



Enamines: efficient nucleophiles for the palladium-catalyzed asymmetric allylic alkylation

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ABSTRACT

Enamines were tested to be efficient nucleophiles for palladium-catalyzed asymmetric allylic alkylation, avoiding the use of unstabilized ketone enolates formed by strong bases. The influence of the chiral metallocene-based ligands upon this reaction was studied in detail. It was shown that planar chirality played an important role in enantioselectivities. Meanwhile, different kinds of enamines and allylic acetate to the reactions were also investigated. High catalytic activity and excellent enantioselectivity (up to 99% ee) were obtained with pyrrolidine enamines of both aliphatic and aromatic ketone.

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1. Introduction

Transition metal-catalyzed reactions have made markedly rapid progress in organic synthesis and have been applied to the synthesis of many kinds of valuable, complex organic molecules in last decades.¹ Particularly, palladium-catalyzed asymmetric allylic alkylation (AAA) has become one of the most powerful tools for constructing chiral centers via carbon–carbon bond forming reactions.² Considerable interest has been made with simple ketones in this AAA reaction recently, which typically has been employed in the form of unstabilized ketone enolates as nucleophilic reagents.³ However, harsh reaction conditions such as the use of potentially unstable and dangerous reagents were required to form these unstabilized ketone enolates.⁴ On the other hand, the ease of access to enamines made them promising nucleophilic reagents instead of unstabilized ketone enolates for asymmetric synthesis since the pioneering work by Stork.⁵ However, recent strategies mainly involved chiral enamines as chiral auxiliaries in asymmetric synthesis,⁶ and only few reports on asymmetric catalysis using enamines instead of ketone enolates as nucleophilic reagents.⁷ To the best of our knowledge, there was no report on Pd-catalyzed asymmetric allylic alkylation with enamine nucleophiles.⁸ Herein, we want to report a Pd-catalyzed asymmetric allylic alkylation with enamines in the presence of chiral metallocene-based ligands.⁹

Metallocene-based ligands with planar chirality had attracted much scientific interest in asymmetric synthesis over the past decades.¹⁰ We recently reported the synthesis of C_2 -symmetric chiral ferrocene-based phosphinooxazoline **1** containing planar chirality as well as central chirality (Fig. 1), and their application for Pd-catalyzed asymmetric allylic alkylation with excellent enantioselectivity (up to 99% ee).¹¹ Subsequently, the central chirality in the oxazoline moiety was removed by ring-opening followed by ester exchange to give C_2 -symmetric ferrocenes **2** with only planar chirality (Fig. 1),¹² acting as efficient ligands for Pd-catalyzed asymmetric allylic alkylation. Very recently, we also reported the synthesis of novel C_2 -symmetric tetrasubstituted ruthenocene ligand **3** and the C_1 -symmetric 1,2-disubstituted phosphinooxazoline ruthenocene ligands **5** and **6** (Fig. 1). These ruthenocene-based ligands and C_1 -symmetric FcPHOX **4** were tested to be effective ones in both Pd-catalyzed AAA reaction and Ru-catalyzed H-transfer hydrogenation of ketones with high catalytic activities and excellent enantioselectivities.^{13,14} In view of their good performance in asymmetric catalysis, these ligands were selected here as chiral ligands for Pd-catalyzed asymmetric allylic alkylation with several enamines as nucleophilic reagents, and excellent enantioselectivities and high yields were afforded.

2. Results and discussion

Firstly, a pyrrolidine enamine of cyclohexanone was selected to examine the nucleophilic behavior in Pd-catalyzed asymmetric allylic alkylation with 1,3-diphenyl-2-propenyl acetate as a model

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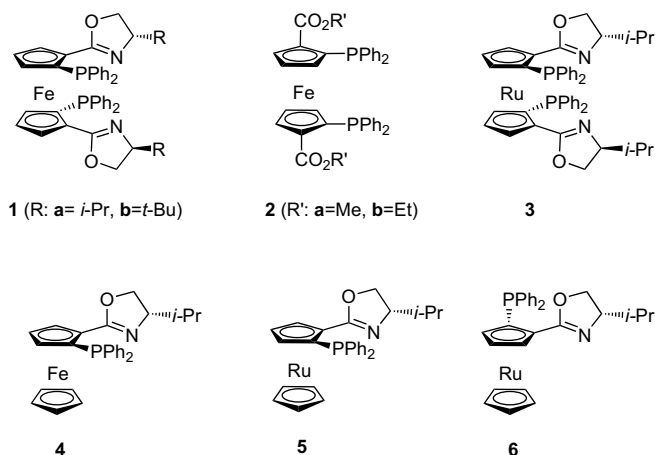


Figure 1. Chiral metallocene-based ligands.

substrate. Excellent enantioselectivity was obtained with both *anti*- and *syn*-configuration. Details are summarized in Table 1.

