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2-(Trifluoromethyl)indoles via Pd(0)-Catalyzed C(sp^3)−H Functionalization of Trifluoroacetimidoyl Chlorides

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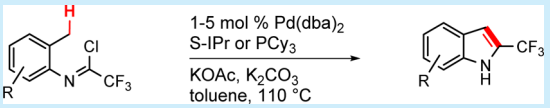
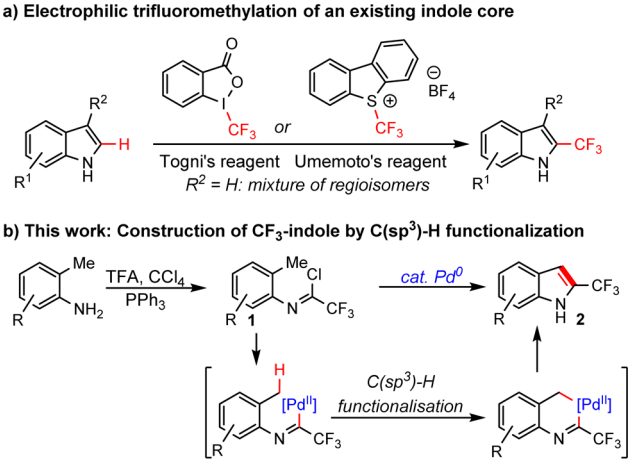
Supporting Information

ABSTRACT: Perfluoroalkylated indoles are valuable compounds in drug discovery. A Pd(0)-catalyzed C(sp^3)−H functionalization enables access to 2-(trifluoromethyl)indoles from trifluoroacetimidoyl chlorides. These are stable compounds, easily obtained from anilines. The cyclization operates with catalyst loadings as low as 1 mol % and accommodates a variety of substituents.



Fluorinated molecules have found extensive applications as active ingredients in pharmaceuticals and agrochemicals. In search of novel development candidates, the systematic introduction of fluorine atoms and perfluoroalkyl groups in scaffolds has become widespread, as such substitution affects the metabolic stability, conformation, and dipole moment of a given molecule, ultimately resulting in altered biological activity.[1] The indole scaffold is a prevalent motif in biologically active natural and unnatural products.[2] The increasing interest in fluorinated derivatives[3] led to the development of methods to access 2-(trifluoromethyl)indoles.[4] These are largely based on the modification of an existing indole ring[5−7] and require a stoichiometric amount of an electrophilic trifluoromethylating reagent such as Togni's[6] or Umemoto's reagent[7] (Scheme 1). Reports on the Fischer indole synthesis using perfluoroalkylated substrates,[8] as well as other cyclization strategies, are known.[9] However, in many cases, one requires either prefunctionalized starting materials or regioselectivity issues pose important limitations, along with the frequent use of protective groups. Transition-metal-catalyzed C−H functionalization became an attractive strategy for the construction of complex molecules often through complementary disconnections.[10] For instance, C−C bond-forming processes initiated by Pd(0)-catalyzed C(sp^3)−H functionalizations have been a focus of investigation over the past years. Whereas a wide range of different C−H groups was investigated,[11−14] the electrophilic partner was mostly limited to aryl halides,[12] vinyl halides,[13] or triflates.[14] In stark contrast, the use of trifluoroacetimidoyl chlorides remains almost completely underdeveloped in this context.[15] This functional group can be conveniently accessed by simply exposing the parent amine to trifluoroacetic acid, CCl_4, and PPh_3. Moreover, it is stable toward silica gel chromatography.[16]

Scheme 1. Complementary Strategies for the Synthesis of 2-(Trifluoromethyl)indoles



Herein we report a method for 2-(trifluoromethyl)indoles **2** via an Pd(0)-catalyzed C(sp^3)−H functionalization of trifluoroacetimidoyl chlorides **1** derived from widely available *o*-methylanilines (Scheme 1). After initial oxidative addition to **1**, the adjacent CH_3 group is activated, enabling reductive elimination and tautomerization to indole **2**.

