DOI: 10.1002/adsc.200900151

Palladium-Catalyzed Asymmetric Allylic Alkylation of 2,3-Allenyl Acetates Using a Chiral Diaminophosphine Oxide

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Received: March 10, 2009; Revised: June 1, 2009; Published online: August 5, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900151.

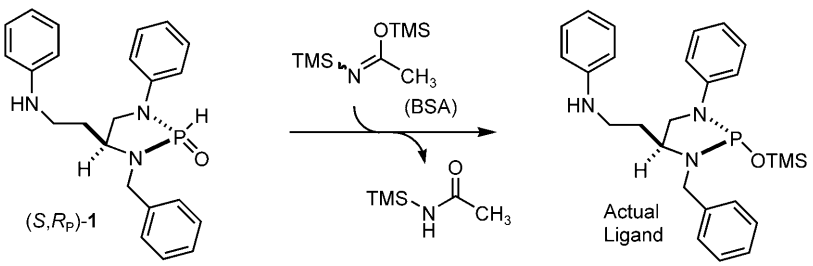
Abstract: An enantioselective synthesis of allenes through palladium-catalyzed asymmetric allylic alkylation using a chiral diaminophosphine oxide is described. The asymmetric allylic alkylations proceeded in the presence of a catalytic amount of lithium acetate at 4 °C, affording the chiral allenes in excellent yield with up to 99% *ee*.

Keywords: allenes; asymmetric allylic alkylation; asymmetric catalysis; diaminophosphine oxides; palladium

Considerable effort has been directed towards the enantioselective synthesis of axially chiral allenes due to their synthetic utility as chiral synthons,[1] as well as their distribution in various biologically active natural products.[2] Typically, chiral allenes are prepared using the optical resolution of racemic allenyl carboxylic acids or chirality transfer of optically active propargyl alcohols.[3–4] In recent years, the direct conversion of racemic or achiral starting materials into optically active allenes through asymmetric catalysis has attracted a great deal of attention from synthetic organic chemists.[5]

In 2000, Hayashi and his co-workers reported a novel method for synthesizing functionalized allenes based on a formal S_N2' substitution of 2-bromo-1,3-butadienes catalyzed by a palladium complex.[6] This method was successfully extended to the asymmetric synthesis of axially chiral allenes using a chiral palladium complex, which was applied to the total synthesis of a natural product, as well as a unique transformation with transfer of axial chirality.[7] Murahashi, Imada, and Naota's group,[8] and Trost's group[9] also reported an enantioselective synthesis of allenes through Pd-catalyzed asymmetric allylic substitution using 2,3-allenyl alcohol derivatives as substrates. Although different electrophiles are utilized in each reaction, both reactions proceed *via* the same α-methylidene π-allylpalladium intermediates, and the enantioselectivity of this type of asymmetric allylic substitution is controlled by a dynamic kinetic asymmetric transformation (DYKAT).[10]

We have intensively studied transition metal-catalyzed asymmetric reactions using chiral diaminophosphine oxide preligands: DIAPHOXs. These pentavalent phosphorus compounds, such as (S,R_P)-**1**, are activated *in situ* by *N,O*-bis(trimethylsilyl)acetamide (BSA)-induced tautomerization to afford trivalent diamidophosphite species, which function as the actual ligand (Scheme 1).[11] This ligand system has been suc-

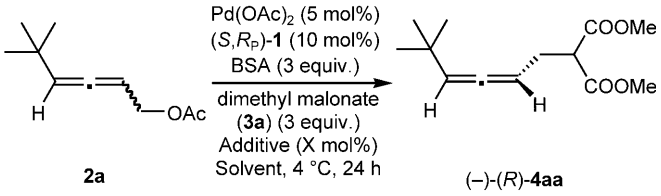


Scheme 1. BSA-induced tautomerization of (S,R_P)-**1**.

cessfully applied to Pd- and Ir-catalyzed asymmetric allylic substitutions, providing synthetically useful chiral products with high enantiomeric purity.[12,13] This background led us to extend the present ligand system to the asymmetric synthesis of allenes based on nucleophilic addition to chiral α-methylidene π-allylpalladium intermediates. Herein, we report the asymmetric allylic alkylation of 2,3-allenyl acetates with malonate nucleophiles using a Pd-DIAPHOX catalyst system, which produces axially chiral allenes in excellent yield with up to 99% *ee*.