The influence of reaction conditions on the allylic alkylation was taken into account. It was shown that solvents had some effect on this reaction and both THF and toluene were tested to be efficient ones based on their catalytic activity and enantioselectivity (Table 1, entries 1–4). It was also found that the values of ee increased with the decrease of temperature, from room temperature to 0 °C (Table 1, entries 4–5). Further decreasing temperature had little effect on this reaction (Table 1, entries 5–7). The substituent R on the oxazolynyl ring had effect on enantioselectivity and a bulkier group gave somewhat better ee values (Table 1, entries 2 vs 8, 4 vs 9). And up to 99% ee was obtained with **1b** with *tert*-butyl groups in THF (Table 1, entry 11).

In order to examine the effect of ligands on the Pd-catalyzed asymmetric allylic alkylation using an enamine as a nucleophilic reagent, several kinds of ligands were used.

C₂-Symmetric diphosphine ferrocene ligands **2** with only planar chirality were applied in this Pd-catalyzed allylic alkylation. Both **2a**

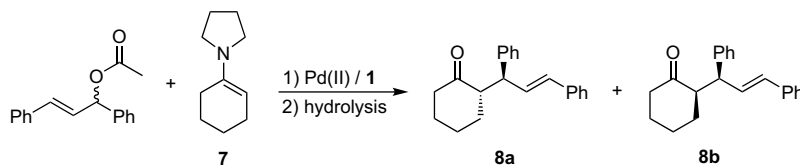
and **2b** provided high catalytic activities and good ee (75–89%) with high yields (Table 2, entries 1–3). The R' in the ester group with greater steric hindrance gave better enantioselectivity (Table 2, entries 2 and 3). It was reported that if an Fe atom between the two Cp rings was replaced by a Ru atom, both catalytic activity and enantioselectivity were altered,^{13,15} mainly due to the different distances between the two Cp rings in ferrocene and ruthenocene (3.32 and 3.68 Å, respectively).¹⁶ Therefore, we also used ruthenocene-based ligand **3** to examine whether a dissimilarity would exist in the same manner. It was shown that all reactions provided good enantioselectivity (Table 2, entries 4 and 5). Meanwhile, ruthenocene-based ligand **3** generally seemed to be a little inferior in enantioselectivity compared to **1** (Table 1, entries 2 and 4 vs Table 2, entries 4 and 5).

For the purpose of examining the influence of C₂-symmetrical factor on the reaction, we selected the C₁-symmetry metallocene-based phosphino-oxazoline ligands **4** and **5**. Ligand **4** was used firstly and the solvents showed obvious effect on the catalytic activity and yield (Table 2, entries 6–9). Up to 95% ee was obtained using **4** as a chiral ligand with THF and CH₂Cl₂ as solvents. Comparable enantioselectivity but much better catalytic activity was obtained with ruthenocene-based ligand **5** in the Pd-catalyzed AAA reaction (Table 2, entry 10). In addition, ligand **6** with opposite planar chirality with **5** was used to investigate the influence of planar chirality factor in this reaction. As a result, the enantioselectivity as well as catalytic activity of the product was dramatically reduced by comparing that caused by **5** (Table 2, entries 10–11). It is evident that the planar chirality plays an important role in this Pd-catalyzed asymmetric allylic alkylation.

On the other hand, the effect of the size of the cycloketone on the reaction was also examined. The reactions were conducted with 1,3-diphenyl-2-propenyl acetate under 0 °C in THF, the optimized conditions obtained from the pyrrolidine enamine of cyclohexanone according to both the reaction rate and enantioselectivity. And **1** was selected as chiral ligands according to their enantioselectivities and reaction activity as well as chemical yield in this asymmetric catalysis. As shown in Table 3, all enamines used here provided excellent enantioselectivity. The size of the cycloketone had somewhat effect on the value of diastereoselectivity. Yield was

Table 1

Allylic alkylation of 1,3-diphenyl-2-propenyl acetate with the enamine **7** with ligands **1**^a



