. Moncarz, N. F. Laritcheva, D. S. Glueck, *J. Am. Chem. Soc.* **2002**, *124*, 13356; l) N. F. Blank, J. R. Moncarz, T. J. Brunker, C. Scriban, B. J. Anderson, O. Amir, D. S. Glueck, L. N. Zakharov, J. A. Golen, C. D. Incarvito, A. L. Rheingold, *J. Am. Chem. Soc.* **2007**, *129*, 6847; m) V. S. Chan, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 15122; n) V. S. Chan, I. C. Stewart, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 2786; o) C. Scriban, D. S. Glueck, *J. Am. Chem. Soc.* **2006**, *128*, 2788; p) V. S. Chan, M. Chiu, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6021; q) L. Hong, W. Sun, C. Liu, D. Zhao, R. Wang, *Chem. Commun.* **2010**, 2856; r) W. Sun, L. Hong, C. Liu, R. Wang, *Org. Lett.* **2010**, *12*, 3914; s) M. Nielsen, C. B. Jacobsen, K. A. Jørgensen, *Angew. Chem.* **2011**, *123*, 3269; *Angew. Chem. Int. Ed.* **2011**, *50*, 3211.

[4] For catalytic asymmetric 1,4-addition of substituted phosphines or phosphine oxides to α,β-unsaturated carbonyl compounds, see: a) A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Angew. Chem.* **2007**, *119*, 4588; *Angew. Chem. Int. Ed.* **2007**, *46*, 4504; b) I. Ibrahem, R. Rios, J. Vesely, P. Hammar, L. Eriksson, F. Himo, A. Córdova, *Angew. Chem.* **2007**, *119*, 4591; *Angew. Chem. Int. Ed.* **2007**, *46*, 4507; c) I. Ibrahem, P. Hammar, J. Vesely, R. Rios, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2008**, *350*, 1875; d) J.-J. Feng, X.-F. Chen, M. Shi, W.-L. Duan, *J. Am. Chem. Soc.* **2010**, *132*, 5562; e) D. Zhao, L. Mao, D. Yang, R. Wang, *J. Org. Chem.* **2010**, *75*, 6756; f) D. Zhao, L. Mao, Y. Wang, D. Yang, Q. Zhang, R. Wang, *Org. Lett.* **2010**, *12*. 1880; g) S. Wen, L. Li, H. Wu, F. Yu, X. Liang, J. Ye, *Chem. Commun.* **2010**, 4806; h) Y. Huang, S. A. Pullarkat, L. Li, P.-H. Leung, *Chem. Commun.* **2010**, 6950; i) A. Russo, A. Lattanzi, *Eur. J. Org. Chem.* **2010**, 6736; j) M.-J. Yang, Y.-J. Liu, J.-F. Gong, M.-P. Song, *Organometallics* **2011**, *30*, 3793; k) D. Du, W.-L. Duan, *Chem. Commun.* **2011**, *47*, 11101; l) X. Luo, Z. Zhou, X. Li, X. Liang, J. Ye, *RSC Advances* **2011**, *1*, 698; m) Y.-R. Chen, W.-L. Duan, *Org. Lett.* **2011**, *13*. 5824; n) Y. Huang, R. J. Chew, Y. Li, S. A. Pullarkat, P.-H. Leung, *Org. Lett.* **2011**, *13*. 5862.

[5] For a review on asymmetric 1,4-addition to nitroalkenes, see: O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877.

[6] a) K. Sumi, T. Ikariya, R. Noyori, *Can. J. Chem.* **2000**, *78*, 697; b) R. Guo, A. J. Lough, R. H. Morris, D. Song, *Organometallics* **2004**, *23*, 5524; c) R. Guo, R. H. Morris, D. Song, *J. Am. Chem. Soc.* **2005**, *127*, 516; d) M. Ito, S. Kitahara, T. Ikariya, *J. Am. Chem. Soc.* **2005**, *127*, 6172; e) J.-B. Xie, J.-H. Xie, X.-Y. Liu, W.-L. Kong, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 4538; f) J.-B. Xie, J.-H. Xie, X.-Y. Liu, Q.-Q. Zhang, Q.-L. Zhou, *Chem. Asian J.* **2011**, *6*, 899.

[7] a) S. Dalili, A. Caiazzo, A. K. Yudin, *J. Organomet. Chem.* **2004**, *689*, 3604; b) Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660; c) K. Yuan, L. Zhang, H.-L. Song, Y. Hu, X.-Y. Wu, *Tetrahedron Lett.* **2008**, *49*, 6262; d) H.-L. Song, K. Yuan, X.-Y. Wu, *Chem. Commun.* **2011**, 1012.

[8] G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, A. Mazzanti, L. Sambri, P. Melchiorre, *Chem. Commun.* **2007**, 722.

[9] a) X. Fu, Z. Jiang, C.-H. Tan, *Chem. Commun.* **2007**, 5058; b) B. Cho, C.-H. Tan, M. W. Wong, *Org. Biomol. Chem.* **2011**, *9*, 4550.

[10] For reviews on pincer metal complexes, see: a) M. Albrecht, G. van Koten, *Angew. Chem.* **2001**, *113*, 3866; *Angew. Chem. Int. Ed.* **2001**, *40*, 3750; b) N. Selander, K. J. Szabó, *Chem. Rev.* **2011**, *111*, 2048.
[11] For synthesis and applications of the chiral PCP-PdCl complex, see: a) J. M. Longmire, X. Zhang, *Tetrahedron Lett.* **1997**, *38*, 1725; b) J. M. Longmire, X. Zhang, M. Shang, *Organometallics* **1998**, *17*, 4374.
[12] A. Caiazzo, S. Dalili, A. K. Yudin, *Org. Lett.* **2002**, *4*. 2597.

