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Z-selective Pd-Catalyzed 2,2,2-Trifluoroethylation of Acrylamides at Room Temperature

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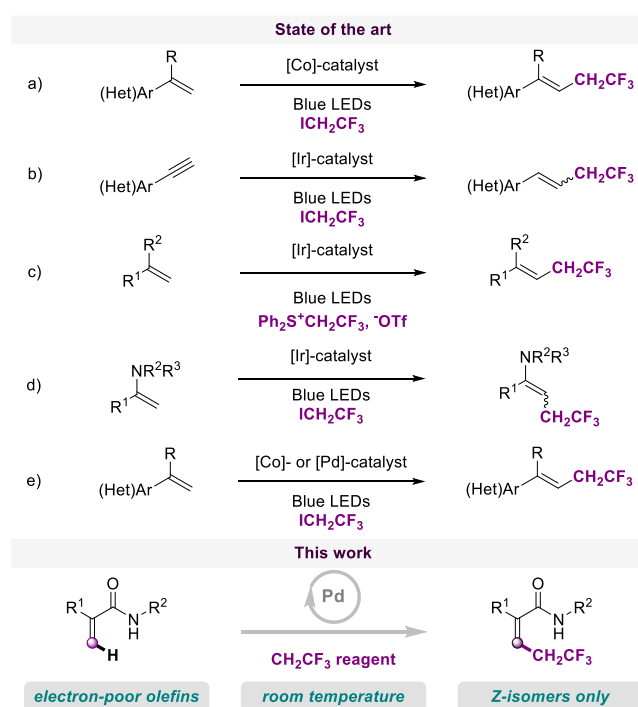
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A straightforward 2,2,2-trifluoroethylation of acrylamides by Pd-catalyzed C–H bond activation was reported by using a fluorinated hypervalent iodine reagent as a coupling partner. At room temperature, this additive-free approach allowed the synthesis of Z-2,2,2-trifluoroethylated acrylamides (19 examples, up to 73% yield) in a stereoselective manner. Under these mild reaction conditions, the methodology turned out to be functional group tolerant and mechanistic studies gave us a better understanding of the transformation.

The diversity of fluorinated moieties and their unique properties^{1a} offer an incredible toolbox for the discovery of new active ingredients because of the possibility of modulating the properties of molecules at will.^{1b} Consequently, the search for original fluorine-containing groups, along with the quest for new methodologies to introduce them onto various scaffolds² is really appealing. These endeavors encouraged researchers to develop new approaches to tackle persisting challenges, resulting in a constantly increasing demand on the part of pharmaceutical and agrochemical industries.³ Besides, transition metal-catalyzed C–H bond activation is nowadays a key modern tool in organic chemistry⁴ and merging C–H bond activation with organofluorine chemistry has already demonstrated its efficiency to straightforwardly access fluorinated derivatives.^{2b,5} In this context, we turned our attention to the 2,2,2-trifluoroethyl group (CH₂CF₃),⁶ an important motif, bioisostere of the ethyl group, found in various compounds of interest⁷ such as the indoleamine 2,3-dioxygenase (IDO) inhibitor.⁸ The synthesis of 2,2,2-trifluoroethylated molecules generally relies on two main retrosynthetic pathways: the trifluoromethylation of a suitable precursor⁹ or the direct introduction of the CH₂CF₃ residue. Although several major contributions were reported for the direct 2,2,2-trifluoroethylation of various classes of compounds,^{10,11} the direct functionalization of non prefunctionalized alkene derivatives was scarcely explored.¹² Among them, Carreira and co-workers reported the Co-catalyzed 2,2,2-trifluoroethylation of styrene derivatives with ICH₂CF₃ under blue light irradiation leading to the expected products as *E*-isomers (Scheme 1, eq. a).^{12a} The functionalization of alkynes,^{12b} alkenes^{12c} and even enamine derivatives^{12d} using Ir-based photocatalysts was studied using either ICH₂CF₃ or a sulfonium salt (Ph₂S⁺CH₂CF₃, [−]OTf) as CH₂CF₃ sources (Scheme 1, eq. b-d). Recently, protocols based on