Entry	Ligand	Solvent	Time (h)	Temp (°C)	Yield ^b (%)	<i>anti/syn</i> ^{c,d}	ee ^e (%)
1	1a	DMF	5	rt	83	60:40	91:91
2	1a	THF	7	rt	71	61:39	94:94
3	1a	CH ₂ Cl ₂	1	rt	94	55:45	83:83
4	1a	Toluene	1	rt	94	61:39	92:92
5	1a	Toluene	6	0	86	53:47	97:97
6	1a	Toluene	48	–15	73	63:37	97:97
7	1a	Toluene	48	–25	75	61:39	95:96
8	1b	THF	2	rt	91	59:41	96:97
9	1b	Toluene	1	rt	94	63:37	94:94
10	1b	THF	14	0	79	59:41	97:96
11	1b	THF	72	–15	56	61:39	99:98
12	1b	THF	72	–25	Trace	—	—

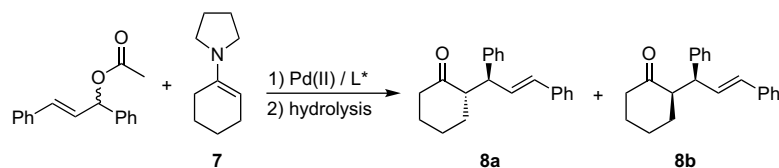
^a Molecular ratio: [Pd(η³-C₃H₅)Cl]₂/ligand/substrate/enamine=2.5:6.0:200:600; reactions were conducted under nitrogen; the catalysts were prepared by treating [Pd(η³-C₃H₅)Cl]₂ with ligands in a suitable solvent at 20 °C for 1 h before use.

^b Isolated yield.

^c Determined by ¹H NMR.

^d The absolute configuration of *syn/anti* products was determined according to Ref. 18.

^e Determined by the HPLC using chiral AD-H column.

Table 2Allylic substitution of 1,3-diphenyl-2-propenyl acetate with the enamine **7** with ligands **2–6**^a

Entry	Ligand	Solvent	Temp (°C)	Time (h)	Yield ^b (%)	anti/syn ^c	ee ^d (%)
1	2a	THF	rt	10	71	57:43	75:75
2	2a	Toluene	rt	1	92	57:43	84:85
3	2b	Toluene	rt	1	93	60:40	88:89
4	3	THF	rt	10	72	57:43	90:90
5	3	Toluene	rt	8	77	56:44	89:89
6	4	DMF	0	13	82	66:34	91:91
7	4	THF	0	10	73	58:42	92:95
8	4	CH ₂ Cl ₂	0	3	93	54:46	94:95
9	4	Toluene	0	12	84	56:44	89:87
10	5	CH ₂ Cl ₂	0	1	95	52:48	94:95
11	6	CH ₂ Cl ₂	0	10	72	58:42	42:37

^a Molecular ratio: [Pd(η³-C₃H₅)Cl]₂/ligand/substrate/enamine=2.5:6.0:200:600; reactions were conducted under nitrogen; the catalysts were prepared by treating [Pd(η³-C₃H₅)Cl]₂ with ligands in a suitable solvent at 20 °C for 1 h before use.

^b Isolated yield.

^c Determined by ¹H NMR.

^d Determined by the HPLC using chiral AD-H column.

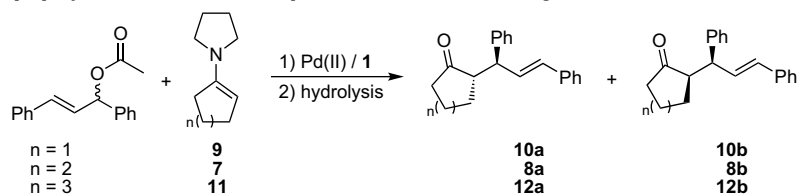
obviously enhanced with the decrease of ring size of the ketone (Table 3, entries 1–6).

Next, in order to investigate the influences of enamines on the reaction, we changed aliphatic ketone to aromatic ketone, 2,3-dihydro-1*H*-inden-1-one. The influence of reaction conditions upon the allylic alkylation was taken into account. First of all, the effect of the solvents on the catalytic reaction was examined with **1a** as chiral ligand (Table 4, entries 1–4). The reaction showed the best balance of rate and selectivity in toluene. The temperature affected the enantioselectivity obviously and up to 98% ee was obtained at 0 °C with **1a** in toluene (Table 4, entries 1 and 5). These results showed that aromatic enamine can also afford high catalytic activity and excellent enantioselectivity. Meanwhile, solvent effect to aromatic enamine was smaller than that to aliphatic enamine.

