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

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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 = dipivaloyImethanato) 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.<sup>1</sup> Recently, other transition metals, including molybdenum<sup>2</sup> and iridium<sup>3</sup> have also been reported to catalyze the asymmetric alkylation. In the reaction, which proceeds through monosubstituted  $\pi$ -allyl intermediates, the regioselectivity in forming a branch chiral isomer is higher with molybdenum and iridium catalysts than with palladium catalysts. Rhodium catalysts<sup>4</sup> have some unique features in the allylic alkylation reactions. Recently, Evans has reported<sup>5</sup> 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.<sup>6</sup> We succeeded in the rhodium-catalyzed asymmetric allylic alkylation with

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<sup>(5) (</sup>a) Evans, P. A.; Nelson, J. D. Tetrahedron Lett. 1998, 39, 1725. (b) Evans, P. A.; Nelson, J. D. J. Am. Chem. Soc. 1998, 120, 5581. (c) Evans, P. A.; Kennedy, L. J. Org. Lett. 2000, 2, 2213. (d) Evans, P. A.; Kennedy, L. J. J. Am. Chem. Soc. 2001, 123, 1234. (e) Evans, P. A.; Robinson, J. E. J. Am. Chem. Soc. 2001, 123, 4609.

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**)<sup>7,8</sup> under one of the standard conditions used for the palladium-catalyzed reactions (Scheme 1). As it was expected



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)( $C_2H_4$ )<sub>2</sub> (**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**)<sup>9</sup> with racemic acetate  $\mathbf{1}^{10,11}$  (Scheme 2). After the complex



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

<sup>*a*</sup> 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. <sup>*b*</sup> Isolated yield by silica gel chromatography (hexane/ethyl acetate = 5:1). <sup>*c*</sup> Determined by <sup>1</sup>H NMR analysis of a crude reaction mixture. <sup>*d*</sup> Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OJ (hexane/2-propanol = 93:7)). <sup>*e*</sup> Slow addition of dimethyl sodiomalonate over 48 h. <sup>*f*</sup> High dilution in 20 mL of THF for 40 h. <sup>*s*</sup> Catalyst = 1 mol %.

lower concentration of the nucleophile, which should prolong the lifetime of the allyl-rhodium intermediates.<sup>12</sup>

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<sub>2</sub>CO<sub>3</sub> as a base in place of sodium hydride brought about higher enantioselectivity (entries 4 and 5).<sup>13</sup> The higher enantioselectivity may be related to the weaker basicity of Cs<sub>2</sub>CO<sub>3</sub>, 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),<sup>14</sup> 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 acetylaceto-

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(9) Generated by mixing Rh(acac)(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub> with (*S*)-*i*-Pr-phox in THF. <sup>31</sup>P NMR (THF):  $\delta$  51.7 (d, J = 206.8 Hz). <sup>1</sup>H NMR (toluene- $d_8$ ):  $\delta$  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) <sup>31</sup>P NMR spectra of a mixture of **6** and **1** showed the generation of two major species in a ratio of 56:44. <sup>31</sup>P NMR (THF):  $\delta$  46.6 (d, J = 143.6 Hz) for the major isomer and  $\delta$  40.7 (d, J = 148.6 Hz) for the minor isomer.

(11) For a recent example of the study on the structure of the corresponding palladium complexes coordinated with the phosphino-oxazoline ligand and monosubstituted  $\pi$ -allyl ligands, see: Kollmar, M.; Steinhagen, H.; Janssen, J, P.; Goldefuss, B.; Makubivsjata, S. A.; Vázquez, J.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2002**, *8*, 3103.

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nato ligand will give us a further chance for higher selectivity. Of the  $\beta$ -diketonato ligands examined, dipivaloylmethanato (dpm) ligand gave the best results. The reaction of acetate **1** with Cs<sub>2</sub>CO<sub>3</sub> and dimethyl malonate in the presence of a rhodium catalyst generated from Rh(dpm)(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub> (**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)( $C_2H_4$ )<sub>2</sub> (**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  $\alpha$ -position of the allyl acetate, to give the corresponding branch products **8** in greater than 90% 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  $\beta$ -diketonato ligand enhanced the enantioselectivity up to 97% ee.

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**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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<sup>(6)</sup> To the best of our knowledge, there has been only one report describing the use of a chiral rhodium catalyst: Selvakumar, K.; Valentini, M.; Pregosin, P. S. *Organometallics* **1999**, *18*, 4591.