VIP Asymmetric Catalysis

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Ruthenium-Catalyzed Enantioselective Propargylation of Aromatic Compounds with Propargylic Alcohols via Allenylidene Intermediates**

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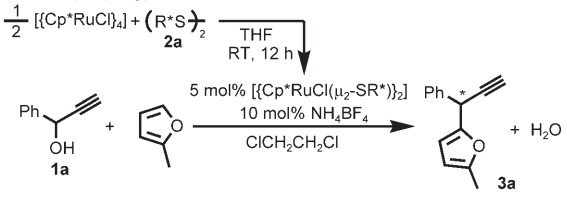
The Friedel–Crafts reaction is one of the most reliable and powerful C–C bond forming tools in organic synthesis.[1] Recently, the development of an asymmetric Friedel–Crafts alkylation of aromatic compounds has received a great deal of attention. This reaction introduces chiral centers at the benzylic position of aromatic compounds,[2] and a variety of Lewis acids and organocatalysts are available to promote the reaction.[2,3] However, the successful examples of asymmetric Friedel–Crafts alkylation are still limited to reactions with three types of electrophiles such as epoxides, carbonyl compounds, activated alkenes, and their analogues.[2,3]

We have recently disclosed the novel catalytic activity[4] of chalcogenolate-bridged diruthenium complexes[5] such as $[\{Cp^*RuCl(\mu_2\text{-}YR)\}_2]$ ($Cp^* = \eta^5\text{-}C_5Me_5$; Y = S, Se, Te; R = Me, *n*Pr, *i*Pr) and $[Cp^*RuCl(\mu_2\text{-}YR)_2RuCp^*(OH_2)]OTf$ (Tf = trifluoromethanesulfonyl) for many organic transformations via ruthenium–allenylidene intermediates.[6] One of these transformations is the propargylation of aromatic compounds with propargylic alcohols.[7–9] We envisaged the development of a catalytic enantioselective propargylation of aromatic compounds as a new type of asymmetric Friedel–Crafts alkylation of aromatic compounds by taking account of our previous development of the ruthenium-catalyzed enantioselective propargylic substitution reactions of propargylic alcohols with acetone (up to 82% *ee*).[10] We report here a successful example of an asymmetric Friedel–Crafts alkylation by using propargylic alcohols as electrophiles.

Treatment of 1-phenyl-2-propyn-1-ol (**1a**) with 2-methylfuran (10 equiv) in $ClCH_2CH_2Cl$ in the presence of a catalytic amount of a chiral thiolate-bridged diruthenium complex **2a**, (prepared in situ from the tetranuclear ruthenium(II) complex $[Cp^*RuCl]_4$ and a chiral disulfide[10b] in THF at room temperature for 12 h), and NH_4BF_4 at 60 °C for 3 h afforded 2-methyl-5-(1-phenyl-2-propynyl)furan (**3a**), which was isolated in 75% yield with 77% *ee* (Table 1, entry 1). A decrease in yield of **3a** was observed at slightly higher temperatures, such as 80 °C (Table 1, entry 2). The formation of the corresponding oligomers was observed as side products in all cases, especially when the reaction was carried out at high temperature. On the other hand, the reaction at lower temperatures, such as 40 °C and at room temperature, proceeded similarly with a slight decrease in the yield of **3a** (Table 1, entries 3 and 4). Even without the use of excess 2-methylfuran, the reaction proceeded, but the yield of **3a** decreased (Table 1, entries 5 and 6). In all cases, the enantioselectivity was not greatly affected.

Table 1: Ruthenium-catalyzed enantioselective propargylation of 2-methylfuran with propargylic alcohol **1a**.[a]



Entry	Equiv of furan[b]	*T* [°C]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	10	60	3	75	77
2	10	80	2	37	79
3	10	40	6	63	75
4	10	RT	9	66	72
5	5	60	3	61	81
6	3	60	6	47	82

[a] All reactions of **1a** (0.20 mmol) with 2-methylfuran were carried out in the presence of a Ru complex (0.010 mmol, generated in situ from $[\{Cp^*RuCl\}_4]$ and **2a**) and NH_4BF_4 (0.020 mmol) in $ClCH_2CH_2Cl$ (5 mL). [b] Equivalent of furan with respect to **1a**. [c] Yield of isolated **3a**. [d] Determined by HPLC (see the Supporting Information for details).

