Ru(II)-catalyzed C7 trifluoromethylthiolation and thioarylation of indolines using bench-stable reagents

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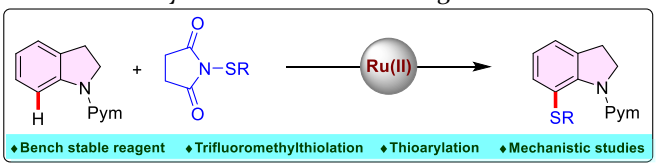
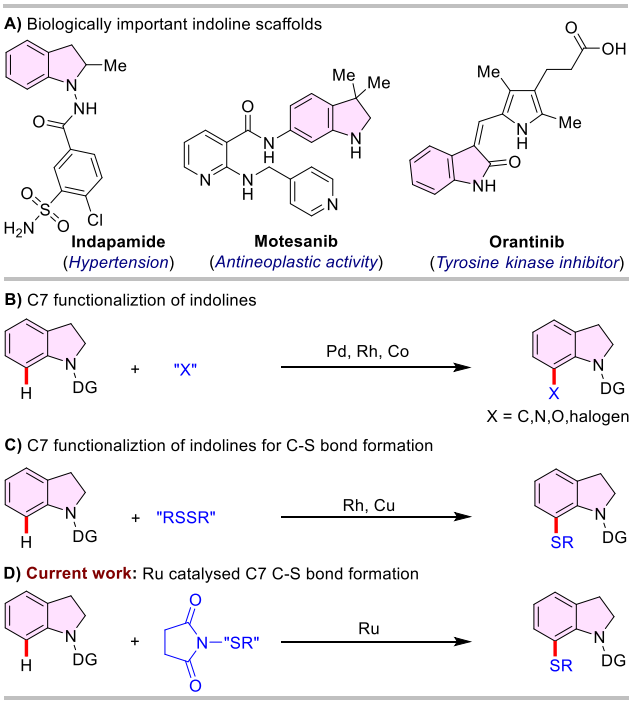
ABSTRACT: A Ru(II)-catalyzed C(sp²)-H trifluoromethylthiolation and thioarylation of indolines using bench-stable reagents have been explored. Diversely substituted indolines were successfully functionalized at C7 position in good to excellent yields. To support the proposed reaction pathway, radical quenching, deuterium labeling, KIE experiments, and reaction order determination were performed. Gram-scale synthesis and post-transformation of the synthesized product have also been performed to demonstrate the applicability of the developed catalytic protocol.



Site-selective C-H functionalization of heterocycles has emerged as a viable tool in modern heterocyclic chemistry.[1] Among the plethora of heterocycles, indoline scaffolds are important because they are found in many lead pharmaceuticals and natural products (**Scheme 1A**).[2] Classically, C7 functionalized indoline can be synthesized *via ortho*-lithation of *N*-carbamate indolines followed by electrophilic addition.[3] With the advancement in modern heterocyclic chemistry, C-H activation strategy provides an atom and step economic protocol for the direct functionalization of indolines. Despite these advancements, the protocols for functionalization of indolines are mainly limited to C-C, C-N, and C-X (X = halogens) bond formations (**Scheme 1B**).[2a, 4] C-S bond imparts some unique characteristics to the molecules such as enhanced bioavailability and lipophilicity and thus improving the pharmacokinetic properties of the molecules. SAr, -SCN, SCF_3 etc., are vital sulfur-containing functional groups whose importance spans pharmaceuticals and agrochemicals.[5] Thus, direct C-H functionalization of the indolines for C-S bond formation would be advantageous. In this direction, Wang group developed a Rh(III)-catalyzed protocol for C_7 thioarylation of indolines using diphenyl sulfide as the coupling partner.[4b] Later on, Song group reported Cu-catalysed C7 sulfonylation of indolines using tosyl chloride (**Scheme 1C**).[6] Recently, there has been an emphasis on utilizing the electrophilic thiolating bench stable reagents for the C-S bond formation.[7] In 2014, Xu and Sen utilized *N*-trifluoromethylthiosuccinimide as a stable reagent for direct C-H thiotrifluoroomethylation of arenes.[8] Later, Tatiana group exploited various reagents for C-S bond formation *via* C-H activation.[9] In 2021, we have developed a protocol for direct thiotrifluoroomethylation of 8-methyl quinolines and oxime using a bench-stable thiotrifluoromethylating agent.[7a] In our ongoing quest on transition metal catalyzed synthesis and functionalization of *N*-heterecycles,[10] herein, we have demonstrated a Ru(II)-catalyzed strategy for the C7 trifluoromethylthiolation and thioarylation of indolines using bench stable reagents (**Scheme 1D**). To our knowledge, there has been no report on the Ru(II)-catalyzed C7 trifluoromethylthiolation and thioarylation of indolines.