We first selected asymmetric allylic alkylation of allenyl acetate **2a** with dimethyl malonate **3a** as the model reaction (Table 1). When 5 mol% of $Pd(OAc)_2$

Table 1. Optimization of the reaction conditions.



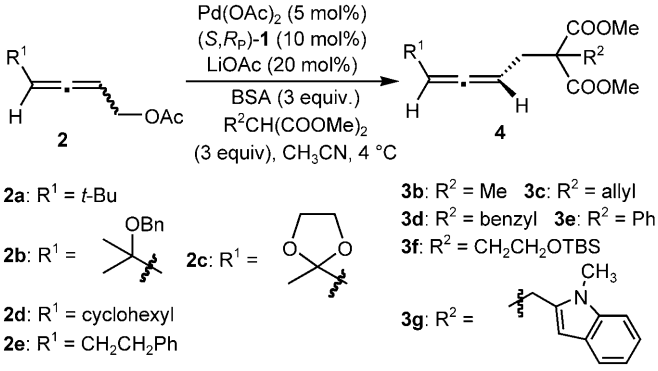
Entry	Additive (mol%)	Solvent	Yield [%][a]	*ee* [%][b]
1	–	CH_3CN	98	69
2	LiOAc (20)	CH_3CN	93	83
3	NaOAc (20)	CH_3CN	92	69
4	KOAc (20)	CH_3CN	91	57
5	CsOAc (20)	CH_3CN	95	63
6	$Mg(OAc)_2$ (20)	CH_3CN	62	60
7	$Zn(OAc)_2$ (20)	CH_3CN	trace	–
8	LiOAc (20)	CH_2Cl_2	98	70
9	LiOAc (20)	DMF	84	65
10	LiOAc (20)	THF	90	74
11	LiOAc (10)	CH_3CN	80	81
12	LiOAc (30)	CH_3CN	92	82

[a] Isolated yield.
[b] Determined by HPLC analysis.

and 10 mol% of (S,R_P)-**1** were used as the catalyst, the reaction proceeded in CH_3CN at 4 °C to provide the corresponding mono-alkylated product (−)-**4aa** in 98% yield with 69% *ee*. The absolute configuration of the major enantiomer was deduced to be (*R*) by the Lowe-Brewster rule.[14] To improve the enantioselectivity, we investigated the effect of adding acetate salts to the reaction (entries 2–7). Enantioselectivity was significantly affected by the counter cations of acetate salts, and LiOAc was the best additive for asymmetric induction (83% *ee*) (entry 2).[15] Further optimization with regard to the solvent, as well as the amount of LiOAc, gave less satisfactory results.

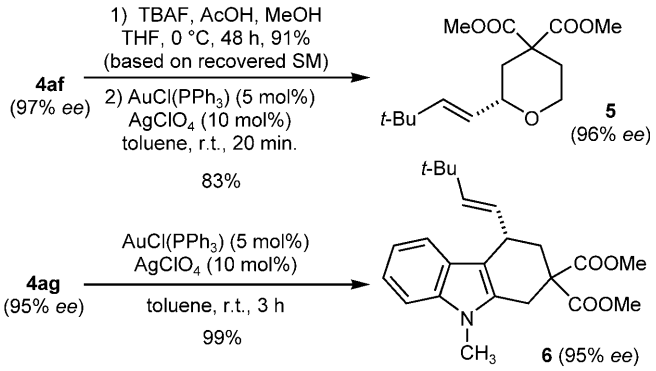
We next examined the scope and limitations of different substrates under the optimized conditions (Table 2). When 5 mol% of $Pd(OAc)_2$ and 10 mol% of (S,R_P)-**1** were used, the asymmetric allylic alkylation of **2a** with dimethyl methylmalonate **3b** proceeded smoothly in the presence of LiOAc, affording chiral allene (−)-**4ab** in 99% yield with much higher enantioselectivity (98% *ee*) than that obtained using dimethyl malonate (entry 1). Moreover, the enantioselectivity was increased when the reaction was performed at a lower temperature (99% *ee*) (entry 2). Other α-monosubstituted dimethyl malonates **3c**–**g** were also applicable to the present catalysis, providing the corresponding chiral allenes (−)-**4ac**–**ag** in excellent yield and enantiomeric excess (91–97% *ee*) (entries 4–9). These reactions could be performed using 1 mol% of $Pd(OAc)_2$ and 2 mol% of (S,R_P)-**1**, and the corresponding products were obtained in good yield without a significant decrease in the enantiomeric excess, compared with that obtained using 5 mol% of the catalyst (entries 3 and 5). Racemic allenyl acetates **2b** and **2c**, bearing a *tert.*-alkyl substituent on the ter-

Table 2. Scope and limitations.



