Asymmetric Catalysis

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Regio- and Enantioselective O-Allylation of Phenol and Alcohol Catalyzed by a Planar-Chiral Cyclopentadienyl Ruthenium Complex**

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Optically active allylic aryl ethers have high potential for use as precursors of biologically active organic molecules.[1,2] Whereas stereospecific allylation of phenol derivatives has been demonstrated with transition-metal catalysts,[3] the enantioselective version catalyzed by chiral palladium complexes has been successfully applied to the synthesis of natural products.[4] However, compared to the myriad reports on enantioselective allylic alkylation and amination, there has been little research on enantioselective allylic substitutions with alcohol and phenol.[5] Recently, an efficient Ir-catalyzed system has been reported to give allyl aryl ethers as well as allyl silyl ethers with high regio- and enantioselectivities.[6,7] Although Ru complexes with chiral bisoxazoline ligands also show catalytic activity towards asymmetric allylic substitution with oxygen nucleophiles, the regio- and enantioselectivities are not very high.[8]

We have been investigating the syntheses and stereoselective reactions of planar-chiral cyclopentadienyl (Cp′; see Eq. (1) for ligand) ruthenium complexes.[9] Previously, we reported the first example of Ru-catalyzed asymmetric allylic amination and alkylation of symmetrically substituted allyl carbonates using planar-chiral Cp′Ru complexes **1**.[10] We describe herein the Ru-catalyzed reaction of unsymmetrically substituted allyl halides with phenol and alcohol to give ethers with high regio- and enantioselectivities.

To optimize the conditions, we chose the reaction of cinnamyl chloride (**2a**, LG = Cl) with *o*-cresol (**3a**) [Eq. (1)]. After careful examination, we found that the reaction of **2a** (2.0 equiv) with **3a** was effectively catalyzed by 3 mol% (*S*)-**1a** in THF at 3 °C in the presence of K_2CO_3 (3.0 equiv) to give the branched ether **4a** with *R* configuration in 92% yield and 95% *ee*, along with a trace amount of the linear ether **5a**. The proper selection of cinnamyl derivatives and Ru catalyst was essential to achieve high selectivity (Table 1). Although methyl- and phenyl-substituted planar-chiral Cp′Ru complexes (*S*)-**1b** and (*S*)-**1c** also catalyzed the reaction with high

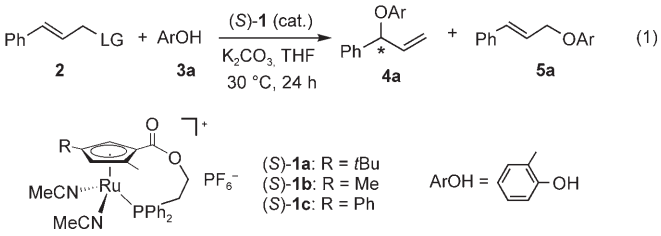

Table 1: Reaction of cinnamyl derivatives **2** with *o*-cresol (**3a**).

Entry	Cat.	**2**, LG	Yield [%] **4a**/**5a**[a]	*ee* [%][b]
1	**1a**	**2a**, Cl	92 (>20:1)	95 (*R*)
2	**1b**	**2a**, Cl	78 (>20:1)	3 (*R*)
3	**1c**	**2a**, Cl	95 (>20:1)	52 (*S*)
4	**1a**	**2b**, Br	91 (20:1)	84 (*R*)
5	**1a**	**2c**, $OP(O)(OEt)_2$	99 (12:8)	22 (*R*)
6	**1a**	**2d** OC(O)O*t*Bu	85 (7:13)	28 (*S*)
7	**1a**	**2e**, OAc	10 (9:11)	5 (*S*)

[a] Yields and ratios of branched and linear ethers were determined from the ^{1}H NMR spectra using hydroquinone dimethyl ether as a standard. [b] Determined by HPLC analysis using a chiral stationary phase. [c] Configuration based on the sign of specific rotation is given in parentheses.

