Asymmetric Allylic Alkylation Using a Palladium Complex of Chiral 2-(Phosphinoaryl)pyridine Ligands

Katsuji Ito,[a*] Risa Kashiwagi,[a] Kazunori Iwasaki,[a] Tsutomu Katsuki[b*]

[a] Department of Chemistry, Fukuoka University of Education, Akama, Munakata, Fukuoka 811-4192, Japan

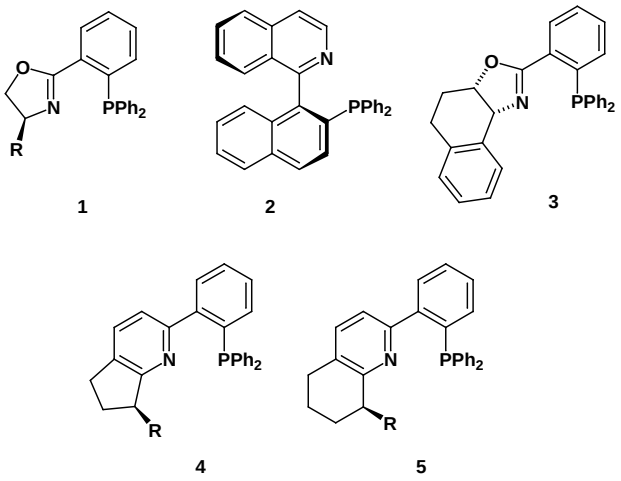
[b] Department of Molecular Chemistry, Graduate School of Science, Kyushu University 33, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

Fax +81-92-642-2607

Received 22 July 1999

Abstract: A palladium complex of newly designed chiral 2-(phosphinoaryl)pyridine (**4b**) was found to be an effective catalyst for asymmetric allylic alkylation. High enantioselectivity was achieved in the reactions of both 1,3-diphenyl-2-propen-1-yl acetate (98% ee) and (2*E*)-1-methyl-2-butenyl phenyl carbonate (93% ee) with dimethyl malonate.

Key words: asymmetric allylic alkylations, asymmetric catalysis, palladium, chiral P,N-ligands

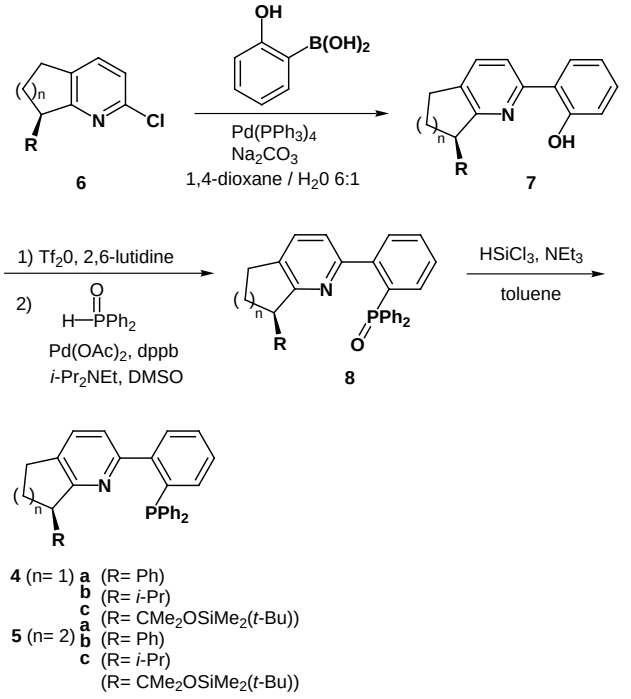


Palladium-catalyzed allylic alkylation is one of the most useful carbon-carbon bond forming reactions, because the reaction proceeds smoothly under mild conditions to give β-functionalized alkenes that are useful building blocks in synthetic organic chemistry.[1] In particular, asymmetric allylic alkylation catalyzed by chiral palladium complex has attracted the attention of synthetic organic chemists.[2] In the early stage of this area of chemistry, C_2-symmetric diphosphine and dinitrogen ligands were extensively used as chiral sources. To achieve high enantioselectivity in allylic alkylation, two factors, the orientation of the allyl moiety in the intermediary π-allyl complexes and regioselection in nucleophilic attack to the complex, have to be controlled strictly. Use of C_2-symmetric ligand removes the first issue but the regiocontrol remains as a difficult problem.[2] Only a few C_2-symmetric diphosphine ligands show high enantioselectivity in the reaction of a wide range of substrates.[3,4] Recently, however, non-symmetric heterobidentate ligands were found to be efficient chiral sources for asymmetric allylic substitution. These new ligands regulate the above two factors through their steric and ligand effects. In particular, the coordination of the ligand atoms of the different rows in periodic table affects the susceptibility of the π-allyl terminal carbons *trans* to the atoms, to nucleophiles in a different way (*trans*-effect) and results in high regioselectivity in the nucleophilic attack.[5,6] Some successful examples in this class of ligands are 2-(phosphinoaryl)oxazolines **1**[5a-c] and (phosphinonaphthyl)isoquinoline (QUINAP) ligand **2**.[5d]