Scheme 1. Importance and C7 functionalization of indolines.



At the outset of the work, we carried out the reaction between *N*-pyrimidylindoline (**1a**) and *N*-(trifluoromethylthio)succinimide (**2a**) in the presence of [Ru(*p*-cymene)Cl_2]$_2$/$AgSbF_6$ in HFIP at 100 °C for 24 h. To our delight, the desired C7 trifluoromethylthiolated was formed in 55% yield (**Table 1, entry 2**). The desired product was confirmed by NMR and ESI-mass spectrometry. No product was obtained in the absence of [Ru(*p*-cymeme)Cl_2]$_2$/$AgSbF_6$ (**Table 1, entry 3**). Other acids, such as PivOH or AdCOOH, in place of AcOH acid afforded inferior results (Table 1, entries 4-5). TFE in lieu of HFIP gave

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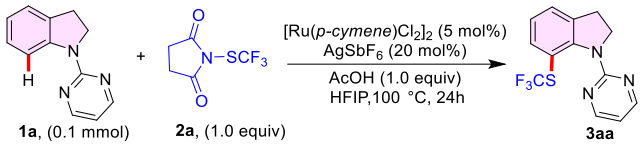
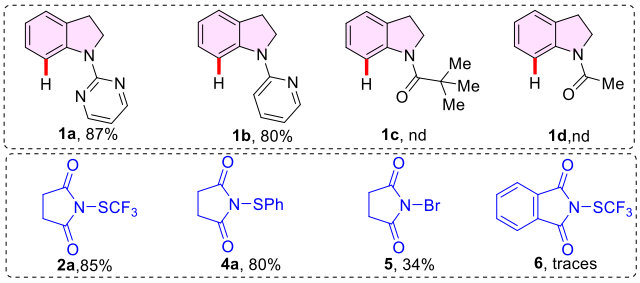
the desired product in 30% yield (**Table 1, entry 6**). Lowering the reaction temperature decreased the reaction yield (**Table 1, entries 7-9**). The use of $[RhCp^*Cl_2]_2$ in place of $[Ru(p\text{-cymene})Cl_2]_2$ provided the desired product in 85% yield (**Table 1, entry 10**). No product was obtained when $CoCp^*(CO)I_2$ was used as a catalyst (**Table 1, entry 11**). Although 2-pyridyl (**1b**) as a directing group gave the desired product in 80% yield, other directing groups were not found compatible under the developed reaction condition (**Table 1, entries 12-13**). Other electrophilic sources, such as *N*-(phenylthio)succinimide (**4a**) and *N*-bromosuccinimide (**5**) gave the corresponding thioarylated and brominated indolines in 80% and 34% yield, respectively, whereas *N*-(trifluoromethylthio)phthalimide (**6**) failed to provide any product. (**Table 1**, **entries 14** and **15**). No product was observed in the absence of the catalyst.[11]

Table 1. Optimization study.[a]



