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Palladium-catalyzed asymmetric allylic alkylation with an enamine as the nucleophilic reagent

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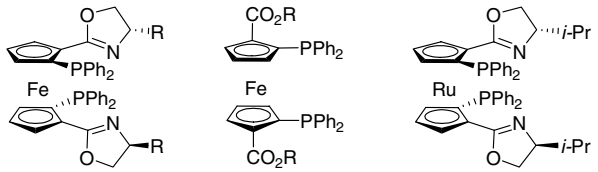
Abstract—An enamine can serve as a good nucleophile for palladium-catalyzed asymmetric allylic alkylation, avoiding the use of an unstablilized ketone enolate formed by strong bases. In the presence of a palladium complex of chiral metallocene-based phosphino-oxazoline ligands, the reaction was carried out smoothly with high catalytic activity and excellent enantioselectivity. Different distances between the two Cp rings of ferrocene and ruthenocene affected the catalytic behavior in the reaction. Furthermore, high catalytic activity and good enantioselectivity were also afforded by the ferrocene-based diphosphine ligands with only planar chirality.

There has been considerable interest in the development of palladium-catalyzed asymmetric allylic alkylation of simple ketones, which typically have been employed in the form of unstablilized ketone enolates as nucleophilic reagents.[1] The most common method to form these ketone enolates generally employed strong bases such as LDA and ClMgN(*i*-Pr)$_2$ to deprotonate the α-hydrogen adjacent to the carbonyl group of the ketones.[2] However, to generate unstablilized ketone enolates, harsh reaction conditions such as the use of potentially unstable and dangerous reagents greatly limit the general utility of this method. In searching for a new approach for Pd-catalyzed asymmetric allylic alkylation of allylic acetate with simple ketones, we tried to introduce enamines instead of the unstablilized ketone enolates as nucleophiles. The ease of access to enamines makes them promising nucleophilic reagents for asymmetric synthesis since the pioneering work by Stork.[3] However, recent strategies mainly involved chiral enamines as chiral auxiliaries in asymmetric synthesis,[4] with only few reports on asymmetric catalysis using enamines instead of ketone enolates as nucleophilic reagents.[5] Hiroi reported an example of Pd-catalyzed allylic alkylation with chiral enamines as nucleophilic reagents.[6] Recently, Crdova reported an unasymmetric Pd-catalyzed allylic alkylation with enamines.[7] We herein report a Pd-catalyzed asymmetric allylic alkylation using an enamine as a nucleophilic reagent with high yield and excellent enantioselectivity.[8]

Ferrocene-based chiral ligands designed for asymmetric synthesis have attracted much scientific interest over the past decades.[9] We recently reported the synthesis of C_2-symmetric chiral ferrocene-based ligands, 1,1′-bis(oxazolinyl)-2,2′-diphenylphosphino ferrocenes (**1**, Fig. 1), and their application for Pd-catalyzed asymmetric allylic alkylation with excellent enantioselectivity (up to 99% ee).[10] This kind of ligand contains planar chirality and central chirality. Subsequently, the central chirality in the oxazoline moiety was removed by ring-opening followed by ester exchange to give C_2-symmetric ferrocenes with only planar chirality (**2**, Fig. 1),[11] acting as efficient ligands for Pd-catalyzed asymmetric allylic alkylation.[11b] We have recently reported the synthesis of novel C_2-symmetric P,N-chelation ruthenocene (**3**, Fig. 1) and demonstrated its utility as an effective ligand



1 (R: **a**= *i*-Pr, **b**=*t*-Bu) **2** (R: **a**=Me, **b**=Et) **3**

Figure 1.

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with high catalytic activity and excellent enantioselectivity for the same asymmetric reaction. In view of their good performance[12] in asymmetric catalysis, **1**, **2**, and **3** were selected as chiral ligands for Pd-catalyzed asymmetric allylic alkylation with the enamine as a nucleophilic reagent. High catalytic activity and excellent enantioselectivity were obtained.

Because 1,3-diphenyl-2-propenyl acetate has been used as a model substrate for Pd-catalyzed asymmetric allylic alkylation,[13] it was selected in this asymmetric catalysis with the enamine as a nucleophilic reagent. Excellent enantioselectivity was obtained with both *anti*-[14] and *syn*-configurations.[15] Details are summarized in Table 1.

