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Ruthenium-Catalyzed Propargylation of Aromatic Compounds with Propargylic Alcohols

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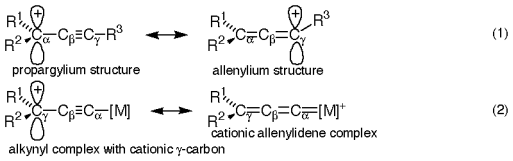
The chemical features of propargyl cations as reactive intermediates as well as persistent species have been one of the interesting subjects in organic and physical chemistry.[1,2] The electronic ground state of propargyl cations is delineated by propargylium and allenylium resonance structures where the positive charge distributes over sp^2- and sp-hybridized carbon atoms (eq 1). Both the electronic and the structural properties of propargyl cations have been extensively investigated by Olah and co-workers, who concluded that propargyl cations can be considered as alkynyl-substituted carbenium ions, and their reactivity is dependent on the kind of substituents at the α- and the γ-positions,[2] affording either propargyl or allenyl products by nucleophilic trapping of propargyl cations.[3]



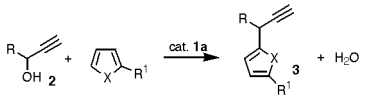
(1)

(2)

The discovery of transition metal stabilization of reactive intermediates not only stimulated a theoretical interest remarkably but also gave a tremendous impact for the application of such species in organic synthesis.[4] Introduction of a transition metal at the γ-position of a propargyl cation without complexation of the triple bond can realize the stabilization and conformational fixation of the propargyl cation (eq 2). It has been reported that the electrophilic aromatic substitution reaction of a *free* propargyl cation gave some polymers as predominant products together with a small amount of a mixture of propargylated and allenylated aromatic compounds.[5] In contrast, the positive charge at the γ-position in the metal complex may promote a desirable electrophilic aromatic substitution reaction. After the detailed investigation, we have actually succeeded in the selective propargylation of aromatic compounds with propargylic alcohols using a diruthenium complex as a catalyst. In this catalytic reaction, the stabilized propargyl cation assisted by the ruthenium complex directly reacted with aromatic compounds. Preliminary results of this novel reaction are described here.

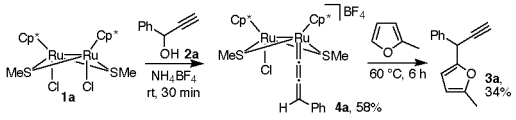
As shown in eq 2, the allenylidene complex exists as another resonance structure of the alkynyl complex with a positive charge at the γ-position. At first, the stoichiometric reaction of the allenylidene complex with aromatic compound was investigated. Heating of the allenylidene complex $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*(C{=}C{=}CHPh)]BF_4$ ($Cp^* = \eta^5\text{-}C_5Me_5$; **4a**) with 10 equiv of 2-methylfuran in $ClCH_2CH_2Cl$ at 60 °C for 6 h led to the formation of 2-methyl-5-(1-phenyl-2-propynyl)furan (**3a**) in 34% yield as a sole product (eq 3). This unprecedented result indicated that an electrophilic aromatic substitution reaction occurred at the γ-carbon of the allenylidene ligand. Reactions of allenylidene complexes with various heteroatom- and carbon-centered nucleophiles at the α- and the γ-carbons have already been reported,[6] but there is no example on the direct reaction of allenylidene ligand with aromatic compounds until now.[7]

Table 1. Propargylation of Heterocyclic Compounds with Propargylic Alcohols[a]