Entry	Allene/ Malonate	Product	Time [h]	Yield [%][a]	*ee* [%][b]
1[c]	**2a**/**3b**	**4ab**	24	99	98 (−)-(*R*)
2[c,d]	**2a**/**3b**	**4ab**	48	98	99 (−)-(*R*)
3[c,e]	**2a**/**3b**	**4ab**	96	99	97 (−)-(*R*)
4	**2a**/**3c**	**4ac**	24	98	96 (−)-(*R*)
5[e]	**2a**/**3c**	**4ac**	96	88	95 (−)-(*R*)
6	**2a**/**3d**	**4ad**	96	99	97 (−)-(*R*)
7[f]	**2a**/**3e**	**4ae**	16	99	91 (−)-(*R*)
8	**2a**/**3f**	**4af**	48	99	97 (−)-(*R*)
9	**2a**/**3g**	**4ag**	48	99	95 (−)-(*R*)
10	**2b**/**3b**	**4bb**	24	86	91 (−)-(*R*)
11	**2c**/**3b**	**4cb**	24	99	92 (−)-(*R*)
12[e]	**2c**/**3c**	**4cc**	24	96	90 (−)-(*R*)
13	**2d**/**3b**	**4db**	48	99	72 (−)-(*R*)
14	**2e**/**3b**	**4eb**	24	99	66 (−)-(*R*)

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.
[c] 30 mol% of LiOAc was used.
[d] Reaction was performed at −4 °C.
[e] 1 mol% of $Pd(OAc)_2$ and 2 mol% of (S,R_P)-**1** were used. The reaction was performed in a 0.4 M solution.
[f] 30 mol% of LiF was used as the additive. (LiOAc as the additive: 72 h, 18% yield, 77% *ee*).



Scheme 2. Transformation of the products.

Table 3. Effect of the amount of LiOAc.[a]

Entry	LiOAc (mol%)	Yield of **4ab** [%]	*ee* of **4ab** [%]
1	0	90	89
2	2.5	92	90
3	5	99	92
4	10	95	94
5	20	98	97
6	30	99	98
7	50	99	97
8	75	99	97

[a] *Additional reaction conditions:* $Pd(OAc)_2$ (5 mol%), (S,R_P)-**1** (10 mol%), BSA (3 equiv.), **3b** (3 equiv.), CH_3CN, 4 °C, 24 h.

minal allenyl carbon, were also effective substrates for this asymmetric catalysis and gave the corresponding products with high enantiomeric excess (90–92% *ee*) (entries 10–12). Decreasing the size of the allene substituent affected the enantioselectivity (entries 13 and 14). Asymmetric allylic alkylation of secondary and primary alkyl-substituted substrates **2d** and **2e** using **3b** gave the corresponding products with 72% *ee* and 66% *ee*, respectively.

Particularly, it is noteworthy that malonate nucleophiles with an additional functionality on the α-substituent are applicable to this catalyst system. Reaction adducts obtained using such nucleophiles are suitable substrates for Au-catalyzed intramolecular hydrofunctionalization (Scheme 2). After deprotection of the TBS group of **4af**,[16] hydroalkoxylation was performed in the presence of 5 mol% of $AuCl(PPh_3)$ and 10 mol% of $AgClO_4$, affording a chiral pyran derivative with an *E*-alkene **5** in 83% yield.[17] Hydroarylation of **4ag** also proceeded under the same catalyst conditions to give a chiral tricyclic compound with an *E*-alkene **6** in 99% yield.[18] Both reactions occurred with transfer of chirality from the allenyl moiety to the newly formed stereogenic carbon atom.[19]