Initially, 2,6-dimethylaniline derivative **1a** was selected as the model substrate (Table 1). Exposure of **1a** to catalytic amounts of Pd(0) and PPh_3 as the ligand provided the desired trifluoromethyl-substituted indole, albeit in a moderate yield of 24% (entry 1). The use of PCy_3 led to a very smooth reaction, giving **2a** in 97% yield (entry 2). The catalyst loading was lowered to 2.0 mol % of $Pd(dba)_2$, and air-stable $PCy_3 \cdot HBF_4$ could be employed with no impact on the reaction performance (entry 3). Moreover, inexpensive KOAc could be used without any loss of reactivity (entry 4). As second model substrate, 2-methylaniline derivative **1b** was selected to expand the methodology to a broader substrate class. However, when monosubstituted trifluoroacetimidoyl chloride **1b** was submitted to previous reaction conditions, only traces of indole **2b**

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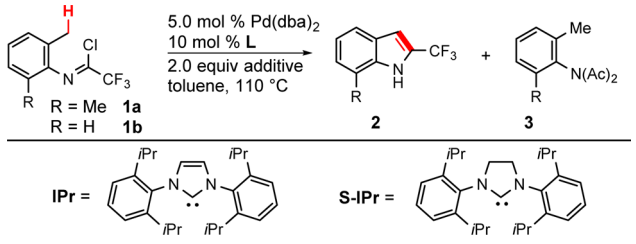
Table 1. Optimisation of the 2-CF_3-indole Formation[a]



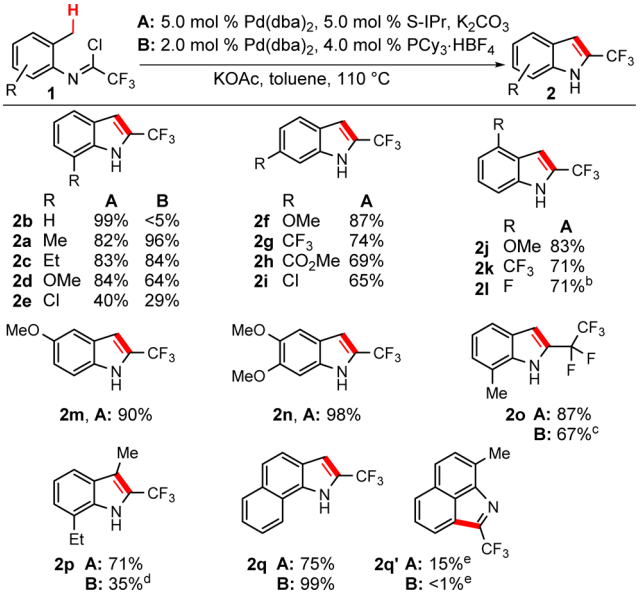
entry	1	L	additive	2[b] (%)	3[b] (%)
1	**1a**	PPh_3	CsOAc	24	
2	**1a**	PCy_3	CsOAc	97	
3[c,d]	**1a**	PCy_3	CsOAc	90	
4[c,d]	**1a**	PCy_3	KOAc	96[e]	
5[c,d]	**1b**	PCy_3	KOAc	<5	
6	**1b**	PCy_3	CsOAc	17	34
7	**1b**	PPh_3	CsOAc	<5	50
8	**1b**	IPr	CsOAc	<5	25
9	**1b**	S-IPr	CsOAc	48	16
10	**1b**	S-IPr	NaOAc	53	10
11	**1b**	S-IPr	KOAc	56	11
12[f]	**1b**	S-IPr	KOAc, K_2CO_3 (2 equiv)	49	<5
13[g]	**1b**	S-IPr	KOAc, K_2CO_3 (3.5 equiv)	99[e]	<1
14[h]	**1b**		CsOAc	0	14

