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High Enantioselectivity in Rhodium-Catalyzed Allylic Alkylation of 1-Substituted 2-Propenyl Acetates

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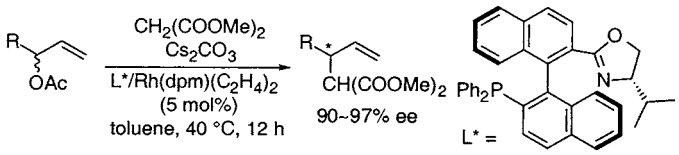
ABSTRACT



R = Ph, C_6H_4Me-4, $C_6H_4CF_3$-4, C_6H_4Cl-4, 1-naphthyl, CH_2CH_2Ph
dpm = dipivaloylmethanato

Rhodium-catalyzed asymmetric allylic alkylation of 1-substituted 2-propenyl acetates with dimethyl malonate proceeded with high enantioselectivity in the presence of cesium carbonate as a base and a rhodium catalyst generated from Rh(dpm)$(C_2H_4)_2$ (dpm = dipivaloylmethanato) and a chiral phosphino-oxazoline whose basic skeleton is axially chiral binaphthyl to give branch alkylation products in greater than 90% ee.

Palladium-catalyzed asymmetric allylic alkylation is one of the most frequently examined asymmetric reactions catalyzed by transition metal complexes because of its easy manipulation, high catalytic activity, and high enantioselectivity.[1] Recently, other transition metals, including molybdenum[2] and iridium[3] have also been reported to catalyze the asymmetric alkylation. In the reaction, which proceeds through monosubstituted π-allyl intermediates, the regioselectivity in forming a branch chiral isomer is higher with molybdenum and iridium catalysts than with palladium catalysts. Rhodium catalysts[4] have some unique features in the allylic alkylation reactions. Recently, Evans has reported[5] that the regiochemistry and the stereochemistry of the starting allylic esters are conserved in the allylic substitution products. Namely, the rhodium-catalyzed substitution takes place at the carbon substituted with the leaving group with net retention of configuration. It seems that the high regio- and stereospecificity in the rhodium-catalyzed system are not compatible with the catalytic asymmetric synthesis using a chiral rhodium catalyst, and as a result, there have been very few reports on the use of chiral rhodium catalysts for the asymmetric allylic substitution reactions.[6] We succeeded in the rhodium-catalyzed asymmetric allylic alkylation with

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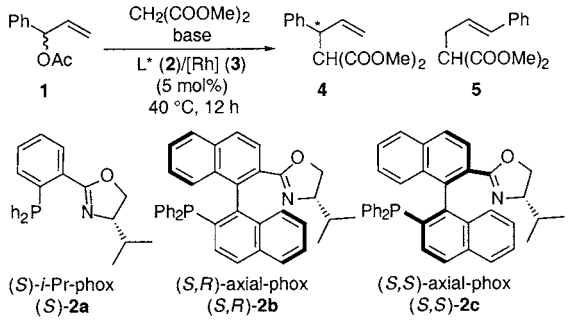
high enantioselectivity by a rational modification of the reaction conditions and fine-tuning of the ligands on the rhodium.

First, we examined the rhodium-catalyzed allylic alkylation of racemic 1-phenyl-2-propenyl acetate (**1**) in the presence of a chiral rhodium catalyst coordinated with (*S*)-*i*-Pr-phox ((*S*)-**2a**)[7,8] under one of the standard conditions used for the palladium-catalyzed reactions (Scheme 1). As it was expected

Scheme 1

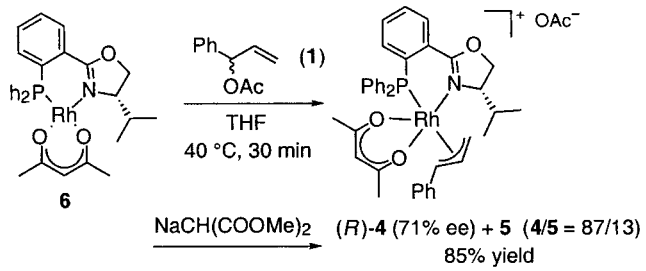


3a: $Rh(acac)(C_2H_4)_2$ (acac = acetylacetonato)
3b: $Rh(dpm)(C_2H_4)_2$ (dpm = dipivaloylmethanato)
3c: $Rh(hfac)(C_2H_4)_2$ (hfac = hexafluoroacetylacetonato)
3d: $Rh(dbm)(C_2H_4)_2$ (dbm = dibenzoylmethanato)

from the high stereospecificity reported by Evans, the enantioselectivity was low. Typically, the reaction of **1** (0.40 mmol) with dimethyl sodiomalonate (1.6 mmol) in the presence of 5 mol % $Rh(acac)(C_2H_4)_2$ (**3a**) and (*S*)-**2a** in THF (2.0 mL) at 40 °C for 12 h gave 90% yield of the allylic alkylation product, which consists of regioisomers **4** and **5** in a ratio of 89:11, and the branch isomer **4** was obtained in 36% ee of the (*R*)-isomer (entry 1 in Table 1). Although the enantioselectivity was this low, the formation of the nonracemic product indicates that the stereospecificity is not perfect, which is probably due to the equilibration between regio- and diastereoisomeric allyl-rhodium intermediates.

