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Rh(I)-Catalyzed Reaction of Trifluoromethylketone *N*-Tosylhydrazones and Arylboronates

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Rh(I)-Catalyzed synthesis of 1,1-difluoro-2,2-diarylalkenes from trifluoromethylketone *N*-tosylhydrazones and arylboronates is presented in this communication. This new synthetic method is based on the Rh(I)-carbene migratory insertion followed by *β*-fluoride elimination. In one particular case the protonation occurs instead of *β*-fluoride elimination, affording 2,2-diaryl trifluoroethane product.

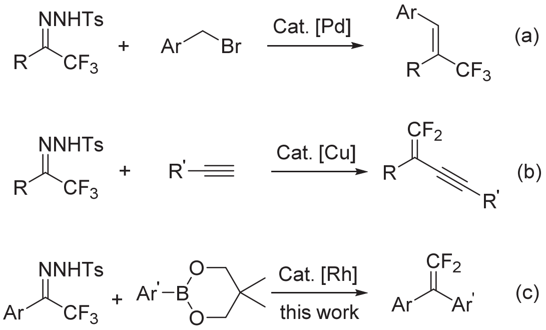
Keywords Rh(I)-catalysis, metal carbene, migratory insertion, *β*-fluoride elimination

Introduction

Owing to the distinct properties of fluorine, organofluorine compounds have found wide applications in various fields, ranging from material science to pharmaceutical chemistry and biological science.[1] As a result, significant efforts have been devoted to the development of efficient synthetic methods toward fluorine-containing organic compounds.[2] Among them, the synthesis based on transition-metal-catalyzed reaction has attracted much attentions in the past decade.

On the other hand, diazo compounds or their equivalents, such as *N*-tosylhydrazones have emerged as a new type of cross-coupling partners in transition-metal-catalyzed reactions.[3] The key process of this type of transformations is the formation of metal carbene species and the subsequent migratory insertion. As an application of this type of coupling reactions in the synthesis of fluorine-containing compounds, we and others have demonstrated that CF_3-bearing *N*-tosylhydrazones or diazo-compounds are versatile building blocks for the synthesis of trifluoromethyl[4a-4d] and difluoromethylene[4e] compounds. For example, we have previously reported the Pd-catalyzed cross-coupling of CF_3-bearing *N*-tosylhydrazones with benzyl bromides for the synthesis of trifluoromethylated trisubstituted olefins (Scheme 1a).[4a] Subsequently, we have demonstrated the Cu(I)-catalyzed cross-coupling of trifluoromethylketone *N*-tosylhydrazones and terminal alkynes to give 1,1-difluoroolefins. The transformation is proposed to undergo carbene migratory insertion and *β*-fluoride elimination (Scheme 1b).[4e] As the continuation of our interests in carbene-based cross-coupling reactions, we have conceived that transition-metal-catalyzed cross-coupling of CF_3-bearing *N*-tosylhydrazones with organboron compounds should also give 1,1-difluoroolefins (Scheme 1c).[5] Herein we report the Rh(I)-catalyzed reaction of trifluoromethylketone *N*-tosylhydrazones and arylboronates, which constitutes a new method for the synthesis of 1,1-difluoro-2,2-diarylalkenes.

Scheme 1 Synthesis of 1,1-difluoroolefins from the cross-coupling with CF_3-bearing *N*-tosylhydrazones



Experimental

General procedure for the Cu(I)-catalyzed reaction

Under N_2 atmosphere, $[Rh(COD)Cl]_2$ (3.0 mg, 0.006 mmol, 3 mol%), LiO*t*Bu (40 mg, 0.5 mmol), and *N*-tosylhydrazone **1** (0.26 mmol) were successively added to a flame-dried 10 mL Schlenk tube. The reaction flask was degassed three times with N_2, and dry MeOH (2.0 mL) was added using syringe. Then a solution of arylboronate **2** (0.2 mmol) in 1.0 mL MeOH was added dropwise in 20 min through syringe. The reaction

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tube was then immersed in a 70 ℃ oil bath. The reaction was heated with stirring for 4 h. Upon cooling down to room temperature, the reaction solution was filtered through a short plug of silica gel (eluted with petroleum ether : EtOAc=5 : 1). Removal of solvent and silica gel column chromatographic separation afforded the pure 1,1-difluoro-2,2-diarylethene product.

