Regio- and Enantioselective Allylation of Indole Catalyzed by a Planar-chiral Cyclopentadienyl–Ruthenium Complex

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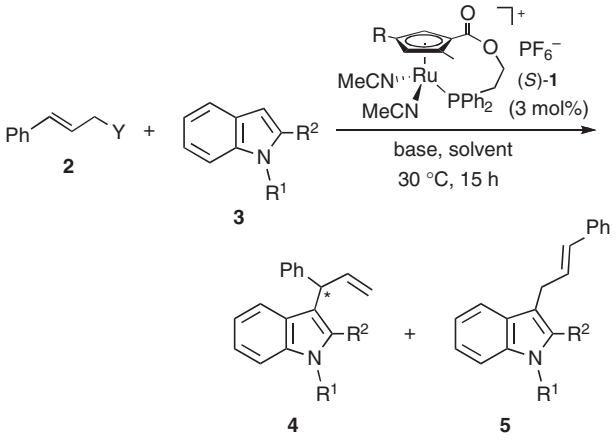
The reaction of cinnamyl chloride with indole in the presence of a ruthenium catalyst possessing a planar-chiral cyclopentadienyl ligand resulted in the substitution at the 3-position of the indole ring to give a branched allylation product with high regio- and enantioselectivities. The stoichiometric reaction clearly revealed that the catalytic reaction proceeded via a π-cinnamyl intermediate.

Transition metal catalyzed asymmetric allylic substitution is a powerful tool to create new C–C, C–N, and C–O bonds with high enantioselectivity.[1] Although palladium complexes possessing a variety of chiral ligands are widely used as common catalysts, a great number of chemists are attracted to other transition-metal complexes that show efficiencies comparable to or better than those of palladium.[2] Whereas palladium catalysts usually produce linear products in the reaction of monosubstituted allylic compounds, other transition metals, such as iridium, molybdenum, and ruthenium, yield branched isomers as the main product.

In the course of our studies on planar-chiral cyclopentadienyl–ruthenium (Cp′Ru) complexes **1**,[3] we developed the first example of Ru-catalyzed asymmetric allylic amination and alkylation of symmetrically 1,3-disubstituted allyl carbonates.[4] Recently, we found that the reaction of monosubstituted allyl halide with phenol or alcohol produced branched allyl–aryl or allyl–alkyl ether with high regio- and enantioselectivities.[5] We then tried to extend our catalytic system to the reaction with indole, which acts as a nucleophile in allylic substitution under appropriate conditions.[6] The development of new synthetic pathways to enantiopure indole derivatives is expected to improve access to biologically active molecules, because indole is an important structural unit in such molecules.[7] We report here the asymmetric allylic substitution of cinnamyl chloride with indole to give a branched product with high selectivity.[8,9]

As illustrated in Scheme 1, treatment of cinnamyl chloride (**2a**: Y = Cl) with indole (**3a**: $R^1 = R^2 = H$) in the presence of 3 mol % planar-chiral Cp′Ru complex (*S*)-**1a** (R = *t*-Bu) led to the selective allylation of indole at the 3-position to give branched product **4a** and linear product **5a**. After an initial screening for the appropriate reaction temperature, reaction time, and substrate molar ratio, we further optimized the reaction conditions, as depicted in Table 1. A reaction using Li_2CO_3 as a base produced a mixture of **4a** and **5a** (**4a**/**5a** = 9/1) in 26% yield, and the enantiopurity of **4a** was 71% ee (Entry 1). When the base was changed to Na_2CO_3, yield and regioselectivity were remarkably increased to 93% and **4a**/**5a** > 99/1, respectively, whereas enantioselectivity was slightly increased (Entry 2). The best regio- and enantioselectivities were observed in the reaction with K_2CO_3, although the yield was slightly lower than that of the reaction with Na_2CO_3 (Entry 3). Changing the base to



Scheme 1.