run	propargylic alcohol	heterocyclic compound	yield of product, %[b]
1	**2a**, R = Ph	X = O, R^1 = Me	**3a**, 85 (>95)[c]
2	**2b**, R = *p*-MeC_6H_4	X = O, R^1 = Me	**3b**, 83
3	**2c**, R = *p*-FC_6H_4	X = O, R^1 = Me	**3c**, 70
4	**2d**, R = 2,4,6-$Me_3C_6H_2$	X = O, R^1 = Me	**3d**, 77
5	**2e**, R = 1-naphthyl	X = O, R^1 = Me	**3e**, 84
6	**2a**, R = Ph	X = O, R^1 = Et	**3f**, 75
7	**2a**, R = Ph	X = O, R^1 = OMe	**3g**, 51
8	**2f**, R = $Ph_2C{=}CH-$	X = O, R^1 = Me	**3h**, 59
9	**2g**, R = cyclohexyl	X = O, R^1 = Me	**3i**, 61
10	**2a**, R = Ph	X = O, R^1 = H	**3j**, 68
11	**2a**, R = Ph	X = NH, R^1 = H	**3k**, 67
12	**2a**, R = Ph	X = NMe, R^1 = H	**3l**, 94
13	**2a**, R = Ph	X = S, R^1 = Me	**3m**, 86

[a] All of the reactions of **2** (0.60 mmol) with heterocyclic compound (6.00 mmol) were carried out in the presence of **1a** (0.03 mmol) and NH_4BF_4 (0.06 mmol) in $ClCH_2CH_2Cl$ (15−30 mL) at 60 °C for 1 h. [b] Isolated yield. [c] GLC yield.



(3)

The result of the above stoichiometric reaction prompted us to investigate the catalytic reaction of aromatic compounds with propargylic alcohols in the presence of thiolate-bridged diruthenium complex[8] $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*Cl]$ (**1a**), because the allenylidene complex **4a** can be readily prepared from the reaction of **1a** with 1 equiv of 1-phenyl-2-propyn-1-ol (**2a**) in the presence of NH_4BF_4.[8b] Treatment of **2a** with 2-methylfuran in $ClCH_2CH_2Cl$ in the presence of **1a** (5 mol %) and NH_4BF_4 (10 mol %) at 60 °C for 1 h afforded **3a** in quantitative yield. Neither other products nor regioisomers of **3a** were observed by GLC and ^1H NMR. The reaction proceeded smoothly even at room temperature for 1 h, **3a** being obtained in 90% yield. Unfortunately, other conventional mono- and diruthenium complexes did not work at all.[9] At present, we consider that one Ru moiety may work as a suitable ligand to another Ru atom in **1a**.

Reactions of other furans with 1-aryl, 1-alkenyl, and 1-alkyl substituted propargylic alcohols in the presence of **1a** proceeded

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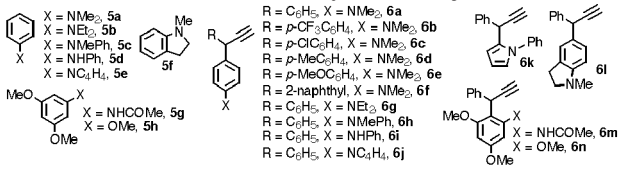
Table 2. Propargylation of Aromatic Compounds with Propargylic Alcohols[a]

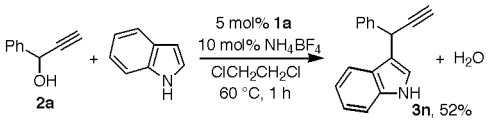
run	propargylic alcohol	aromatic compound	reaction time (h)	yield of product, %[b]
1	**2a**, R = Ph	**5a**	2	**6a**, 50
2	**2h**, R = *p*-$CF_3C_6H_4$	**5a**	2	**6b**, 58
3	**2i**, R = *p*-ClC_6H_4	**5a**	2	**6c**, 53
4	**2b**, R = *p*-MeC_6H_4	**5a**	5	**6d**, 23
5	**2j**, R = *p*-$MeOC_6H_4$	**5a**	3	**6e**, —[c]
6	**2k**, R = 2-naphthyl	**5a**	6	**6f**, 30
7	**2a**, R = Ph	**5b**	5	**6g**, 23
8	**2a**, R = Ph	**5c**	3	**6h**, 49
9	**2a**, R = Ph	**5d**	2	**6i**, 63
10	**2a**, R = Ph	**5e**	3	**6j** + **6k**, 60[d]
11	**2a**, R = Ph	**5f**	1	**6l**, 48
12	**2a**, R = Ph	**5g**	3	**6m**, 52
13	**2a**, R = Ph	**5h**	2	**6n**, 38

