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# Synthesis of $CF_3$-Containing Isoindolinone Derivatives through Rhodium-Catalyzed Oxidative Coupling of Benzamides with 2-Trifluoromethylacrylate

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# Synthesis of $CF_3$-Containing Isoindolinone Derivatives through Rhodium-Catalyzed Oxidative Coupling of Benzamides with 2-Trifluoromethylacrylate

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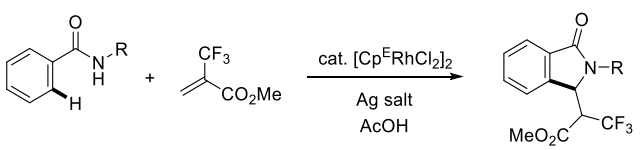
The oxidative coupling of benzamides with methyl 2-trifluoromethylacrylate proceeds smoothly under rhodium(III) catalysis to produce trifluoromethyl-substituted isoindolinone derivatives. The catalyst system $[Cp^ERhCl_2]_2/AgSbF_6$ is effective for the oxidative coupling, while $[Cp^*RhCl_2]_2/AgSbF_6$ leads to their redox-neutral coupling predominantly. The oxidative coupling reactions with related acrylates have also been examined. Keywords: rhodium catalyst; oxidative coupling; isoindolinone; organofluorine compound

Nitrogen-containing fused heterocyclic frameworks can be seen in naturally occurring and synthetic bioactive molecules.[1] Among them, variously substituted isoindolinone derivatives have been recognized as nonbenzodiazepine sedative and anti-anxiety agents.[2] Especially, isoindolinones possessing a trifluoromethyl group, which is known to affect their lipophilicity as well as metabolic robustness, have attracted much attention and their synthetic methods have been developed.[3] Recently, Wang's group reported a copper-catalyzed intramolecular aminotrifluoromethylation of *o*-vinylbenzamides using Togni's reagent for preparing $CF_3$-containing isoindolinones.[3b] Zhang's group also disclosed a similar cyclization using $CF_3SO_2Na$ as a $CF_3$ source.[3a] However, less accessible disubstituted aromatic substrates were usually required to be employed in these procedures to impose synthetic limitation.

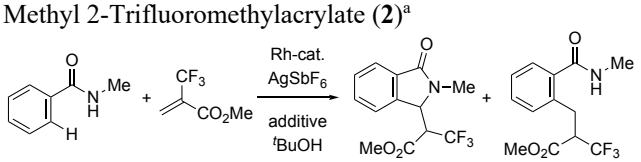
Meanwhile, transition-metal-catalyzed C-H functionalization has been developed and widely utilized in organic synthesis.[4] The direct coupling of aromatic substrates bearing a heteroatom-containing directing group with unsaturated compounds is one of the most powerful tools for constructing fused heterocyclic compounds from readily available monosubstituted aromatic substrates.[5] During our continuous studies on rhodium(III)-catalyzed direct annulative coupling reactions,[6] we found that simple benzamides[7] undergo direct coupling with methyl 2-trifluoromethylacrylate under rhodium(III) catalysis to produce $CF_3$-containing isoindolinones (Scheme 1).[8] The new findings are described herein.




**Scheme 1.**

In an initial attempt, *N*-methylbenzamide (**1a**) (0.5 mmol) was treated with methyl 2-trifluoromethylacrylate (**2**) (0.5 mmol) in the presence of $[Cp^*RhCl_2]_2$ ($Cp^*$ = 1,2,3,4,5-pentamethylcyclopentadienyl, 0.02 mmol), $AgSbF_6$ (0.2 mmol), and AcOH (1 mmol) under argon in $^t$BuOH (3 mL) at 60 °C for 24 h. As a result, the desired isoindolinone, methyl 3,3,3-trifluoro-2-(2-methyl-3-oxoisoindolin-1-yl)propanoate (**3a**), was formed as an oxidative coupling product in a low yield (7%, entry 1 in Table 1). Instead, a redox-neutral coupling product, methyl 3,3,3-trifluoro-2-(2-(methylcarbamoyl)benzyl)propanoate (**4a**), was obtained predominantly (60%) as in our previous report.[8a] Neither **3a** nor **4a** was formed when $[RhCl(cod)]_2$ was employed in place of $[Cp^*RhCl_2]_2$ (entry 2). Interestingly, the use of $[Cp^ERhCl_2]_2$ ($Cp^E$ = 1,3-bis(ethoxycarbonyl)-2,4,5-trimethylcyclopentadienyl), which was developed by Tanaka's group,[9] as a catalyst altered the product distribution dramatically. Thus, **3a** was produced in 54% yield,[10] no **4a** being detected (entry 3). In the case without AcOH, the yield of **3a** decreased (entry 4). As expected, the addition of $Ag_2CO_3$ (1 mmol) as an oxidant significantly enhanced the **3a** yield to 81% (entry 5). Increasing the reaction temperature to 80 °C somewhat decreased the reaction efficiency (entry 6). To our delight, **3a** was obtained in a good yield (97%), when the reaction temperature was reduced to 40 °C (entry 7). The NMR spectra of **3a** indicated that it consists of two diastereoisomers (see the Supporting Information). It was confirmed that the addition of AcOH is essential for