As shown in Tables 1, 3 and 4, there was no remarkable effect on the values of ee and de in spite of changing the size and species of

ketone. Then the pyrrolidine ring with small hindrance was replaced by large ones, *N*-methylcyclohexylamine and *N*-methyl-aniline. Initially, much effort was made to carry out the reaction of enamine **15**, derived from cyclohexanone and *N*-methylbenzenamine, with 1,3-diphenyl-2-propenyl acetate for the Pd-catalyzed AAA reaction. However, no reaction occurred, possibly due to its weak nucleophilic ability (Scheme 1). Then, the *N*-cyclohexyl-*N*-methylcyclohex-1-en-1-amine (**16**) was used in this reaction. Grati-fyingly, excellent enantioselectivity and good yield were obtained with dichloromethane as solvent. Meantime, it was found that the dosage of catalyst had great effect on the catalytic activity with similar enantioselectivity. As shown in Scheme 2, when the dosage of catalyst was changed from 2.5 mol % to 10 mol %, the catalytic activity is enhanced obviously (Scheme 2).

Cyclohex-2-enyl acetate was also used instead of 1,3-diphenyl-2-propenyl acetate in this Pd-catalyzed AAA reaction. High catalytic activity and moderate enantioselectivity were obtained (Scheme 3).

Table 3Allylic substitution of 1,3-diphenyl-2-propenyl acetate with different aliphatic enamines **7**, **9**, **11** with ligands **1**^a

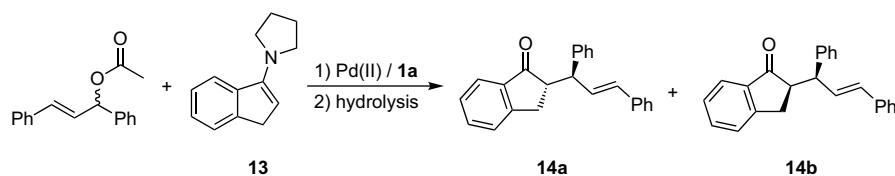
Entry	Ligand	<i>n</i>	Time (h)	Yield (%) ^b	anti/syn ^c	ee (%) ^d
1	1a	1	1.5	95	52:48	87:85
2	1b	1	3	90	57:43	94:94
3	1a	2	8	72	58:42	97:96
4	1b	2	14	79	59:41	97:96
5	1a	3	2	74	65:35	93:88
6	1b	3	5	71	64:36	96:97

^a Molecular ratio: [Pd(η³-C₃H₅)Cl]₂/ligand/substrate/enamine=2.5:6.0:200:600; reactions were conducted under nitrogen; the catalysts were prepared by treating [Pd(η³-C₃H₅)Cl]₂ with ligands in a suitable solvent at 20 °C for 1 h before use.

^b Isolated yield.

^c Determined by ¹H NMR.

^d Determined by the HPLC using chiral AD-H column.

Table 4Allylic substitution of 1,3-diphenyl-2-propenyl acetate with aromatic enamine **13** with ligand **1a**^a

Entry	Solvent	Time (h)	Temp (°C)	Yield ^b (%)	anti/syn ^c	ee ^d (%)
1	Toluene	1	rt	92	56:33	95:94
2	CH ₂ Cl ₂	1	rt	91	55:45	92:91
3	THF	3	rt	87	54:46	93:92
4	DMF	1	rt	91	53:47	94:94
5	Toluene	3	0	89	52:48	98:97

^a Molecular ratio: [Pd(η³-C₃H₅)Cl]₂/ligand/substrate/enamine=2.5:6.0:200:600; reactions were conducted under nitrogen; the catalysts were prepared by treating [Pd(η³-C₃H₅)Cl]₂ with ligands in a suitable solvent at 20 °C for 1 h before use.

^b Isolated yield.

^c Determined by ¹H NMR.

^d Determined by the HPLC using chiral AD-H column.

It was reasonable that allylic acetate with less steric hindrance gave lower ee value in this reaction.

3. Conclusion

In summary, enamines could serve as efficient nucleophilic reagents for Pd-catalyzed asymmetric allylic alkylation, avoiding the use of unstabilized ketone enolate via powerful bases. The effect of chiral ligands on the reaction was investigated. The chiral metallocene-based phosphinooxazoline ligands afforded excellent enantioselectivity. Different distances between the two Cp rings in C₂-symmetric ligands had some effects on the enantioselectivities while had little effect on the enantioselectivities with C₁-symmetric ligands. It was also found that high catalytic activity and good enantioselectivity were also afforded by the ferrocene-based diphosphine ligands with only planar chirality. Furthermore, the planar chirality played an important role in enantioselectivities by comparing ligands with opposite planar chirality.