A variety of optically active disulfides were investigated as chiral ligands in the reaction of **1a** with 2-methylfuran as shown in Scheme 1. The presence of three aryl groups in the 2-, 3-, and 5-positions of the benzene ring of the chiral disulfide was necessary to achieve the high enantioselectivity. In fact, the use of chiral disulfides (**2b**–**2f**) with one or two phenyl groups on the benzene ring apparently decreased the enantioselectivity. A similar tendency has been observed in the catalytic propargylation of acetone with propargylic alcohols.[10b]

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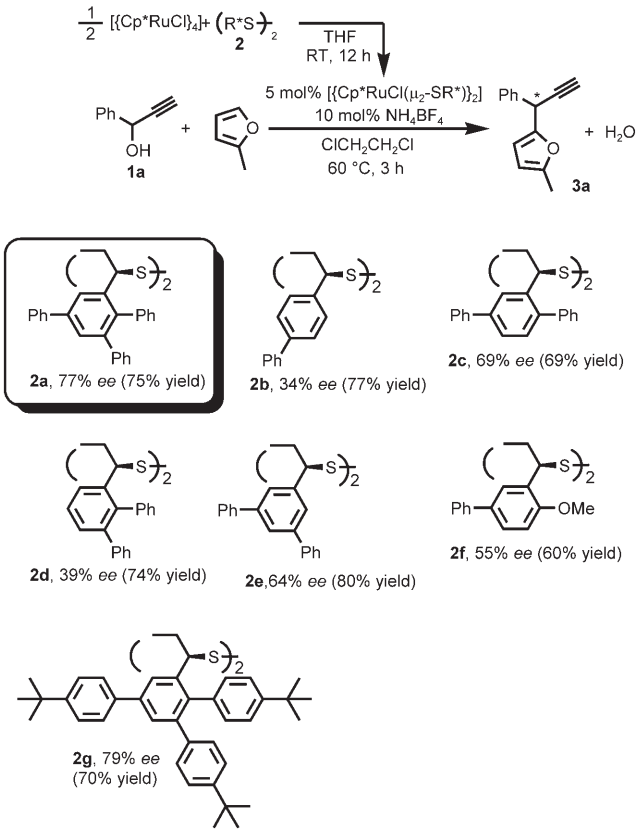
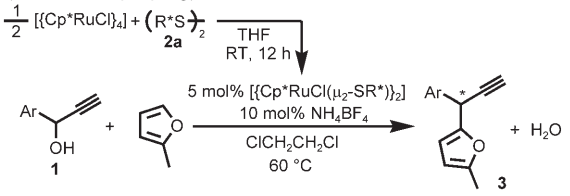


Scheme 1. Reactions of 1-phenyl-2-propyn-1-ol (**1a**) with 2-methylfuran in the presence of chiral thiolate-bridged diruthenium complexes, generated in situ from [{Cp*RuCl}$_4$] and chiral disulfides **2**.

Next, the catalytic propargylation of 2-methylfuran with other propargylic alcohols was investigated by using **2a** as a chiral ligand. Typical results are shown in Table 2. The presence of a substituent in the benzene ring of the propargylic alcohols greatly affected the enantioselectivity. The introduction of a methyl or methoxy moiety in the *para* or *ortho* position of the benzene ring of **1a** slightly improved the enantioselectivity (Table 2, entries 2–4), while introduction of a chlorine moiety decreased the enantioselectivity (Table 2, entry 5). The introduction of one or two phenyl groups on the benzene ring of the propargylic alcohols, as well as the use of 1-naphthyl-2-propyn-1-ols, increased the enantioselectivity (Table 2, entries 6–10). For example, the reaction with a propargylic alcohol with a phenyl group on the *ortho* position of the benzene ring gave the highest enantioselectivity (94% *ee*; Table 2, entry 6). The use of 2-ethylfuran (10 equiv) in place of 2-methylfuran gave the corresponding propargylated furan **3k** in 59% yield and 79% *ee* (Table 2, entry 11). After one recrystallization, an optically pure propargylated aromatic compound was obtained in some cases.

