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Planar-Chiral Cyclopentadienyl-Ruthenium-Catalyzed Regio- and Enantioselective Asymmetric Allylic Alkylation of Silyl Enolates under Unusually Mild Conditions

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Abstract: We report the asymmetric allylic alkylation of allylic chlorides with silyl enolates as a carbon nucleophile using a planar-chiral cyclopentadienyl-ruthenium (Cp′Ru) catalyst. The reaction proceeds under unusually mild conditions to give the desired branched products with complete regioselectivity and high enantioselectivity, and reactive functional groups, such as aldehyde, can be tolerated. In this reaction system, Cp′Ru plays an important role in activating both silyl enolate and allylic chloride.

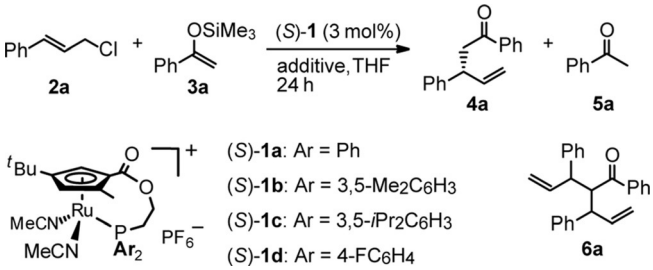
Keywords: asymmetric allylic substitution; cyclopentadienyl-ruthenium; enantioselective catalysis; planar chirality; silyl enolates

Enantioselective allylic alkylation catalyzed by transition metal complexes has become a convenient synthetic method for the asymmetric formation of carbon-carbon bonds.[1] In fact, reactions between monosubstituted allylic substrates and various carbon nucleophiles have been reported, affording the corresponding products in good yields and high regio- and enantioselectivities, leading to their widespread application in organic synthesis. In such systems, stabilized enolates[2] such as β-carbonyl compounds have been mainly used. On the other hand, simple non-stabilized ketone enolates are the most important class of nucleophiles for the formation of carbon-carbon bonds in allylic alkylation.[3] Trost[4] and Hou[5] have demonstrated the palladium-catalyzed asymmetric allylic alkylation using unstable alkali metal enolates as the 'hard' carbanion to give α-allylic ketones with high selectivity. In contrast, the nucleophilicity and basicity of the alkali metal enolates are liable to result in undesired side reactions. For instance, carbonyl groups, which are sensitive with enolates, will interfere with the reaction. Therefore, it is necessary to develop other types of asymmetric allylic alkylation that can be achieved under milder reaction conditions.[6]

Silyl enolates are valuable nucleophiles in organic synthesis, because silyl enolates are stable enough to be isolated and can be easily handled in comparison with other metal enolates. Therefore silyl enolates are capable of forming carbon-carbon bonds under mild conditions,[7] such as in the Mukaiyama aldol reaction.[8] As silyl enolates are much less reactive than other metal enolates, Lewis acids or bases are needed to activate silyl enolates to react. In the aldol reactions, with the less reactive silyl enolates, Lewis acids are usually used to increase the positive charge on the carbonyl carbon atom enough to be attacked nucleophilically. For asymmetric allylic substitutions, an efficient Ir-catalyzed system using silyl enolates as the nucleophile under mild conditions has been reported by Hartwig and co-workers.[9] In this reaction system, the carbonate anion, which was generated from the oxidative addition of an allylic carbonate to the Ir complex, serves as an activator of silyl enol ether.[9e]

The cyclopentadienyl(Cp)-ruthenium complex is an effective catalyst for stereoselective allylic substitutions,[10] and several types of reaction using simple non-stabilized ketone enolates have been reported. For example, Tunge and Lacour have reported a stereoselective allylic alkylation using the decarboxylative Carroll rearrangement to give homoallylic ketones under mild conditions.[10e–g] On the other hand, we have already shown that planar-chiral ruthenium (Cp′Ru) complexes [(*S*)-**1**, see Table 1][11] are proficient catalysts for regio- and enantioselective allylic substitutions of monosubstituted allylic halides.[12] In this catalytic system, the Cp′Ru catalyst exhibited characteristic reactivity towards less-reactive nucleo-

Table 1. Optimization of the Cp′Ru-catalyzed asymmetric allylic alkylation using silyl enolates.[a]



