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Enantioselective Synthesis of Allylic Esters via Asymmetric Allylic Substitution with Metal Carboxylates Using Planar-Chiral Cyclopentadienyl Ruthenium Catalysts

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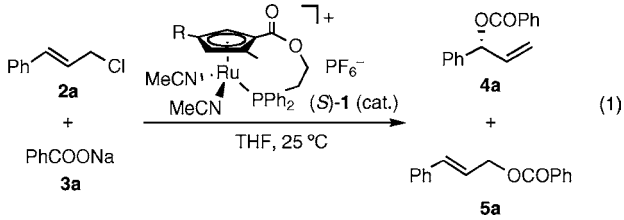
Optically active allylic alcohols and their derivatives are valuable building blocks for organic synthesis.[1] An efficient approach to these compounds involves transition-metal-catalyzed allylic substitution with oxygen nucleophiles.[2,3] However, most of these processes are limited to the synthesis of allylic ethers. Although asymmetric allylic substitution with carboxylates seems to be a fascinating direct process, few reports are available,[4] probably because of the high reactivity of the resulting allylic esters with metal catalysts. Overman disclosed the Pd-catalyzed asymmetric synthesis of chiral allylic esters from (*Z*)-allylic trichloroacetimidates and carboxylic acid.[5] However, this system is not applicable to the *E* isomer, and the relatively large leaving group is unfavorable from the viewpoint of atom economy. Feringa and co-workers offered another route to allylic esters via Cu-catalyzed asymmetric allylic alkylation of 3-bromopropenyl esters,[6] but the use of a Grignard reagent led to some limitations.

As an extension of our study of asymmetric allylic substitution catalyzed by planar-chiral cyclopentadienyl ruthenium (Cp′Ru) complexes (**1**),[7,8] we recently reported the regio- and enantioselective reaction of monosubstituted allylic halides with phenol and indole.[9] When allylic acetate was used as the substrate in these reactions, the desired allylation products were furnished in low yields, and most of the starting allylic acetate was recovered. The low reactivity of Cp′Ru catalysts **1** with allylic esters prompted us to examine the allylic substitution using carboxylate as the nucleophile. We present herein the catalytic asymmetric allylic substitution with sodium carboxylates to give allylic esters with high regio- and enantioselectivities.

We started our investigation by optimizing the reaction conditions using cinnamyl derivatives and metal benzoates and found that the reaction of cinnamyl chloride (**2a**) with sodium benzoate (**3a**) in THF at 25 °C for 2 h in the presence of 3 mol % (*S*)-**1a** (R = ^{t}Bu) was suitable for the present system (eq 1).[10]



(1)

Although the methyl- and phenyl-substituted Cp′Ru complexes (*S*)-**1b** (R = Me) and (*S*)-**1c** (R = Ph) also catalyzed the reaction, no enantioselectivity was observed in those reactions.[9a,11] Furthermore, controlling the substrate ratio (**2a**/**3a**) was crucial to achieving high regioselectivity (Table 1). The reaction of **3a** with an equimolar amount of **2a** produced branched and linear allylic esters (**4a** and **5a**) in 97% yield in a 13:7 ratio with 89% ee for **4a** (entry 4). The reaction with 0.5 equiv of **2a** showed similar regioselectivity but lower enantioselectivity (entry 1). Extension of the reaction time decreased the regioselectivity of **4a**, and **5a** was obtained as the sole product in the reaction conducted for 7 h (entries 2 and 3), indicating that **4a** was converted into **5a** under these conditions.[12] Use of 1.3 equiv of **2a** slightly improved the regioselectivity to **4a**/**5a** = 18:2 (entry 5). The reaction with 2 equiv of **2a** selectively produced **4a** in 98% yield with 95% ee (entry 6), and no loss of regio- and enantioselectivity was observed when the reaction was conducted for 12 h (entry 7). These results suggest that the presence of excess **2a** prevents the isomerization of **4a** into **5a**. In the reaction of racemic **4a** with (*S*)-**1a** in the presence of **3a**, no significant kinetic resolution was observed.