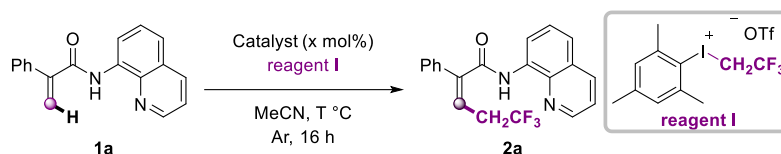
visible light induced 2,2,2-trifluoroethylation of styrenes under Co-^{12e} and Pd^{12f}-catalysis were reported (Scheme 1, eq. e). Worth mentioning that in all cases, those methodologies provided a selective access to *E*-isomers or eventually to *E/Z* mixtures, except in case of the work of Loh^{12d} (Scheme 1, eq. d), for which a single example of *Z*-enamide was reported. Despite these advances, a general method for the *Z*-selective 2,2,2-trifluoroethylation of functionalized electron-poor olefins is yet to be developed. As some limitations exist with the ICH₂CF₃ reagent, such as the slow oxidative addition of the metal to the C-I bond and the undesired I-F elimination side-reaction,¹³ we thought to use the mesityl(trifluoroethyl)iodonium triflate (reagent I), an electrophilic reagent developed by the Novák group.^{6a,c,e} As part of our research program,¹⁴ we report herein the Pd-catalyzed 2,2,2-trifluoroethylation of acrylamides at room temperature, providing a straightforward access to highly functionalized and difficult-to-build up 2,2,2-trifluoroethylated scaffolds as only *Z* isomers.



Scheme 1. State of the art and present work.

At the beginning of this study, the *p*-phenyl acrylamide **1a** was reacted with the reagent I at 120 °C using Pd(TFA)₂ as the catalyst (table 1, entry 1). Gratifyingly, the expected 2,2,2-trifluoroethylated product **2a** was observed in 38% ¹⁹F NMR yield. It turned out that tuning the temperature of the reaction was crucial to favor the expected transformation, probably due to the low stability of the reagent I at high temperature (Table 1, entries 1-3). Indeed, when the reaction was carried out at 25 °C, **2a** was isolated in 49% yield as a single diastereoisomer. The catalyst loading was then studied and using 15 mol% Pd catalyst, **2a** was isolated in 52% yield (Table 1, entry 4). When the ratio between the acrylamide **1a** and the reagent I was changed, **2a** was obtained in a lower yield (Table 1, entry 5). Pleasingly, switching Pd(TFA)₂ for Pd(OAc)₂ had a beneficial effect on the outcome of the reaction, as **2a** was isolated in 66% yield (Table 1, entry 6). The reaction temperature and the catalyst loading were then investigated again and the transformation was even possible at 10 or 0 °C, although **2a** was

obtained in lower yields (Table 1, entries 7-9). Using DMF as the solvent led to a complete shutdown of the reactivity (Table 1, entry 10). When the 2-iodo-1,1,1-trifluoroethane was used as the coupling partner instead of the reagent **I** or in the absence of the palladium catalyst, no reaction occurred (Table 1, entries 11 and 12). These control experiments highlighted the key importance of the use of the Pd(OAc)₂ and the need of the reagent **I** in this transformation.