As reported from our previous studies,[7] *N*,*N*-dimethylaniline is less reactive than 2-alkylfuran in the propargylation of aromatic compounds with propargylic alcohols catalyzed by the methanethiolate-bridged diruthenium complex. Although a large excess of *N*,*N*-dimethylaniline was necessary to fully convert the starting propargylic alcohols into product

Table 2: Ruthenium-catalyzed enantioselective propargylation of 2-methylfuran with propargylic alcohols **1**.[a]



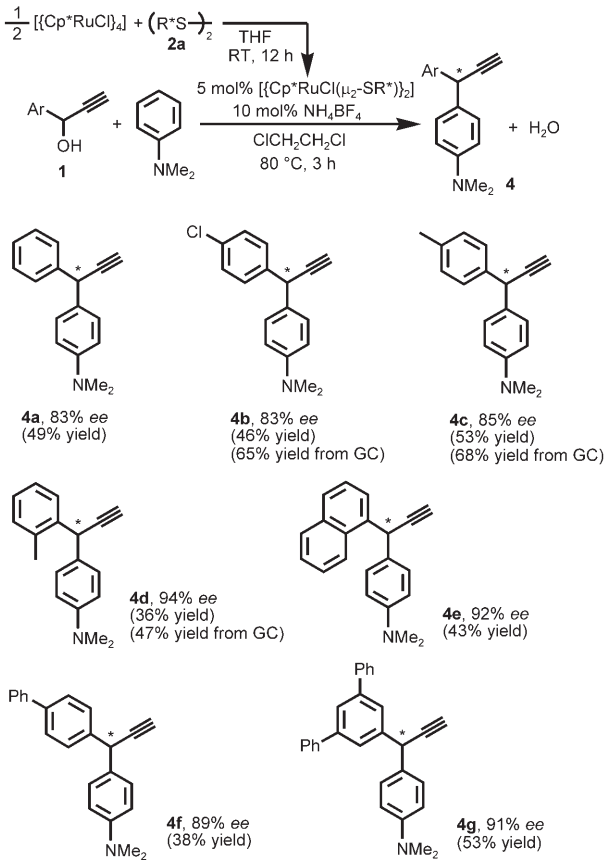
Entry	Ar	*t* [h]	Yield of **3** [%][b]	*ee* of **3** [%][c]
1	**1a**, Ph	3	**3a**, 75	77
2	**1b**, *p*-MeC_6H_4	3	**3b**, 67	82
3	**1c**, *o*-MeC_6H_4	3	**3c**, 44	86
4	**1d**, *p*-MeOC_6H_4	6	**3d**, 40	81
5	**1e**, *p*-ClC_6H_4	3	**3e**, 63	68
6	**1f**, *o*-PhC_6H_4	6	**3f**, 52	94
7	**1g**, *p*-PhC_6H_4	3	**3g**, 77	89
8	**1h**, 3,5-$Ph_2C_6H_3$	3	**3h**, 83	76
9	**1i**, 1-napthyl	6	**3i**, 59	86
10	**1j**, 2-naphthyl	3	**3j**, 67	83
11[d]	**1a**, Ph	2	**3k**, 59	79

[a] All reactions of **1** (0.20 mmol) with 2-methylfuran (2.00 mmol) were carried out in the presence of a Ru complex (0.010 mmol, generated in situ from [{Cp*RuCl}$_4$] and **2a**) and NH_4BF_4 (0.020 mmol) in $ClCH_2CH_2Cl$ (5 mL) at 60 °C. [b] Yield of isolated product. [c] Determined by HPLC (see the Supporting Information for details). [d] 2-Ethylfuran (2.00 mmol; 10 equiv) was used in place of 2-methylfuran at 80 °C.

under the same reaction conditions, the reactions of propargylic alcohols **1** with *N*,*N*-dimethylaniline (10 equiv) gave the corresponding *N*,*N*-dimethyl-4-(1-aryl-2-propynyl)anilines **4** in high enantioselectivity (Scheme 2). In all cases, only moderate yields of the isolated products were obtained because of formation of the corresponding oligomers as side-products and/or loss of the product on purification.