Results and Discussion

The initial experiment was carried out at 60 ℃ with CF_3-bearing *N*-tosylhydrazone **1a** and (*p*-phenyl)-phenyl boronic acid **2a** as substrates, LiO*t*-Bu as the base and dioxane as the solvent. However, no product could be detected (Table 1, Entry 1). The addition of CuI as the catalyst to the reaction system also did not give the coupling product and the starting materials were recovered unchanged (Table 1, Entry 2). This might be attributed to the fact that transmetalation of boronate with Cu(I) catalyst is not efficient under the current reaction conditions. Then Rh(I) catalysts were examined. To our delight, the expected 1,1-difluoro-2,2-diarylethene product was obtained in 30% isolated yield (Table 1, Entry 3). However, most of the boronic acid was directly protonated to give biphenyl as the side product.

Next, we examined the reaction with pinacol (*p*-phenyl)phenylboronate **2b**, but only 25% yield of the product was obtained (Table 1, Entry 4). In this case, the boronate **2b** was largely remained unchanged due to its stability and low reactivity. The reaction with more reactive boronate **2c** gave the product with improved yield (Table 1, Entry 5). In this case, the protonation byproduct was still formed in small amount. We then tried to add the boronate **2c** dropwise by using a syringe, but the poor solubility of **2c** resulted in the failure of the experiment. Then we turned to the boronate substrate **2d**, which has high solubility in methanol. Under the same reaction conditions as mentioned above, a 50% yield of the coupling product could be obtained (Table 1, Entry 6). By slowly adding **2d**, the yield of the cross-coupling products could be improved to 70% (Table 1, Entry 7).

Surprisingly, the reaction with boronate **2e** as the substrate gave the pronation product **4**, and no 1,1-difluoroolefin could be detected (Eq. 1).

Scheme 2 The boronic acid and boronates employed for the reaction condition optimization

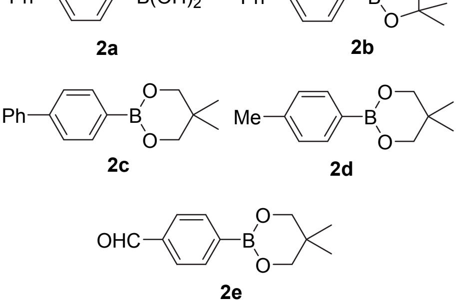
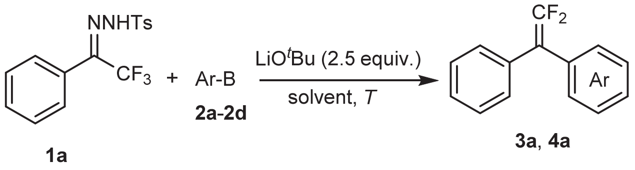
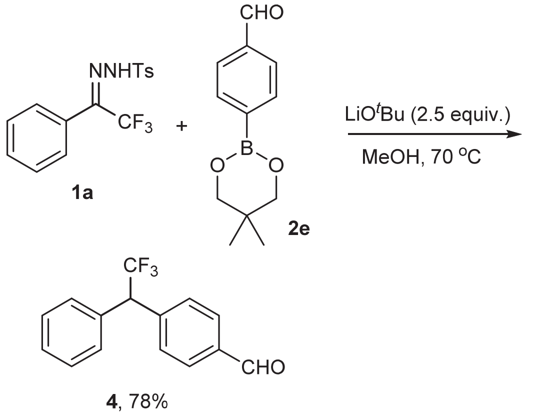


Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (*x* mol%)	Ar-*B*	*T*/℃	Solvent	(**3a**/**4a**)[b]/%
1	None	**2a**	60	Dioxane	N.R.
2	CuI (20)	**2a**	60	Dioxane	N.R.
3	$[Rh(COD)Cl]_2$ (3)	**2a**	70	MeOH	30/0
4	$[Rh(COD)Cl]_2$ (3)	**2b**	70	MeOH	25/0
5	$[Rh(COD)Cl]_2$ (3)	**2c**	70	MeOH	57/0
6	$[Rh(COD)Cl]_2$ (3)	**2d**	70	MeOH	50/0
7[c]	$[Rh(COD)Cl]_2$ (3)	**2d**	70	MeOH	70/0
8[c]	$[Rh(COD)Cl]_2$ (3)	**2e**	70	MeOH	0/78

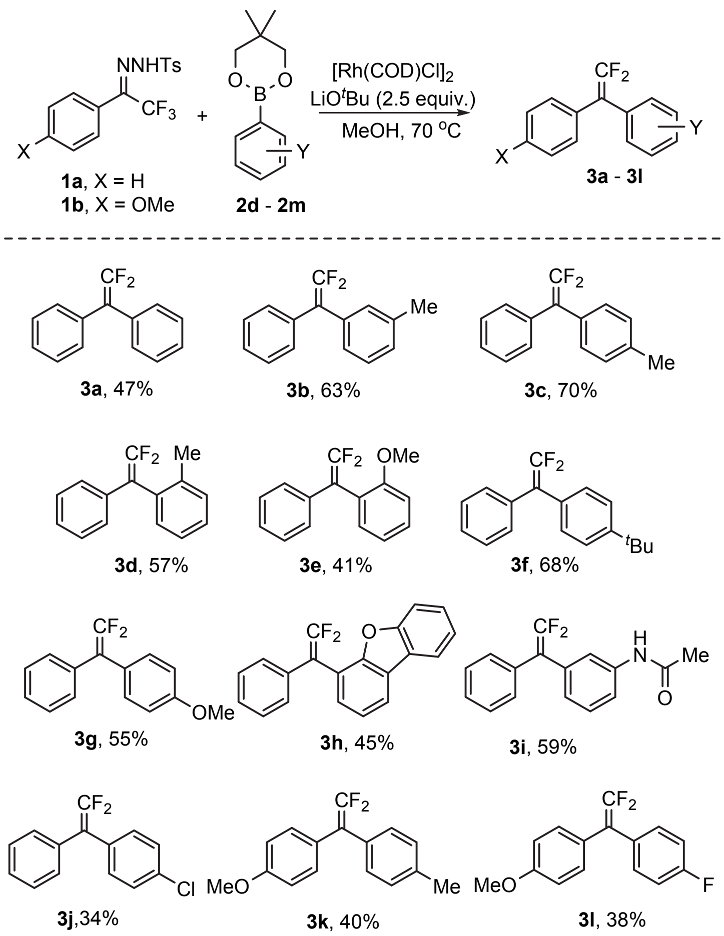
[a] All the reactions were carried out in 0.2 mmol scale, **1a** : **2**=1.3 : 1; solvent (3 mL). [b] Isolated yields. [c] The borate was added dropwise in 20 min.



(1)

With the optimized reaction conditions in hand, the substrates scope of this cross-coupling reaction was investigated with a series of CF_3-bearing *N*-tosylhydrazones and arylboronates. As illustrated in Scheme 3, the *N*-tosylhydrazone **1a** could react with a series of arylboronates to afford corresponding 1,1-difluoroolefin products in moderate yields. Notably, the boronates bearing *ortho*-substituted aryl moiety also gave the coupling products (**3d**, **3e**). *N*-Tosylhydrazones bearing electron-donating *p*-methoxy group could afford the 1,1-difluoroolefin products, albeit in diminished yields (**3k**, **3l**). The reaction with boronates bearing hetero aromatic moiety and *m*-acetamido substituted phenyl group also worked well (**3h**, **3i**). Interestingly, as shown in Eq. 1, the reaction with arylboronates bearing electron-withdrawing substituent did not afford the corresponding 1,1-difluoroolefin product. Instead, CF_3-bearing products were isolated. When the boronate with aromatic moiety bearing moderately electron-with-

