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Palladium-Catalyzed Trifluoromethylation of Aromatic C–H Bond Directed by an Acetamino Group

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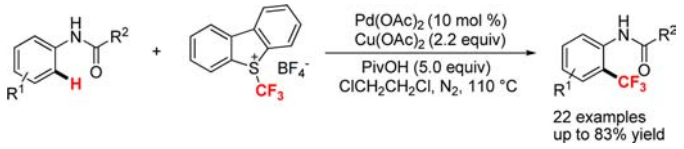
ABSTRACT



The first palladium-catalyzed *ortho*-trifluoromethylation of the aromatic C–H bond directed by an acetamino group is reported. This method provides an efficient and green approach to synthesize the highly biological potential key structure of *ortho*-CF_3 acetanilides and anilines.

Presently, the trifluoromethyl group has been incorporated into significant structural motifs to improve the physical, chemical, and biological properties of a large number of organic compounds, such as pharmaceutical molecules and drug candidates, because of its electronic properties, special size, and great metabolic stability.[1] Especially trifluoromethyl-substituted arenes have played an important role in many synthetically valuable organic compounds.[2] Recently several Pd- and Cu-catalyzed trifluoromethylation reactions of aryl halides[3] and aryl boronic acids[4] have been reported, providing available methods to synthesize trifluoromethyl-substituted arenes.

For a direct transformation from the aromatic C–H bond to the C–CF_3 bond, various efficient methods, involving electrophilic substitution and a Minisci type reaction, have also been developed.[5] Furthermore, to achieve the

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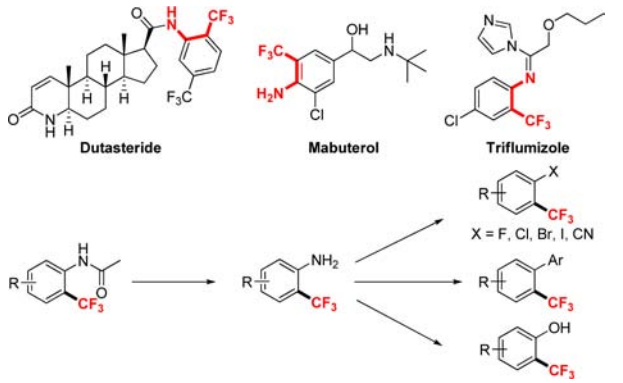
selective transformation of the aromatic C−H bond to the $C-CF_3$ bond through direct C−H activation *via* transition metal catalysis, several effective methods have also been reported. Sanford et al. reported Ag-mediated trifluoromethylation of arenes using $TMSCF_3$[6b] and Pd-catalyzed C−H perfluoroalkylation of arenes.[6c] Brase et al. developed the Ag-mediated selective *ortho*-triluoromethylation of functionalized aromatic triazenes.[7] Yu et al. reported the Pd(II)-catalyzed *ortho*-trifluoromethylation of 2-phenylpyridines and *N*-arylbenzamides derived from readily available benzoic acids.[8a,b] Hartwig and Shen simultaneously reported the highly selective trifluoromethylation of 1,3-disubstituted arenes through the sequence of Ir-catalyzed borylation of arenes and subsequent trifluoromethylation.[9] Qing et al. developed Cu-catalyzed direct C−H oxidative trifluoromethylation of heteroarenes.[10] Liu et al. reported palladium-catalyzed oxidative trifluoromethylation of indoles at rt.[11b] Herein we report the Pd(II)-catalyzed trifluoromethylation of the aromatic C−H bond directed by an acetamino group, which provides an efficient and green approach to produce the highly biological potential key structure of *ortho*-CF_3 acetanilides and anilines such as Dutasteride,[12a] Mabuterol,[12b] and Triflumizole.[12c] Notably, the utility of the acetamino group provided other opportunities to transform it into different functional groups through existing methods (Scheme 1).