[a]Conditions: 0.1 mmol of **1**, 5.0 mol % of $Pd(dba)_2$, 10.0 mol % of **L**, 2.0 equiv of additive, 0.1 M in toluene, 110 °C for 12 h. [b]Determined by ^1H NMR with an internal standard. [c]2.0 mol % of $Pd(dba)_2$, 4.0 mol % of **L**. [d]0.2 M. [e]Isolated yield. [f]0.5 equiv of KOAc. [g]5.0 mol % of **L**. [h]No $Pd(dba)_2$.

were detected (entry 5). An increased catalyst loading of 5.0 mol % formed **2b** in 17% yield along with 34% of side product **3b** (entry 6). Among the tested ligands (entries 6–9), S-IPr delivered the most promising result, giving 48% yield of the desired indole **2b** and just 16% of **3b** (entry 9). Further screening revealed that KOAc is superior (56% **2b**, entry 11). Moreover, the addition of K_2CO_3 almost completely suppressed the formation of side product **3b** (entry 12). Adjustments of the amount and ratio of the two additives as well as the Pd/ligand ratio to 1:1 furnished **2b** in nearly quantitative yield (entry 13). Surprised by the fact that the amounts of formed imide **3b** strongly depended on the employed ligand, substrate **1b** was exposed to reaction conditions in the absence of the palladium catalyst. In this case, imide **3b** is observed in minor quantity (14%, entry 14), suggesting a contribution of the Pd catalyst to its formation.

Next, the cyclization of a range of trifluoroacetimidoyl chlorides was investigated (Scheme 2). For the C–H functionalization of 6-substituted imidoyl chlorides, the Pd(0)/S-IPr catalyst system (conditions A) showed often superior performance compared to the Pd(0)/PCy_3 system (conditions B). Both conditions were well suited for the synthesis of 7-alkylindoles **2a** and **2c**, and higher yields of heteroatom-containing **2d**,**e** were obtained using conditions A. Moreover, trifluoroacetimidoyl chlorides **1f**–**l** substituted in *meta*-position to the *N*-atom underwent cyclization delivering indoles decorated with functional groups such as methyl ester (**2h**), CF_3 (**2g**, **2k**) and halogen atoms (**2i**, **2l**) in good to excellent yields. 2-Methyl-1-naphthyl derivative **1q** reacted well with the Pd(0)/S-IPr catalyst but provided a 5:1 mixture of **2q** and its C(sp^2)–H functionalization product **2q′**. In contrast, the Pd(0)/PCy_3 catalyst system gave exclusive rise to indole **2q**

Scheme 2. 2-CF_3-indoles Scope of the C(sp^3)–H Functionalization[a]

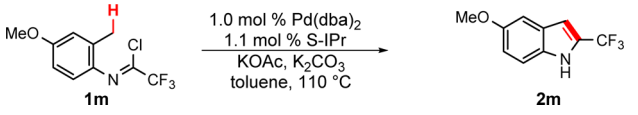


[a]Conditions A: 0.1 mmol of **1**, 5.0 mol % of $Pd(dba)_2$, 5.0 mol % of S-IPr, 2.0 equiv of KOAc, 3.5 equiv of K_2CO_3, 0.1 M in toluene, 110 °C for 12 h. Conditions B: 0.1 mmol of **1**, 2.0 mol % of $Pd(dba)_2$, 4.0 mol % of PCy_3·HBF_4, 2.0 equiv of KOAc, 0.2 M in toluene, 110 °C for 12 h; isolated yields. [b]0.5 mmol scale. [c]83% conversion. [d]53% conversion. [e]^1H NMR yield.

in almost quantitative yield. Besides trifluoromethyl, longer fluorinated chains such as the C_2F_5 group (**1o**) provide the corresponding indole in very good yield (87%, conditions A; 67%, conditions B). Moreover, the transformation accommodates in addition to the methyl group activation as well methylene groups. For instance, ethyl-substituted substrate **1p** provides selectively 2,3-disubstituted indole **2p**. Conditions A, using S-IPr as the ligand, were found to provide the better reactivity.

