Homogeneous Catalysis

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Cooperative Catalytic Reactions Using Organocatalysts and Transition-Metal Catalysts: Enantioselective Propargylic Alkylation of Propargylic Alcohols with Aldehydes**

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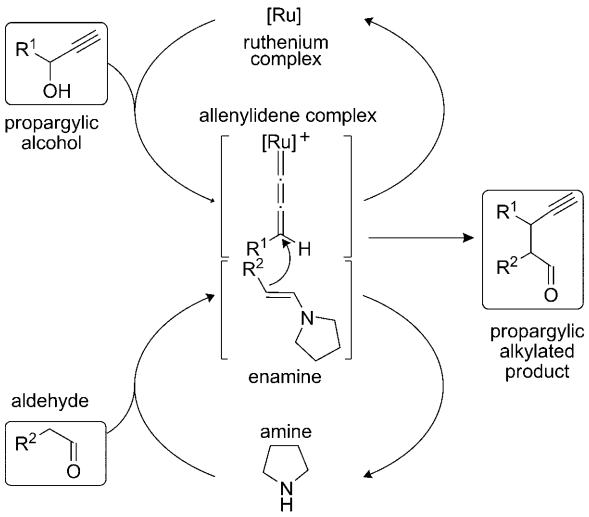
In the last decade, remarkable progress has been made toward the development of asymmetric reactions using organocatalysts under operationally simple and environmentally friendly reaction conditions.[1] Especially secondary amines derived from naturally available compounds worked as effective catalysts to promote asymmetric reactions of electrophiles with carbonyl compounds, such as aldol condensations and 1,4-conjugate additions, with high to excellent enantioselectivity.[2] In these reaction systems, enamines generated in situ from carbonyl compounds, such as aldehydes and ketones, and secondary amines worked as suitable carbon-centered nucleophiles. Nowadays, the methodology using organocatalysts realizes the diastereo- and enantioselective preparation of highly functionalized compounds such as (−)-Oseltamivir.[3,4]

We have previously found that the ruthenium-catalyzed propargylic alkylation of propargylic alcohols with acetone as a carbon-centered nucleophile gives the corresponding products with a high enantioselectivity (up to 82% *ee*).[5] Unfortunately, the use of an excess amount of simple ketones such as acetone was necessary to promote the propargylic alkylation. We have envisaged that the enamines generated in situ from aldehydes and secondary amines can be applied as carbon-centered nucleophiles for the asymmetric propargylic alkylation. As an extension of our study on enantioselective propargylic substitution reactions,[6] we have now found the ruthenium-catalyzed propargylic alkylation of propargylic alcohols with aldehydes in the presence of a catalytic amount of a secondary amine as an organocatalyst gives the corresponding products in high yields with an excellent enantioselectivity. In the present reaction system, both the transition-metal catalyst (ruthenium complex) and organocatalyst (secondary amine) activate the propargylic alcohol and aldehyde, respectively, thereby cooperatively promoting the enantioselective propargylic alkylation (Scheme 1). We believe that the method herein may provide a new type of dual catalytic reaction using both organocatalysts and transition-metal catalysts.[7,8] Preliminary results are described herein.



Scheme 1. Cooperative catalytic reactions using organocatalysts and transition-metal catalysts.

Treatment of 1-phenyl-2-propyn-1-ol (**1a**) with 3-phenylpropanal (**2a**) in the presence of catalytic amounts of (*S*)-α,α,-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethyl silyl ether (**3a**), methanethiolate-bridged diruthenium complex [{Cp*RuCl(μ_2-SMe)}$_2$] (Cp* = η^5-C_5Me_5; **4a**), and NH_4BF_4 in toluene at room temperature for 140 hours gave 2-benzyl-3-phenyl-4-pentynal (**5a**) exclusively (Scheme 2). After the reduction of **5a** using $NaBH_4$ at 0 °C for one hour, 2-benzyl-3-phenyl-4-pentyn-1-ol (**6a**) was isolated in 87% yield as a mixture of two diastereoisomers (*syn*-**6a**/*anti*-**6a** = 2.2:1) with 94% *ee* for *syn*-**6a** and 88% *ee* for *anti*-**6a**. Only two equivalents of **2a** relative to **1a** were used as a carbon-centered nucleophile; this is in sharp contrast to the previous reaction system for propargylic alkylation, wherein a large amount (i.e., as solvent) of the simple ketone was necessary to promote the propargylic alkylation.[5] The reaction proceeded more smoothly when three equivalents of **2a** relative to **1a** were used under the same reaction conditions. Other secondary amines such as (5*S*)-2,2,3-tri-