**Table 1.** Reaction of *N*-Methylbenzamide (**1a**) with Methyl 2-Trifluoromethylacrylate (**2**)[a]




**1a** **2** **3a** **4a**

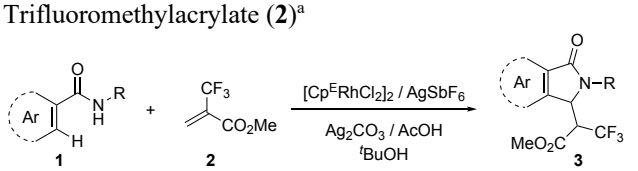
| entry | Rh-cat. | additive(s) | temp. (°C) | yield (%)[b] | |
|---|---|---|---|---|---|
| | | | | **3a** | **4a** |
| 1 | $[Cp^*RhCl_2]_2$ | AcOH | 60 | 7 | 60 |
| 2 | $[RhCl(cod)]_2$ | AcOH | 60 | 0 | 0 |
| 3 | $[Cp^ERhCl_2]_2$ | AcOH | 60 | 54 | 0 |
| 4 | $[Cp^ERhCl_2]_2$ | - | 60 | 23 | 0 |
| 5 | $[Cp^ERhCl_2]_2$ | AcOH / $Ag_2CO_3$ | 60 | 81 | 0 |
| 6 | $[Cp^ERhCl_2]_2$ | AcOH / $Ag_2CO_3$ | 80 | 60 | 0 |
| 7 | $[Cp^ERhCl_2]_2$ | AcOH / $Ag_2CO_3$ | 40 | 97 (97)[c] | 0 |
| 8 | $[Cp^ERhCl_2]_2$ | $Ag_2CO_3$ | 40 | 26 | 0 |
| 9 | $[Cp^*RhCl_2]_2$ | AcOH / $Ag_2CO_3$ | 40 | 8 | 40 |

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), Rh-cat. (0.01 mmol), $AgSbF_6$ (0.2 mmol), additive (1 mmol) in $^t$BuOH (3 mL) under Ar for 24 h. [b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] **3a** was obtained as a mixture of diastereoisomers (64 : 36).

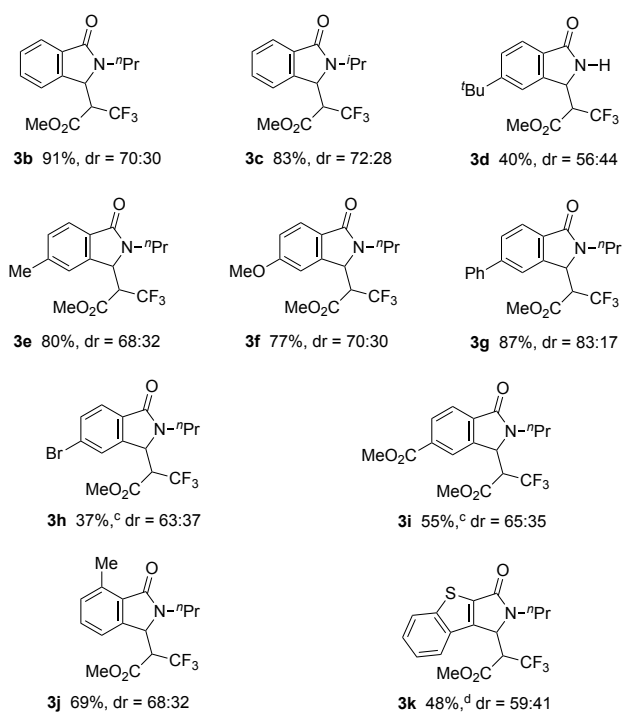
conducting the reaction efficiently. Without it, the yield of **3a** considerably decreased (entry 8). Even in the presence of AcOH and $Ag_2CO_3$, **4a** was obtained as a major product again in the case using $[Cp^*RhCl_2]_2$ as a catalyst (entry 9).

Under the optimized conditions (entry 7 in Table 1), we next examined the reactions using various benzamides **1** with **2** (Table 2). Both *N*-*n*- and *N*-*i*-propylbenzamides underwent the reaction smoothly to produce **3b** and **3c**, respectively, as diastereoisomer mixtures. In addition to these secondary amides, a primary amide, *N*-unsubstituted 4-*t*-butylbenzamide could also be employed for the present reaction to give *N*-H isoindolinone **3d**. The reactions of relatively electron-rich *N*-*n*-propylbenzamides possessing methyl, methoxy, and phenyl groups proceeded efficiently to afford **3e**-**g** in 77-87% yields. In contrast, the reactions of 4-bromo- and 4-methoxycarbonylbenzamides were sluggish even at 80 °C to give **3h** and **3i** in moderate yields. 2-Methyl substituted *N*-*n*-propylbenzamide coupled with **2** effectively to produce **3j**. Besides these benzamides, *N*-*n*-propylbenzo[*b*]thiophene-2-carboxamide also underwent the reaction at 60 °C to give 1,2-dihydro-3*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-3-one (**3k**) selectively.

