Rhodium(III)-Catalyzed Redox-Neutral Coupling of α-Trifluoromethylacrylic Acid with Benzamides through Directed C–H Bond Cleavage

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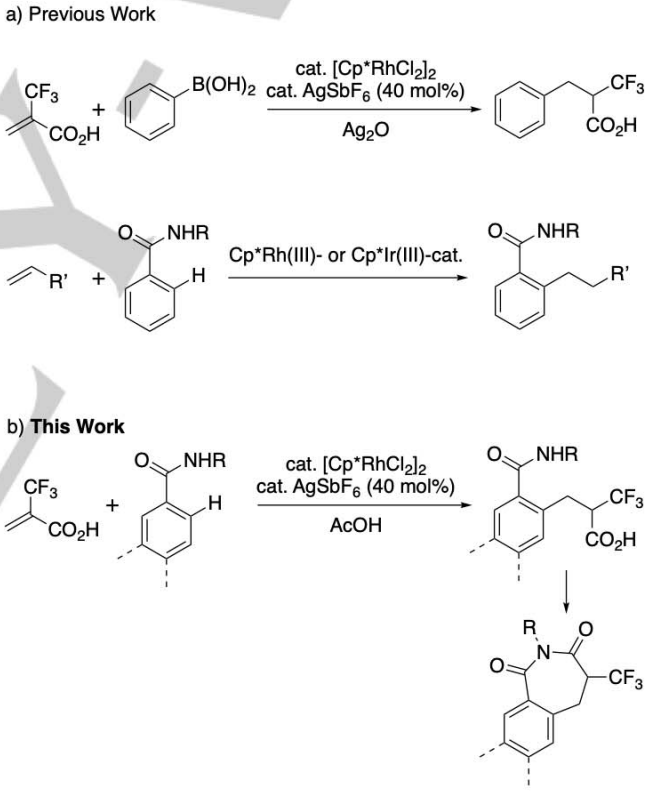
Risa Yoshimoto,[a] Yoshinosuke Usuki,[a] and Tetsuya Satoh*[a]

Abstract: The rhodium(III)-catalyzed redox-neutral coupling of α-trifluoromethylacrylic acid with bezamides proceeds smoothly accompanied by amide-directed C–H bond cleavage to produce β-[2-(aminocarbonyl)phenyl]-α-trifluoromethylpropanoic acid derivatives. One of products can be transformed to a trifluoromethyl substituted heterocyclic compound. In addition, the redox-neutral coupling of α-trifluoromethylacrylic acid with related aromatic substrates possessing a nitrogen-containing directing group can also be conducted under similar conditions.

Introduction

Organofluorine chemistry has gained recognition for its importance especially in the fields of material and medicinal industries.[1] The demand from such fields has led to the development of synthetic methods for organofluorine compounds. Compared to fluorination and trifluromethylation using activated reagents such as selectfluor and Togni's reagent,[2] the transition-metal-catalyzed cross-coupling reactions of more stable fluorine-containing substrates are preferred because of their wide applicability and usability. α-Trifluoromethylacrylic acid is one of such stable, readily available building-blocks and has been utilized in palladium-,[3] rhodium-,[4] iridium-,[5] and ruthenium-catalyzed[6] cross-coupling reactions. We also recently reported the rhodium-catalyzed coupling of α-trifluoromethylacrylic acid with arylboronic acids to selectively produce 1,4-conjugate addition products, β-aryl-α-trifluoromethylpropanoic acid derivatives (Scheme 1a).[7] It should be noted that this type of fluorine-containing molecules has been receiving increasing attention due to their biological activities and utilities as important synthetic intermediates in fine chemicals production processes.[8] However, the coupling reactions with arylmetal reagents as well as their preparation steps bring about undesired waste formation. From atom- and step-economical points of view, the direct coupling with arenes through C–H bond cleavage is more attractive to provide straightforward synthesis pathways.[9] Recently, the Cp*Rh(III)- and Cp*Ir(III)-catalyzed redox-neutral coupling reactions of alkenes with benzamides have been developed.[10] During our continuous studies on transition-metal-catalyzed C–H functionalization,[11] we found that α-trifluoromethylacrylic acid undergoes redox-neutral coupling with benzamides under rhodium catalysis via *ortho* C–H bond cleavage to produce β-[2-(aminocarbonyl)phenyl]-α-trifluoromethylpropanoic acid derivatives (Scheme 1b). This can be an environmentally-benign approach toward β-aryl-α-trifluoromethylpropanoic acid derivatives, because no metal-containing reagents other than catalysts are needed for the reaction. It has been shown that one of products can be transformed to a trifluoromethyl substituted heterocyclic compound. These new findings are described herein.