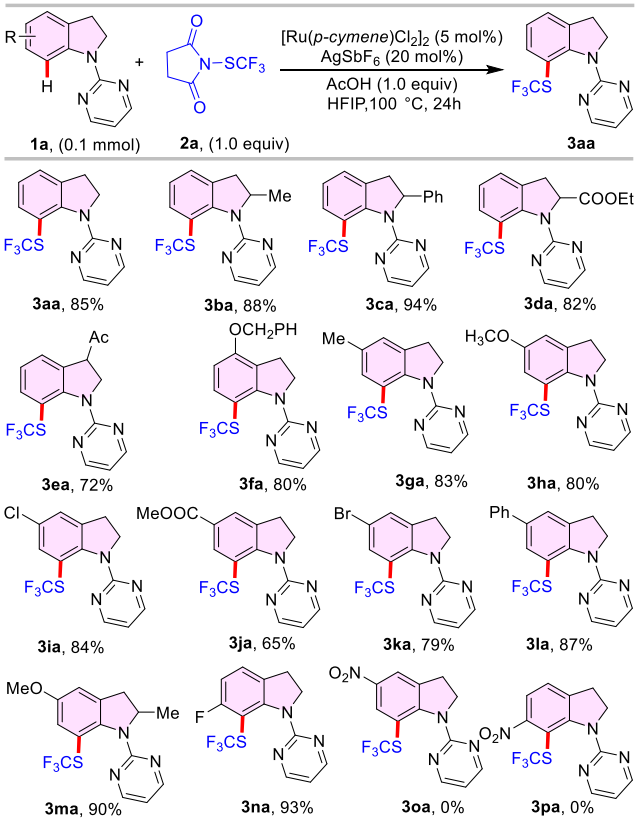
Sr. no.	Variation from standard condition	yield (%)[b]
1.	-	87 (85)[c]
2	Without AcOH	55
3	Without $[Ru(p\text{-cymene})Cl_2]_2$/$AgSbF_6$	nd
4	PivOH instead of AcOH	42
5	AdCOOH instead of AcOH	54
6	TFE instead of HFIP	30
7	At 80 °C	60
8	At 60 °C	50
9	At RT	23
10	Rh(III) instead of $[Ru(p\text{-cymene})Cl_2]_2$	85
11	Co(III) instead of $[Ru(p\text{-cymene})Cl_2]_2$	Nd
12	**1b** instead of **1a**	80
13	**1c** or **1d** instead of **1a**	nd
14	**4a** instead of **2a**	80
15	**5** instead of **2a**	34



[a]Reaction conditions: **1a** (0.10 mmol), **2a** (1.0 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), AcOH (1.0 equiv), HFIP (0.5 mL), 100 °C, 24 h. [b]NMR yield of crude reaction mixture using tetrachloroethane as an internal standard. [c]Isolated yield in parentheses, nd = not detected. Rh(III) = $[RhCp^*Cl_2]_2$; Co(III) = $CoCp^*(CO)I_2$

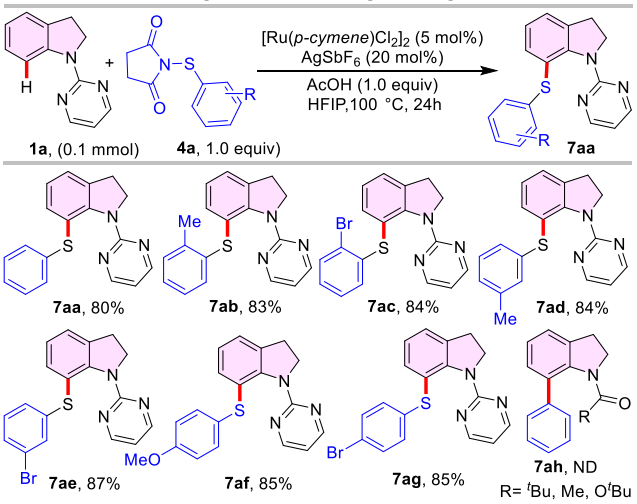
Next, diversely substituted indolines were tested under the developed reactions (**Scheme 2**). C2 substituted indolines gave the desired product in excellent yield (**3ba-3da**). Indolines substituted with acetyl at C3 position (**3ea**) and benzyloxy at C4 position (**3fa**) reacted smoothly to provide the desired product in good yields. Both electron-donating and electron-withdrawing groups at C5 position were well tolerated and gave the desired products in good to excellent yields (**3ga-3ma**). Indoline substituted with fluro at C6 position provided the desired product in 93% yield (**3na**). Unfortunately, nitro-substituted indolines failed to react (**3oa-3pa**).