Table 1. Effect of base and solvent in the reaction of **2a** with **3a**[a]

Run	Base	Solvent	Yield/%	**4a**:**5a**[b]	ee/%[c]
1	Li_2CO_3	THF	26	90:10	71
2	Na_2CO_3	THF	93	>99:1	76
3	K_2CO_3	THF	79	>99:1	83
4	Cs_2CO_3	THF	41	94:6	70
5	Et_3N	THF	0	—	—
6	*i*-Pr_2EtN	THF	29	97:3	78
7	K_2CO_3	CH_2Cl_2	76	>99:1	65
8	K_2CO_3	Acetone	50	97:3	85
9	K_2CO_3	MeCN	21	75:25	22
10	K_2CO_3	DMF	15	96:4	34

[a]**2a** (0.5 mmol), **3a** (1.0 mmol), (*S*)-**1a** (3 mol %), base (1.5 mmol), solvent (2 mL), 30 °C, 15 h. [b]Determined by GLC. [c]Determined by HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 99/1).

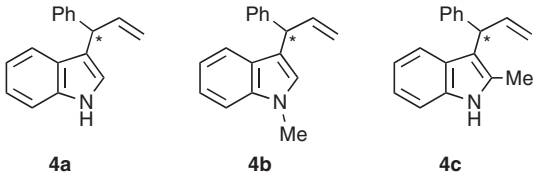
Cs_2CO_3 decreased both yield and regio- and enantioselectivities (Entry 4). Poor results were obtained when tertiary amine was used (Entries 5 and 6). The solvent effect on this reaction was also examined. Compared to the reaction in THF, slightly low yield or enantioselectivity was observed in the reaction using CH_2Cl_2 or acetone while the regioselectivity was comparable (Entries 7 and 8). Use of acetonitrile and DMF let to the decrease in yield and/or selectivity (Entries 9 and 10).

We then examined the effect of the leaving group of the cinnamyl compound and the substituent on the Cp′ ring of the ruthenium catalyst. Representative results are summarized in Table 2. Although the reaction of *t*-butyl cinnamyl carbonate (**2b**) produced **4a** with high regioselectivity, the enantioselectivity was low (Entry 2). No reaction took place when cinnamyl acetate (**2c**) was used as substrate (Entry 3). Ruthenium complexes (*S*)-**1b** and (*S*)-**1c**, which have a methyl group and a phenyl group at the 4-position of the Cp′ ring, respectively, also cata-

Table 2. Reactions of **2** with **3a**[a]

Run	Substrate	Catalyst	Yield/%	**4a**:**5a**[b]	ee/%[c]
1	**2a** (Y = Cl)	**1a** (R = *t*-Bu)	79	>99:1	83
2	**2b** (Y = OCO_2t-Bu)	**1a**	70	92:8	18
3	**2c** (Y = OAc)	**1a**	0	—	—
4	**2a**	**1b** (R = Me)	47	94:6	2
5	**2a**	**1c** (R = Ph)	76	>99:1	25

[a]**2** (0.5 mmol), **3a** (1.0 mmol), (*S*)-**1** (3 mol %), K_2CO_3 (1.5 mmol), THF (2 mL), 30 °C, 15 h. [b]Determined by GLC. [c]Determined by HPLC (Daicel Chiralcel AD-H, hexane/^{i}PrOH = 99/1).

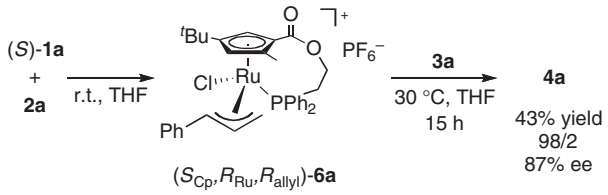


4a 79% yield, >99/1, 83% ee

4b 75% yield, >95/5, 33% ee

4c 28% yield, >95:5, 89% ee

Chart 1.



Scheme 2.

lyzed the reaction with high regioselectivity. However, the enantioselectivity was much lower than that with **1a** (Entries 4 and 5).

This catalytic system was applied to three indole derivatives (Chart 1). The reaction of 1-methylindole (**3b**) gave corresponding branched product **4b** in good yield but with low enantioselectivity, whereas the reaction of 2-methylindole (**3c**) produced **4c** in low yield but with high enantioselectivity. In both reactions, high regioselectivity was observed.