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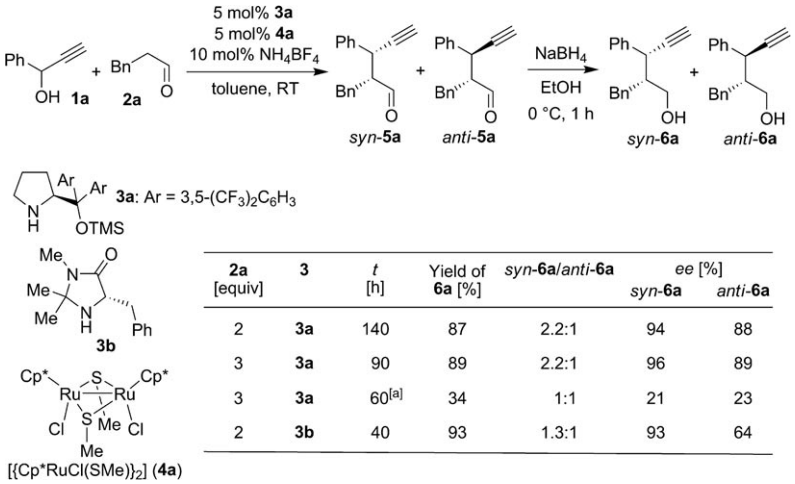


2a [equiv]	3	t [h]	Yield of 6a [%]	syn-6a/anti-6a	ee [%] syn-6a	ee [%] anti-6a
2	3a	140	87	2.2:1	94	88
3	3a	90	89	2.2:1	96	89
3	3a	60[a]	34	1:1	21	23
2	3b	40	93	1.3:1	93	64

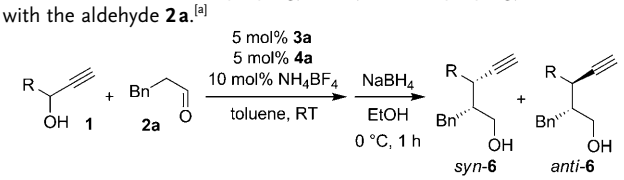
Scheme 2. Enantioselective propargylic alkylation of propargylic alcohols with aldehydes. [a] 1,2-Dichloroethane was used as a solvent in place of toluene. Bn = benzyl, TMS = trimethylsilyl.

methyl-5-benzyl-4-imidazolidinone (**3b**) worked effectively, but a substantially lower diastereo- and enantioselectivity were observed. Separately, we confirmed that the use of either **3a** or **4a** did not promote the propargylic alkylation. This result indicates that both **3a** and **4a** cooperatively work as catalysts to promote the catalytic reaction enantioselectively.

Next, alkylation of a variety of propargylic alcohols was carried out by using **3a** and **4a** as co-catalysts. Typical results are shown in Table 1. The introductuion of methyl, fluoro, chloro, or methoxy group at the *para* position of the benzene ring appended to the propargylic alcohols did not significantly affect the reactivity and enantioselectivity of the reaction (Table 1, entries 2–5). Interestingly, the introductuion of a methoxy group at the *ortho* position of the benzene ring appended to the propargylic alcohol substantially increased the enantioselectivity (Table 1, entry 6). Similarly, a high enantioselectivity was observed when naphthyl-2-propyn-1-ols (**1g** and **1f**) were used as substrates (Table 1, entries 7 and 8). No reaction occurred when 1-cyclohexyl-2-propyn-1-ol (**1i**) was used as a substrate under the same reaction conditions (Table 1, entry 9). These results indicate that the presence of an aryl moiety at the propargylic position of **1** is necessary to promote the catalytic reaction with a high enantioselectivity.

Propargylic alkylation with other aldehydes also proceeded smoothly to give the corresponding products with a high enantioselectivity. Typical results are shown in Table 2. The reaction of **1a** with 3-(4-chloro)phenylpropanal (**2b**) under the same reaction conditions gave the corresponding alkylated product with a similarly high enantioselectivity (Table 2, entry 1). When other aldehydes such as heptanal (**2c**), 3-cyclohexylpropanal (**2d**), and 6-chlorohexanal (**2e**) were used the corresponding products were obtained in high yields as a mixture of two diastereoisomers, each with high enantioselectivity (Table 2, entries 2–4). Reactions of 1-(2-methoxyphenyl)-2-propyn-1-ol (**1f**) with aldehydes also gave a similar result (Table 2, entries 5–8). These results indicate that a variety of aldehydes are available for the propargylic alkylation.