Scheme 1. β-Arylation of α-trifluoromethylacrylic acid.

Results and Discussion

In an initial attempt, α-trifluoromethylacrylic acid (**1**) (0.5 mmol) was treated with *N*-methylbenzamide (**2a**) (0.5 mmol) in the presence of catalytic amounts of $[Cp^*RhCl_2]_2$ (0.01 mmol; 2 mol%) and $AgSbF_6$ (0.2 mmol; 40 mol%) and 2 equiv. of AcOH in ^{t}BuOH (3 mL) at 80 °C for 24 h under Ar. As a result, the desired redox-neutral coupling product was selectively formed, and it was subsequently methyl-esterified for its quantification to afford methyl β-[2-(*N*-methylcarbamoyl)phenyl]-α-

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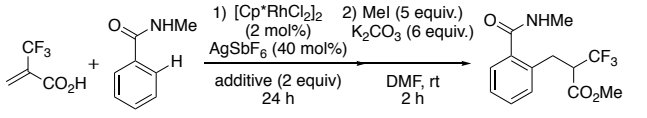
trifluoromethylpropanoate (**3a**) in 62% GC yield (entry 1 in Table 1). At 60 °C, the yield was slightly improved to 70% (entry 2). In this case, no other products including a 2:1 coupling product were formed. Under conditions using an excess amount of **1** (1 mmol), a trace amount of 2:1 coupling product was detected by GC and GC-MS along with **3a** (entry 3). Further decreasing the reaction temperature to 40 °C resulted in lower efficiency (entry 4). Both decreasing the amount of $AgSbF_6$ to 20 mol% at 60 °C and using $AgNTf_2$ in place of $AgSbF_6$ at 80 °C also reduced the yield of **3a** (entries 5 and 6). The reaction was sluggish in the absence of AcOH (entry 7). Other carboxylic acids such as $EtCO_2H$ and PivOH were less effective as additive than AcOH (entries 8 and 9). The reaction proceeded with lower efficiency in ^{t}AmOH and 1-octanol (entries 10 and 11) and did not proceed at all in DMF, *o*-xylene, and AcOH (entries 12-14).

Table 1. Reaction of α-Trifluoromethylacrylic acid (**1**) with *N*-Methylbenzamide (**2a**)[a]

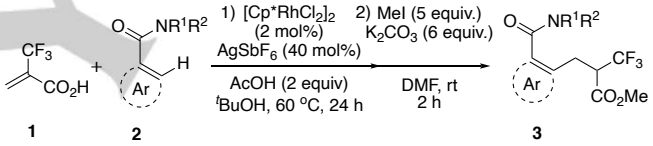


1 **2a** **3a**

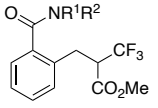
entry	additive	solvent	temp. [°C]	Yield of **3a** [%][b]
1	AcOH	^{t}BuOH	80	62
2	AcOH	^{t}BuOH	60	70 (52)
3[c]	AcOH	^{t}BuOH	60	61[d]
4	AcOH	^{t}BuOH	40	41
5[e]	AcOH	^{t}BuOH	60	56
6[f]	AcOH	^{t}BuOH	80	38
7	–	^{t}BuOH	60	44
8	$EtCO_2H$	^{t}BuOH	60	43
9	PivOH	^{t}BuOH	60	55
10	AcOH	^{t}AmOH	60	44
11	AcOH	1-octanol	60	35
12	AcOH	DMF	60	0
13	AcOH	*o*-xylene	60	0
14	–	AcOH	60	0