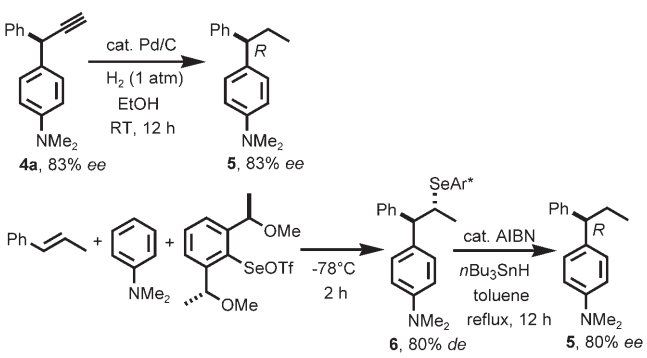
To obtain more information about the enantioselective propargylation of aromatic compounds, the stereochemistry of the propargylated product **4a** was determined. Hydrogenation of the propargylated product **4a** in the presence of a catalytic amount of Pd/C under one atmosphere of H_2 at room temperature for 12 h gave 1-[4-(*N*,*N*-dimethylamino)phenyl]-1-phenylpropane (**5**) in quantitative yield (Scheme 3). The absolute configuration of **5** thus obtained was in accord with (*R*)-**5** obtained by the reported method[11] (Scheme 3), which shows that the original propargylated product **4a** has an *R* absolute configuration. These results support our previously proposed reaction pathway for the propargylation of acetone,[10] in which the π–π interaction of phenyl rings between the chiral ligand and allenylidene moieties plays an important role in the achievement of high enantioselectivity (Figure 1). Here, *N*,*N*-dimethylaniline should attack the alkynyl complex **7′** with a cationic γ-carbon atom, which is a resonance structure of the allenylidene complex (**7**) prepared from a propargylic alcohol and the diruthenium complex, from the *Si* face (Scheme 4).[4,7] Thus, this asymmetric Friedel–Crafts alkylation reaction offers a rare example of a stereoselective reaction via carbocations as reactive intermediates.

Finally, we carried out the reactions of optically active propargylic alcohols (*R*)- and (*S*)-**1a** with 2-methylfuran using



Scheme 2. Reactions of 1-aryl-2-propyn-1-ols **1** with *N*,*N*-dimethylaniline in the presence of chiral thiolate-bridged diruthenium complex, generated in situ from [{Cp*RuCl}$_4$] and chiral disulfide **2a**. All yields are of the isolated product.

2a as a chiral ligand. In both cases, the propargylated product **3a** was obtained in almost the same yield with a similar enantioselectivity and the same absolute configuration (Scheme 5). As expected, no optical activity was observed in **1a** recovered from the reaction carried out under the conditions shown in Scheme 5a. Thus, there is no substantial reactivity difference between (*R*)-**1a** and (*S*)-**1a**, which indicates that the isomerization occurs easily at the chiral allenylidene intermediates before the attack of 2-methylfuran.



Scheme 3. Determination of the absolute configuration of the propargylated aromatic compound **4a**. AIBN = 2,2′-azobisisobutyronitrile.

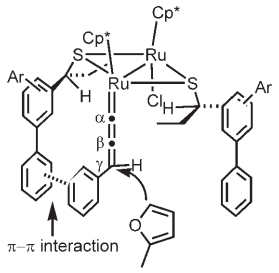
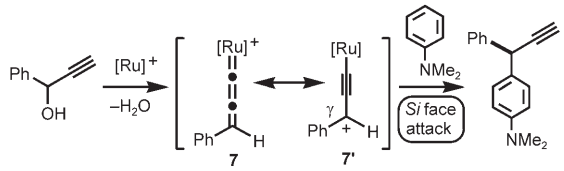
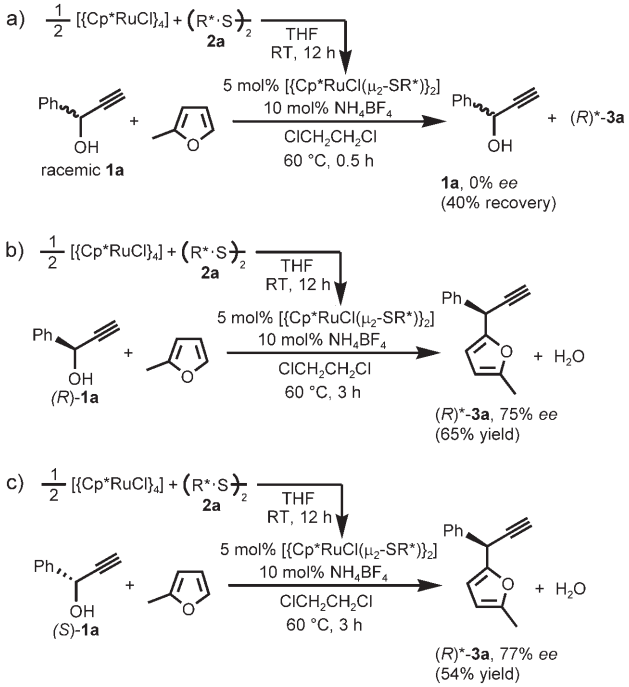


