Asymmetric Hydroxylation

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Ruthenium-Catalyzed Regio- and Enantioselective Allylic Substitution with Water: Direct Synthesis of Chiral Allylic Alcohols**

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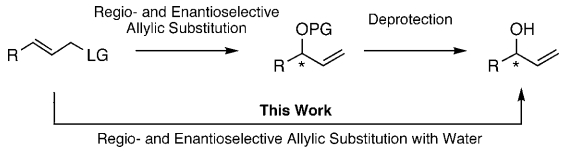
Enantioselective allylic substitution catalyzed by transition-metal complexes is an important process in organic synthesis.[1] For many years, mainly palladium complexes that contain chiral ligands have been employed as efficient catalysts in these reactions. Recent studies have demonstrated that chiral catalysts based on other transition metals show different regioselectivity in the synthesis of branched allylic products via monosubstituted π-allyl intermediates.[2] Although a variety of carbon and nitrogen nucleophiles can be used in those reactions, applicable oxygen nucleophiles are still limited to phenols and alcohols, which produce allylic ethers.[3] Thus, enantioenriched branched allylic alcohols, which serve as useful chiral building blocks, are often synthesized by other processes, such as the hydrogenation of α,β-unsaturated ketones,[4] the nucleophilic addition of vinyl-metal reagents to aldehydes and ketones,[5] and the kinetic resolution of racemic allylic alcohols.[6] Recently, new ways to access these compounds have been developed, and they involve allylic substitution by a two-step conversion involving allylic esters and silyl ethers (Scheme 1; OPG = ester or silyl ether).[7,8] In the reaction of allylic chlorides with boronic acids in the presence of a ruthenium catalyst, the allylic alcohols were synthesized but high regio- and enantioselectivities were not achieved.[9] Herein, we describe the direct synthesis of chiral allylic alcohols by the regio- and enantioselective allylic substitution using water as the nucleophile.[10]

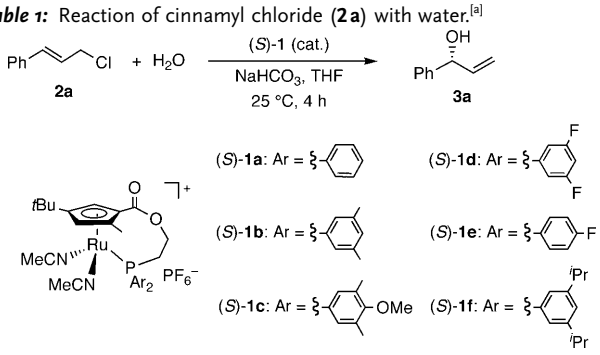


Scheme 1. Synthesis of chiral allylic alcohols by allylic substitution. LG = leaving group.

Previously, we reported the enantioselective allylic substitution of 1,3-disubstituted allylic carbonates with amine and carbon nucleophiles catalyzed by planar-chiral cyclopentadienyl ruthenium (Cp′Ru) complexes (**1**; see Table 1).[11] This system was successfully extended to the regio- and enantioselective allylic substitution of monosubstituted allylic halides with oxygen and carbon nucleophiles.[12] From those studies, we found that Cp′Ru catalysts showed characteristic reactivity towards the less reactive nucleophiles. Thus, we started an examination of the enantioselective allylic substitution with water using Cp′Ru catalysts.

Treatment of cinnamyl chloride (**2a**) with water in the presence of 1 mol% of the Cp′Ru complex (*S*)-**1a** resulted in the selective formation of the branched allylic alcohol (**3a**; see equation in Table 1). After optimization of the reaction conditions, we found that the reaction in a mixture of THF/water (8:1) at 25 °C with sodium hydrogen carbonate (1.2 equiv), produced **3a** after 4 hours in 99% yield with 81% *ee*.[13] Notably, the linear allylic alcohol was not formed at all. To improve the enantioselectivity, we examined the effect of the aryl groups on the phosphine ligand of the Cp′Ru catalyst (Table 1). Replacement of the phenyl groups with 3,5-dimethylphenyl and 4-methoxy-3,5-dimethylphenyl groups led to an increase in enantioselectivity to 88% *ee* and 90% *ee*, respectively (Table 1, entries 2 and 3). Complexes **1d** and **1e**, which have 3,5-difluorophenyl and 4-fluorophenyl groups, quantitatively produced **3a** in 88% *ee* and 87% *ee*, respec-

Table 1: Reaction of cinnamyl chloride (**2a**) with water.[a]



Entry	Cat.	Yield [%][b]	*ee* [%][c,d]
1	(*S*)-**1a**	99	81 (*R*)
2	(*S*)-**1b**	99	88 (*R*)
3	(*S*)-**1c**	99	90 (*R*)
4	(*S*)-**1d**	99	88 (*R*)
5	(*S*)-**1e**	99	87 (*R*)
6	(*S*)-**1f**	97	81 (*R*)

[a] Reaction conditions: **2a** (1.0 mmol), cat. (10 μmol), $NaHCO_3$ (1.2 mmol), THF (4 mL), and H_2O (0.5 mL), 25 °C, 4 h. [b] Yields of the isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Configuration is given in parentheses. THF = tetrahydrofuran.