[a] Reaction conditions: 1) **1** (0.5 mmol), **2a** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.2 mmol), and additive (1 mmol) in solvent (3 mL) under Ar (1 atm) for 24 h, unless otherwise noted: 2) With the addition of MeI (2.5 mmol), K_2CO_3 (1.5 mmol), and DMF (2 mL) at rt for 2 h. [b] GC yield based on the amount of **1** used. Value in parentheses indicates yield after purification. [c] **1** (1 mmol) was used. [d] A 2:1 coupling product was also detected (1%). [e] With $AgSbF_6$ (0.1 mmol). [f] With $AgNTf_2$ (0.2 mmol) in place of $AgSbF_6$.

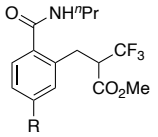
Under the optimized conditions (entry 2 in Table 1), the coupling reactions of variously substituted benzamides **2** with **1** were next examined (Scheme 2). *N*-*n*-Propyl- (**2b**) and *N*-*i*-propylbenzamides (**2c**) reacted with **1** smoothly to give **3b** and **3c** in 83 and 69% yields, respectively. The reaction of a sterically hindered amide, *N*-(2,6-dimethylphenyl)benzamide (**2d**), was sluggish to afford **3d** in a lower yield even at 80 °C. Not only secondary but also tertiary benzamides underwent the present coupling. Thus, treatment of *N,N*-dimethylbenzamide (**2e**) and phenyl(piperidin-1-yl)methanone (**2f**) with **1** gave **3e** and **3f** in moderate yields. 4-Methoxy- (**2g**), -methyl- (**2h**), -pheny- (**2i**), and -bromo-*N*-*n*-propylbenzamides (**2j**) coupled with **1** efficiently to afford **3g-j** in fair to good yields. 4-Chloro- (**2k**) and -trifluoromethyl- (**2l**) substituted benzamides gave **3k** and **3l** in moderate yields. The reaction efficiency of 4-methoxycarbonyl-*N*-*n*-propylbenzamides (**2m**) was improved at 80 °C to yield **3m** in 70% yield. Besides these 4-substituted ones, 3- and 2-substituted *N*-*n*-propylbenzamides **2n**-**2r** also underwent the coupling to produce **3n**-**3r**. The low yields in cases with **2q** and **2r** even at 80 °C seem to be due to a steric reason. In addition to benzamides, *N*-propyl-2-naphthamide (**2s**) also reacted with **1** at 80 °C through regioselective C–H bond cleavage at the C3-position to give **3s** in 59% yield. The reaction of *N*-propylbenzo[*b*]thiophene-2-carboxamide (**2t**) also took place at the C3-position to afford **3t** selectively. In contrast to **2t**, related heteroarene-2-carboxamides such as *N*-propylbenzofuran-2-carboxamide and 1-methyl-*N*-propyl-1*H*-indole-2-carboxamide showed low reactivity. The corresponding coupling products were detected by GC and GC-MS in less than 10% yields. In the latter case at higher temperature (100 °C), 3-(*t*-butyl)-1-methyl-*N*-propyl-1*H*-indole-2-carboxamide (**4**) was also produced via Friedel-Crafts alkylation with solvent ^{t}BuOH in 36% yield.



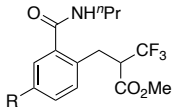
1 **2** **3**



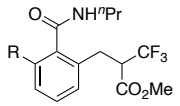
3b: R^1 = ^{n}Pr, R^2 = H, 83%
3c: R^1 = ^{i}Pr, R^2 = H, 69%
3d: R^1 = 2,6-$Me_2C_6H_3$, R^2 = H, 38%[a]
3e: R^1 = R^2 = Me, 41%[a]
3f: $–R^1R^2–$ = $–(CH_2)_5–$, 58%[a]



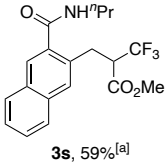
3g: R = OMe, 66%
3h: R = Me, 59%
3i: R = Ph, 87%
3j: R = Br, 62%
3k: R = Cl, 40%
3l: R = CF_3, 41%
3m: R = CO_2Me, 70%[a]