Entry	Cat.	Additive	Temp. [°C]	**4a** [%][b]	*ee* [%][c]	**5a** [%][b]
1	**1a**	CsF	30	10	N.D.	86
2	**1a**	$KHCO_3$	30	67	79	3
3	**1a**	K_2CO_3	30	71	78	20
4	**1a**	$NaHCO_3$	30	95	78	5
5	**1a**	Na_2CO_3	30	95	78	5
6	**1a**	Li_2CO_3	30	9	N.D.	9
7	**1a**	Cs_2CO_3	30	0	N.D.	99
8	**1a**	$(i\text{-Pr})_2EtN$	30	0	–	0
9	**1a**	$NaHCO_3$	35	97	80	3
10	**1a**	$NaHCO_3$	40	97	80	3
11	**1a**	$NaHCO_3$	45	97	75	3
12	**1a**	$NaHCO_3$	20	65	72	7
13	**1b**	$NaHCO_3$	35	99	79	1
14	**1c**	$NaHCO_3$	35	99	70	1
15	**1d**	$NaHCO_3$	35	96	78	>0

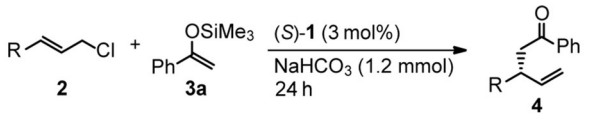
[a] *Reaction conditions:* **2a** (0.6 mmol), **3a** (0.4 mmol), cat. (3 mol%), additive (1.2 mmol), THF 2.0 mL for 24 h.
[b] Determined by ^1H NMR based on **3a**.
[c] Determined by HPLC analysis on a chiral stationary phase.

philes such as metal carboxylates,[12b] water[12c] and *N*-alkoxybenzamides.[12d] Most recently, when a β-diketone was used as the nucleophile, the reaction in the presence of $NaHCO_3$ as base, proceeded with quantitative conversion despite the latter being a weak base.[12e] Herein, we describe the Cp′Ru-catalyzed asymmetric allylic alkylation of monosubstituted allylic chlorides with silyl enolates which proceeds to give good yield with high regio- and enantioselectivities. Because activator reagents to generate the free enolate anion are not used, the concentration of free enolate anion in the reaction system is extremely low and reactive functional groups can be tolerated. The Cp′Ru complex plays an important role in activating both the silyl enolate and the allylic chloride.

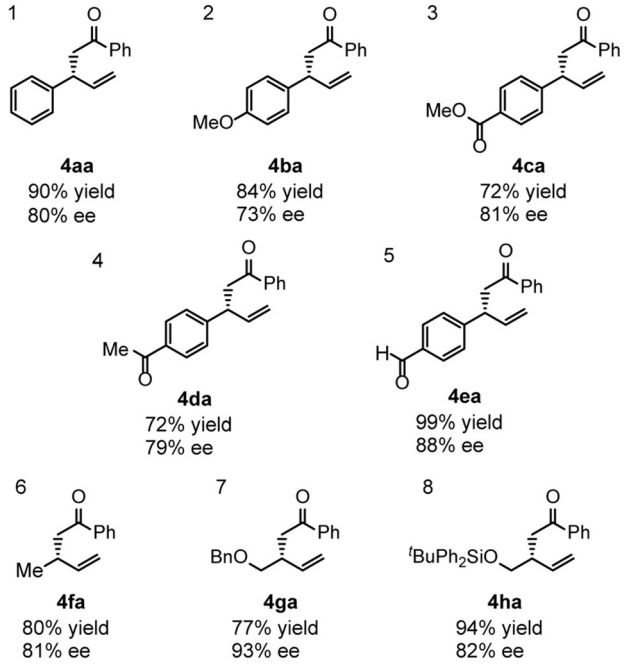
We initially examined the use of the Cp′Ru complex (**1a**: Ar = Ph, 3 mol%) to catalyze the reaction of cinnamyl chloride (**2a**: R = Ph) with the silyl enolate (**3a**) that was derived from acetophenone and trimethylsilyl chloride (Table 1). First, CsF was used to cleave the Si–O bond (entry 1). Unfortunately, the desired allylic product (**4a**) was generated in only 10% yield, and the majority of **3a** was decomposed to acetophenone (**5a**) by fluoride. Other fluoride additives, e.g., LiF, NaF and KF, provided similar results (Figure S1, see the Supporting Information). As the polarities of **4a** and **5a** are quite similar, the complete isolation of **4a** using silica gel chromatography was difficult in the presence of **5a**. Thus, preventing the decomposition of **4a** was crucial. When metal carbonates, such as $KHCO_3$, $NaHCO_3$ and Na_2CO_3, were used as additive, the production of **5a** was reduced (entries 2, 4 and 5). The reaction in the presence of $KHCO_3$ proceeded in 67% yield with 79% *ee*, and only a slight amount of **5a** was observed (entry 2). When $NaHCO_3$ and Na_2CO_3 were used as base, the reaction proceeded in 95% yield with high enantioselectivity (entries 4 and 5). In contrast, when K_2CO_3 was used as base, the reaction also proceeded, but 20% of **5a** was formed (entry 3). In addition, the reactions with $KHCO_3$ and K_2CO_3 formed small amounts of the diallylation product **6a**. The reactions with other metal carbonates such as Li_2CO_3 and Cs_2CO_3 gave only trace amounts of the desired product (entries 6 and 7). When a tertiary amine was used as the additive, the reaction did not proceed at all (entry 8). Next, various reaction temperatures were screened with $NaHCO_3$ as additive. When the reaction temperature was increased to 35–40 °C, the enantioselectivity improved (80% *ee*, entries 9 and 10). Meanwhile, lower reactivity and enantioselectivity were observed at a lower temperature (entry 12). We previously reported that the aryl group on the phosphine ligand in the Cp′Ru complex plays an important role in achieving high enantioselectivity in allylic substitution. However, when the reactions were conducted using (*S*)-**1b–d** as catalysts (entries 13–15), the enantioselectivities of the resulting products were slightly lower than those observed for the reaction with (*S*)-**1a**. The reactions of cinnamyl bromide and cinnamyl carbonate were not suitable for the present reaction owing to low reactivity (Figure S2, see the Supporting Information).