We have already reported that π-cinnamylruthenium complex ($S_{Cp}, R_{Ru}, R_{allyl}$)-**6a** was selectively formed in the reaction of (*S*)-**1a** with **2a**. ($S_{Cp}, R_{Ru}, R_{allyl}$)-**6a** exhibits metal-centered chirality at the ruthenium center and planar chirality on the π-cinnamyl ligand, and the control of both chiralities is very important to achieve high regio- and enantioselectivities.[5] When the reaction of **2a** with **3a** was performed using ($S_{Cp}, R_{Ru}, R_{allyl}$)-**6a** as catalyst, allylation products **4a** and **5a** were obtained in 76% yield with regio- and enantioselectivities of 98/2 and 87% ee, respectively. The stoichiometric reaction of ($S_{Cp}, R_{Ru}, R_{allyl}$)-**6a** with **3a** in the presence of K_2CO_3 produced **4a** and **5a** in 43% yield with regio- and enantioselectivities of 98/2 and 87% ee, respectively (Scheme 2). These results clearly indicate that the present catalytic reaction also proceeds via the π-cinnamyl intermediate. Because we were unable to determine the absolute configuration of **4**, the details of the nucleophilic attack of indole are still unclear.

In summary, we have developed a novel allylation reaction of indole at the 3-position that gave high regio- and enantioselectivities by using a planar-chiral Cp′Ru catalyst.[10] Further studies that focus on the scope and limitations of the present reaction as well as its application to the efficient synthesis of biologically active compounds are in progress.

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References and Notes

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1 For reviews, see: B. M. Trost, D. L. V. Vranken, *Chem. Rev.* **1996**, *96*, 395; G. Helmchen, *J. Organomet. Chem.* **1999**, *576*, 203; B. M. Trost, *J. Org. Chem.* **2004**, *69*, 5813; J. T. Mohr, B. M. Stoltz, *Chem. Asian J.* **2007**, *2*, 1476; Z. Lu, S. Ma, *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

2 For reviews, see: O. Belda, C. Moberg, *Acc. Chem. Res.* **2004**, *37*, 159; C. Bruneau, J.-L. Renaud, B. Demerseman, *Chem.—Eur. J.* **2006**, *12*, 5178; G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675.

3 N. Dodo, Y. Matsushima, M. Uno, K. Onitsuka, S. Takahashi, *J. Chem. Soc., Dalton Trans.* **2000**, 35; K. Onitsuka, N. Dodo, Y. Matsushima, S. Takahashi, *Chem. Commun.* **2001**, 521; K. Onitsuka, Y. Ajioka, Y. Matsushima, S. Takahashi, *Organometallics* **2001**, *20*, 3274; Y. Matsushima, K. Onitsuka, S. Takahashi, *Organometallics* **2004**, *23*, 2439; Y. Matsushima, K. Onitsuka, S. Takahashi, *Organometallics* **2004**, *23*, 3763.

4 Y. Matsushima, K. Onitsuka, T. Kondo, T. Mitsudo, S. Takahashi, *J. Am. Chem. Soc.* **2001**, *123*, 10405; K. Onitsuka, Y. Matsushima, S. Takahashi, *Organometallics* **2005**, *24*, 6472.

5 K. Onitsuka, H. Okuda, H. Sasai, *Angew. Chem., Int. Ed.* **2008**, *47*, 1454.

6 A. V. Malkov, S. L. Davis, I. R. Baxendale, W. L. Mitchell, P. Kočovský, *J. Org. Chem.* **1999**, *64*, 2751; M. Bandini, A. Melloni, A. Umani-Ronchi, *Org. Lett.* **2004**, *6*, 3199; H. Y. Cheung, W.-Y. Yu, F. L. Lam, T. T.-L. Au-Yeung, Z. Zhou, T. H. Chan, A. S. C. Chan, *Org. Lett.* **2007**, *9*, 4295.

7 J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030; D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 10780; R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem., Int. Ed.* **2005**, *44*, 6576; B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314; B. M. Trost, Y. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 14548.

8 Recently, a similar reaction using chiral Ir catalysts was reported. W.-B. Liu, H. He, L.-X. Dai, S.-L. You, *Org. Lett.* **2008**, *10*, 1815.

9 Reactions of allyl alcohol derivatives with indole in the presence of achiral Ru catalysts were reported. S. Gruber, A. B. Zaitsev, M. Wörle, P. S. Pregosin, L. F. Veiros, *Organometallics* **2008**, *27*, 3796; A. B. Zaitsev, S. Gruber, P. A. Pluss, P. S. Pregosin, L. F. Veiros, M. Worle, *J. Am. Chem. Soc.* **2008**, *130*, 11604.

10 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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