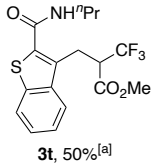
3n: R = Me, 55%
3o: R = OMe, 52%
3p: R = Br, 43%



3q: R = Me, 27%[a]
3r: R = Br, 16%[a]



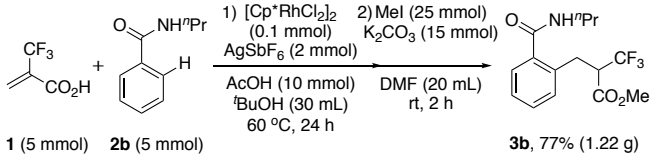
3s, 59%[a]



3t, 50%[a]

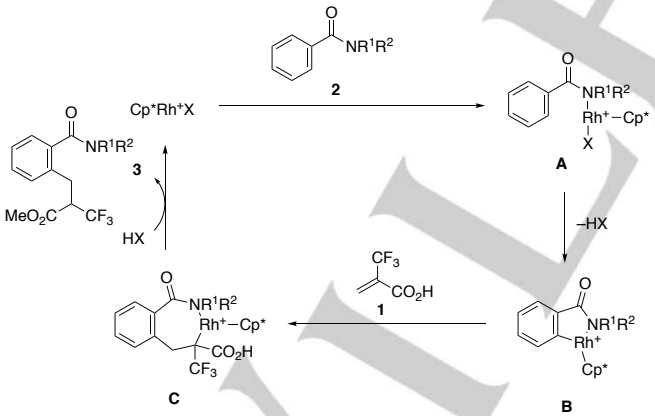
Scheme 2. Reaction scope of aromatic and heteroaromatic amides. Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.2 mmol), and AcOH (1 mmol) in ^{t}BuOH (3 mL) under Ar (1 atm) at 60 °C for 24 h, unless otherwise noted. Yields after purification were listed. [a] At 80 °C.

Considering that stoichiometric amounts of metal-containing reagents are not required, the present reaction can be readily scaled up to a gram scale. Thus, **3b** was obtained in 77% isolated yield (1.22 g) from **1** (5 mmol) and **2b** (5 mmol) (Scheme 3).



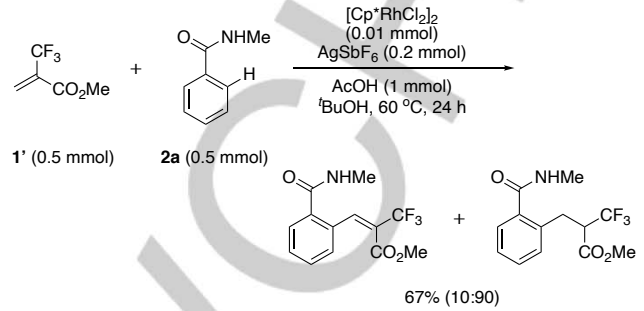
Scheme 3. Gram scale synthesis of **3b**.

A plausible mechanism for the reaction of **1** with benzamides **2** is illustrated in Scheme 4. Coordination of the amide function of **2** toward a cationic Cp^*RhX^+ species forms intermediate **A**. Then, **A** undergoes cyclorhodation through amide-directed C–H bond cleavage at the *ortho*-position to provide a five-membered rhodacycle intermediate **B**. As previously proposed for the coupling of **1** with arylboronic acids,[7] **1** inserts into the formed aryl-rhodium bond of **B** to give a seven-membered intermediate **C**. Finally, protonation of the formed alkyl-rhodium bond of **C** may occur to release the product **3** and regenerate an active Cp^*RhX^+ species.