regioselectivity, the enantioselectivities were lower than that obtained with (*S*)-**1a** (Table 1, entries 1–3). The substituent at the 4-position on the Cp′ ring has a similarly large effect on the enantioselectivity in the allylic aminations and alkylations.[10] The reaction of cinnamyl bromide (**2b**) also produced **4a** in good yield, albeit with slightly lower enantioselectivity than the reaction of **2a** (Table 1, entry 4). When cinnamyl phosphate (**2c**) or cinnamyl carbonate (**2d**) was used as a substrate, a mixture of **4a** with low enantioselectivities and **5a** was obtained in good yield (Table 1, entries 5 and 6). Cinnamyl acetate (**2e**) was not suitable for the present reaction owing to its low reactivity (Table 1, entry 7).

The scope of the present O-allylation catalyzed by (*S*)-**1a** under the optimized conditions was examined [Eq. (2)], and the results are summarized in Table 2. The reactions of **2a** with various phenol derivatives **3** selectively produced the corresponding branched ethers **4** in good yields with more than 90% *ee* even when the phenol has a bulky substituent at

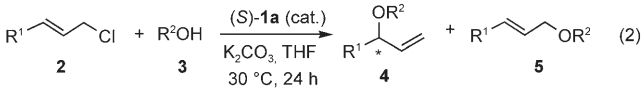

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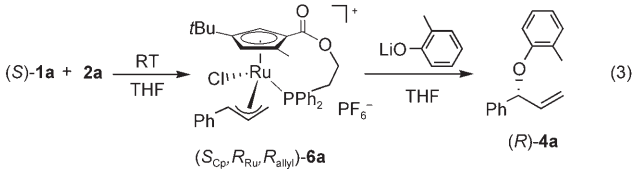
Table 2: Reaction of substituted allyl chlorides **2** with phenol and primary alcohols **3**.

Entry	**2**, R^1	**3**, R^2	Yield [%][a]	Regioselectivity[b]	*ee* [%][c]
1	**2a**, Ph	**3a**, *o*-MeC_6H_4	91	**4a/5a** > 20:1	95 (*R*)
2	**2a**, Ph	**3b**, Ph	99	**4b/5b** > 20:1	92
3	**2a**, Ph	**3c**, *m*-MeC_6H_4	91	**4c/5c** > 20:1	93
4	**2a**, Ph	**3d**, *p*-MeC_6H_4	95	**4d/5d** > 20:1	93
5	**2a**, Ph	**3e**, *o*-*t*BuC_6H_4	86	**4e/5e** > 20:1	93
6	**2a**, Ph	**3f**, *o*-PhC_6H_4	85	**4f/5f** > 20:1	91
7	**2a**, Ph	**3g**, *p*-$CF_3C_6H_4$	99	**4g/5g** > 20:1	91 (*R*)
8	**2a**, Ph	**3h**, *p*-ClC_6H_4	98	**4h/5h** > 20:1	93
9	**2a**, Ph	**3i**, $PhCH_2$	88	**4i/5i** > 20:1	87 (*R*)
10	**2a**, Ph	**3j**, Me	69	**4j/5j** > 20:1	83
11	**2f**, *p*-$CF_3C_6H_4$	**3b**, Ph	90	**4k/5k** > 20:1	94
12	**2g**, *p*-ClC_6H_4	**3b**, Ph	96	**4l/5l** = 20:1	86
13	**2h**, *o*-$MeOC_6H_4$	**3b**, Ph	63	**4m/5m** > 20:1	95
14	**2i**, 1-naphthyl	**3b**, Ph	98	**4n/5n** > 20:1	82
15	**2j**, Me	**3b**, Ph	36	**4o/5o** > 20:1	80

[a] Yields of isolated products. [b] Ratio of branched and linear ethers was determined from the ^{1}H NMR spectrum. [c] Determined by HPLC analysis using a chiral stationary phase. Configuration based on the sign of specific rotation is given in parentheses.

the *ortho* position (Table 2, entries 2–8). This system was successfully applied to the reaction of alcohol to give allyl alkyl ethers with high enantioselectivities (Table 2, entries 9 and 10). The reactions of substituted cinnamyl chlorides proceeded smoothly giving the branched ethers in good yields with high enantioselectivities (Table 2, entries 11–14), while the reaction of crotyl chloride produced the branched ether in 36% yield with 80% *ee* (Table 2, entry 15).