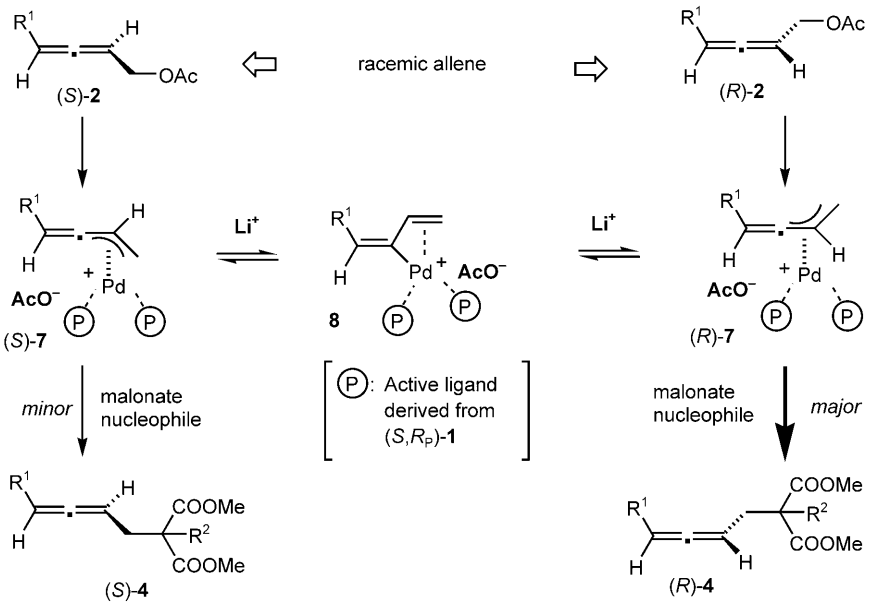
To gain preliminary insights into the reaction mechanism of this catalyst system, we performed several mechanistic studies using asymmetric allylic alkylation of **2a** with **3b**. As shown in Table 1, the counter cations of the acetate salt mainly affected the enantioselectivity. To confirm the coherence with the data shown in Table 1, we first performed the reaction in the absence of LiOAc, or using 20 mol% of LiOAc, providing **4ab** in 90% yield with 89% *ee*, and in 98% yield with 97% *ee*, respectively (Table 3, entries 1 and 5). The analogous improvement in the enantiomeric excess led us to investigate into the effect of the amount of LiOAc in detail (Table 3). There was a gradual increase in the enantioselectivity until 30 mol% of LiOAc was added, and no further changes were observed with additional LiOAc. To elucidate the effect of the counter anions of the lithium salt, we performed the reaction in the presence of several lithium salts (Table 4). Although there were only slight changes in the enantioselectivity, the reactivity was dramatically affected by the counter anions (entries 1–7). Similar results were obtained when the reaction was performed using $PdCl_2$ or $Pd(OOCCF_3)_2$ as the palladium source (entries 8 and 9). These results clearly indicate that the acetate anion has an important role in controlling the catalytic activity. In addition, these experimental data led us to hypothesize that a catalytic amount of lithium cation would relate to the asymmetric induction of this catalyst system.

As mentioned in the introduction, enantiodifferentiation of this type of asymmetric allylic substitution is achieved by a dynamic kinetic asymmetric transformation. In this process, there is an equilibrium between the two diastereomeric π-allylpalladium complexes *via* π-σ-π interconversion, which is faster than nucleophilic addition. When the reaction of **2a** with **3b** using the optimized conditions was quenched after 4 h and 8 h, (−)-(*R*)-**4ab** was isolated in 30% yield

Table 4. Effect of the counter anions of the Li salt and Pd source.[a]

Entry	Pd Source	LiX	Yield of **4ab** [%]	*ee* of **4ab** [%]
1	$Pd(OAc)_2$	X = AcO	99	98
2	$Pd(OAc)_2$	X = F	74	90
3	$Pd(OAc)_2$	X = Cl	21	95
4	$Pd(OAc)_2$	X = Br	trace	–
5	$Pd(OAc)_2$	X = CF_3COO	38	97
6	$Pd(OAc)_2$	X = BF_4	12	93
7	$Pd(OAc)_2$	X = PF_6	trace	–
8	$Pd(OOCCF_3)_2$	X = AcO	49	97
9	$PdCl_2$	X = AcO	14	98
10	$[\eta^3\text{-}C_3H_5PdCl]_2$	X = AcO	99	98

[a] *Additional reaction conditions:* Pd catalyst (5 mol%), (S,R_P)-**1** (10 mol%), LiX (30 mol%), BSA (3 equiv.), **3b** (3 equiv.), CH_3CN, 4 °C, 24 h.



Scheme 3. A plausible reaction mechanism.