Next, we tested the scope of the asymmetric allylic alkylation under optimized conditions; the results are summarized in Table 2. In all the reactions, as described below, regioselectivity was high because linear products were not formed at all. The reactions of **3a** with substituted cinnamyl chloride possessing electron-rich and electron-deficient groups produced the corresponding branched products (**4ba–4ea**) in a high yield with moderate enantioselectivities (entries 2–5). Because the reaction conditions are mild, carbonyl groups such as aldehydes can be tolerated in this reaction. The present reaction also proceeded with alkyl-substituted allylic chlorides **2f–2h** to give **4fa–4ha**, respectively (entries 6–8). Particularly, the reaction of **2g** proceeded with high enantioselectivity (93% *ee*, entry 7).

Table 2. Effect of the substituent on the allylic chlorides.[a]



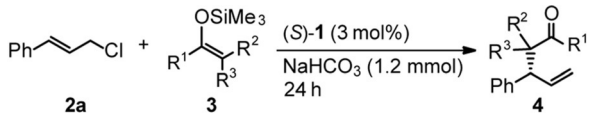
2 3a 4



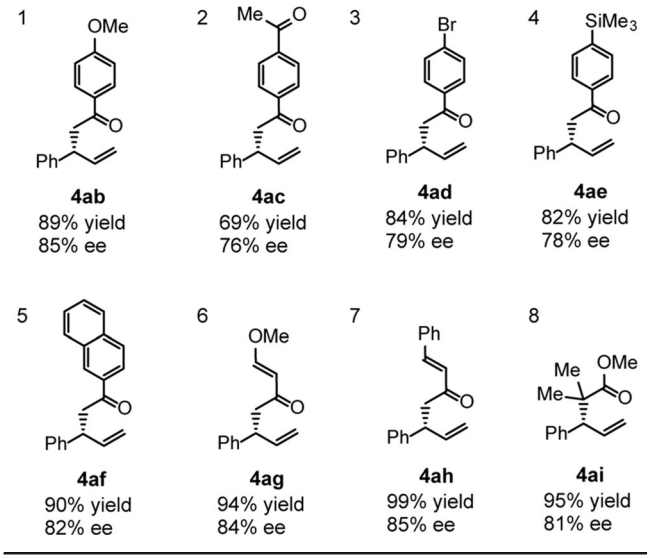
4aa 90% yield 80% ee
4ba 84% yield 73% ee
4ca 72% yield 81% ee
4da 72% yield 79% ee
4ea 99% yield 88% ee
4fa 80% yield 81% ee
4ga 77% yield 93% ee
4ha 94% yield 82% ee

[a] *Reaction conditions:* **2** (0.60 mmol), **3a** (0.40 mmol), cat. **1a** (0.012 mmol, 3 mol%) at 35 °C, $NaHCO_3$ (1.2 mmol), THF (2.0 mL) for 24 h. Yield of isolated product after column chromatography. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