Scheme 2. Trifluoromethylthiolation of *N*-pyrimidylindoline.[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.0 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%), AcOH (1.0 equiv), HFIP (1.0 mL), 100 °C, 24 h

Scheme 3. Thioarylation of *N*-pyrimidylindoline.[a]

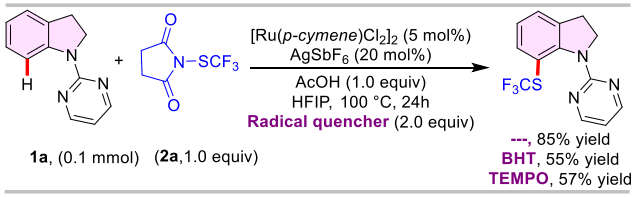


[a]Reaction conditions: **1a** (0.1 mmol), **4a** (1.0 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%), AcOH (1.0 equiv), HFIP (1.0 mL), 100 °C, 24 h

After exploring the trifluoromethylthiolation of indolines, C7 thioarylation of indolines was explored (**Scheme 3**). Initially, **1a** was reacted with **4a,** to get the desired thiaolated product **7aa** in 80% yield. The electron-donating and electron-withdrawing substituents at the *ortho*-position of aryl ring did not affect the reaction outcome and provided the desired products with excellent yields (**7ab-7ac**). The methyl and bromo groups have also been well tolerated and gave the desired product in good yields (**7ad-7ae**). Excellent yields were obtained with *para*-substituted aryl ring (**7af-7ag**).

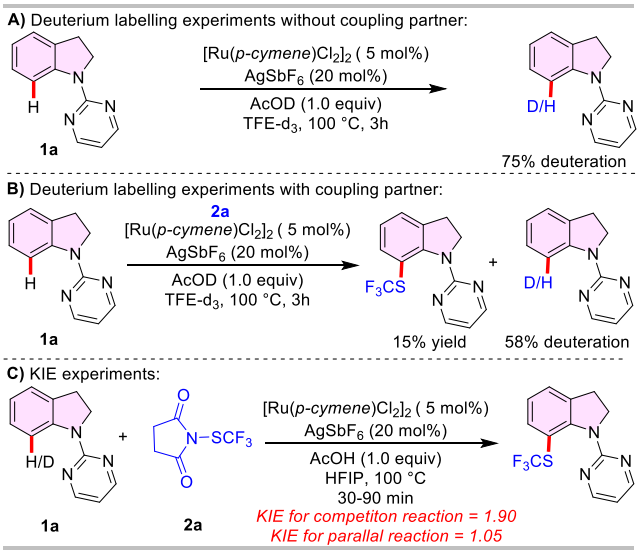
Next, a few mechanistic experiments were carried out to understand the course of the reaction. To check the radical pathway, the reaction was carried out in the presence of two different radical quenchers (**Scheme 4**). The desired product was obtained in 55% and 57% yield, implying that a radical pathway might not be involved under current reaction condition. **Int-A** was observed in the crude reaction mixture's ESI-MS analysis, further confirming a radical pathway's non-involvement.

Scheme 4. Radical quenching experiments.