Scheme 1. Drug Molecules and Possible Transformations of the Acetamino Moiety into a Series of Functional Groups



With this in mind, we initially chose acetanilide **1a** as the starting material, which had shown relatively high reactivity in our previous studies (Table 1).[13] The first reaction was performed in dichloroethane with $Pd(OAc)_2$ as the catalyst and Togni's reagent[14] as the trifluoromethylation reagent, which has been broadly used and shows high reactivity (entry 1). Although we observed a trace amount of desired product of *ortho*-trifluoromethylation, the transformation could also occur in the absence of any transition metal catalyst, which confirmed that Togni's reagent might decompose and generate a CF_3 radical under relatively high temperature.[5b] We next tried to explore the $TESCF_3/F^-$ system[11] with $PhI(OAc)_2$ as the oxidant to achieve the conversion *via* the Pd(IV) pathway (entry 2). Unfortunately, several products with *ortho*-, *meta*-, and *para*- trifluoromethylation were observed in a trace amount detected by GC-MS, but we failed to promote the selectivity to approach a sole product. Subsequently, we tested Umemoto's reagent **2**,[15] combined with different oxidants such as $PhI(OAc)_2$, $K_2S_2O_8$, BQ, *N*-fluorobenzenesulfonimide, and $Ce(SO_4)_2$ as well as Ag and Cu salts in the presence of $Pd(OAc)_2$ as the catalyst (entreis 3−7). Actually, the yield could be slightly improved with $Cu(OAc)_2$, CuF_2, or $Cu(TFA)_2$ in the system compared with other various oxidants. 15% of desired product **3a** (by GC with *n*-dodecane as the internal standard) was obtained in the presence of $Cu(OAc)_2$ (1.0 equiv) (entry 7). To our delight, PivOH (10.0 equiv) improved the yield to 49% (by GC), while either other acids or bases were not efficient. Increasing or decreasing the amount of PivOH slightly diminished the yield (entries 10−15). To our delight, the yield of product was promoted to 65% when the amount of $Cu(OAc)_2$ was increased to 2.0 equiv (entries 16−17). Moreover, the yield was further enhanced by increasing the amount of Umemoto's reagent to 1.5 equiv (entry 18). Finally, we found the yield reached an optimal level when 2.2 equiv of $Cu(OAc)_2$ were used (entry 19). A further increase of $Cu(OAc)_2$ did not affect the efficiency (entries 19−20). Other transition metal catalysts, such as $[Cp^*Rh(MeCN)_3](SbF_6)_2$ or $[Cp^*RhCl_2]_2$, did not promote the transformation.

With the above optimized conditions in hand, we further investigated various acetanilides to explore the application of the reaction (Scheme 2). To explore the influence of directing groups, we first tested different substrates with carbonyl groups. Other than the acetyl group, pivaloyl and benzoyl groups showed partial reactivity

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Table 1. Optimization of Reaction Conditions

entry[a]	oxidant (equiv)	additive (equiv)	yield[b]
1	–	–	trace[c]
2	$PhI(OAc)_2$ (1.0)	CsF (2.0)	trace[d]
3	$PhI(OAc)_2$ (1.0)	–	0%
4	$K_2S_2O_8$ (1.0)	–	trace
5	BQ (1.0)	–	trace
6	AgOAc (1.0)	–	trace
7	$Cu(OAc)_2$ (1.0)	–	15%
8	$Cu(OAc)_2$ (1.0)	TFA (10.0)	16%
9	$Cu(OAc)_2$ (1.0)	AcOH (10.0)	15%
10	$Cu(OAc)_2$ (1.0)	PivOH (10.0)	49%
11	$Cu(OAc)_2$ (1.0)	PivOH (20.0)	46%
12	$Cu(OAc)_2$ (1.0)	PivOH (50.0)	trace
13	$Cu(OAc)_2$ (1.0)	–	0%[e]
14	$Cu(OAc)_2$ (1.0)	PivOH (5.0)	53%
15	$Cu(OAc)_2$ (1.0)	PivOH (2.0)	50%
16	$Cu(OAc)_2$ (1.5)	PivOH (5.0)	58%
17	$Cu(OAc)_2$ (2.0)	PivOH (5.0)	65%
18[f]	$Cu(OAc)_2$ (2.0)	PivOH (5.0)	72%
19[f]	$Cu(OAc)_2$ (2.2)	PivOH (5.0)	76% (69%)
20[f]	$Cu(OAc)_2$ (2.5)	PivOH (5.0)	76%
21[f]	$Cu(OAc)_2$ (2.2)	PivOH (5.0)	0%[g]
22[f]	$Cu(OAc)_2$ (2.2)	PivOH (5.0)	43%[h]

[a] Reaction conditions: 0.10 mmol of acetanilide, 0.12 mmol of Umemoto's reagent, 0.01 mmol $Pd(OAc)_2$ as the catalyst, 1.0 mL of $ClCH_2CH_2Cl$, 24 h. [b] Yields are determined by GC analysis using *n*-dodecane as an internal standard. Yields of isolated product are given within parentheses. [c] 0.12 mmol of Togni's reagent was used. [d] 0.20 mmol of $TESCF_3$ was used. [e] PivOH was used as the solvent. [f] 0.15 mmol of Umemoto's reagent. [g] Without $Pd(OAc)_2$ as the catalyst. [h] At 90 °C.