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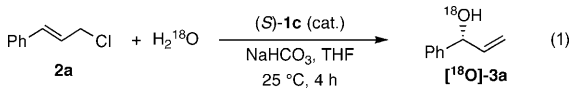
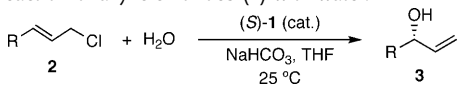
tively (Table 1, entries 4 and 5). These results indicate that the enantioselectivity is not affected by the electronic properties of the aryl group but is affected by the steric properties of the aryl group. Complex **1f** (Table 1, entry 6) showed the same enantioselectivity as **1a**, thus indicating the catalyst containing the large 3,5-diisopropylphenyl groups (**1f**) was not suitable for this reaction.

Gais and co-workers reported the palladium-catalyzed deracemization of 1,3-disubstituted allylic carbonates to give chiral allylic alcohols.[14] On the basis of some control experiments, they concluded that the reaction proceeded through the nucleophilic attack of the hydrogen carbonate ion, and subsequent decarboxylation. In contrast, in our reaction water actually functions as a hydroxide source. The reaction using sodium formate instead of sodium hydrogen carbonate also produced **3a** in 64% yield with 80% *ee*.[13] Critical evidence was obtained in the isotope labeling experiment. The reaction using $H_2{}^{18}O$ led to the selective formation of [^{18}O]-**3a** instead of **3a** [Eq. (1)], and this result was unequivocally confirmed by mass spectrometry.[15] To the best of our knowledge, this is a rare example of an allylic substitution that uses water as the nucleophile to give the chiral allylic alcohol in good yield and high enantioselectivity.[10]



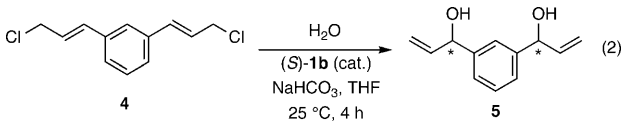
The scope of the present allylic hydroxylation is summarized in Table 2. The reactions of cinnamyl chloride derivatives, which possess various substituents, selectively produced the corresponding branched allylic alcohols **3** in good yields with high enantioselectivities (Table 2, entries 1–5), although substrates with electron-withdrawing groups required longer reaction times for complete conversion. Although Bruneau and co-workers reported that **3c** easily isomerizes into 1-(4-methoxyphenyl)propanone with a ruthenium catalyst,[16] no isomerization was observed in the present system (Table 2, entry 2). Moreover, because the reaction conditions are very mild, methoxycarbonyl and formyl groups are well tolerated in this reaction (Table 2, entries 4 and 5). The reactions of naphthyl and dienyl derivatives **2g–2i** produced the corresponding allylic alcohols (Table 2, entries 6–8). The present reaction also proceeded with alkyl-substituted allylic chlorides **2j–2m** to give **3j–3m**, respectively (Table 2, entries 9–12). Although the yields of **3k** and **3l** were not very high, the substrates were completely consumed and no by-products were formed. Technical difficulties in the isolation of **3k** and **3l** resulted from their relatively low boiling points, thus resulting in lower yields. Meanwhile, the reaction of *m*-bis(chloropropenyl)benzene (**4**) gave allylic diol (**5**) in 90% yield with 99% *ee* and 82% *de* [Eq. (2)]. This result indicates that the configuration in the first allylic hydroxylation does not affect the enantioselectivity of the second reaction. In all the reactions described above, regioselectivity was high because the formation of linear products was not observed.

Table 2: Reaction of allylic chlorides (**2**) with water.[a]