And then, it was shown that the size of cycloketones had little effect on enantioselectivity, while had somewhat effect on diastereoselectivity. High catalytic activity and excellent enantioselectivity were obtained with pyrrolidine enamines of both aliphatic and aromatic ketone. *N*-Methylcyclohexamine enamine could also serve as efficient nucleophilic reagent while the reaction could not occur with *N*-methylbenzylamine enamine possibly due to the weak nucleophilic ability of nitrogen atom. High catalytic activity and moderate enantioselectivity were also obtained with cyclohex-2-enyl acetate and cyclohexanone enamine **7**.

4. Experimental section

4.1. General

All reactions were performed under a nitrogen atmosphere and the workup was carried out in air. The reaction solvents were distilled prior to used (tetrahydrofuran was distilled from sodium-benzophenone ketyl; dichloromethane, *N,N*-dimethylformamide, and toluene were distilled from CaH₂). The commercially available

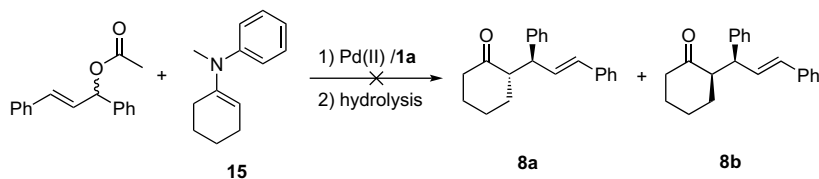
reagents were used without further purification. The substrate of asymmetric allylic alkylation was prepared according to the literature procedure.¹⁷ TLC was run on 2 cm×5 cm silica plate. Column chromatography was run on silica gel (100–200 mesh). ¹H NMR (400 MHz) spectra were recorded on a Varian MERCURY plus-400 spectrometer. The ee values were determined by HPLC using a Daicel Chiralcel AD-H column.

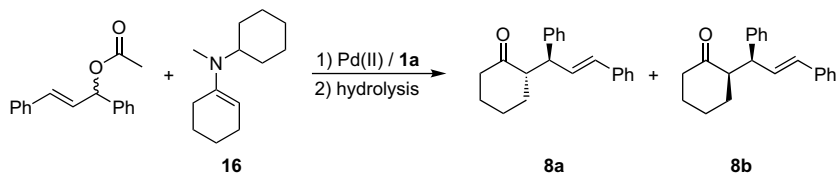
4.2. Procedures and analytical data

4.2.1. Preparation of enamines

4.2.1.1. 1-Cyclohexenylpyrrolidine (7)¹⁸. Cyclohexanone (20.0 g, 0.200 mol) was dissolved in cyclohexane (250 mL) and then anhydrous magnesium sulfate (120 g) was added in one portion under a nitrogen atmosphere. The mixture was cooled to 0 °C with an ice bath and pyrrolidine (84.0 mL, 1.00 mol) was added dropwise via a syringe over a 0.5 h period. After the reaction mixture had been stirred for additional 30 min at 0 °C, the ice bath was removed and the mixture was stirred overnight at room temperature. Magnesium sulfate was removed by filtration and rinsed thoroughly with dry cyclohexane (3×50 mL). The combined filtrate and rinsings were concentrated under reduced pressure to give crude product as an orange oil, which was distilled under reduced pressure (69 °C/1 mmHg) to give **7** as a colorless oil (28.7 g, 93% yield). ¹H NMR (CDCl₃, 400 Hz): δ 1.49–1.55 (m, 2H), 1.62–1.68 (m, 2H), 1.78–1.82 (m, 4H), 2.05–2.09 (m, 2H), 2.14–2.17 (m, 2H), 2.95–2.98 (m, 4H), 4.24–4.26 (m, 1H). ¹³C NMR (CDCl₃, 100 Hz): δ 23.2, 23.6, 24.7, 24.7, 27.7, 47.6, 93.7, 143.5.

4.2.1.2. 1-Cyclopentenylpyrrolidine (9)¹⁸. This enamine was prepared from cyclopentanone by a similar procedure with **7**. It was distilled under reduced pressure (42 °C/1 mmHg) to give **9** as a colorless oil (31.0 g, 95% yield). ¹H NMR (CDCl₃, 400 Hz): δ 1.78–1.85 (m, 6H), 2.29–2.32 (m, 2H), 2.37–2.41 (m, 2H), 3.00–3.03 (m, 4H), 4.00 (br s, 1H). ¹³C NMR (CDCl₃, 100 Hz): δ 23.2, 25.3, 30.8, 33.0, 48.9, 92.2, 149.4.