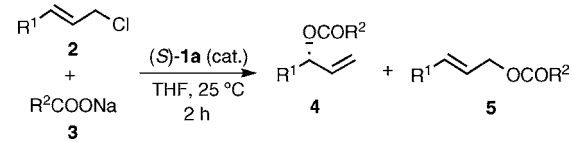
Table 1. Effect of the Ratio of Cinnamyl Chloride (**2a**) to Sodium Benzoate (**3a**)

entry	**2a**/**3a**	time (h)	yield (%)[a]	**4a**/**5a**[b]	ee (%)[c]
1	0.5	2	98	13:7	69
2	0.5	5	98	4:16	65
3	0.5	7	98	<1:20	−
4	1.0	2	97	13:7	89
5	1.3	2	98	18:2	82
6	2.0	2	98	>20:1	95
7	2.0	12	98	>20:1	94

[a] Isolated yield. [b] Determined from the ^{1}H NMR spectrum. [c] Determined by HPLC analysis using a column with a chiral stationary phase.

The scope of the present asymmetric allylic substitution with sodium carboxylate catalyzed by (*S*)-**1a** is summarized in Table 2.

Table 2. Reactions of Allylic Chlorides (**2**) with Sodium Carboxylates (**3**)[a]



entry	R^1, R^2	yield (%)[b]	regioselectivity[c]	ee (%)[d,e]
1	Ph (**2a**), Ph (**3a**)	98	**4a**/**5a** > 20:1	95 (*R*)
2	4-$CF_3C_6H_4$ (**2b**), Ph (**3a**)	98	**4b**/**5b** > 20:1	97 (*R*)
3	Me (**2c**), Ph (**3a**)	99	**4c**/**5c** > 20:1	82 (*S*)
4	^{n}Pr (**2d**), Ph (**3a**)	88	**4d**/**5d** > 20:1	81 (*S*)
5	Ph (**2a**), 2-PhC_6H_4 (**3b**)	99	**4e**/**5e** > 20:1	91 (*R*)
6	Ph (**2a**), 4-ClC_6H_4 (**3c**)	97	**4f**/**5f** > 20:1	88 (*R*)
7	Ph (**2a**), 4-MeC_6H_4 (**3d**)	80	**4g**/**5g** > 20:1	93 (*R*)
8	Ph (**2a**), Me (**3e**)	99	**4h**/**5h** > 20:1	92 (*R*)
9	Ph (**2a**), ^{t}Bu(**3f**)	97	**4i**/**5i** > 20:1	91 (*R*)
10	Ph (**2a**), Cy (**3g**)	99	**4j**/**5j** > 20:1	93 (*R*)

[a] Sodium carboxylates were generated in situ from carboxylic acids with Na_2CO_3, except for **3a**. [b] Isolated yield. [c] Determined from the ^{1}H NMR spectrum. [d] Determined by HPLC analysis. [e] Absolute configurations are indicated in parentheses.

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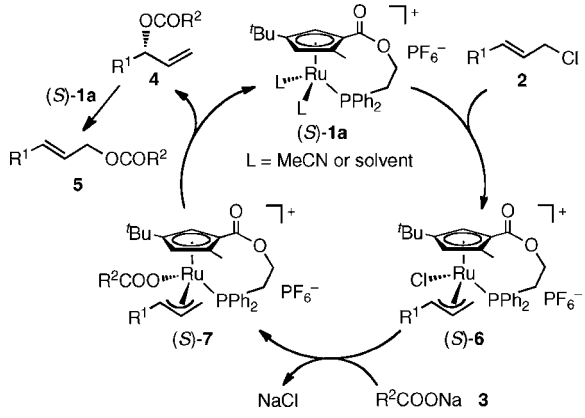
Not only aryl-substituted allylic chloride **2b** but also alkyl-substituted allylic chlorides **2c** and **2d** produced the corresponding allylic esters in good yields with high regio- and enantioselectivities (entries 2−4). Substituted sodium benzoates (**3b**−**d**) also produced optically active allylic esters selectively even when a bulky group occupied the ortho position of the aromatic ring (entries 5−7). The present reaction was successfully applied to aliphatic carboxylates (**3e**−**g**; entries 8−10). In all of the reactions, allylic esters **4a**−**j** were obtained in good yields with high enantioselectivities.

