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Palladium-catalyzed asymmetric allylic alkylation with an indenide

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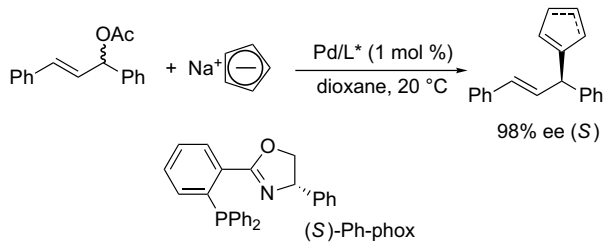
Abstract—Catalytic asymmetric synthesis of a chiral indene (97% ee) was realized by asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate with an indenide generated from indene and cesium carbonate in the presence of a palladium catalyst coordinated with (*S*)-Ph-phox. The stereochemistry of the allylic substitution with the indenide was demonstrated to be net retention.

1. Introduction

Palladium-catalyzed allylic substitution of allyl esters is recognized to be one of the most useful reactions catalyzed by transition metal complexes,[1] and it has been applied to catalytic asymmetric synthesis involving several types of nucleophiles represented from malonate esters.[2] We have previously reported that a cyclopentadienide anion[3,4] can participate in the palladium-catalyzed asymmetric allylic alkylation giving a cyclopentadiene substituted with a chiral allylic side chain with high enantioselectivity (Scheme 1) where the enantioselectivity is strongly dependent on the concentration of the cyclopentadienide.[5] The chiral cyclopentadiene was readily converted into chiral metallocenes.



Scheme 1. Palladium-catalyzed asymmetric allylic substitution with cyclopentadienide.

We have successfully extended this palladium-catalyzed asymmetric allylic alkylation to the reaction with an indenide anion as the nucleophile. Here we wish to report the fine tuning of the reaction conditions for high enantioselectivity.

2. Results and discussion

Before starting the asymmetric reaction, we studied the stereochemistry of the palladium-catalyzed allylic substitution[1] with the indenide nucleophile. One report has appeared on the stereochemical pathway of the allylic substitution with indenide.[4] It was suggested that the indenide behaves as a hard carbon nucleophile attacking the palladium metal rather than π-allyl moiety. In our studies using a cyclohexenyl acetate, on the contrary, it was demonstrated that the indenide behaves as a soft carbon nucleophile attacking the π-allyl moiety from the side opposite to palladium. Thus, the reaction of *cis*-5-methoxycarbonyl-2-cyclohexenyl acetate[6] **1** with sodium indenide, generated from indene and sodium hydride, in the presence of $[PdCl(\pi\text{-}C_3H_5)]_2$ and dppe (5 mol% Pd) in THF at 20 °C gave a high yield of allylated indene **2** (Scheme 2). ^{1}H NMR studies on **2** showed that the stereochemistry between the carbomethoxy and indenyl groups is *cis*. Both of the coupling constants between H^3 and H^4 and between H^4 and H^5 are larger than 11 Hz, indicating that both H^3 and H^5 are pseudo-axial.

Because the reaction mechanism for the palladium-catalyzed allylic substitution with the indenide nucleophile is similar to that with cyclopentadienide,[3] the asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **3** with the indenide (Scheme 3) was first examined under the same conditions used for cyclopentadienide.[5] The reaction of acetate **3** with sodium indenide (2 equiv to **3**), generated from indene and sodium hydride, in the

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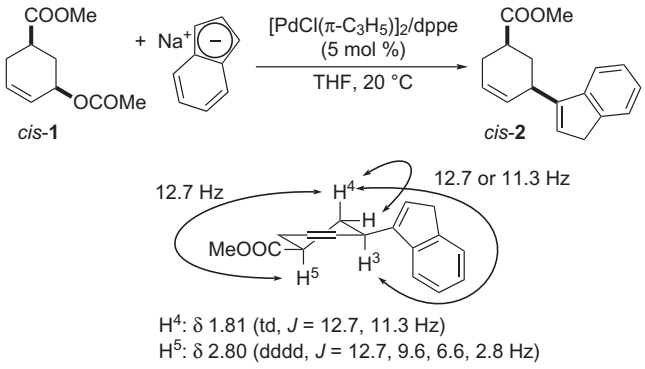
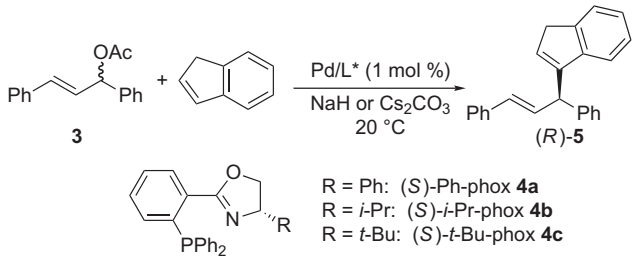
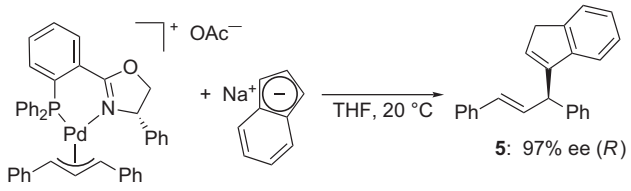


Scheme 2. Stereochemistry in the palladium-catalyzed allylic substitution with indenide.