Further investigations were conducted with substrate **1m** toward the scalability of the process (Table 2). First, the

Table 2. Scale-up and Reduced Catalyst Loadings[a]



entry	1m (mmol)	c (M)	conv[b] (%)	2m[b] (%)
1	2.0	0.50	46	30
2	2.0	0.40	84	70
3	2.0	0.25	100	85[c]
4	10	0.25	100	77[c]

[a]Conditions: **1m**, 1.0 mol % of $Pd(dba)_2$, 1.1 mol % of S-IPr, 2.0 equiv of KOAc, 3.2 equiv of K_2CO_3, toluene, 110 °C for 20 h. [b]Determined by ^1H NMR with an internal standard. [c]Isolated yield.

catalyst loading was lowered to 1.0 mol % while the concentration was increased 5-fold (entry 1). Indole **2m** was obtained in 30% yield, and the reaction stalled at 46% conversion. The concentration has a significant influence (entries 1–3), and an optimum was found at 0.25 M, giving **2m** in 85% isolated yield. These conditions proved to be

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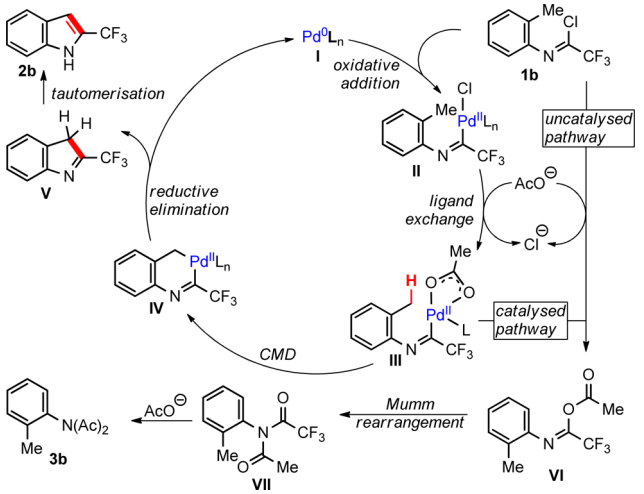
suitable for further scale up, and 2.5 g (10.0 mmol) of **1m** delivered **2m** in 77% isolated yield (entry 4).

On the basis of previous work,[17] the following reaction mechanism is likely (Scheme 3). Following the oxidative

Scheme 3. Proposed Reaction Mechanism



addition of the Pd(0) catalyst to the C−Cl bond of substrate **1b**,[18] ligand exchange leads to intermediate **III**. The desired pathway proceeds with carboxylate-assisted concerted metalation−deprotonation (CMD),[19] forming palladacycle **IV**. Upon C−C bond-forming reductive elimination, the catalyst is regenerated and intermediate **V** readily tautomerizes to furnish indole **2b**. The observed imide side product **3b** can be formed via two distinct pathways. A simple nucleophilic substitution with acetate anion at trifluoroacetimidoyl chloride **1b** could lead to intermediate **VI**. Alternatively, **VI** can be formed by reductive elimination forming the C−O bond from complex **III**. Experimental evidence suggests that both pathways are operative for monosubstituted substrate **1b**, with the catalytic one dominating with certain ligands. Mumm rearrangement of **VI** forms intermediate **VII**. In turn, the trifluoroacetyl group of the mixed imide is substituted by acetate, leading to the observed side product **3b**.

In conclusion, we report convenient access to a range of valuable (trifluoromethyl)indoles employing a Pd(0)-catalyzed C(sp^3)−H functionalization of trifluoroacetimidoyl chlorides. It represents a complementary access to this class of compounds avoiding the use of expensive electrophilic trifluoromethylating reagents. Our study showcases the good potential of stable trifluoroacetimidoyl chlorides as electrophilic partners for C(sp^3)−H functionalization reactions. Moreover, the reaction operates efficiently at low catalyst loadings of 1 mol % of Pd and is readily scalable to gram amounts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00795.

Experimental procedures and analytical and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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