To obtain information on the reaction mechanism, we examined the stoichiometric reactions [Eq. (3)]. Treatment of



(3)

(*S*)-**1a** with 10 equiv of **2a** in THF at room temperature led to the quantitative formation of the η^3-cinnamyl ruthenium complex **6a**, which was isolated in 80% yield.[9f] Although chirality was generated not only at the Ru center but also on the η^3-cinnamyl plane, the NMR spectra of the reaction mixture suggested that **6a** was a single diastereomer. The configuration of **6a** was unequivocally determined by X-ray crystallographic analysis of the racemic sample to be $S^*_{Cp},R^*_{Ru},R^*_{allyl}$, as shown in Figure 1.[11] It should be noted that the chloro ligand on the Ru atom is located at a position close to the phenyl group of the η^3-cinnamyl ligand. When the reaction was conducted in an NMR tube, no ^{31}P NMR signals other than those of (*S*)-**1a** and (S_{Cp},R_{Ru},R_{allyl})-**6a** were detected; this is consistent with kinetic control of the configuration around Ru in the reaction of **1** with allyl chloride.[9f] The reaction of **2a** with **3a** was also catalyzed by (S_{Cp},R_{Ru},R_{allyl})-**6a** to give (*R*)-**4a** with 92% *ee* (yield of ether: 98%; **4a**/**5a** > 20:1). Although (S_{Cp},R_{Ru},R_{allyl})-**6a** did not react with *o*-cresol even in the presence of K_2CO_3, the reaction with 2 equiv of lithium *o*-methylphenoxide led to the regioselective formation of (*R*)-**4a** in 54% yield with > 99% *ee*, suggesting that (S_{Cp},R_{Ru},R_{allyl})-**6** is a reasonable intermediate.[12]

The plausible reaction mechanism is illustrated in Scheme 1. Oxidative addition of **2** to (*S*)-**1a** produces (S_{Cp},R_{Ru},R_{allyl})-**6a** selectively. Then, nucleophilic attack of phenol derivatives takes place to give **4** and regenerate (*S*)-**1a**. There are two possible pathways for this step: One is the direct attack on the η^3-cinnamyl group from outside, and the other proceeds by substitution of chloride with phenoxide on the Ru atom and subsequent reductive elimination (inside attack). Judging from the retention of stereochemistry

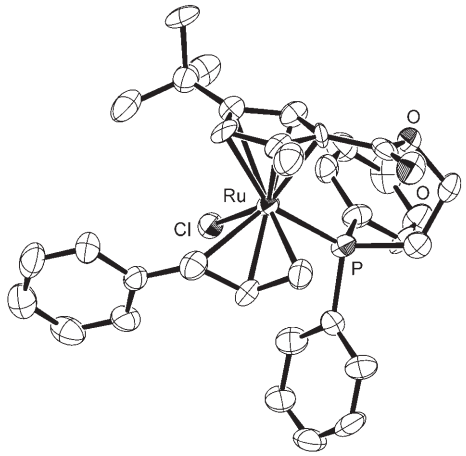
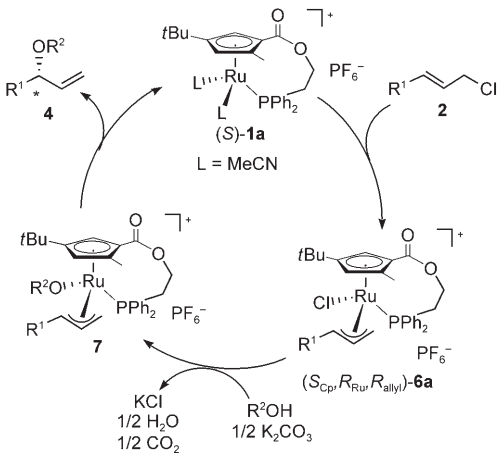