Scheme 3. Palladium-catalyzed asymmetric allylic substitution with indenide.

presence of 1 mol% of a palladium catalyst coordinated with Ph-phox[7] **4a** in dioxane proceeded smoothly to give 90% isolated yield of 1,3-diphenyl-3-(3*H*-inden-1-yl)-propene **5**, which is the *R* enantiomer of 82% ee (entry 1 in Table 1). The reaction in THF under the same conditions gave (*R*)-**5** of 68% ee (entry 2). As had been observed for the reaction of sodium cyclopentadienide,[3] the enantioselectivity is dependent on the solubility of the sodium indenide, the lower concentration giving the higher enantioselectivity. The concentration of the saturated solution of sodium indenide was measured to be 0.5 mol/L in THF and 0.04 mol/L in dioxane. Higher enantioselectivity was observed in the slow addition of a THF solution of sodium indenide over a period of 12 h, which gave the product (*R*)-**5** of 95% ee (entry 3). These data suggest that the nucleophilic attack of sodium indenide after the equilibration of π-allylpalladium intermediates brings about higher enantioselectivity, and it is consistent with the high stereoselectivity observed in the stoichiometric reaction of an isolated π-allylpalladium complex (Scheme 4). The addition of sodium indenide in THF to a THF solution of [Pd(1,3-diphenyl-π-allyl)(Ph-phox **4a**)]$^{+}$OAc^{-5} at 20 °C gave 91% yield of (*R*)-**5**, which is 97% ee.



Scheme 4. Stoichiometric reaction of a π-allylpalladium complex with sodium indenide.

Although the high enantioselectivity (95% ee) was obtained by the slow addition of sodium indenide in the catalytic reaction, the slow addition procedure is not a practically useful method. We further examined other reaction conditions and found that the use of cesium carbonate as a base increases the enantioselectivity. Thus, a mixture of allyl acetate **3** (0.40 mmol), indene (0.8 mmol), cesium carbonate (0.8 mmol), and the palladium catalyst (1 mol% Pd) generated from [PdCl(π-C_3H_5)]$_2$ and Ph-phox **4a** in 1.6 mL of dioxane was stirred at 20 °C for 12 h to give a quantitative yield of the allylation product (*R*)-**5** with 97% ee (entry 4). The enantioselectivity was also high in the reaction carried out in THF (entry 5). Under the same conditions, *i*-Pr-phox **4b** and *t*-Bu-phox **4c** gave (*R*)-**5** of 92% ee and 94% ee, respectively (entries 6 and 7). The role of cesium carbonate on the high enantioselectivity remains to be clarified but it is likely that the reaction of indene with cesium carbonate generating cesium indenide is slow enough for its concentration to be kept very low.

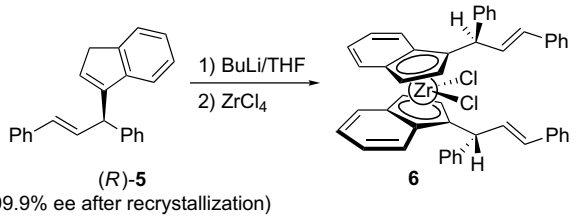
The chiral allylated indene (*R*)-**5** (97% ee) was readily made enantiomerically pure (>99.9% ee) by recrystallization from hexane with high recovery (91%). The lithium indenide, generated from enantiomerically pure indene (*R*)-**5** with butyllithium in THF, was allowed to react with $ZrCl_4$. Recrystallization gave a C_2-symmetric

Table 1. Palladium-catalyzed asymmetric allylic substitution of **3** with indenide[a]

Entry	Ligand L*	Solvent	Base	Yield (%) of **5**[b]	ee of **5** (%)[c,d]
1	(*S*)-Ph-phox **4a**	Dioxane	NaH	90	82 (*R*)
2	(*S*)-Ph-phox **4a**	THF	NaH	91	68 (*R*)
3[e]	(*S*)-Ph-phox **4a**	THF	NaH	89	95 (*R*)
4	(*S*)-Ph-phox **4a**	Dioxane	Cs_2CO_3	99	97 (*R*)
5	(*S*)-Ph-phox **4a**	THF	Cs_2CO_3	96	95 (*R*)
6	(*S*)-*i*-Pr-phox **4b**	Dioxane	Cs_2CO_3	95	92 (*R*)
7	(*S*)-*t*-Bu-phox **4c**	Dioxane	Cs_2CO_3	96	94 (*R*)