Table 1: Enantioselective propargylic alkylation of propargylic alcohols **1** with the aldehyde **2a**.[a]

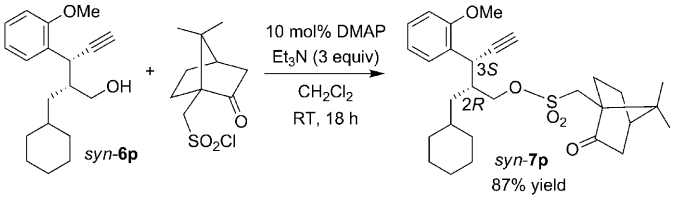


Entry	1	t [h]	Yield of 6[b] [%]	syn-6/anti-6[c]	ee [%][d] syn-6	ee [%][d] anti-6
1	R = Ph (**1a**)	90	89 (**6a**)	2.2:1	96	89
2	R = *p*-MeC$_6$H$_4$ (**1b**)	50	90 (**6b**)	2.5:1	97	86
3	R = *p*-FC$_6$H$_4$ (**1c**)	120	88 (**6c**)	2.1:1	95	87
4	R = *p*-ClC$_6$H$_4$ (**1d**)	120	85 (**6d**)	2.2:1	95	84
5	R = *p*-MeOC$_6$H$_4$ (**1e**)	120	85 (**6e**)	2.0:1	92	68
6	R = *o*-MeOC$_6$H$_4$ (**1f**)	40	93 (**6f**)	3.3:1	99	93
7	R = 1-naphthyl (**1g**)	90	91 (**6g**)	3.1:1	96	84
8	R = 2-naphthyl (**1h**)	120	87 (**6h**)	3.0:1	97	86
9	R = cyclohexyl (**1i**)	90	0 (**6i**)	–	–	–

[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.60 mmol), **3a** (0.01 mmol), **4a** (0.01 mmol), and NH_4BF_4 (0.02 mmol) were combined in toluene (6 mL) at room temperature. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis.

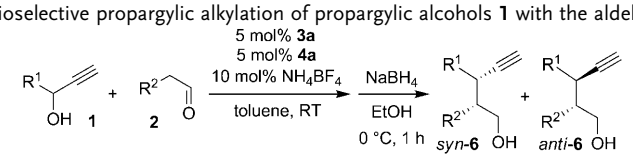
To obtain some information on the enantioselective propargylic alkylation, the stereochemistry of the product *syn*-**6p** was determined. The reaction of diastereochemically pure *syn*-**6p** with (1*S*)-10-camphorsulfonyl chloride and triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) was run at room temperature for 18 hours to give *syn*-**7p** in 87 % yield upon isolation (Scheme 3). After one recrystallization of *syn*-**7p**, the enantio- and diastereomerically pure *syn*-**7p** was isolated, and its absolute configuration was determined as [(2*R*,3*S*)] by X-ray analysis.[9]

We investigated the stoichiometric and catalytic reactions to gain insight into the reaction pathway. Treatment of a ruthenium–allenylidene complex **8g**[10] with three equivalents of **2a** and one equivalent of **3a** at room temperature for 45 hours and subsequent reduction with $NaBH_4$ gave **6g** in 49 % yield as a mixture of two diastereoisomers [*syn*-**6g**/*anti*-**6g** = 3.0:1; *syn*-**6g** (94 % *ee*), *anti*-**6g** (86 % *ee*)] as shown in Scheme 4. Furthermore, the reaction of **1g** with **2a** in the presence of catalytic amounts of **8g** and **3a** at room temper-



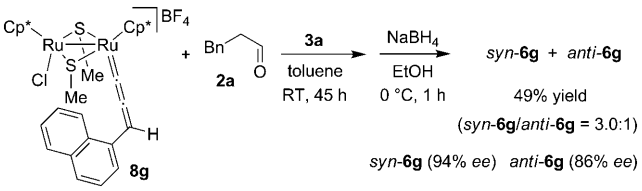
Scheme 3. The stereochemistry of the propargylic alkylated product.