These first generation heterobidentate ligands showed high enantioselectivity in the allylic alkylation of 1,3-diphenyl-substituted allyl (*i.e.* α,γ-diphenylallyl) substrates, but they gained a limited success in the reaction of 1,3-dimethyl-substituted allyl (*i.e.* α,γ-dimethylallyl) or cyclic allyl substrates. It is clear that the chiral coordination sphere constructed by heterobidentate ligands regulates the orientation of the allyl moiety but the regulation is not sufficient for the latter reaction. Following these pioneering studies, various second generation heterobidentate ligands have been introduced and the scope of asymmetric allylic alkylation has been extended.[5e-t,6] Quite recently, Helmchen *et al* reported that highly enantioselective allylic alkylation of 1,3-dimethyl-substituted allyl substrates using new type of 2-(phosphinoaryl)oxazolines **3** (up to 89.5% ee).[5p,7]

Several years ago, we found that chiral bipyridine ligands showed high enantioselectivity in cyclopropanation and ring-enlargement reactions.[8] Therefore we were intrigued by the heterobidentate ligands **4** and **5** bearing chiral pyridine ligands as chiral auxiliaries, in which the substituent at the chiral center was fixed to direct toward the allyl-palladium moiety and therefore expected to efficiently control the orientation of the allyl moiety.[5p] Here we wish to report our preliminary results on the synthesis of 2-(phosphinoaryl)pyridine ligands and their application to palladium-catalyzed asymmetric allylic alkylation.

The synthesis of chiral 2-(phosphinoaryl)pyridines **4** and **5** started with the corresponding chiral chloropyridines **6**, which are key intermediates for the chiral bipyridine synthesis (Scheme 1).[8c] Suzuki cross-coupling of the chloropyridines **6** with 2-hydroxyphenylboronic acid gave pyridylphenols **7**. Pyridylphenols **7** were converted into the desired 2-(phosphinoaryl)pyridines **4** and **5**, respectively, in a conventional manner.[9]



Scheme 1

With chiral 2-(phosphinoaryl)pyridines **4** and **5** in hand, we first examined the allylic alkylation of 1,3-diphenyl-2-propen-1-yl acetate with dimethyl malonate in the presence of the palladium complex of **4** or **5** in dichloromethane using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate as the base (Table 1).[10] The catalytic activity of the palladium complexes and their asymmetric induction depended on the ligands used. Although all the reactions completed to give the product in quantitative yield at room temperature, the reaction time varied with the ligands. The reaction using ligand **4c** or **5c** having a bulky substituent at the stereogenic carbon was slow and required longer reaction times (entries 3 and 6). When **5c** was used as the ligand, the enantioselectivity also suffered. As expected, however, the other new ligands served as efficient chiral auxiliaries and high enantioselectivity greater than 90% ee was attained. The most effective one was **4b**, the Pd complex of which showed the best enantioselectivity of 97% ee together with high catalytic activity (entry 2). Ligand **5a** was almost equally effective to **4b**. Absolute configuration of all the products was determined to be *S* by chiroptical comparison with the published value.[3b,4] This sense of asymmetric induction by these ligands was identical with that by chiral 2-(phosphinoaryl)oxazolines **1**, suggesting the present reaction proceeds through a similar transition state proposed by Helmchen *et al*.[5b]

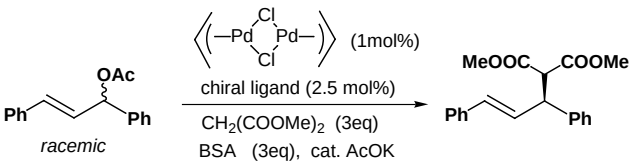


Table 1 Asymmetric allylic alkylation of 1,3-diphenyl-2-propen-1-yl acetate.[a)]

entry	ligand	time (min)	yield (%)	% ee[b)]	confign.[c)]
1	**4a**	35	100	91	*S*
2	**4b**	30	100	97	*S*
3	**4c**	150	100	91	*S*
4	**5a**	30	100	96	*S*
5	**5b**	75	100	93	*S*
6	**5c**	120	100	64	*S*
7	**4b**[d)]	60	100	98	*S*

a) Reactions were carried out at room temperature in dichloromethane unless otherwise mentioned.
b) Enantiomeric excess was determined by HPLC using optically active column (Daicel Chiralpak AD; hexane : *i*-PrOH= 9 : 1).
c) Determined by chiroptical comparison with the published value (references 4 and 5a).
d) Reaction was carried out in acetonitrile at 0 °C in the presence of 15-crown-5 by using NaH as the base instead of BSA.