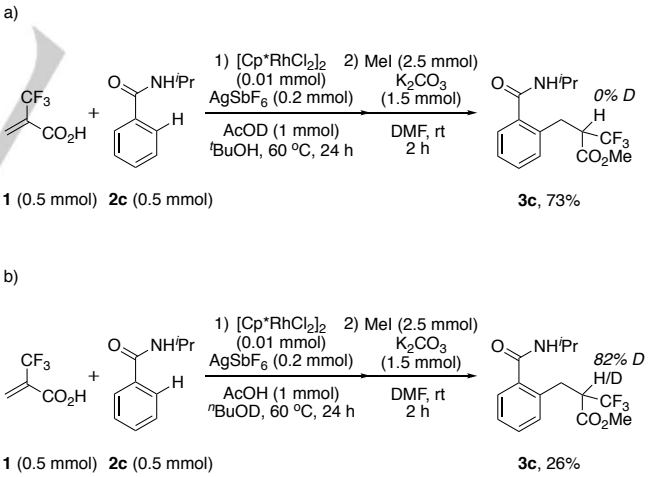
Scheme 4. Plausible mechanism.

In the reactions of **1** with **2** under standard conditions, no dehydrogenative coupling products were observed. Therefore, β-hydrogen elimination from intermediate **C** seems to be a difficult pathway compared to protonation. In constast, in the case using methyl α-trifluoromethylacrylate (**1'**) in place of **1** with **2a**, a small amount of dehydrogenative coupling product was detected by GC and GC-MS along with **3a** (10:90) (Scheme 5). The resulting mixture was found to be inseparable. This result indicates that the carboxylic group of **1** appears to play an important role for the exclusive formation of redox-neutral coupling product **3**.



Scheme 5. Reaction of **1'** with **2a**.

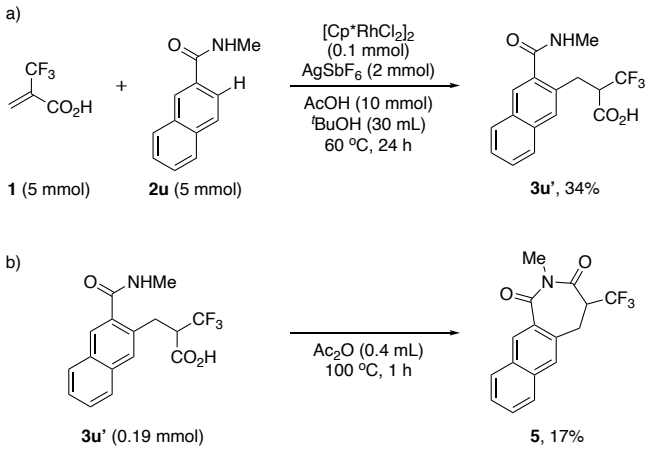
Some deuterium labeling studies were carried out to gain mechanistic information. First, the reaction of **1** with **2c** was performed under standard conditions except using AcOD (1 mmol). In this case, no deuterium incorporation was observed in obtained **3c** (Scheme 6a). In contrast, when the same reaction was conducted in ^{n}BuOD, deuterium was significantly incorporated at the α-position of **3c** (Scheme 6b). These results indicate that the dominant proton source at the protonolysis step of intermediate **C** in Scheme 4 seems to be an alcoholic solvent.



Scheme 6. Reactions of **1** with **2c** using deuterium labeling reagents.

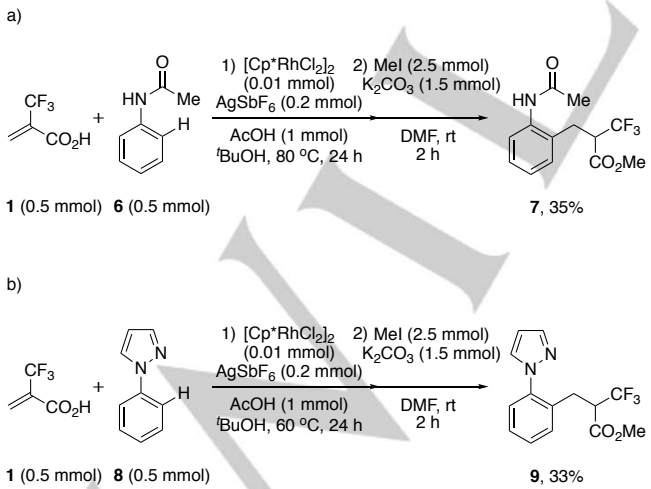
The present coupling provides a series of β-[2-(*N*-methylcarbamoyl)phenyl]-α-trifluoromethylpropanoic acids as shown in Scheme 2. The products possessing amide- and carboxyl functions are expected to be precursor of CF_3-substituted heterocyclic compounds. As an initial attempt, the sequence of the coupling of *N*-methyl-2-naphthamide (**2u**) with **1** and following cyclization using Ac_2O was examined.[12] Thus,