Figure 1. Transition state of the reaction of an allenylidene intermediate with 2-methylfuran.

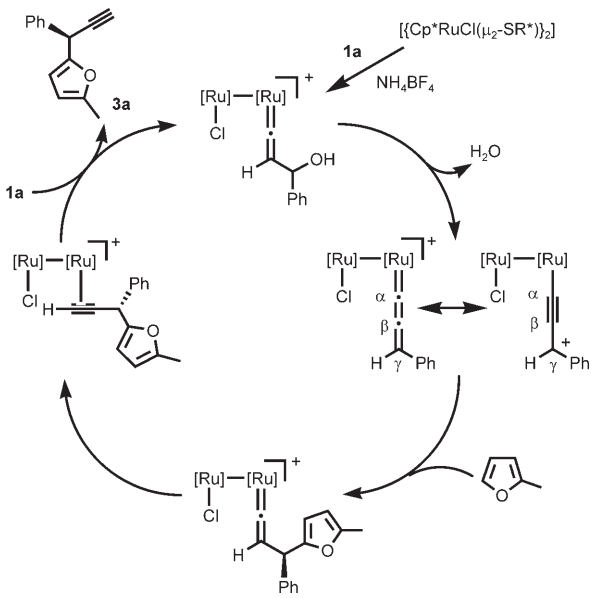


Scheme 4. Attack of the aromatic compound on the *Si* face at the Cγ atom of the allenylidene complex.

By considering the above experimental results, a reaction pathway of this enantioselective propargylation of aromatic compounds is proposed in Scheme 6 for the propargylation of 2-methylfuran as a representative example. Initially, a vinylidene complex is formed in the reaction of a chiral diruthenium complex with **1a** in the presence of NH_4BF_4. Dehydration of the vinylidene complex leads to an allenylidene complex, in which the racemization of the allenylidene moiety rapidly occurs via the corresponding alkynyl complex when an optically active propargylic alcohol is used as a substrate.



Scheme 5. Reactions of optically active 1-phenyl-2-propyn-1-ols (**1a**) with 2-methylfuran in the presence of chiral thiolate-bridged diruthenium complex, generated in situ from [{Cp*RuCl}$_4$] and **2a**.



Scheme 6. Proposed reaction pathway.

Subsequent nucleophilic attack of 2-methylfuran on the C_γ atom of the allenylidene ligand results in the formation of another vinylidene complex. This vinylidene complex is then transformed into a η^2-coordinated alkyne complex, which liberates the propargylated furan **3a** by reaction with a propargylic alcohol **1a,** and regenerates the starting complex. We proposed a similar catalytic cycle for the sulfur-bridged diruthenium-catalyzed propargylic substitution reactions of propargylic alcohols with nucleophiles in our previous studies, along with a DFT calculation.[4a,c] It has already been proposed that the synergistic effect in the diruthenium complex is quite important for the promotion of the catalytic reaction.[4a,c]

In summary, we have found that the ruthenium-catalyzed enantioselective propargylation of aromatic compounds such as 2-alkylfurans and *N*,*N*-dimethylaniline with propargylic alcohols affords the corresponding propargylated aromatic compounds selectively in good yields with high enantioselectivity (up to 94% *ee*). This is the first example of asymmetric propargylation of aromatic compounds. The synthetic method described in this article provides a novel protocol for the catalytic asymmetric Friedel–Crafts alkylation of aromatic compounds, by using propargylic alcohols as a new type of electrophiles, because, to date, the selective propargylation of aromatic compounds is known to be quite difficult.[12]

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