We next examined the reaction of 3-penten-2-yl acetate which is an unmanageable substrate among 1,3-dialkyl-substituted allyl acetates, using **4b** as the chiral source (Table 2). Reaction in dichloromethane using BSA as the base proceeded smoothly but the enantioselectivity was moderate (entry 1). It is well-known that the enantioselectivity of allylic alkylation was affected by the base used in many cases.[2] Thus, we next examined the effect of the base on enantioselectivity. Rapid reaction was observed by using sodium hydride as the base in THF, but the enantioselectivity was decreased to a considerable extent (entry 2).[11] In contrast, the reaction in acetonitrile using sodium hydride in the presence of 15-crown-5[5d] showed the greatly improved enantioselectivity of 82% ee (entry 3). The reaction at 0 °C otherwise under the same conditions further improved the enantioselectivity to 86% ee (entry 5). Although enantioselectivity was improved to 88% ee by further depressing the temperature (-15 °C), the reaction rate became slow (entry 6). Except for the last run, the starting material was completely consumed in these reactions but the chemical yields of the desired product were unsatisfactory (entries 2-5).[12] This indicated that elimination of acetic acid occurred competitively during the reaction. To suppress this undesired side-reaction, we examined the reaction of the substrates bearing alkyl carbonyloxy groups[1a,3b] that are less potent leaving groups than acetoxy group. The reactions of these substrates proceeded smoothly with better chemical yields (entries 7-9) and an equal level of enantioselectivity was observed when the phenyl carbonate was used as a substrate (entry 9). Enantioselectivity increased as reaction temperature was decreased and high enantioselectivity of 93% ee as well as good chemical yield of 85% were achieved when the reaction was performed at -25 °C (entry 11).[13]

Under the conditions using sodium hydride as the base in the presence of 15-crown-5, we re-examined the allylic alkylation of 1,3-diphenyl-2-propen-1-yl acetate with

dimethyl malonate and found that high enantioselectivity of 98% ee and quantitative yield were realized (Table 1, entry 7).

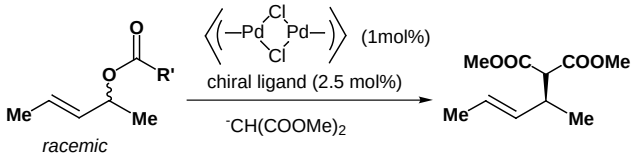


Table 2 Asymmetric allylic alkylation of 1,3-dimethyl-substituted allyl substrates using **4b** as the chiral source.[a)]

entry	substrate (R')	base	temp (°C)	time	yield (%)	ee[b)] (%)	confign.[c)]
1[d)]	Me	BSA	rt	40 min	77	71	*S*
2[e)]	"	NaH	rt	3 min	66	41	*S*
3	"	NaH	rt	40 min	66	82	*S*
4	"	NaH[f)]	rt	75 min	52	72	*S*
5	"	NaH	0	50 min	44	86	*S*
6	"	NaH	-15	72 h	36	88	*S*
7	OMe	NaH	rt	20 min	82	78	*S*
8	OPr-*i*	NaH	rt	25 min	75	81	*S*
9	OPh	NaH	rt	20 min	75	83	*S*
10	"	NaH	0	150 min	70	88	*S*
11	"	NaH	-25	48 h	85	93	*S*

a) Reactions were carried out in acetonitrile unless otherwise mentioned.
b) Enantiomeric excess was determined by ^{1}H NMR analysis in the presence of chiral shift reagent Eu(hfc)$_3$.
c) Determined by chiroptical comparison with the published value (references 3b, 4 and 5a).
d) Reaction was carried out in dichloromethane.
e) Reaction was carried out in THF.
f) Reaction was carried out in the absence of 15-crown-5.

In conclusion, we were able to disclose that the newly designed 2-(phosphinoaryl)pyridines were promising chiral ligands for palladium-catalyzed asymmetric allylic alkylation. Further studies on the optimization of the ligands and application to other asymmetric reactions are in progress in our laboratory.

Acknowledgment

Financial support from a Grant-in-Aid for Scientific Research (10740338) from the Ministry of Education, Science, Sports and Culture, Japan is gratefully acknowledged.