Table 3. Effect of the substituent on the silyl enolate.[a]



2a 3 4

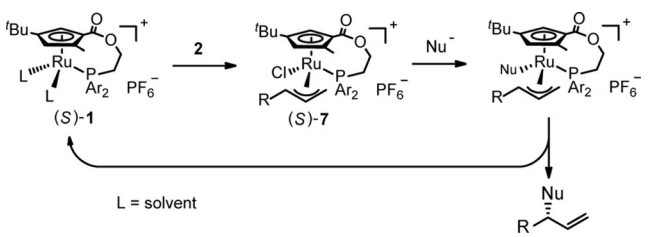


4ab 89% yield 85% ee
4ac 69% yield 76% ee
4ad 84% yield 79% ee
4ae 82% yield 78% ee
4af 90% yield 82% ee
4ag 94% yield 84% ee
4ah 99% yield 85% ee
4ai 95% yield 81% ee

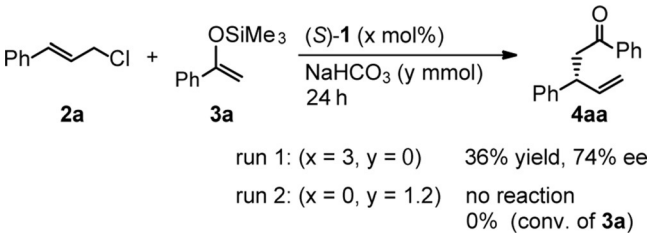
[a] *Reaction conditions:* **2a** (0.60 mmol), **3** (0.40 mmol), cat. **1a** (0.012 mmol, 3 mol%) at 35 °C, $NaHCO_3$ (1.2 mmol), THF (2.0 mL) for 24 h. Yield of isolated product after column chromatography. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

The scope of this reaction was also tested using various silyl enolates **3** (Table 3). Substituents on the phenyl moiety of the silyl enolate, such as OMe, COOMe, Br and $SiMe_3$, and even its replacement with 2-naphthyl, were well tolerated and the corresponding branched product **4** was obtained in 69–90% yield with 76–85% *ee* (entries 1–5). The reaction system tolerated the presence of the trimethylsilyl group, because a metal fluoride to cleave the Si–O bond was not used (entry 4). The mild conditions allowed us to use the nucleophiles of **3g** and **3h** that were derived from unsaturated ketones, the reactions proceeded in a good yield without any side reactions, such as aldol condensation or Michael additions (entries 6 and 7), because of the mild reaction conditions. Additionally, the reaction can be applied to ketene silyl acetals (entry 8). When **3i** was used as the ketene silyl acetal, the product containing a trisubstituted α-carbon was formed in a good yield with 81% *ee*.[13]

In recent years, we have reported the reaction mechanism of asymmetric allylic substitutions catalyzed by **1**.[12a] Thus, the reaction proceeds *via* the formation of a π-allyl intermediate (*S*)-**7**, which is generated by oxidative addition of allylic chloride with high diastereoselectivity. From mechanistic studies, the reaction is thought to occur by an inner-sphere mechanism, in which the nucleophilic anion coordinates to the ruthenium with high diastereoselectivity at the metal center prior to the attack of the π-allyl group. The reaction proceeds by an inside attack of the coordinated nucleophile at the substituted allylic carbon atom of the π-allyl group (Scheme 1). Because the absolute configuration of the resulting branched product **4** is in agreement with the conventional reaction mechanism,[15] it is likely that the present asymmetric allylic alkylation catalyzed by **1** using silyl enolates proceeds through the inner-sphere pathway *via* a ruthenium enolate complex.[14] However, the step of cleaving the Si–O bond is unclear in the present



Scheme 1. Proposed reaction mechanism for asymmetric allylic substitution catalyzed by (*S*)-**1**.

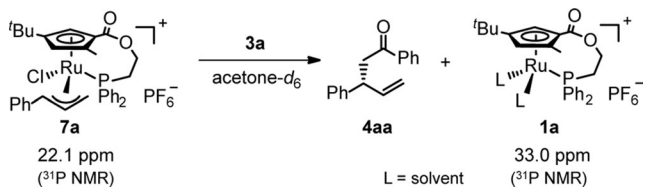


Scheme 2. Reaction for investigation of the reaction mechanism.