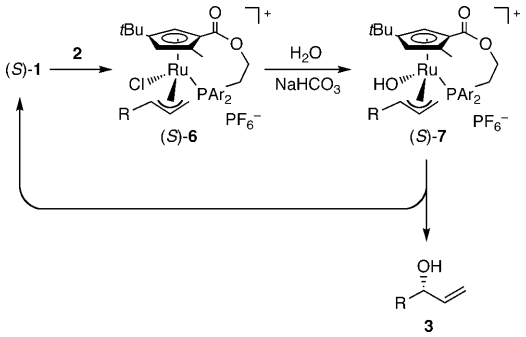


Entry	Substrate	Cat.	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	**2b** (R = 4-MeC_6H_4)	(*S*)-**1d**	4	99	90 (*R*)
2	**2c** (R = 4-MeOC_6H_4)	(*S*)-**1b**	4	99	76 (*R*)
3	**2d** (R = 4-$CF_3C_6H_4$)	(*S*)-**1c**	12	99	94 (*R*)
4	**2e** (R = 4-$MeO_2CC_6H_4$)	(*S*)-**1c**	12	99	93 (*R*)
5	**2f** (R = 4-OHCC_6H_4)	(*S*)-**1c**	12	93	93 (*R*)
6	**2g** (R = 1-naphthyl)	(*S*)-**1c**	4	99	90 (*R*)
7	**2h** (R = 2-naphthyl)	(*S*)-**1c**	7	95	89 (*R*)
8	**2i** (R = (*E*)-PhCH=CH)	(*S*)-**1b**	4	96	96 (*R*)
9	**2j** (R = $PhCH_2CH_2$)	(*S*)-**1d**	12	99	85 (*S*)
10	**2k** (R = *n*-C_5H_{11})	(*S*)-**1d**	18	78	83 (*S*)
11	**2l** (R = *c*-C_6H_{11})	(*S*)-**1b**	18	87	97 (*R*)
12	**2m** (R = *t*BuPh_2SiOCH_2)	(*S*)-**1c**	12	99	90 (*R*)

[a] Reaction conditions: **2** (1.0 mmol), cat. (10 μmol), $NaHCO_3$ (1.2 mmol), THF (4 mL), and H_2O (0.5 mL), 25 °C, 4 h. [b] Yields of the isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Configuration is given in parentheses.



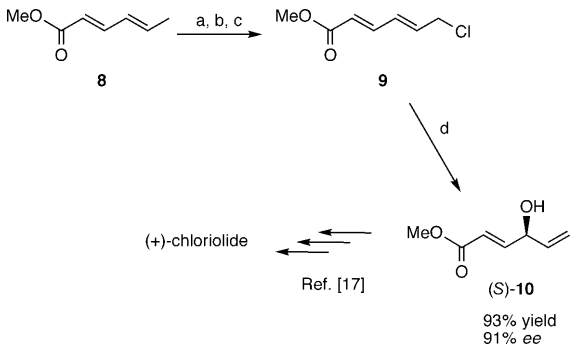
Similar to other asymmetric allylic substitutions using **1**,[12] the reaction proceeds via the π-allyl intermediates (*S*)-**6** that are generated by the oxidative addition of allylic chloride with high diastereoselectivity (Scheme 2). Indeed, treatment of



Scheme 2. Proposed reaction pathway for asymmetric allylic hydroxylation.

(*S*)-**6a** (Ar = R = Ph) with H_2O and sodium hydrogen carbonate in CH_3CN resulted in the quantitative formation of **3a** (R = Ph) with 93% *ee*. The absolute configuration of **3** is in agreement with the reaction mechanism involving an attack of the coordinated hydroxy group at the substituted allylic carbon atom of the π-allyl group in complex (*S*)-**7**, which is the key to the high regio- and enantioselectivities.

This reaction was successfully applied to the synthesis of a known intermediate enroute to the 12-membered macrolide (+)-chloriolide (Scheme 3). Kirsh and Haug prepared the chiral allylic alcohol (*S*)-**10** from the readily available



Scheme 3. Enantioselective formal synthesis of (+)-chloriolide. a) **8**, NBS, AIBN, PhCl; b) $NaHCO_3$ aq., acetone, 48% (2 steps); c) NCS, DMS, CH_2Cl_2, 90%; d) (*R*)-**1b** (1 mol%), $NaHCO_3$, THF, 25 °C, 12 h (see the Supporting Information for details). AIBN = 2,2′-azoisobutyronitrile, DMS = dimethylsulfide, NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide.

trichloroacetimidate in seven steps, which included the Overman allylic esterification.[17] Although our attempt at the direct chlorination of the commercially available methyl sorbate **8** failed, the allylic chloride **9** was prepared in three steps through the corresponding allylic bromide and alcohol, in 43% yield. The reaction of **9** using (*R*)-**1b** gave the target allylic alcohol (*S*)-**10** in 93% yield with 91% *ee*, and this can be converted into (+)-chloriolide in nine steps.

In conclusion, we have developed a synthetic route to chiral allylic alcohols that involves allylic substitution with water. Complete regioselectivity and high enantioselectivity were achieved by using the planar-chiral Cp′Ru catalysts. The simplicity and availability of the nucleophile, the mild reaction conditions, and the broad scope of the allylic chlorides are the attributes of the present system. Further studies to extend the reaction to other nucleophiles are ongoing.

Experimental Section

General procedure: $NaHCO_3$ (101 mg, 1.2 mmol) and Cp′Ru catalyst **1** (10 μmol, 1 mol%) were added to a solution of allylic chloride **2** (1.0 mmol) in THF (4.0 mL) and water (0.5 mL), and the reaction mixture was stirred for 4 h at 25 °C. After dilution with diethyl ether, the reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate, 10:1) to give a colorless oil.

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[15] MS (EI): **3a**: *m/z* 134 (59) [M^+], 133 (100) [$(M-H)^+$], 117 (66) [$(M-OH)^+$]; [^{18}O]-**3a**: *m/z* 136 (55) [M^+], 135 (100) [$(M-H)^+$], 117 (98) [$(M-^{18}OH)^+$].

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