References and Notes

(1) Reviews: a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. b) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds; Pergamon Press: Oxford, 1982, Vol. 8, pp. 799.
(2) Reviews: a) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993, pp.325. b) Trost, B. M.; van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395.
(3) a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. b) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520. The best enantioselectivity (92% ee) in the so far reported allylic alkylations of 1,3-dimethyl-substituted allyl substrates reaction has been achieved by using cyclohexanediamidodiphosphine-Pd complex as a catalyst. However, the catalyst can not be successfully applied to 1,3-diphenyl-substituted allyl substrate.
(4) Dierkes, P.; Ramdeehul, S.; Barloy, L.; De Cian, A.; Fischer, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A.; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3116.
(5) Some recent examples of asymmetric allylic substitution of 1,3-disubstituted allyl substrates using P,N-chelate ligands: a) von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566. b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. d) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493. e) Kubota, H.; Koga, K. *Tetrahedron Lett.* **1994**, *36*, 6689. f) Wimmer, P.; Widhalm, M. *Tetrahedron: Asymmetry* **1995**, *6*, 657. g) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R.; *J. Am. Chem. Soc.* **1996**, *118*, 1031. h) Evans, P. A.; Brandt, T. A. *Tetrahedron Lett.* **1996**, *37*, 9143. i) Saitoh, A.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3567. j) Brunel, J. -M.; Constantieux, T.; Labande, A.; Lubatti, F.; Buono, G. *Tetrahedron Lett.* **1997**, *38*, 5971. k) Bourghida, M.; Widhalm, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1073. l) Ogasawara, M.; Yoshida, K.; Kamei, H.; Kato, K.; Uozumi, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1779. m) Zhang, W.; Yoneda, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1998**, *9*, 3371. n) Cahill, J. P.; Guiry, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 4301. o) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1998**, *39*, 4343. p) Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727. q) Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *Chem. Commun.* **1999**, 415. r) Saitoh, A.; Misawa, M.; Morimoto, T. *Synlett*, **1999**, 483. s) Hiroi, K.; Suzuki, Y.; Abe, I. *Tetrahedron: Asymmetry* **1999**, *10*, 1173. t) Suzuki, Y.; Ogata, Y.; Hiroi, K. *Tetrahedron: Asymmetry* **1999**, *10*, 1219. See also reference 2b.
(6) Efficient regio- and enantioselective allylic alkylation of 1- and 3-aryl-2-propenyl acetates has been reported with chiral palladium catalysts: a) Pretoto, R.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 323. b) Pretot, R.; Lloyd-Jones, G. C.; Pfaltz, A. *Pure Appl. Chem.* **1998**, *70*, 1035. For regio- and enantioselective allylic alkylation using the catalysts other than palladium catalysts, see: c) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 462. d) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025. e) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741. See also reference 6b.
(7) Highly enantioselective allylic alkylation of cyclic allyl substrates using P,N-chelate ligands has also been reported: Kudis, S.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3047.
(8) a) Ito, K.; Katsuki, T. *Tetrahedron Lett.* **1993**, *34*, 2661. b) Ito, K.; Katsuki, T. *Chem. Lett.* **1994**, 1857. c) Ito, K.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, *52*, 3905. d) Ito, K.; Yoshitake, M.; Katsuki, T. *Heterocycles*, **1996**, *42*, 305.
(9) a) Uozumi, Y.; Suzuki, N.; Ogiwara, A.; Hayashi, T. *Tetrahedron* **1994**, *50*, 4293. b) Valk, J. -M.; Claridge, T. D. W.; Brown, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2597.
(10) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.

(11) In contrary to our results, Helmchen *et al* reported that high enantioselectivity was observed using sodium hydride as the base in THF with their new phosphinooxazoline-palladium complex (reference 5p).

(12) The formation of the corresponding (*Z*) product was not detected spectroscopically.

(13) **Typical experimental procedure:**
Preparation of a solution of palladium catalyst: To a solution of allylpalladium chloride dimer (2.7 mg, 7.4 µmol) in acetonitrile (0.6 ml) was added ligand **4b** (7.8 mg, 18.5 µmol) under argon. After being stirred for 1h at room temperature, the resulting orange solution was used for allylic alkylation.
Preparation of a malonate solution: Sodium hydride (40 mg, 60% in mineral oil, 1 mmol) was placed in flask under nitrogen, washed three times with acetonitrile and suspended in acetonitrile (3.7 ml). To this suspension was added dimethyl malonate (117 µl, 1 mmol). After being stirred for 30 min at room temperature, 15-crown-5 (200 µl, 1 mmol) was added to the mixture and the resulting solution was used for allylic alkylation.
Asymmetric allylic alkylation: To the above malonate solution (1.5 ml) was added (2*E*)-1-methyl-2-butenyl phenyl carbonate (43.6 mg, 0.21 mmol) and cooled to -25 °C. To this mixture was added the solution of palladium catalyst (168 µl) and further stirred at the temperature for 48 h. The mixture was quenched with saturated aqueous NH_4Cl, allowed to warm to room temperature, and extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1) gave the desired product (36.1 mg, 85%) as an oil. Enantiomeric excess of the product was determined to be 93% by ^1H NMR analysis in the presence of chiral shift reagent $Eu(hfc)_3$.

Article Identifier:
1437-2096,E;1999,0,10,1563,1566,ftx,en;Y14699ST.pdf