**Scheme 1.** Allylic substitution of 1,3-diphenyl-2-propenyl acetate with the enamines **15** with ligand **1a**.



Scheme 2. Allylic substitution of 1,3-diphenyl-2-propenyl acetate with the enamines **16** with ligand **1a**. (1) Molecular ratio: $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2/\text{ligand}/\text{substrate}/\text{enamine}=2.5:6.0:200:600$, completed within 3 h, yield: 73%, de: 62:38, ee: 91:93. (2) Molecular ratio: $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2/\text{ligand}/\text{substrate}/\text{enamine}=10:24:200:600$, completed within 1 h, yield: 95%, de: 51:49, ee(%): 91:92.

4.2.1.3. 1-Cycloheptenylpyrrolidine (11**)¹⁸.** This enamine was prepared from cycloheptanone by a similar procedure with **7**. It was distilled under reduced pressure (82 °C/1 mmHg) to give **11** as a colorless oil (27.1 g, 92% yield). ^1H NMR (CDCl_3 , 400 Hz): δ 1.42–1.54 (m, 4H), 1.62–1.71 (m, 2H), 1.79–1.82 (m, 4H), 2.06–2.09 (m, 2H), 2.33–2.35 (m, 2H), 2.92 (br s, 4H), 4.44–4.48 (m, 1H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 24.8, 26.3, 27.2, 29.1, 31.3, 33.0, 48.7, 99.3, 99.4, 151.7.

4.2.1.4. 1-(3H-Inden-1-yl)pyrrolidine (13**)¹⁹.** 1-Indenone (13.2 g, 0.100 mol) was dissolved in cyclohexane (250 mL) in a three-necked flask under a nitrogen atmosphere. The mixture was cooled to 0 °C with an ice-bath and pyrrolidine (38.0 mL, 0.400 mol) was added dropwise via a syringe over a 0.5 h period. And then, solution of titanium tetrachloride (5.0 mL) in cyclohexane (50 mL) was added in the three-necked flask. After the reaction mixture had been stirred for an additional 30 min at 0 °C, the ice bath was removed and the mixture was stirred overnight at room temperature. The mixture was filtered through kieselguhr and rinsed thoroughly with dry cyclohexane (3×50 mL). The combined filtrate and rinsings were concentrated under reduced pressure to give crude product as a black oil (16.7 g, 90% yield). ^1H NMR (CDCl_3 , 400 Hz): δ 1.96–1.99 (m, 4H), 3.34 (d, $J=2.0$ Hz, 2H), 3.44 (t, $J=6.0$ Hz, 4H), 5.10 (t, $J=2.4$ Hz, 1H), 7.18 (t, $J=7.6$ Hz, 1H), 7.26 (t, $J=7.6$ Hz, 1H), 7.43 (d, $J=6.8$ Hz, 1H), 7.63 (d, $J=8.0$ Hz, 1H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 25.4, 35.7, 50.5, 101.0, 120.7, 124.2, 124.6, 125.9, 126.9, 134.8, 145.5.

4.2.1.5. N-Cyclohexenyl-N-methylbenzenamine (15**)²⁰.** Cyclohexanone (20.0 g, 0.200 mol) and the ring-substituted N-methylaniline (21.0 g, 0.200 mol) were refluxed in toluene in the presence of toluene-*p*-sulfonic acid (0.40 g, 2 mg/mmol) in a Dean–Stark apparatus. When separation of water was complete, the reaction mixture was concentrated and the product was distilled under reduced pressure (110 °C/1 mmHg) to give **15** as a pale yellow oil (36.3 g, 95% yield). ^1H NMR (CDCl_3 , 400 Hz): δ 1.69–1.76 (m, 4H), 2.09 (br s, 2H), 2.23 (br s, 2H), 3.08 (s, 3H), 5.46 (br s, 1H), 6.89–6.91 (m, 3H), 7.25–7.33 (m, 2H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 22.8, 23.5, 25.2, 26.7, 30.4, 39.7, 116.6, 117.9, 119.3, 129.1, 144.3, 149.3.

