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Rhodium(III)-catalyzed sp^2 C–H bond addition to CF_3-substituted unsaturated ketones†

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Rhodium(III)-catalyzed conjugate addition of aromatic and olefinic C–H bonds to CF_3-substituted unsaturated ketones was efficiently achieved. Both arene and olefin substrates bearing a chelate assisted-directing group were coupled with a variety of β-trifluoromethyl-α,β-unsaturated ketones with excellent atom-economy, high yields, and broad substrate scopes.

The introduction of a trifluoromethyl moiety to an organic molecule dramatically modifies its biological activities and physical properties such as solubility, lipophilicity, and metabolic stability. Trifluoromethylated compounds have recently received great attention in their application to pharmaceutical, agricultural, and material sciences.[1] In general, two synthetic strategies can be employed for the incorporation of a CF_3 group: (i) direct trifluoromethylation by means of trifluoromethylating reagents such as Ruppert–Prakash reagent, Togni reagent, and Umemoto's reagent;[2] and (ii) the reactions with a CF_3-containing molecule without cleaving the X–CF_3 bond.[3] Although the direct method has been well developed, the latter has been proved to be an important supplement in this area. CF_3-substituted unsaturated ketones are readily available for diverse organic transformations. In this aspect, β-trifluoromethyl-α,β-unsaturated ketones have been known for Michael additions,[4] Diels–Alder reactions,[5] Friedel–Crafts reactions,[6] metal-mediated conjugate additions,[7] and other transformations[8] to indirectly access CF_3-containing compounds.

Transition-metal-catalyzed C–H activation has recently emerged as a promising method in organic synthesis without prefunctionalization of substrates.[9] Rhodium compounds are one among the class of the most important catalysts in this type of transformation due to their high reactivity, applicability under mild conditions, and high tolerance of functional groups in the substrates.[10] Rhodium(III)-catalyzed direct C–H addition to unsaturated compounds has attracted much attention for the construction of C–C bonds because such a process features step- and atom-economy.[11] Rh(III) complex catalysts have been reported to promote C–H bond addition to C≡C,[12] C=C,[13] C=O,[14] C=N,[15] and other multiple bonds.[16] Rhodium-catalyzed conjugate addition of arylboronic acids and arylstannanes to β-trifluoromethyl-α,β-unsaturated ketones was also documented.[17] Thus, we reasonably envisioned transition-metal-catalyzed C–H addition to CF_3-substituted unsaturated ketones. Herein, we report the efficient Rh(III)-catalyzed sp^2 C–H addition to β-trifluoromethyl-α,β-unsaturated ketones. In our case, both arenes and olefins with a chelate assisted-directing group are compatible in the reactions to bring in a CF_3 group.

Initially, the reaction of 2-phenylpyridine (**1a**) with (*E*)-4,4,4-trifluoro-1-*p*-tolylbut-2-en-1-one (**2a**) in a 1.5 : 1 molar ratio was conducted to screen the reaction conditions (see the ESI,† Table S1). In the presence of 2.5 mol% of $[Cp^*RhCl_2]_2$ and 10 mol% of $AgSbF_6$ as the catalyst in 1,2-dichloroethane (DCE) at 80 °C, the desired product **3a** was formed in 86% yield within 20 h. Among the screened solvents, toluene promoted the reaction most efficiently, affording **3a** in 96% isolated yield. Lowering the reaction temperature to 60 °C lessened the yield to 94%. Both $Rh(COD)BF_4$ and $[Ru(p\text{-cymene})Cl_2]_2$ were not effective catalysts for the reaction. With a lower catalyst loading, that is, 1.25 mol% $[Cp^*RhCl_2]_2$ and 5 mol% of $AgSbF_6$, the reaction efficiency was remarkably deteriorated to give **3a** in 10% yield. The variation in the molar ratio of **1a** to **2a** to 1.2 : 1 led to **3a** in a relatively low yield (88%).

Under the optimal conditions, the scope of β-trifluoromethyl-α,β-unsaturated ketones (**2**) was explored in the reactions with 2-phenylpyridine (**1a**) (Table 1). Substrates **2** containing a non-substituted phenyl group or an aryl group substituted by an electron-donating or an electron-withdrawing group, such as methyl, methoxy, chloro and fluoro, efficiently reacted with **1a**