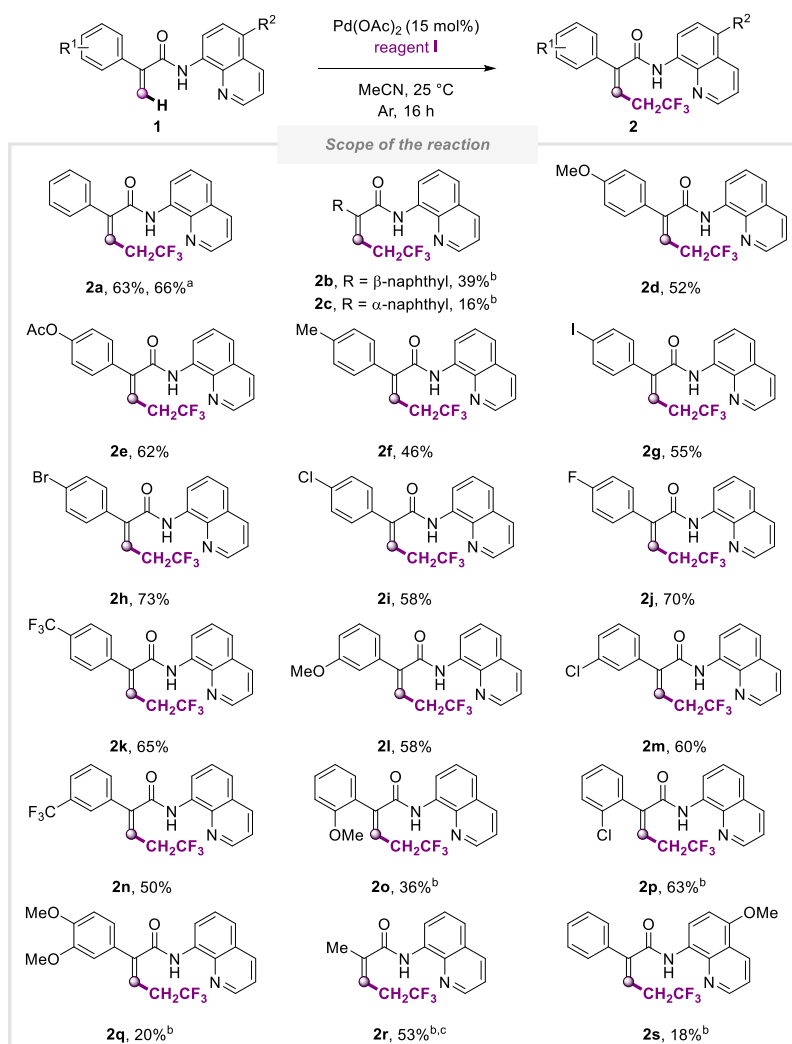


entry	catalyst	X	T (°C)	yields (%)
1	Pd(TFA) ₂	10	120	(38) ^a
2	Pd(TFA) ₂	10	50	41
3	Pd(TFA) ₂	10	25	49
4	Pd(TFA) ₂	15	25	52
5 ^b	Pd(TFA) ₂	15	25	43
6	Pd(OAc)₂	15	25	66
7	Pd(OAc) ₂	15	10	62
8	Pd(OAc) ₂	15	0	45
9	Pd(OAc) ₂	10	25	20
10 ^c	Pd(OAc) ₂	15	25	NR
11 ^d	Pd(OAc) ₂	15	25	NR
12	None	/	25	NR

Reaction conditions: **1a** (0.2 mmol), **I** (0.1 mmol), catalyst (10 or 15 mol%), MeCN (0.5 mL), T (°C), 16 h, Argon. Isolated yields were given. ^a ¹⁹F NMR yields using the α,α,α-trifluoroacetophenone as an internal standard. ^b **1a** (0.1 mmol) and **I** (0.2 mmol) were used. ^c DMF instead of MeCN. ^d ICH₂CF₃ instead of **I**. NR: no reaction

With the best reaction conditions in hand, we investigated the scope of the reaction (Scheme 2). In general, the 2,2,2-trifluoroethylation of various *para*-aryl acrylamides derived from the 8-aminoquinoline as a directing group went smoothly, affording the products (**2a-q**) in moderate to good yields. With the assistance of the bidentate directed group, the approach was fully stereoselective towards the formation of the challenging *Z*-isomer **2**. The stereochemistry of the compounds was ascertained by 2D NOESY NMR experiments on the compounds **2d** and **2g**.¹⁵ Note that in some cases (compounds **2b-c**, **2o-s**), solubility issues have been encountered and bypassed using a 2:8 mixture of CH₂Cl₂/MeCN.¹⁶ Acrylamides substituted with a naphthyl group were 2,2,2-trifluoroethylated and the transformation turned out to be sensitive to the steric hindrance, as **2b** was obtained in a better yield than **2c**. Then, an array of *para*-substituted *para*-aryl acrylamides bearing electron donating groups (**1d-f**), halogens (**1g-j**) and a trifluoromethyl residue **1k** was functionalized and the expected products (**2d-k**) were isolated in moderate to good yields. The 2,2,2-trifluoroethylation of *meta*- and *ortho*-substituted *para*-aryl acrylamides (**1l-p**) went smoothly under our reaction conditions showcasing that the substitution pattern of the aromatic substituents did not affect the reaction outcome. The transformation was tolerant to various functional groups such as ester (**1e**) and halogens (Cl, Br and even I, compounds **1g-j**, **1m**, **1p**), allowing the possibility of post-functionalization reactions. The disubstituted compound **1q** was also a suitable substrate,

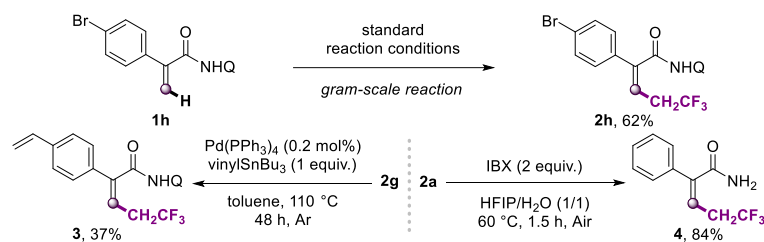
albeit **2q** was isolated in 20% yield. Pleasingly, the 2-methyl acrylamide **1r** was 2,2,2-trifluoroethylated, giving **2r** in 53% yield. A change of the directing group has a significant impact in this process. Indeed, with the amide derived from the 5-methoxy-8-aminoquinoline, the corresponding product **2s** was obtained in a poor 18% yield. Note that when styrene was used, no reaction occurred, reinforcing the importance of the directing group in the transformation.^{12f,15}