[a] All of the reactions of **2** (0.60 mmol) with aromatic compound (6.00 mmol) were carried out in the presence of **1a** (0.03 mmol) and NH_4BF_4 (0.06 mmol) in $ClCH_2CH_2Cl$ (15−30 mL) at 60 °C for 1 h. [b] Isolated yield. [c] A small amount of **6e** was detected by GC-MS. [d] **6j**:**6k** = 1:5.



smoothly to give the corresponding propargylated furans (**3**) in high yields with a complete regioselectivity. A slightly lower yield of 2-(1-phenyl-2-propynyl)furan (**3j**) was obtained when furan was used as a substrate (Table 1, run 10). Pyrrole, *N*-methylpyrrole, and thiophene can be propargylated with **2a** (Table 1, runs 11−13). In all cases, propargylation occurred selectively at the α-position of heterocyclic rings, and the reaction of indole with **2a** afforded the *β*-propargylated indole (**3n**) in 52% yield with a complete selectivity (Scheme 1). These results accord exactly with the regioselectivity of electrophilic substitution reactions of heterocyclic compounds.[10]

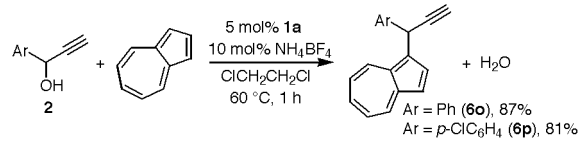
Scheme 1



N,*N*-Dimethylaniline (**5a**) reacted with several 1-aryl-2-propyn-1-ol **2** at 60 °C for 2−6 h to give the corresponding *N*,*N*-dimethyl-4-(1-aryl-2-propynyl)anilines (**6a**−**6f**) in good yields with a complete regioselectivity (Table 2). In this case, the aryl groups in **2** were found to have a strong influence on catalytic activity. The introduction of an electron-withdrawing group such as *p*-CF_3 and *p*-Cl increased the product yield slightly, while the introduction of an electron-releasing group such as *p*-Me and *p*-MeO decreased it (Table 2, runs 1−5). It is worth noting that electrophilic substitution reactions occurred exclusively at the *para*-position of anilines. These results support a reaction pathway via an electrophilic attack of the cationic *γ*-carbon in the alkynyl complex, which is considered to be a resonance structure of the allenylidene complex (vide supra). The reactions of **2a** with other aniline derivatives proceeded to give the corresponding propargylated anilines in moderate to good yields. A mixture of **6j** and **6k** was obtained in a ratio of 1 to 5 by the reaction of **2a** with *N*-phenylpyrrole (**5e**) (Table 2, run 10).

The reactions of 3,5-dimethoxyacetanilide (**5g**) and 1,3,5-trimethoxybenzene (**5h**) with **2a** proceeded smoothly and selectively to afford the corresponding propargylated aromatic compounds (**6m** and **6n**[11]) in moderate yields (Table 2, runs 12 and 13). In contrast, no propargylation occurred when acetanilide, 1,3-dimethoxybenzene, 1,3,5-trimethylbenzene, *p*-xylene, and toluene were used as aromatic compounds.[9] Thus, this catalytic propargylation proceeded only when electron-rich arenes[12] were used. Interestingly, the formation of 1-propargylated azulenes (**6o** and **6p**) was observed in the reactions of propargylic alcohols with azulene (Scheme 2).

Scheme 2



In summary, we have found a novel ruthenium-catalyzed propargylation of aromatic compounds with propargylic alcohols to afford the corresponding propargylated aromatic products in good yields with a complete regioselectivity. The Nicholas reaction has been known to be effective for propargylation of aromatic compounds by using a *stoichiometric* amount of $Co_2(CO)_8$, where several steps are necessary to obtain propargylated products from propargylic alcohols via cationic propargyl complexes $[(propargyl)Co_2(CO)_6]^+$.[13] Further investigations involving the elucidation of the detailed reaction mechanism[14] are currently in progress.

Supporting Information Available: Experimental procedures and spectral data for all of the new compounds (PDF), and crystallographic data for **6n** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) At the present stage, we cannot exclude the possibility that the reaction proceeded via a charge-transfer mechanism including radical cation intermediates.

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