[a] All reactions were carried out with allyl acetate **3** (0.40 mmol), indene (0.8 mmol), base (0.8 mmol), and 1 mol% of palladium catalyst generated from [PdCl(π-C_3H_5)]$_2$ and a chiral ligand in 1.6 mL of a solvent at 20 °C for 12 h under nitrogen.
[b] Isolated yield by silica gel chromatography (ethyl acetate/hexane 1/10).
[c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H (hexane/2-propanol 500/1)).
[d] The absolute configuration was tentatively assigned by similarity of the reaction with cyclopentadienide (Ref. 5).
[e] A solution of sodium indenide (0.8 mmol) in THF was added over a period of 12 h.

homochiral bis(indenyl)zirconium **6**, which contains the chiral allylic side chain on both indenyl rings in 15% yield (Scheme 5).



Scheme 5. Synthesis of a chiral zirconocene from the indene (*R*)-**5**.

In summary, we have achieved high enantioselectivity (up to 97% ee) in the palladium-catalyzed asymmetric allylic alkylation with indenide by use of cesium carbonate as a base. The enantiomerically pure metallocenes derived from the chiral indene should find applications as chiral ligands or chiral catalysts in catalytic asymmetric reactions.

3. Experimental

3.1. General

All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. NMR spectra were recorded on a JEOL JNM LA-500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR and chloroform-*d* (δ 77.0) for ^{13}C.

3.2. Materials

Palladium complex, $[Pd(OAc)(1,3\text{-diphenyl-}\pi\text{-allyl})]_2$ was prepared by the reaction of $[PdCl(1,3\text{-diphenyl-}\pi\text{-allyl})]_2$ with AgOAc according to the reported procedures,[8] and it was converted into [Pd(1,3-diphenyl-π-allyl)(Ph-phox (**4a**))]OAc by addition of the phox ligand.[9] Phosphino-oxazoline ligands ((*S*)-Ph-phox, (*S*)-*i*-Pr-phox, and (*S*)-*t*-Bu-phox) were prepared according to the reported procedures.[7,10] THF, dioxane, toluene, and diethyl ether were dried over sodium benzophenone ketyl and distilled prior to use.

3.3. Palladium-catalyzed allylic alkylation of allyl acetate 1 with sodium indenide

To a solution of $[PdCl(\pi\text{-}C_3H_5)]_2$ (3.7 mg, 0.01 mmol), 1,2-bis(diphenylphosphino)ethane (dppe) (8.0 mg, 0.02 mmol), and *cis*-5-methoxycarbonyl-2-cyclohexenyl acetate (**1**) (79.3 mg, 0.40 mmol) in THF (0.5 mL) was added sodium indenide (110 mg, 0.80 mmol) in THF (1.0 mL), and the mixture was stirred at 20 °C for 1 h. Water (1 mL) was added and the mixture was extracted with ether. The organic layer was washed with aqueous sodium chloride and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel PTLC (hexane/ethyl acetate 20/1) to give 71.7 mg (70% yield) of *cis*-5-methoxycarbonyl-3-(3*H*-inden-1-yl)cyclohexene (**2**). **2**: ^1H NMR ($CDCl_3$) δ 1.81 (td, $J = 12.7$, 11.3 Hz, 1H), 2.35–2.43 (m, 3H), 2.80 (dddd, $J = 12.7$, 9.6, 6.6, 2.8 Hz, 1H), 3.31 (s, 2H), 3.58 (m, 1H), 3.67 (s, 3H), 5.81–5.83 (m, 2H), 6.24 (dd, $J = 2.9$, 2.0 Hz, 1H), 7.18 (td, $J = 7.4$, 1.1 Hz, 1H), 7.27 (td, $J = 7.4$, 0.9 Hz, 1H), 7.41 (d, $J = 7.5$ Hz, 1H), 7.44 (dt, $J = 7.3$, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 27.7, 31.6, 35.7, 37.6, 39.9, 51.7, 119.5, 123.9, 124.6, 125.7, 125.9, 127.8, 129.5, 144.2, 144.8, 147.0, 175.9. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 79.88; H, 7.21%.