Table 2: Enantioselective propargylic alkylation of propargylic alcohols **1** with the aldehydes **2**.[a]



Entry	1	2	t [h]	Yield of 6[b] [%]	syn-6/anti-6[c]	ee [%][d] syn-6	ee [%][d] anti-6
1	R^1 = Ph (**1a**)	R^2 = *p*-$ClC_6H_4CH_2$ (**2b**)	90	90 (**6j**)	2.2:1	96	87
2	R^1 = Ph (**1a**)	R^2 = $Me(CH_2)_4$ (**2c**)	90	91 (**6k**)	1.7:1	92	85
3	R^1 = Ph (**1a**)	R^2 = $CyCH_2$ (**2d**)[e]	90	81 (**6l**)	2.1:1	96	78
4	R^1 = Ph (**1a**)	R^2 = $Cl(CH_2)_4$ (**2e**)	120	80 (**6m**)	1.8:1	88	89
5	R^1 = *o*-$MeOC_6H_4$ (**1f**)	R^2 = *p*-$ClC_6H_4CH_2$ (**2b**)	40	85 (**6n**)	3.0:1	97	95
6	R^1 = *o*-$MeOC_6H_4$ (**1f**)	R^2 = $Me(CH_2)_4$ (**2c**)	40	90 (**6o**)	2.1:1	97	52
7	R^1 = *o*-$MeOC_6H_4$ (**1f**)	R^2 = $CyCH_2$ (**2d**)[e]	70	86 (**6p**)	2.1:1	98	92
8	R^1 = *o*-$MeOC_6H_4$ (**1f**)	R^2 = $Cl(CH_2)_4$ (**2e**)	60	91 (**6q**)	2.5:1	98	90

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.60 mmol), **3a** (0.01 mmol), **4a** (0.01 mmol), and NH_4BF_4 (0.02 mmol) were combined in toluene (6 mL) at room temperature. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis. [e] 3-Cyclohexylpropanal. Cy = cyclohexyl.

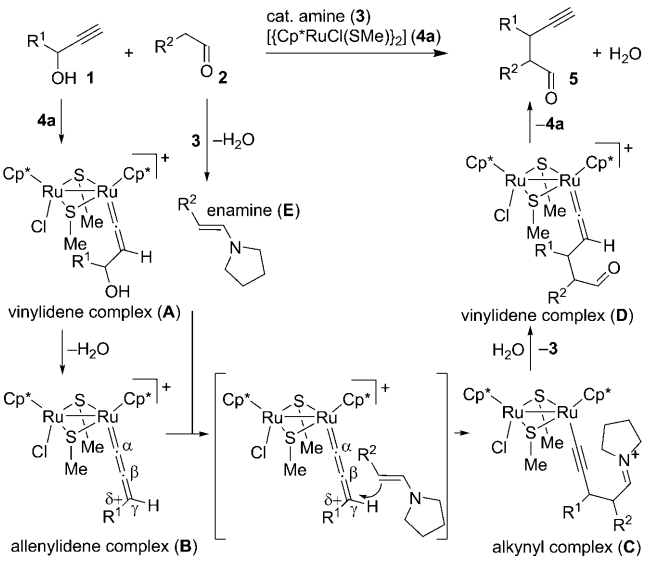


Scheme 4. The stoichiometric reaction of ruthenium–allenylidene complex with an aldehyde in the presence of an amine.

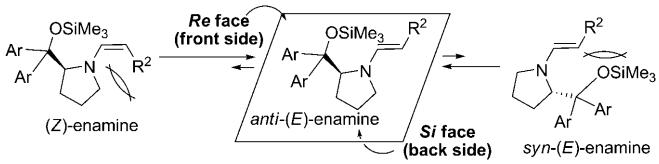
ature for 90 hours and subsequent $NaBH_4$ reduction afforded **6g** in 85% yield as a mixture of two diastereoisomers [*syn*-**6g**/*anti*-**6g** = 3.0:1; *syn*-**6g** (97% *ee*), *anti*-**6g** (85% *ee*)]. Independently, we confirmed that no reaction occurred when the reaction of the propargylic alcohol bearing an internal alkyne moiety was carried out under the same reaction conditions. These results clearly indicate that this propargylic alkylation proceeded with ruthenium–allenylidene complexes serving as the key reactive intermediates.[11]

A proposed reaction pathway is shown in Scheme 5. The initial step is the formation of the allenylidene complex **B** by the reaction of propargylic alcohol **1** with **4a** via the vinylidene complex **A**. Subsequent attack of the enamine **E**, generated in situ from aldehyde **2** and amine **3**, upon the γ-carbon atom of **B** results in the formation of the vinylidene complex **D** via the alkynyl complex **C**. Then, the alkylated product **5** is formed from **D** by ligand exchange with another propargylic alcohol **1**. As described in our previous reports,[10] we believe that the synergistic effect between two ruthenium atoms in the diruthenium complexes is also quite important to promote this catalytic reaction.