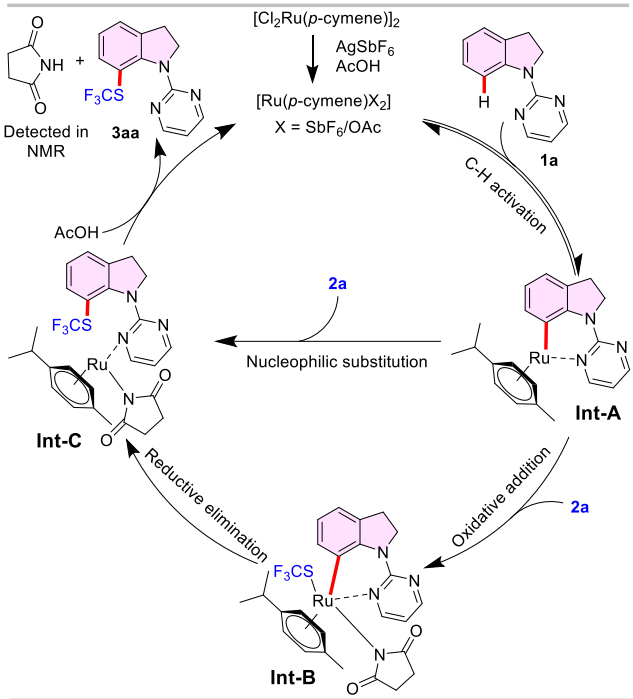
Deuterium labeling experiments were performed by reacting **1a** with or without **2a** under standard reaction condition in the presence of AcOD and TFE-d_3 for 3h to get 75% and 58% deuteration, respectively, at the C7 position of the recovered **1a,** suggesting the reversible nature of the C-H activation step (**Scheme 5**). Competition and parallel reaction (performed using the initial rate method) suggested that C-H activation might not be the rate-determining step. The reaction order was found to be first with respect to **1a** and second with respect to **2a**. The total order of the reaction was found to be three.[11] These experiments further confirmed that C-H activation step might not be the rate-determining step.

Scheme 5. Deuterium labelling and KIE experiments.



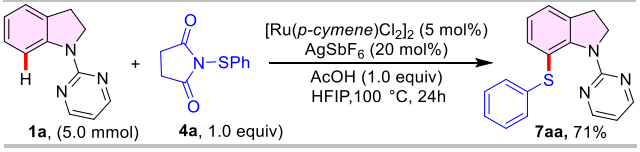
Based upon these preliminary mechanistic experiments and literature reports,[4a, 7a, 12] a plausible reaction mechanism was proposed (**Scheme 6**). The reactive Ru(II) species was generated initially, which reacted with **1a** *via* C-H activation to yield **Int-A**. Now, **2a** can react with **Int-A** to provide **Int-C** through nucleophilic substitution or oxidation addition followed by reductive elimination. **Int-C** in the presence of AcOH provided the desired product **3aa**, succinimide along with the regeneration of active Ru(II)-species to continue the cycle.

Scheme 6. Plausible mechanism.



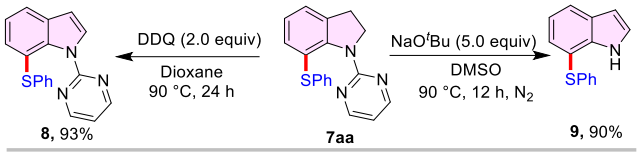
The reaction proceeded smoothly at the gram scale to provide the desired product in 71% yield (**Scheme 7**).

Scheme 7: Gram scale synthesis.



The title compound (**7aa**) was further subjected to post-transformation reaction (**Scheme 8**).[4a] The oxidation and deprotection of the **7aa** gave the desired product in 93% 90% yields, respectively.

Scheme 8: Post transformations



Conclusion

We have successfully developed Ru(II)-catalyzed novel strategy for trifluoromethylthiolation and thioarylation of indolines using an electrophilic thiolating reagent. The reaction was applicable up to gram-scale synthesis. The synthetic utility of the developed protocol further defined by easy uninstallation of directing group and transformation of functionalized indoline to indole. Preliminary mechanistic experiments were performed to support the proposed reaction pathway.

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ASSOCIATED CONTENT

Supporting Information

Notes

The authors declare no competing financial interest.

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