3.4. Palladium-catalyzed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate (±)-3 with cesium indenide

The reaction conditions and results are shown in Table 1. A typical procedure is given for the reaction with indene and Cs_2CO_3 in dioxane (entry 4). To a solution of $[PdCl(\pi\text{-}C_3H_5)]_2$ (0.7 mg, 0.002 mmol), (*S*)-2-[2-(diphenylphosphino)phenyl]-4-phenyloxazoline **4a** [(*S*)-Ph-phox] (1.7 mg, 0.004 mmol), cesium carbonate (260 mg, 0.80 mmol), and 1,3-diphenyl-2-propenyl acetate **3** (100 mg, 0.40 mmol) in dioxane (1.6 mL) was added indene (92 mg, 0.80 mmol) and the mixture was stirred at 20 °C for 12 h. Water (5 mL) was added and the mixture was extracted with ether. The organic layer was washed with aq sodium chloride and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel (hexane/ethyl acetate 10/1) to give 121.9 mg (99% yield) of 1,3-diphenyl-3-(3*H*-inden-1-yl)propene **5**, which is a single olefinic isomer at the indene moiety. The enantiomeric purity was determined to be 97% ee by HPLC analysis with Chiralcel OD-H (hexane/2-propanol 500/1). Recrystallization of the obtained indene from hexane gave 110.9 mg (91% yield) of (*R*)-**5**, which is enantiomerically pure (>99.9% ee). Spectral and analytical data for the 1,3-diphenyl-3-(3*H*-inden-1-yl)propene **5** are shown below: ^1H NMR ($CDCl_3$) δ 3.34 (s, 2H), 4.79 (d, $J = 7.4$ Hz 1H), 6.23 (s, 1H), 6.34 (d, $J = 15.9$ Hz 1H), 6.61 (dd, $J = 15.9$, 7.4 Hz, 1H), 7.09–7.39 (m, 13H), 7.39 (d, $J = 3.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 37.78, 48.12, 120.23, 123.71, 124.56, 125.93, 126.29 (2C), 126.57, 127.23, 128.46 (2C), 128.49 (2C), 128.51 (2C), 130.48, 131.02, 131.42, 137.31, 141.70, 144.42, 144.54, 145.83. Anal. Calcd for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 93.37; H, 6.64. $[\alpha]_D^{20} = -74.3$ (*c* 1.02, $CHCl_3$).

3.5. Reaction of lithium 1-(1,3-diphenyl-2-propenyl)indenide with zirconium tetrachloride giving zirconocene 6

To a suspension of 7.63 g (33.1 mmol) of $ZrCl_4$ in 150 mL of toluene was added at −78 °C a cold solution of 20.7 g (66.1 mmol) of lithium 1-(1,3-diphenyl-2-propenyl)indenide prepared from (*R*)-1,3-diphenyl-3-(3*H*-inden-1-yl)propene **5** (>99.9% ee) and *n*-butyllithium in

150 mL of THF. The mixture was allowed to warm to ambient temperature over a period of 6 h with stirring and then kept at 70 °C for 12 h. Solvent was removed in vacuo. Methylene chloride (150 mL) was added to the residue, and the precipitated lithium chloride was removed by filtration. Concentration of the solution in vacuo brought about crystallization to give 3.84 g (15% yield) of the pure isomer **6**. (*R*,*R*)-$ZrCl_2$ [η^5-C_9H_6-1-CHPh(CH=CHPh)]$_2$ **6**: ^{1}H NMR ($CDCl_3$) δ 5.54 (d, $J = 6.9$ Hz, 2H), 6.09 (d, $J = 3.0$ Hz, 2H), 6.25 (d, $J = 15.9$ Hz, 2H), 6.35 (d, $J = 3.0$ Hz, 2H), 6.64 (dd, $J = 15.9$, 6.9 Hz, 2H), 6.92 (dd, $J = 8.7$, 8.5 Hz,, 2H), 6.98 (d, $J = 7.4$ Hz, 4H), 7.12–7.26 (m, 12H), 7.31 (t, $J = 7.4$ Hz, 4H), 7.40 (d, $J = 7.4$ Hz, 4H), 7.51 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 47.38 (2C), 97.07 (2C), 119.77 (2C), 124.33 (2C), 124.84 (2C), 125.67 (2C), 125.74 (2C), 125.82 (2C), 126.39 (4C), 126.58 (2C), 127.04 (2C), 127.43 (2C), 128.42 (4C), 128.46 (4C), 128.58 (4C), 128.73 (2C), 131.04 (2C), 132.04 (2C), 137.15 (2C), 142.02 (2C). Anal. Calcd for $C_{48}H_{38}ZrCl_2$: C, 74.20; H, 4.93. Found: C, 73.65; H, 5.11. $[\alpha]_D^{20} = +95.2$ (*c* 0.96, $CHCl_3$).

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