4.2.1.6. N-Cyclohexyl-N-methylcyclohex-1-enamine (16**)¹⁹.** This enamine was prepared from cycloheptanone by a similar procedure with **13**. It was distilled under reduced pressure (162 °C/1 mmHg) to give **16** as a pale yellow oil (18.9 g, 96% yield). ^1H NMR (CDCl_3 , 400 Hz): δ 0.98–1.09 (m, 1H), 1.16–1.35 (m, 6H), 1.49–1.70 (m, 7H),

2.06–2.10 (m, 4H), 2.43 (br s, 3H), 3.10–3.18 (m, 1H), 4.47–4.49 (m, 1H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 23.2, 23.9, 25.0, 26.3, 26.5, 27.7, 29.7, 31.3, 56.1, 98.4, 144.4.

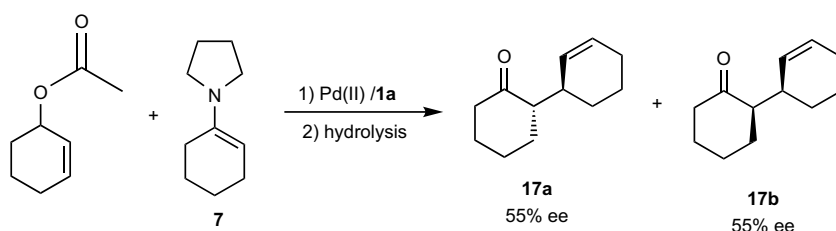
4.2.2. General procedure for palladium-catalyzed asymmetric allylic alkylation

A mixture of ligand (15 μmol) and $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ (2.3 mg, 6.3 μmol) in dry solvent (1 mL) was stirred at room temperature under nitrogen for 1 h and 1,3-diphenyl-2-propenyl acetate (126 mg, 0.500 mmol) was added for another 10 min followed by the addition of enamine (1.50 mmol). The reaction was monitored by TLC for the disappearance of 1,3-diphenyl-2-propenyl acetate. The reaction mixture was quenched by iced saturated NH_4Cl solution (10 mL) for 2 h and the aqueous layer was extracted with ethyl ether (5 mL×3). The combined organic extracts were washed with water, brine, dried over Na_2SO_4 , and concentrated under reduced pressure after filtration. The ratio of *anti*- and *syn*-configuration^{4d} was determined by ^1H NMR of the mixture and the residue was purified on silica gel column chromatography with petrol ether–ethyl acetate (10:1) to afford pure product of *anti*-configuration and *syn*-configuration, respectively. For the determination of ee value by HPLC, a mixture of the products of *anti*- and *syn*-configuration was used.

4.2.2.1. (S)-2-((S,E)-1,3-Diphenylallyl)cyclohexanone (8a**).** ^1H NMR (CDCl_3 , 400 Hz): δ 1.33–1.41 (m, 1H), 1.56–1.63 (m, 1H), 1.70–1.81 (m, 3H), 1.90–1.95 (m, 1H), 2.31–2.46 (m, 2H), 2.83–2.89 (m, 1H), 3.87 (t, $J=8.4$ Hz, 1H), 6.32 (d, $J=16$ Hz, 1H), 6.44 (dd, $J=8.0$, 16 Hz, 1H), 7.12–7.32 (m, 10H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 24.2, 28.8, 32.4, 42.5, 48.6, 56.1, 126.5, 126.8, 127.4, 128.6, 128.7, 128.9, 130.7, 132.2, 137.6, 140.1, 212.7.

4.2.2.2. (R)-2-((S,E)-1,3-Diphenylallyl)cyclohexanone (8b**).** ^1H NMR (CDCl_3 , 400 Hz): δ 1.57–1.77 (m, 3H), 1.86–2.10 (m, 2H), 2.15–2.37 (m, 3H), 2.85–2.91 (m, 1H), 3.97 (t, $J=8.4$ Hz, 1H), 6.25 (dd, $J=9.6$, 15.6 Hz, 1H), 6.45 (d, $J=15.6$ Hz, 1H), 7.14–7.33 (m, 10H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 24.8, 28.6, 32.1, 42.6, 48.7, 55.9, 126.5, 126.6, 127.5, 128.1, 128.7, 128.8, 131.3, 131.6, 137.5, 143.5, 211.8.

4.2.2.3. (S)-2-((R,E)-1,3-Diphenylallyl)cyclopentanone (10a**).** ^1H NMR (CDCl_3 , 400 Hz): δ 1.70–1.78 (m, 1H), 1.93–2.03 (m, 3H), 2.16–2.23 (m, 1H), 2.27–2.34 (m, 1H), 2.55–2.61 (m, 1H), 4.09–4.12 (m, 1H), 6.40 (d, $J=4.4$ Hz, 1H), 6.41 (s, 1H), 7.17–7.35 (m, 10H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 20.9, 26.1, 39.1, 48.0, 55.1, 126.5, 126.7, 127.6, 128.1, 128.7, 128.8, 129.3, 132.6, 137.4, 143.0, 219.3.