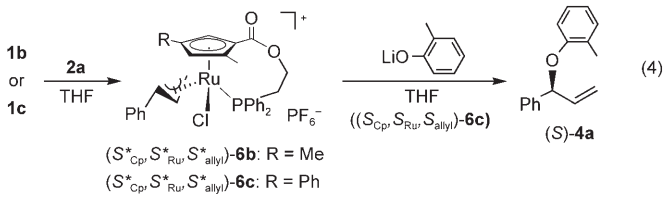
Figure 1. X-ray crystal structure of ($S^*_{Cp},R^*_{Ru},R^*_{allyl}$)-**6a**. Ellipsoids at the 50% probability level; PF_6^- and hydrogen atoms are omitted for clarity.



Scheme 1. Plausible reaction mechanism for the enantioselective O-allylation.

between (S_{Cp},R_{Ru},R_{allyl})-**6a** and (*R*)-**4a**, the latter pathway forming intermediate **7a** seems to be reasonable,[13,14] because (*S*)-**4a** and/or linear ether **5a** should be provided by means of the former mechanism. Moreover, the highly regioselective formation of **4** can be explained if phenoxide binds to Ru at the position of the chloride ligand of (S_{Cp},R_{Ru},R_{allyl})-**6**. However, we cannot completely exclude the possibility of the mechanism that includes S_N2'-type nucleophilic attack on the η^1-cinnamyl complex at this stage.[15]

The reaction of a racemic mixture of **1b** with **2a** resulted in the quantitative formation of η^3-cinnamyl ruthenium complex (S^*_{Cp},S^*_{Ru},S^*_{allyl})-**6b** [Eq. (4)], X-ray analysis of



which revealed that the configuration at the Ru center and the coordination plane of the η^3-cinnamyl group are opposite to those of (S^*_{Cp},R^*_{Ru},R^*_{allyl})-**6a**.[11,16] The reaction of **1c** with **2a** also produced (S^*_{Cp},S^*_{Ru},S^*_{allyl})-**6c** quantitatively.[11,16] When an enantiomerically pure sample of (S_{Cp},S_{Ru},S_{allyl})-**6c** was treated with lithium *o*-methylphenoxide, (*S*)-**4a** was selectively formed in 76% yield with 91% *ee* (**4a**/**5a** 20:1). These results, which support with the reaction mechanism including inside attack of phenoxide, clearly suggest the reason why the reaction using (*S*)-**1c** as a catalyst does not produce (*R*)-**4a** but (*S*)-**4a** as a major enantiomer (Table 1, entry 3). Because the regioselectivity of the resulting ether is high, the moderate enantioselectivity may result from partial isomerization of (S_{Cp},S_{Ru},S_{allyl})-**6c** to (S_{Cp},R_{Ru},R_{allyl})-**6c** during the catalytic reaction. The lower enantioselectivity of (*S*)-**1b** (Table 1, entry 2) can be explained by assuming that isomerization of (S_{Cp},S_{Ru},S_{allyl})-**6b** to (S_{Cp},R_{Ru},R_{allyl})-**6b** is significantly faster than that of (S_{Cp},S_{Ru},S_{allyl})-**6c** to (S_{Cp},R_{Ru},R_{allyl})-**6c**.

In conclusion, we have described the highly regio- and enantioselective O-allylation of phenol and alcohol. The planar chirality of the Cp′ ligand on the Ru catalyst controls not only the Ru-centered chirality but also the planar chirality of the η^3-cinnamyl group of the intermediate. Nucleophilic attack of phenoxide to the η^3-cinnamyl ruthenium complex from the inside is the key to the high regio- and enantioselectivity. Although allylation often takes place at the more substituted allylic carbon in the reactions catalyzed by transition-metal complexes other than palladium, no logical explanation is available so far.[17] Studies focusing on the extension to other allylic substitutions as well as further clarification of the reaction mechanism are in progress.

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