Considering that a longer lifetime of the allyl intermediate will give us a chance for higher enantioselectivity, we examined a stoichiometric reaction of a rhodium complex that was generated by mixing Rh(acac)((*S*)-*i*-Pr-phox) (**6**)[9] with racemic acetate **1**[10,11] (Scheme 2). After the complex

Scheme 2



was kept in THF at 40 °C for 30 min, dimethyl sodiomalonate was added to give (*R*)-**4** in 71% ee and **5** in a ratio of 87:13. It follows that the catalytic reaction will produce the branch isomer **4**, whose enantiomeric purity is as high as 71% if the lifetime of the allyl intermediate in the catalytic reaction is sufficiently long. Slow addition of the nucleophile over 48 h to the solution containing the **3a**/(*S*)-*i*-Pr-phox (**2a**) catalyst and acetate **1** (entry 2) or the reaction in a high dilution condition (entry 3) gave (*R*)-**4** in 66% ee, the ee value being close to that observed in the stoichiometric reaction. Thus, the enantioselectivity became higher with the

Table 1. Rhodium-Catalyzed Asymmetric Allylic Alkylation of Acetate **1** with Dimethyl Malonate[a]

entry	ligand L*	[Rh]	solvent	base	yield (%) of **4** and **5**[b]	ratio of **4**:**5**[c]	% ee **4**[d]
1	(*S*)-**2a**	**3a** (acac)	THF	NaH	90	89:11	36 (*R*)
2[e]	(*S*)-**2a**	**3a** (acac)	THF	NaH	63	87:13	66 (*R*)
3[f]	(*S*)-**2a**	**3a** (acac)	THF	NaH	79	90:10	66 (*R*)
4	(*S*)-**2a**	**3a** (acac)	THF	Cs_2CO_3	91	91:9	45 (*R*)
5	(*S*)-**2a**	**3a** (acac)	dioxane	Cs_2CO_3	97	87:13	59 (*R*)
6	(*S*,*R*)-**2b**	**3a** (acac)	dioxane	Cs_2CO_3	93	96:4	73 (*S*)
7	(*S*,*S*)-**2c**	**3a** (acac)	dioxane	Cs_2CO_3	95	87:13	58 (*R*)
8	(*S*,*R*)-**2b**	**3b** (dpm)	dioxane	Cs_2CO_3	98	97:3	90 (*S*)
9	(*S*,*R*)-**2b**	**3c** (hfac)	dioxane	Cs_2CO_3	59	79:21	58 (*S*)
10	(*S*,*R*)-**2b**	**3d** (dbm)	dioxane	Cs_2CO_3	76	89:11	67 (*S*)
11	(*S*,*R*)-**2b**	**3a** (acac)	toluene	Cs_2CO_3	94	96:4	87 (*S*)
12	(*S*,*R*)-**2b**	**3b** (dpm)	toluene	Cs_2CO_3	94	98:2	97 (*S*)
13[g]	(*S*,*R*)-**2b**	**3b** (dpm)	toluene	Cs_2CO_3	73	99:1	97 (*S*)
14	(*S*,*R*)-**2b**	**3c** (hfac)	toluene	Cs_2CO_3	64	92:8	81 (*S*)
15	(*S*,*R*)-**2b**	**3d** (dbm)	toluene	Cs_2CO_3	75	97:3	87 (*S*)

[a] All reactions were carried out with allyl acetate **1** (0.40 mmol), dimethyl malonate (1.6 mmol), base (1.6 mmol), and 5 mol % rhodium catalyst generated from a rhodium precursor **3** and a chiral ligand **2** in 2.0 mL of a solvent at 40 °C for 12 h under nitrogen. [b] Isolated yield by silica gel chromatography (hexane/ethyl acetate = 5:1). [c] Determined by ^1H NMR analysis of a crude reaction mixture. [d] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OJ (hexane/2-propanol = 93:7)). [e] Slow addition of dimethyl sodiomalonate over 48 h. [f] High dilution in 20 mL of THF for 40 h. [g] Catalyst = 1 mol %.