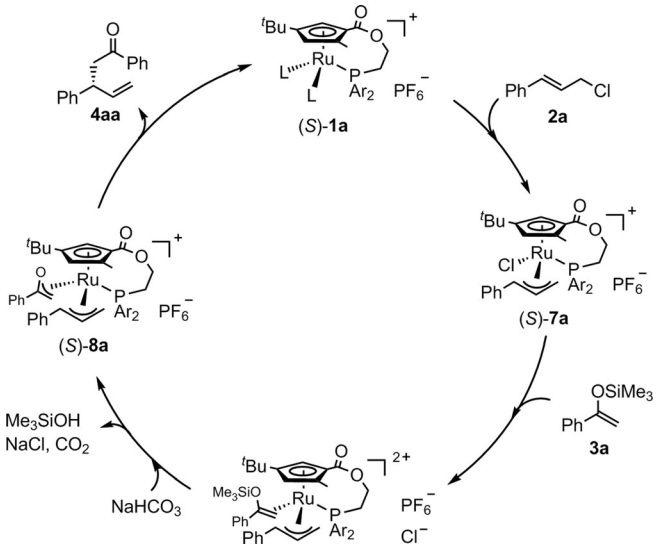
mechanism. Additionally, the reaction proceeds under unusually mild conditions in comparison with other methods[3e,g,4,5] for allylic substitution using enolates as nucleophile; substituents bearing carbonyl groups sensitive to enolate ions, such as aldehydes and esters, can be used in this reaction. These facts demonstrate that the concentration of free enolate anion in the reaction system must be extremely low.

To obtain information on the mechanism of the Si–O bond activation, some experiments were conducted. In the absence of the additive, the reaction of **2a** and **3a** proceeded in 36% yield with 74% *ee*; the enantioselectivity was similar in the presence of the additive $NaHCO_3$ (Scheme 2). On the other hand, the absence of (*S*)-**1a** caused a drastic reduction in conversion of **3a** (0%, Scheme 2). Therefore, the Cp′Ru catalyst is needed to activate the Si–O bond. To further clarify this, an NMR experiment was conducted. The ^{31}P NMR spectrum of the cationic Ru(IV) species of **7a** (Ar = Ph) showed a peak at 22.1 ppm, which was assigned to the anchoring phosphine moiety. Treatment of **7a** with **3a** in acetone-d_6 resulted in the quantitative conversion of **7a** and the branched product **4aa** was observed,[15] which was confirmed by ^1H NMR. In the ^{31}P NMR, the resonance of **1a** was observed at 33.0 ppm (Scheme 3). These results support that **7** is involved in the activation of the Si–O bond.

A proposed reaction mechanism is shown in Scheme 4. In this reaction, π-allyl complex **7a** is an important intermediate as in the previous reactions. Additionally, the electron-deficient high-valence cationic Ru(IV) species **7a** can probably serve as a Lewis acid to activate the Si–O bond of **3**, which accelerates the transmetallation of **7a** to form the Ru-enolate



Scheme 3. Stoichiometric reaction of **7a** with **3a** in acetone-d_6.



Scheme 4. Proposed reaction mechanism for asymmetric allylic alkylation catalyzed by (*S*)-**1a** using silyl enolates

complex **8a**. This process is further promoted by interaction of the hydrogen carbonate ion on the Si atom. Subsequently, the resulting complex **8** can immediately undergo reductive elimination *via* an inside attack of the coordinated enolate anion at the π-allyl group to yield the branched chiral product **4aa**. Thus, a low concentration of free enolate ion is achieved in this system.

In conclusion, we have demonstrated the asymmetric allylic alkylation of monosubstituted allylic chlorides with silyl enolates catalyzed by (*S*)-**1a**. The mild conditions and broad scope of the allylic chlorides and silyl enolates are the key attributes of this reaction system. Furthermore, substrates containing reactive groups that do not tolerate the presence of free enolate anion, such as aldehydes, can be used in this reaction. We have also shown that the Cp′Ru catalyst plays an important role in activating the silyl enolate for cleavage of the Si–O bond and formation of Cp′Ru enolate complex. Further development of this reaction system using these specific reactivities is now in progress.

Experimental Section

General Procedure

To Cp′Ru catalyst **1** (0.012 mmol, 3 mol%) and $NaHCO_3$ (1.2 mmol) was added a THF (1.0 mL) solution of **2** (0.60 mmol) and the mixture was stirred at 35 °C. After 20 min, a THF (1.0 mL) solution of **3** (0.40 mmol) was then added by a syringe and the reaction mixture was stirred for 24 h at 35 °C. After dilution with ether, the insoluble parts were filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by SiO_2

column chromatography to give branched allylic compound (**4**) as colorless oil.

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