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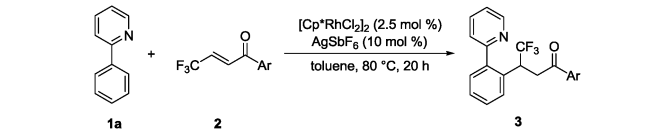
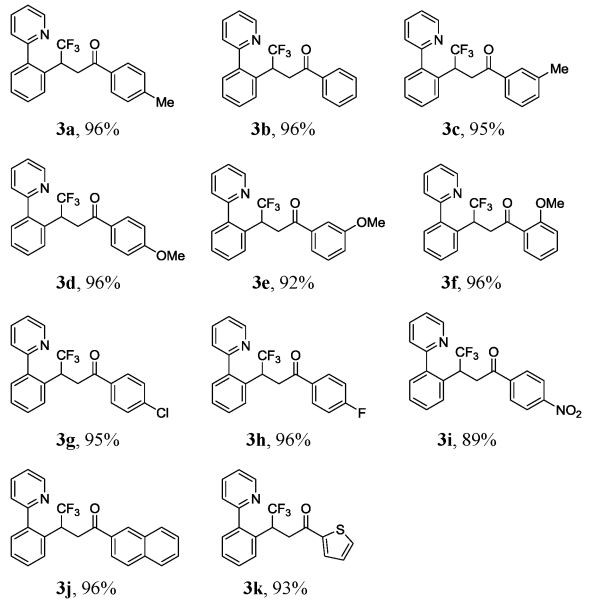
Table 1 Scope of β-trifluoromethyl-α,β-unsaturated ketones (**2**)[a,b]

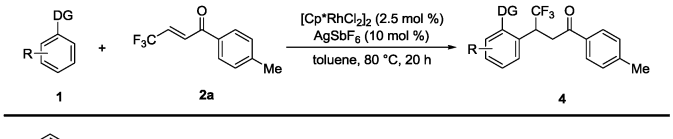


1a 2 3

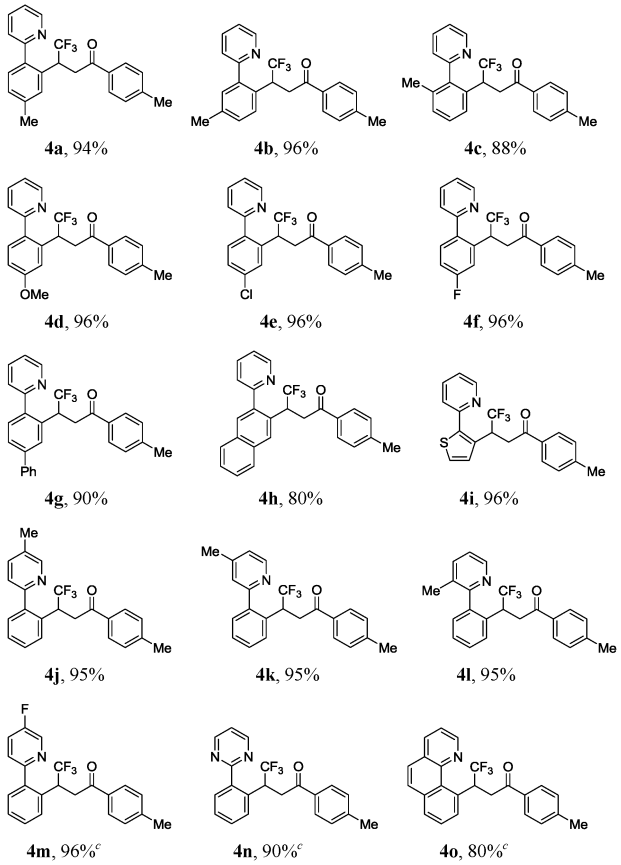


[a] Conditions: **1a** (0.3 mmol), **2** (0.2 mmol), toluene (2 mL), 80 °C, 20 h, 0.1 MPa N_2. [b] Yields refer to the isolated products.

Table 2 Scope of arene subtrates (**1**)[a,b]



1 2a 4



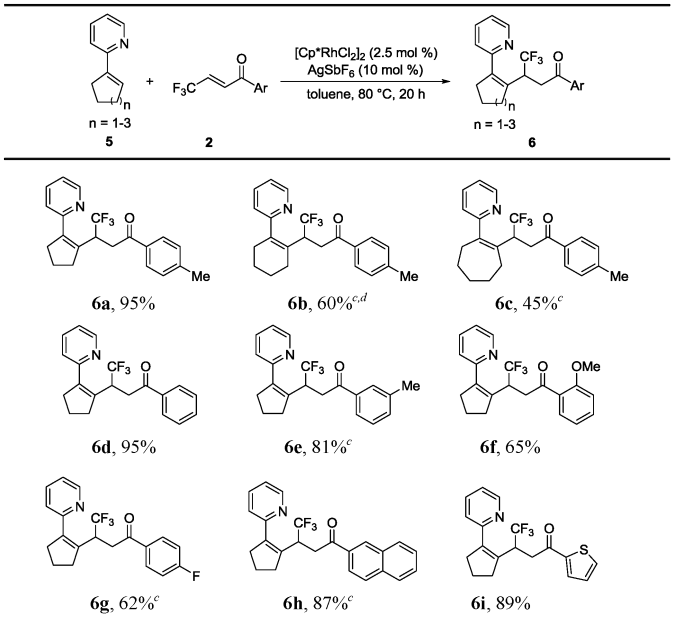
[a] Conditions: **1** (0.3 mmol), **2a** (0.2 mmol), toluene (2 mL), 80 °C, 20 h, 0.1 MPa N_2. [b] Yields refer to the isolated products. [c] 110 °C. DG = directing group.