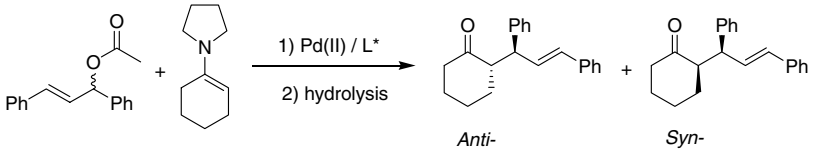
The influence of reaction conditions on the allylic alkylation was taken into account. First, the effect of solvents on this reaction was examined with **1a** (Table 1, entries 1–4). Both THF and toluene were efficient based on their catalytic activity and enantioselectivity. Temperature also affected enantioselectivity. Up to 97% ee was obtained at 0 °C with **1a** in both THF and toluene (Table 1, entries 5 and 6). There was little effect on the reaction with lower temperature and the ee was reduced to −25 °C (Table 1, entries 7 and 8). The substituent R on the oxazolinyl ring had an effect on enantioselectivity and a bulkier group gave somewhat better ee values (Table 1, entries 2 vs 9, 4 vs 10). When **1b**, having *tert*-butyl groups, was used as a chiral ligand, up to 99% ee was obtained in the allylic alkylation (Table 1, entry 12). It is interesting that much higher catalytic activity and yield were observed with **1b** than **1a** in THF (Table 1, entries 2 and 9).

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,[12,16] mainly due to the different distances between the two Cp rings in ferrocene and ruthenocene (3.32 and 3.68 Å, respectively).[17] Therefore, we also used ruthenocene-based ligand **3** to examine whether a dissimilarity exists in the same manner (Table 1, entries 14–17).

It was shown that all reactions provided excellent enantioselectivity. The solvents showed little effect on the enantioselectivity, but great effect on the catalytic activity. Meanwhile, the enantioselectivity generally seems to be a little inferior compared to **1**.

Furthermore, C_2-symmetric diphosphine ferrocene ligands **2** with only planar chirality were also applied in this Pd-catalyzed allylic alkylation (Table 1, entries

Table 1. Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with the enamine[a]



Entry	Ligand	Solvent	Time (h)	*T* (°C)	Yield[b] (%)	*Anti*/*syn*[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_2Cl_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**	THF	8	0	72	58/42	97/96
7	**1a**	Toluene	48	−15	73	63/37	97/97
8	**1a**	Toluene	48	−25	75	61/39	95/96
9	**1b**	THF	2	rt	91	59/41	96/97
10	**1b**	Toluene	1	rt	94	63/37	94/94
11	**1b**	THF	14	0	79	59/41	97/96
12	**1b**	THF	72	−15	56	61/39	99/98
13	**1b**	THF	72	−25	Trace	—	—
14	**3**	DMF	3	rt	84	59/41	88/88
15	**3**	THF	10	rt	72	57/43	90/90
16	**3**	CH_2Cl_2	1	rt	92	55/45	86/86
17	**3**	Toluene	8	rt	77	56/44	89/89
18	**2a**	DMF	1	rt	91	53/47	85/84
19	**2a**	THF	10	rt	71	57/43	75/75
20	**2a**	CH_2Cl_2	1	rt	93	50/40	76/76
21	**2a**	Toluene	1	rt	92	57/43	84/85
22	**2b**	CH_2Cl_2	2	rt	93	51/49	83/79
23	**2b**	Toluene	1	rt	93	60/40	88/89

[a] Molecular ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/substrate/enamine = 2.5/6.0/200/600; reactions were conducted under nitrogen; the catalysts were prepared by treating $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 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. 2d.

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

18–23). As shown in Table 1, both **2a** and **2b** provided high catalytic activity and good enantioselectivity with high yields (71–93%). The R in the ester group with greater steric hindrance gave better enantioselectivity (Table 1, entries 20–23).

In summary, an enamine can serve as a good nucleophilic reagent for Pd-catalyzed asymmetric allylic alkylation, avoiding the use of an unstablilized ketone enolate generated via strong bases and harsh reaction conditions. Using chiral metallocene-based P,N-ligands, the reaction was carried out smoothly, producing high catalytic activity and excellent enantioselectivity. Different distances between the two Cp rings in ferrocene and ruthenocene also affected the catalytic behavior in the reactions. Furthermore, high catalytic activity and good enantioselectivity were also afforded by the ferrocene-based diphosphine ligands with only planar chirality. Further study, including the improvement of diastereoselectivity and the application of other allylic substrates and enamines as nucleophilic reagents, is ongoing in our laboratory, and the results will be reported in due course.

Acknowledgements

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14. *Data for product of anti-configuration*: ^{1}H 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 24.16, 28.77, 32.42, 42.48, 48.64, 56.05, 126.50, 126.81, 127.39, 128.64, 128.74, 128.86, 130.69, 132.16, 137.56, 140.13, 212.70.
15. *Data for product of syn-configuration*: ^{1}H 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 24.76, 28.63, 32.14, 42.64, 48.72, 55.93, 126.45, 126.55, 127.48, 128.12, 128.71, 128.75, 131.25, 131.55, 137.48, 143.53, 211.84.
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