(98% *ee*) and 51% (98% *ee*), accompanied by the recovery of (−)-(*R*)-**2a** with 4% *ee* and 9% *ee*, respectively. This finding indicates that there is little static kinetic resolution in the formation of π-allylpalladium complexes. In addition, a positive non-linear effect was observed in this reaction,[20] suggesting that a cationic π-allylpalladium complex with two chiral ligands and an acetate anion functions as the active species. These data led us to propose a plausible mechanism for this asymmetric catalysis (Scheme 3).

First, oxidative addition of racemic allene **2** forms two diastereomeric π-allylpalladium complexes (*S*)-**7** and (*R*)-**7** in a nearly 1:1 ratio. (*S*)-**7** and (*R*)-**7** are in rapid equilibrium *via* σ-allylpalladium complex **8**. The absolute configuration of the products suggests that nucleophilic addition of a malonate nucleophile to (*R*)-**7** proceeds preferentially to afford (*R*)-**4** with high enantiomeric excess. Kinetic experiments revealed that the reaction rate of asymmetric allylic alkylation of **2a** with **3b** was not affected by the concentration of LiOAc,[20] suggesting that the lithium cations are not related to the rate-determining nucleophilic addition. Based on this information, we speculate that, at the present stage, lithium cations would facilitate the dynamic kinetic resolution process by accelerating the equilibrium between (*S*)-**7** and (*R*)-**7**, resulting in increased enantioselectivity.

In conclusion, we have achieved a Pd-catalyzed asymmetric allylic alkylation of 2,3-allenyl acetates with malonate nucleophiles using a Pd-DIAPHOX catalyst system, which afforded axially chiral allenes in excellent yields with up to 99% *ee*. Studies on the application to other nucleophiles, as well as more detailed mechanistic investigations, are in progress.

Experimental Section

Typical Procedure for the Pd-Catalyzed Asymmetric Allylic Alkylation

To a stirred solution of **2a** (25.2 mg, 0.15 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol, 5 mol%), (S,R_P)-**1** (5.9 mg, 0.015 mmol, 10 mol%), and LiOAc (3.0 mg, 0.045 mmol, 30 mol%) in CH_3CN (0.9 mL) at room temperature was added BSA (110 μL, 0.45 mmol), and the resulting brown solution was stirred for 10 min at the same temperature. After the reaction had been cooled down to 4 °C, dimethyl methylmalonate (60 μL, 0.45 mmol) was added, and the resulting mixture was stirred for 24 h. After the reaction mixture had been concentrated under reduced pressure, the crude residue was purified by flash column chromatography (hexane/AcOEt = 40/1) to give (−)-(*R*)-**4ab** as a colorless oil; yield: 37.8 mg (99%, 98% *ee*).

Acknowledgements

This work was supported by a Grant-in Aid for Scientific Research on Priority Areas, Chemistry of Concerto Catalysis, and Grant-in Aid for Encouragement of Young Scientist (B) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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[15] Dialkylated product was isolated in 1–2% yield (entries 1–5). As shown in entries 6 and 7, there was a remarkable decrease in the reactivity when $Mg(OAc)_2$ or $Zn(OAc)_2$ were used as an additive. Although no reasonable explanation for the decreased reactivity can be offered at the present stage, the obtained results imply that these metal acetates have an inhibiting effect on reaction promotion.

[16] Deprotected compound was isolated in 73% yield, and 20% of **4af** was recovered. A prolonged reaction time decreased the yield due to lactone formation.

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6684; h) C. Deutsch, B. Gockel, A. Hoffmann-Röder, N. Krause, *Synlett* **2007**, 1790; see also: i) Z. Zhang, R. A. Widenhoefer, *Org. Lett.* **2008**, *10*, 2079; j) N. Nishina, Y. Yamamoto, *Tetrahedron* **2009**, *65*, 1799.

[18] For examples of Au-catalyzed intramolecular hydroarylation of allenes with indole nucleophiles, see: a) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 9066; b) C. Liu, R. A. Widenhoefer, *Org. Lett.* **2007**, *9*, 1935; see also: c) Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 10352; d) T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2007**, *9*, 4821; e) M. A. Tarselli, M. R. Gagne, *J. Org. Chem.* **2008**, *73*, 2439.

[19] The stereochemistry of **5** and **6** was deduced based on the transition state reported by Widenhoefer et al.[18a] Both reactions did not proceed in the absence of Au catalyst.

[20] See the Supporting Information for details.