Scheme 2. Scope of the 2,2,2-trifluoroethylation reaction. Reaction conditions: acrylamide **1** (0.8 mmol, 2 equiv.), **I** (0.4 mmol, 1 equiv.), Pd(OAc)₂ (15 mol %), MeCN (2 mL), 25 °C, 16 h, argon. Isolated yields were given. ^a Reaction on 0.1 mmol scale. ^b A CH₂Cl₂/MeCN mixture (2:8) was used. ^c Reaction on 0.2 mmol scale.

To further illustrate the synthetic utility of this methodology, a scale-up of the reaction was conducted and when 1 gram of **1h** was used, the corresponding product **2h** was isolated in 62% yield (Scheme 3). In addition, taking benefit from the functional group tolerance of the transformation, a post-functionalization of **2g** was possible, offering an access to the product **3** thanks to a Stille reaction.¹⁷ Pleasingly, the directing group was efficiently cleaved in the

presence of IBX, and the corresponding primary amide **4** was isolated in a high yield.¹⁸ This highlighted the key advantage of using a simple and cleavable directing group.



Scheme 3. Scale-up and post-functionalization reactions. See supporting information for details. Isolated yields were given. Q = 8-quinolyl.

To gain insights on the reaction mechanism involved in the transformation, several experiments were conducted (Scheme 4a-e).¹⁵ First, radical trapping experiments were performed, and the results suggested that a free radical pathway might be ruled out. Indeed, in the presence of the 3,5-di-*tert*-4-butylhydroxytoluene (BHT, 2 equiv.) as a radical quencher, no impact on the outcome of the reaction was observed. However, in case of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl, 2 equiv.), **2a** was observed in only 16% ¹⁹F NMR yield, probably due to a competitive side-reaction between the reagent **I** and TEMPO, as the TEMPO-CH₂CF₃ adduct was detected by HRMS upon mixing.^{11c,15,19} Then, a scrambling experiment was carried out and no H/D exchange was observed.¹⁵ In addition, a kinetic isotopic effect (KIE) of 1.8²⁰ was determined with parallel experiments starting either from **1a** or [D]-**1a**. Competition experiments were also carried out in a one pot process and a KIE of 2.4 was measured.¹⁵ All these observations suggested that the C–H bond palladation was irreversible and probably the rate-determining step. Finally, the palladacycle **Int-1a** was successfully prepared from **1a** and Pd(OAc)₂ in MeCN.^{15,21} When this latter was reacted with the reagent **I**, the expected product was isolated in 24% yield (48% ¹⁹F NMR yield), suggesting the plausible involvement of this palladacycle as a reaction intermediate. Considering these results and the literature data,^{14a-e} the following reaction mechanism was suggested (Scheme 4). The intermediate **A** was generated *via* the chelation of the palladium catalyst to the directing group. Then, the formation of the palladacycle **B** occurred, presumably by means of a C–H concerted metalation deprotonation (CMD) process. This latter underwent an oxidative addition with the reagent **I** (species **C**) followed by a reductive elimination to afford the expected product and regenerate the catalyst.

In summary, we have developed a straightforward protocol enabling the Pd-catalyzed 2,2,2-trifluoroethylation of a panel of β -substituted acrylamide derivatives (19 examples, up to 73% yield) at room temperature using a hypervalent iodine reagent as the CH₂CF₃ source. With a practical and simple catalytic system, the transformation was completely stereo-selective. The mechanistic studies shed light on the key steps involved in this catalytic cycle. Compared to existing methods, this approach constitutes a unique synthetic pathway towards *Z*-isomers. We do believe that this methodology has an untapped potential to access 2,2,2-

trifluoroethylated molecules and materials and will be of high interest for the scientific community.

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Conflicts of interest

There are no conflicts to declare.

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For more details, see the Supporting Information.

Note that in some cases some solubility issues were observed and the products were obtained in a lower yield. To tackle that issue, the replacement of acetonitrile by a 2:8 CH₂Cl₂/MeCN mixture was beneficial.

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