When (*Z*)-2-hexenyl chloride (*Z*)-**2d** was treated with **3a**, a 4:16 mixture of branched and linear products **4d** and **5d** was obtained in 63% yield with 27% ee, in sharp contrast to the result for the *E* isomer (*E*)-**2d** (Table 2, entry 4). This result clearly shows that the present reaction is applicable to only (*E*)-allylic chlorides and is complementary to the Pd-catalyzed system.[5]

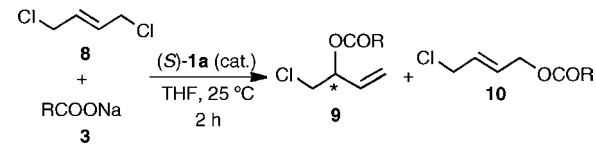
Scheme 1. Plausible Reaction Mechanism



A plausible reaction mechanism is illustrated in Scheme 1. High regio- and enantioselectivities as well as the absolute configuration of the product can be determined by diastereoselective formation of π-allyl intermediate (*S*)-**6** followed by an inside attack of the carboxylate via Ru carboxylate complex (*S*)-**7**.[9a] In the reaction using an excess amount of allylic chloride, the catalytic cycle would stop at the stage involving (*S*)-**6**, which does not react with branched allylic esters **4**. On the other hand, when the amount of allylic chloride in the system is insufficient, regenerated (*S*)-**1a** would slowly react with **4** to provide thermodynamically stable linear allylic ester **5**. This explanation is supported by the following experimental results: (i) No isomerization of **4a** into **5a** took place without the Ru catalyst. (ii) Although (*S*)-**6a** (R^1 = Ph) did not catalyze the isomerization of **4a**, the addition of **3a** led to the quantitative formation of **5a**. (iii) When the reaction of **4g** with **1a** was performed in the presence of **3a**, not only **5g** but also **5a** and **4a** were formed. Thus, we believe that the isomerization of **4** proceeds via oxidative addition to **1a**.

Finally, we examined the reaction of a difunctional allylic substrate (Table 3).[13] Treatment of (*E*)-1,4-dichloro-2-butene (**8**) with **3a** resulted in the formation of branched product **9a** in 90% yield with **9a**/**10a** > 20:1 and 88% ee for **9a** (entry 1). Substituted sodium benzoates **3b** and **3c** also reacted with **8** to give **9b** and **9c**, respectively, in good yields with high selectivities (entries 2 and 3). Because not only the ester group and the olefinic part but also the residual chloride can undergo further transformation, the resulting allylic esters **9** should be useful as a highly tunable chiral synthon.

Table 3. Reaction of 1,4-Dichloro-2-butene (**8**) with Sodium Carboxylates (**3**)[a]



entry	R	yield (%)[b]	regioselectivity[c]	ee (%)[d]
1	Ph (**3a**)	90	**9a**/**10a** > 20:1	88
2	2-PhC_6H_4 (**3b**)	90	**9b**/**10b** > 20:1	88
3	4-ClC_6H_4 (**3c**)	93	**9c**/**10c** > 20:1	78

[a] Sodium carboxylates were generated in situ from carboxylic acids with Na_2CO_3, except for **3a**. [b] Isolated yield. [c] Determined from the ^{1}H NMR spectrum. [d] Determined by HPLC analysis.

In conclusion, we have demonstrated the efficient synthesis of optically active allylic esters via asymmetric allylic substitution with carboxylates. We anticipate further development of asymmetric carbon−carbon and carbon−heteroatom bond-forming reactions using the characteristic reactivity of planar-chiral Cp′Ru catalysts.

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Supporting Information Available: Experimental procedures for the catalytic reactions and details of the optimization of reaction conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) See the Supporting Information.

(11) (*S*)-**1b**: 80% yield, **4a**/**5a** = 18:2, 2% ee. (*S*)-**1c**: 82% yield, **4a**/**5a** = 15:5, 2% ee.

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