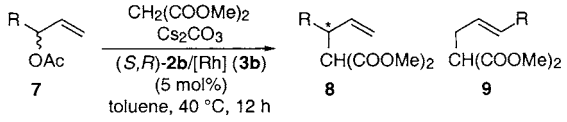
lower concentration of the nucleophile, which should prolong the lifetime of the allyl-rhodium intermediates.[12]

Although slow addition or high dilution conditions increased the enantioselectivity, these methods are not convenient from a practical point of view because the reaction requires a longer reaction time and the yields are generally not sufficiently high. The use of cesium carbonate Cs_2CO_3 as a base in place of sodium hydride brought about higher enantioselectivity (entries 4 and 5).[13] The higher enantioselectivity may be related to the weaker basicity of Cs_2CO_3, which will keep the concentration of the nucleophile lower, resulting in a longer lifetime of the allyl-rhodium intermediates. The reaction with phosphino-oxazoline ligand (*S*,*R*)-axial-phox (**2b**),[14] whose basic skeleton is axially chiral binaphthyl, was found to be more enantioselective than that with (*S*)-*i*-Pr-phox (**2a**). The reaction of acetate **1** with cesium carbonate and dimethyl malonate in dioxane in the presence of rhodium catalyst **3a**/(*S*,*R*)-axial-phox (**2b**) gave (*S*)-**4** in 73% ee and **5** in a ratio of 96:4 (entry 6).

One of the characteristic features of the rhodium catalysts used here is that they have an acetylacetonato-type ligand in addition to the phox ligand **2**, which cannot be incorporated into the palladium catalysts due to the limitation of coordination number. Thus, modification of the acetylacetonato ligand will give us a further chance for higher selectivity. Of the β-diketonato ligands examined, dipivaloylmethanato (dpm) ligand gave the best results. The reaction of acetate **1** with Cs_2CO_3 and dimethyl malonate in the presence of a rhodium catalyst generated from Rh(dpm)$(C_2H_4)_2$ (**3b**) and (*S*,*R*)-**2b** in dioxane gave 98% yield of (*S*)-**4** (90% ee) and **5** in a 97:3 ratio (entry 8). The enantioselectivity was further improved (up to 97% ee) by carrying out the reaction in toluene with the rhodium catalyst of **3b**/(*S*,*R*)-**2b** (entry 12). The regioselectivity in giving **4** is also higher (**4**:**5** = 98:2). With the rhodium catalyst precursors **3c** and **3d** coordinated with hfac and dbm, respectively, the enantioselectivity was not higher than that with the acac-rhodium catalyst **3a** (entries 9, 10, 14, and 15).

Using Rh(dpm)$(C_2H_4)_2$ (**3b**) and (*S*,*R*)-**2b** as a catalyst in toluene for the allylic alkylation with Cs_2CO_3 and dimethyl malonate, a high enantioselectivity ranging between 94 and 97% ee was observed for 1-(substituted phenyl)-2-propenyl acetates **7a**−**c** (Scheme 3). The enantioselectivity was also high for acetates **7d** and **7e**, which are substituted with 1-naphthyl and an alkyl substituent, respectively, at the α-position of the allyl acetate, to give the corresponding branch products **8** in greater than 90% ee.

Scheme 3



7a: R = C_6H_4Me-4 — 97% yield, **8a**/**9a** = 88/12, 94% ee
7b: R = $C_6H_4CF_3$-4 — 97% yield, **8b**/**9b** = 99/1, 97% ee
7c: R = C_6H_4Cl-4 — 93% yield, **8c**/**9c** = 97/3, 95% ee
7d: R = 1-naphthyl — 94% yield, **8d**/**9d** = 60/40, 95% ee

To summarize, we succeeded in asymmetric allylic alkylation with high enantioselectivity in the rhodium-catalyzed reaction. The low concentration of the malonate nucleophile increased the enantioselectivity of the catalytic reaction by keeping the long lifetime of allyl-rhodium intermediates, which causes equilibration between the isomeric rhodium intermediates. A fine-tuning of the chiral rhodium catalysts by modification of the β-diketonato ligand enhanced the enantioselectivity up to 97% ee.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Generated by mixing Rh(acac)$(C_2H_4)_2$ with (*S*)-*i*-Pr-phox in THF. ^{31}P NMR (THF): δ 51.7 (d, J = 206.8 Hz). ^{1}H NMR (toluene-d_8): δ 0.59 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 7.1 Hz, 3H), 1.83 (s, 3H), 2.25 (s, 3H), 3.38 (dsep, J = 3.0, 6.9 Hz, 1H), 3.86 (dd, J = 10.0, 8.6 Hz, 1H), 4.08 (dd, J = 8.6, 4.4 Hz, 1H), 5.58 (ddd, J = 10.0, 4.4, 3.0 Hz, 1H), 5.63 (s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.27−7.30 (m, 3H), 7.34−7.41 (m, 3H), 7.50 (t, J = 8.0 Hz, 1H), 8.01−8.07 (m, 2H), 8.10−8.17 (m, 3H).

(10) ^{31}P NMR spectra of a mixture of **6** and **1** showed the generation of two major species in a ratio of 56:44. ^{31}P NMR (THF): δ 46.6 (d, J = 143.6 Hz) for the major isomer and δ 40.7 (d, J = 148.6 Hz) for the minor isomer.

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