**Table 2.** Reaction of Benzamides **1** with Methyl 2-Trifluoromethylacrylate (**2**)[a]

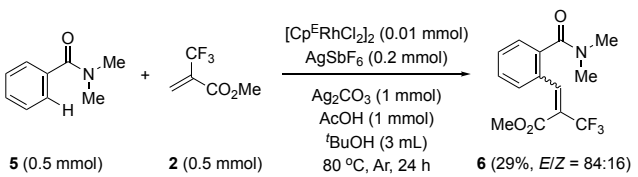



product yield (%)[b]



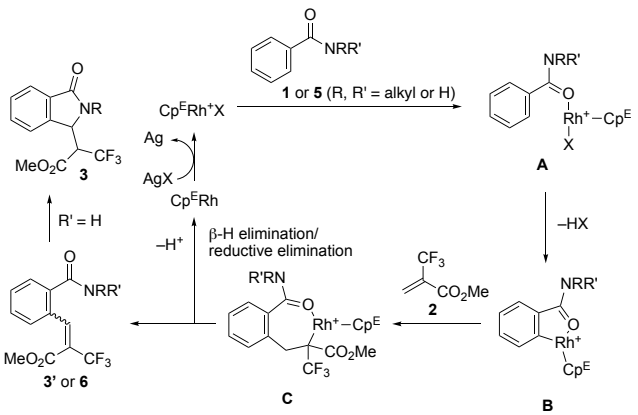

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $[Cp^ERhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.2 mmol), $Ag_2CO_3$ (1 mmol), AcOH (1 mmol) in $^t$BuOH (3 mL) under Ar at 40 °C for 24 h, unless otherwise noted. [b] dr (diastereomer ratio) was determined by $^1$H NMR. Isolated yield includes both diastereomers. [c] Reaction was conducted at 80 °C. [d] Reaction was conducted at 60 °C.

In addition to secondary and primary amides, a tertiary benzamide, *N*,*N*-dimethylbenzamide (**5**), also underwent the oxidative coupling with **2**. As expected, an acyclic *ortho*-alkenylated product **6** was formed as a mixture of geometric isomers, albeit with a low yield (Scheme 2).



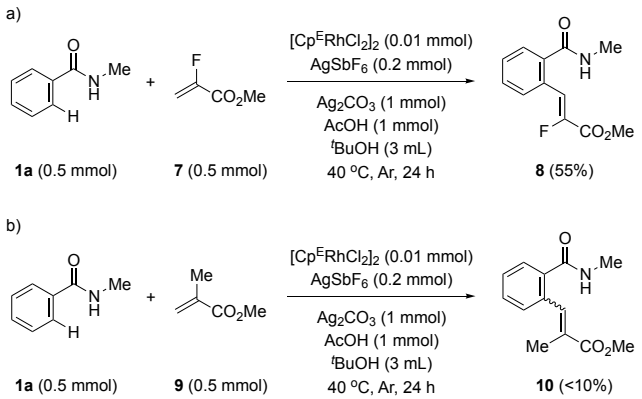

**Scheme 2.**

A plausible mechanism for the reaction of benzamides **1** and **5** with methyl 2-trifluoromethylacrylate (**2**) is illustrated in Scheme 3. As proposed in our previous paper for the redox-neutral coupling of **1** with 2-trifluoromethylacrylic acid,[8a] a seven-membered intermediate **C** seems to be formed through coordination of the amide directing group to a cationic $Cp^ERh^+$ species,[11] cyclorhodation at the *ortho*-position of **A**, and the insertion of **2** into the C-Rh bond of **B**. Subsequently, β-hydrogen elimination to liberate an *ortho*-alkenylated benzamide **3'** or **6** and reductive elimination may take place to form a $Cp^ERh(I)$ species, which is then oxidized by a silver salt to regenerate an active $Cp^ERh^+$ species. Finally, **3'** may undergo intramolecular nucleophilic addition to form isoindolinone **3**.




**Scheme 3.**

It was found that a strongly electron-withdrawing $CF_3$ group on the alkene moiety of **3'** is essential for inducing the intramolecular nucleophilic addition step. Thus, treatment of **1a** with methyl 2-fluoroacrylate (**7**) in place of **2** under standard conditions gave an acyclic *ortho*-alkenylated product **8** in 55% yield (Scheme 4a). No isoindolinone derivative was detected at all. In addition, the reaction of **1a** with methyl methacrylate (**9**) was sluggish to form only a small amount of *ortho*-alkenylbenzamide **10** as a geometric mixture (Scheme 4b).




**Scheme 4.**

In summary, we have demonstrated that isoindolinone derivatives possessing a trifluoromethyl group can be constructed from readily available benzamides and methyl 2-trifluoromethylacrylate. The oxidative coupling reaction of these substrates proceeds efficiently under rhodium catalysis through *ortho* C–H bond cleavage of benzamides. The choice of ligand for the rhodium(III) catalyst has been found to be important to promote the oxidative coupling. However, the exact role of ligand is obscure at the present stage. Work is underway for further understanding the effect of ligand.

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Supporting Information is available electronically on J-STAGE.

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