The *E* conformation of the enamine is energetically favored over its *Z* conformation, and the large aryl and silyl substituents at the α position of the pyrrolidine ring disfavored the *syn* form of enamine (Scheme 6).[12] To account for the highly enantioselective formation of both diastereoisomers (*syn*-**5** and *anti*-**5**), we propose transition states between the ruthenium–allenylidene complex and the enamine as shown in Scheme 7. The bulky substituents on the pyrrolidine ring efficiently shield the *Re* face of the favored *anti*-(*E*)-enamine (Scheme 6).[12] For the formation of *syn*-**5** (Scheme 7a), the *Si* face of enamine attacks the *Re* face of allenylidene complex leading to the carbon–carbon bond formation. In contrast, for the formation of *anti*-**5** (Scheme 7b), the *Si* face of enamine attacks the *Si* face of allenylidene complex for the carbon–carbon bond formation. The predominant formation of *syn*-**5** is a result of the steric repulsion between the phenyl group at the γ-carbon atom of the allenylidene

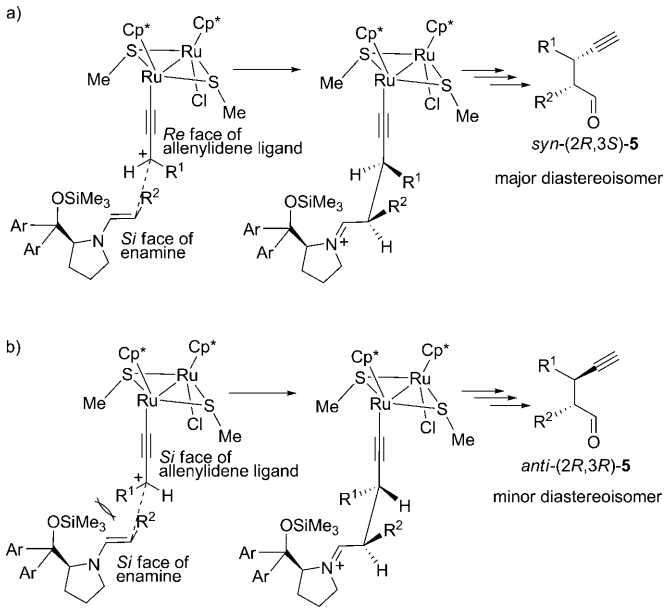


Scheme 5. Reaction pathway for the propargylic alkylation of propargylic alcohols with aldehydes.



Scheme 6. The conformation of enamines generated from amines and aldehydes.

ligand and the bulky substituents in the enamine. At present, we observed only the moderate diastereoselectivity of the alkylated products **5**, but this is the first successful example of the enantioselective propargylation of aldehydes with propargylic alcohols to give the corresponding chiral β-ethynyl aldehydes.[13]



Scheme 7. The high enantioselectivity of propargylic alkylated products. a) Path for the formation of the major diastereoisomer. b) Path for the formation of the minor diastereoisomer.

In summary, we have found the enantioselective propargylic alkylation of propargylic alcohols with aldehydes in the presence of a thiolate-bridged diruthenium complex and a secondary amine as the co-catalysts to give the corresponding propargylic alkylated products in excellent yields as a mixture of two diastereoisomers, each with high enantioselectivity (up to 99% *ee*). This catalytic reaction is considered to be a new type of enantioselective propargylic substitution reaction,[14] wherein the enamines generated in situ from aldehydes enantioselectively attack the ruthenium–allenylidene complexes. In the present reaction system, both the transition-metal catalyst (ruthenium complex) and organocatalyst (secondary amine) activate propargylic alcohols and aldehydes, respectively, and cooperatively work to promote the enantioselective propargylic alkylation. We believe that the finding described herein will open a new aspect of not only dual catalytic reactions using both organocatalysts and transition-metal catalysts, but also the enantioselective α-alkylation of aldehydes.[15,16] Additional work is currently in progress to apply this strategy to other reaction systems.

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