treatment of **2u** with **1** under standard conditions without the methyl-esterification process gave β-[3-(*N*-methylcarbamoyl)naphthalen-2-yl]-α-trifluoromethylpropanoic acid (**3u'**) in 34% yield (Scheme 7a). Then, **3u'** was treated with Ac_2O at 100 °C for 1 h. As a result, cyclization took place to produce **5,** albeit with a low yield. (Scheme 7b).



Scheme 7. Preparation and cyclization of **3u'**.

We also examined the direct coupling reactions using a few aromatic substrates possessing other directing groups beyond benzamides. Treatment of acetanilide (**6**) with **1** under standard conditions at 80 °C and following methyl-esterification gave the corresponding redox-neutral coupling product, methyl 2-(2-acetamidobenzyl)-3,3,3-trifluoropropanoate (**7**) (Scheme 8a). A pypazolyl function was also found to act as a directing group in the present coupling. Thus, 1-phenylpyrazole (**8**) coupled with **1** accompanied by pyrazolyl-directed C–H bond cleavage to afford an expected product **9** (Scheme 8b).



Scheme 8. Reactions of **6** and **8** with **1**.

Conclusions

We have demonstrated that α-trifluoromethylacrylic acid undergoes redox-neutral coupling with benzamides, acetanilide, and 1-phenylpyrazole in the presence of a rhodium(III) catalyst through regioselective C−H bond cleavage to produce the corresponding β-aryl-α-trifluoromethylpropanoic acid derivatives. The remaining functional groups in the products can be utilized for further transformations. Work is underway toward the further development of the procedures in our group.

Experimental Section

General procedure for Rh-catalyzed redox-neutral coupling of α-trifluoromethylacrylic acid (1) with benzamides 2: A mixture of α-trifluoromethylacrylic acid (**1**) (0.5 mmol, 70 mg), benzamide **2** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol, 6 mg), $AgSbF_6$ (0.2 mmol, 69 mg), AcOH (1 mmol, 60 mg), and 1-methylnaphthalene (ca. 20 mg) as internal standard was stirred in *tert*-butanol (3 mL) under argon at 60 °C for 24 h. After the reaction, MeI (2.5 mmol), K_2CO_3 (1.5 mmol) and DMF (2 mL) were added to the mixture and stirred at rt for 2 h. Then the reaction mixture was diluted by CH_2Cl_2 (15 mL). The organic layer was washed by 1 N HCl (15 mL), water (15 mL), and brine (15 mL) and dried over Na_2SO_4. After evaporation of the solvents under vacuum, product **3** was isolated by gel permeation chromatography using EtOAc as eluant.

Acknowledgements

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Keywords: alkylation • C–H activation • C–C coupling • cross-coupling • rhodium

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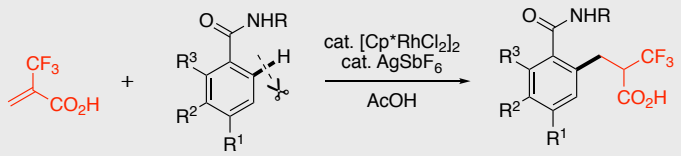

Redox-neutral Coupling of α-trifluoromethylacrylic acid with bezamides was achieved under rhodium(III) catalysis via regioselective C–H bond cleavage to produce β-aryl-α-trifluoromethylpropanoic acid derivatives. One of products was found to be transformed to a trifluoromethyl substituted heterocyclic compound. In addition, the redox-neutral coupling of α-trifluoromethylacrylic acid with related aromatic substrates could also be conducted under similar conditions.

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Rhodium(III)-catalyzed Redox-neutral Coupling of α-Trifluoromethylacrylic Acid with Benzamides through Directed C–H Bond Cleavage