Scheme 3. Allylic substitution of cyclohex-2-enyl acetate with the enamine **7** with ligand **1a**. Molecular ratio: $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2/\text{ligand}/\text{substrate}/\text{enamine}=2.5:6.0:200:600$, completed within 5 h, yield: 91%, de: 51:49, ee(%): 55:55.

4.2.2.4. (*R*)-2-((*R,E*)-1,3-Diphenylallyl)cyclopentanone (**10b**). ^1H NMR (CDCl_3 , 400 Hz): δ 1.70–1.86 (m, 1H), 1.94–2.11 (m, 3H), 2.18–2.28 (m, 1H), 2.29–2.38 (m, 1H), 2.58–2.64 (m, 1H), 4.05–4.10 (m, 1H), 6.44 (d, $J=3.2$ Hz, 1H), 6.45 (s, 1H), 7.20–7.41 (m, 10H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 21.0, 26.1, 39.1, 48.0, 55.1, 126.4, 126.6, 128.7, 129.2, 129.3, 132.5, 132.6, 132.7, 137.4, 143.1, 219.3. HRMS (EI) calcd for $\text{C}_{20}\text{H}_{20}\text{O}$ 275.1514; found 275.1515.

4.2.2.5. (*S*)-2-((*R,E*)-1,3-Diphenylallyl)cycloheptanone (**12a**). ^1H NMR (CDCl_3 , 400 Hz): δ 1.23–1.28 (m, 4H), 1.62–1.66 (m, 2H), 1.85–1.88 (m, 2H), 2.44–2.49 (m, 2H), 3.06–3.12 (m, 1H), 3.80–3.84 (dd, $J=6.4$, 10 Hz, 1H), 6.34–6.36 (m, 2H), 7.24–7.37 (m, 10H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 24.6, 28.5, 29.0, 29.8, 43.5, 51.4, 57.4, 126.5, 126.9, 127.4, 128.6, 128.6, 128.9, 130.9, 132.0, 137.5, 142.0, 215.1.

4.2.2.6. (*R*)-2-((*R,E*)-1,3-Diphenylallyl)cycloheptanone (**12b**). ^1H NMR (CDCl_3 , 400 Hz): δ 1.20–1.39 (m, 4H), 1.63–1.72 (m, 2H), 1.83–1.89 (m, 2H), 2.23–2.34 (m, 2H), 3.03–3.12 (m, 1H), 3.81–3.86 (t, $J=9.6$ Hz, 1H), 6.27–6.33 (dd, $J=10$, 16 Hz, 1H), 6.45 (d, $J=16$ Hz, 1H), 7.13–7.35 (m, 10H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 24.1, 28.8, 29.0, 29.6, 44.1, 51.4, 56.9, 126.5, 126.6, 127.5, 127.8, 128.7, 128.8, 131.0, 131.8, 137.4, 143.1, 214.9. HRMS (EI) calcd for $\text{C}_{22}\text{H}_{24}\text{O}$ 304.1827; found 304.1829.

4.2.2.7. (*E*)-2-(1,3-Diphenylallyl)-2,3-dihydro-1H-inden-1-one (**14a** and **14b**). ^1H NMR (CDCl_3 , 400 Hz): δ 2.90–3.30 (m, 6H), 4.14–4.21 (t, 1H), 4.34–4.41 (dd, $J=2.8$, 7.6 Hz, 1H), 6.21–6.74 (m, 4H), 7.11–7.78 (m, 28H). HRMS (EI) calcd for $\text{C}_{24}\text{H}_{20}\text{O}$ 324.1514; found 324.1511.

4.2.2.8. 2-(Cyclohex-2-enyl)cyclohexanone (**17a** and **17b**). ^1H NMR (CDCl_3 , 400 Hz): δ 1.05–2.41 (m, 15H), 2.52–2.75 (m, 1H), 5.35–5.52 (m, 1H), 5.59–5.72 (m, 1H). ^{13}C NMR (CDCl_3 , 100 Hz): δ 21.9, 22.1, 24.8, 24.0, 25.2, 25.3, 25.4, 27.2, 28.0, 28.2, 29.5, 29.9, 33.5, 34.2, 42.4, 42.5, 55.1, 55.8, 128.2, 128.4, 129.0, 131.0, 213.0.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.003.

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