Scheme 3 The substrate scope of the reaction

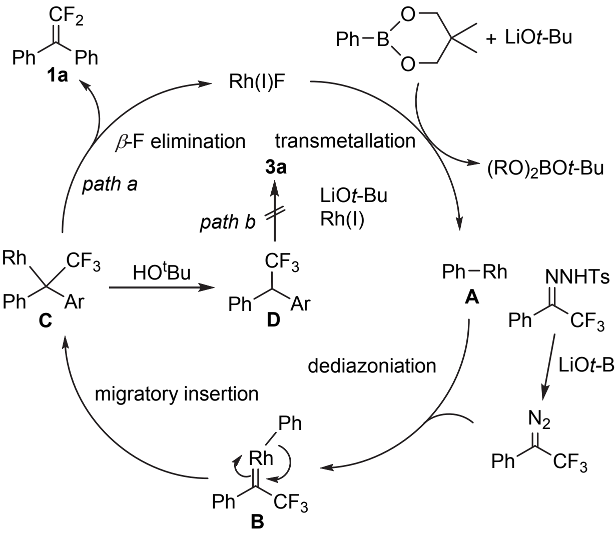


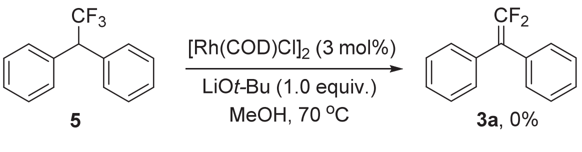
drawing substituent was employed, the reaction afforded a mixture of CF_3-bearing product and 1,1-difluoroolefin. Apparently, the chemo-selectivity of the reaction is dependent on electronic nature of substrates.

According to our previous study on Cu(I)-catalyzed reaction involving β-fluoride elimination,[4e] we propose the following reaction mechanism (Scheme 4). Firstly, aryl rhodium species is generated through transmetallation. The aryl rhodium species then reacts with the *in situ* generated diazo compounds to afford the Rh(I) carbene intermediate **B**, which is followed by migratory insertion to generate intermediate **C**. From intermediate **C** the catalytic cycle can be completed in two ways: β-fluoride elimination (*path a*) and protonation of carbon rhodium bond (*path b*). The *path a* gives the 1,1-difluoroolefin product, and *path b* gives the CF_3-bearing product **D**. In *path a*, we suggest that rhodium fluoride is formed, which undergoes transmetallation with arylboronate.[6]

To verify the possible involvement of *path b* in the reaction mechanism, (2,2,2-trifluoroethane-1,1-diyl)dibenzene **5** was subjected to the identical reaction conditions. The 1,1-difluoroolefin product **3a** was not detected (Eq. 2). The result does not support the involvement of path *b* in the reaction mechanism. The formation of 1,1-difluoroolefin product **3a** seems to exclusively follow path *a*.

Scheme 4 Proposed reaction mechanism





(2)

Traditional β-fluoride elimination is the α-anion derived elimination,[7] while β-fluoride elimination from organorhodium species is rare.[4e,8] In the current reaction, the β-fluoride elimination needs some driving force. It is postulated that the carbon linked to the rhodium will develop partial positive charge in the process of the β-fluoride elimination. Thus the electron-donating substituent on the aromatic ring can stabilize the transition state. On the contrary, in our previously reported Cu(I)-catalyzed similar reaction, the β-fluoride elimination was less affected by the electronic effects.[4e] Presumably, this is because carbon copper bond is more polarized. Moreover, Cu(I) has more ionic character and is easier to associate with fluoride.

Conclusions

In summary, we have demonstrated a new method to synthesize 1,1-difluoro-2,2-diaryl olefins or 2,2-diaryl trifluoroethanes.[9] The chemo-selectivity of the reaction is dominated by the electronic nature of the substrates. Mechanistically, this reaction follows a pathway involving transmetallation, carbene formation, migratory insertion, and β-fluoride elimination or protonation. This reaction further demonstrates the application of CF_3-bearing *N*-tosylhydrazones in the synthesis of fluorine-containing organic compounds.

Acknowledgement

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