to form the desired products **3a–h** in 92–96% yields, exhibiting no obvious substituent effect. However, the electron-withdrawing 4-nitro group showed a negative substituent effect, rendering **3i** to be produced in 89% yield. Both 2-naphthyl and 2-thienyl β-trifluoromethyl-α,β-unsaturated ketones efficiently reacted with **1a** to afford **3j** (96%) and **3k** (93%), respectively. The molecular structures of compounds **3** were further confirmed by the X-ray single crystal structural determination of **3f** (see ESI†). Huang and co-workers recently reported rhodium-catalyzed C–H addition to chalcones, in which the substituent effect from the aryl functionality in chalcones was remarkable.[13e] For example, the introduction of an electron-donating group on the phenyl group bound to the carbonyl moiety greatly reduced the product yields. However, in our case, no obvious substituent effect was observed. These differences are presumably attributed to the presence of the strong electron-withdrawing β-CF_3 group, which enhances the electrophilicity of β-CF_3-α,β-unsaturated ketones.

Next, the arene substrates **1** were investigated by reacting with (*E*)-4,4,4-trifluoro-1-*p*-tolylbut-2-en-1-one (**2a**) (Table 2). 2-Arylpyridines (**1**) are well tolerated with the electron-donating or -withdrawing substituents such as methyl, methoxy, chloro, fluoro, and phenyl on their aryl functionality, giving the desired products **4a**, **4b**, and **4d–4f** in excellent yields (94–96%), while a 2-methyl or 4-phenyl substituent reduced the product yields to some extent, that is, resulting in **4c** (88%) and **4g** (90%), respectively. The sterically hindered 2-(2-naphthyl)-pyridine reacted with **2a** to form **4h** in a lower yield (80%). Interestingly, 2-(2-thienyl)pyridine exhibited a high reactivity to interact with **2a** to produce **4i** (96%). The electron-donating substituent such as methyl on the pyridyl moiety did not affect the reactivity of **1**. Thus, 5-, 4-, and 3-methyl-substituted 2-phenylpyridines were efficiently transformed to the corresponding trifluoromethylated products **4j–4l** in 95% yield. Both 5-fluoro-2-phenylpyridine and 2-phenylpyrimidine showed lower reactivities to **2a**, and their reactions had to be performed at an elevated temperature, *i.e.*, 110 °C, giving products **4m** (96%) and **4n** (90%), respectively. For benzo[*h*]quinoline, although its reaction was conducted at 110 °C, the desired product **4o** was obtained only in a relatively low yield (80%), exhibiting an obvious steric effect from both the phenyl and pyridyl moieties in **1**.

Although C–H bond activation of arenes has been well investigated, relatively less attention has been paid to C–H bond activation of olefins.[18] Then, the protocol was applied to olefinic substrates in order to further expand the C–H bond scope (Table 3). Cyclic olefins of type **5** were chosen as the C–H substrates.[15b,19] The ring size effect of the olefin substrates

Table 3 Olefinic C–H addition to β-trifluoromethyl-α,β-unsaturated ketones[a,b]



[a] Conditions: **1a** (0.3 mmol), **2** (0.2 mmol), toluene (2 mL), 80 °C, 20 h, 0.1 MPa N_2. [b] Yields refer to the isolated products. [c] 110 °C. [d] 5 mol% $[Cp^*RhCl_2]_2$ and 20 mol% $AgSbF_6$ were used.

was tested at first. To our delight, cyclopentene with a 2-pyridyl as the directing group, that is, 2-(cyclopent-1-en-1-yl)pyridine (**5a**), reacted with **2a** to form **6a** in 95% yield. However, the corresponding six- and seven-membered cyclic olefin analogues demonstrated much lower reactivities even at a higher temperature and/or catalyst loading, forming **6b** (60%) and **6c** (45%), respectively. A 4-methyl on the phenyl moiety of substrates **2** did not affect their reaction efficiency with **5a**, thus both **6a** and **6d** were obtained in 95% yield. However, in most of the cases using **5a** the substituent effect was obvious from the aryl moiety of the ketone substrates that 3-methyl lessened the product yield to 81% for **6e** even at 110 °C, and 2-methoxy and 4-fluoro further deteriorated the reaction efficiency to give **6f** and **6g** in 62–65% yields. Unexpectedly, 2-naphthyl and 2-thienyl-substituted β-trifluoromethyl-α,β-unsaturated ketones effectively reacted to form **6h** and **6i** in 87–89% yields. As compared to Huang and Li's work on aryl C–H addition to α,β-unsaturated ketones,[13e,f] the present work expands the C–H substrate scope to olefins. A plausible mechanism is proposed, involving rhodium-catalyzed C–H activation, insertion of the olefinic C=C bond to form oxa-π-allylrhodium, and the subsequent protonation (see ESI†).

In conclusion, we have developed an efficient Rh(III)-catalyzed C–H addition of arenes and olefins to β-CF_3-α,β-unsaturated ketones. A CF_3 group was indirectly introduced to molecules bearing a *N*-heteroaryl functionality. The present method provides a promising route to CF_3-containing compounds through C–H activation under rhodium catalysis.

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