(**3w**−**x**). Methyl-*N*-phenylacetamide is not a proper substrate, and no conversion was observed (**3v**). Later on, we tested various substituted acetanilides. To our interest, *para*-substituents did not obviously affect the efficacy. For instance, with alkyl groups at the *para*-position, such as methyl and *tert*-butyl groups, the desired product **3b** and **3c** were obtained in 63% and 77% yields, respectively. To our delight, chloro-, bromo-, and fluoro- groups at the *para*-position were compatible and afforded the desired products in 72%, 66%, and 71% yields (**3e**−**g**). Surprisingly, the reaction tolerated the existence of the most active C−I bond at the *para*-position, affording the desired product in 48% yield (**3h**). Such group tolerances provided great potential for orthogonal functionalization.[16] No observation of the trifluoromethylation of C−X bonds indicated that such a transformation did not go through the sequence of halogenation/trifluoromethylation though the halogenation is possible under this condition. In fact, a trace amount of chlorination product was observed with 1,2-dichloroethane as the solvent. Moreover, electron-withdrawing groups such as $-CO_2Et$, $-CO_2Me$, and −COPh were also well tolerated under the reaction conditions and provided the product in 83%, 64%, and 72% yields, respectively (**3i**−**k**). Comparably, the acetyl group gave a lower yield with starting material remaining (**3l**). Notably, the acetoxyl group, which is similar to the

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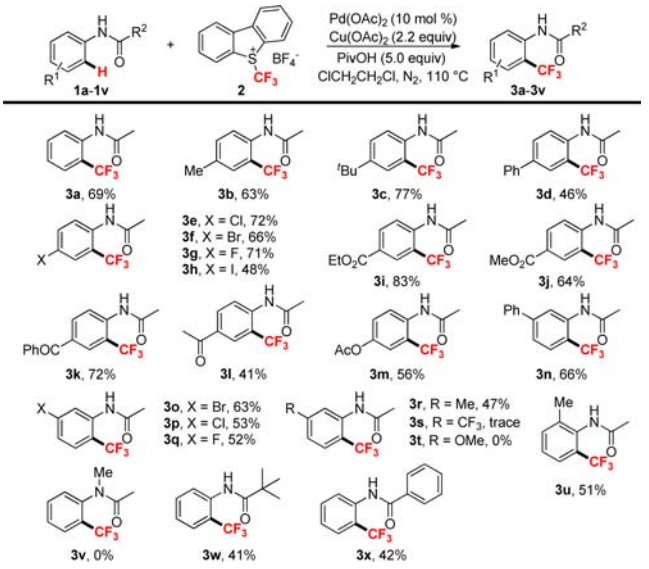
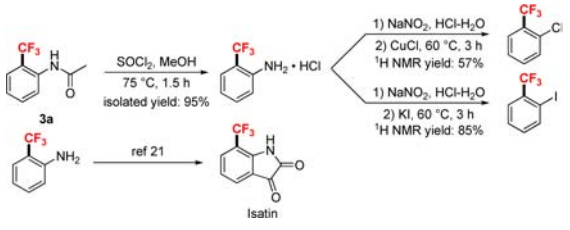
Scheme 2. Palladium-Catalyzed *ortho*-Trifluoromethylation of Different Acetanilides **1** Using Umemoto's Reagent **2**[a,b]



[a] Reaction conditions: 0.10 mmol of substrate, 0.15 mmol of Umemoto's reagent, 0.01 mmol $Pd(OAc)_2$ as the catalyst, 0.22 mmol of $Cu(OAc)_2$, 0.50 mmol of PivOH, 1.0 mL of $ClCH_2CH_2Cl$, 24 h. [b] Isolated yield. The details for reaction conditions are described in the Supporting Information.

directing acetamino group, was also accommodated in our method (**3m**). The presence of a phenyl group at the *para*-position decreased the yield to 46% due to its incomplete conversion within 24 h (**3d**). *ortho*-Methyl substituted acetanilide was submitted, and an isolated yield of 51% was achieved (**3u**). The test of the substituents at the *meta*-position indicated that, in most cases, only a sole product was isolated at the less hindered position in 47−66% yields, which may arise from steric effects (**3n**−**r**). Unfortunately, a methoxyl group or a trifluoromethyl group at the *meta*-position obviously inhibited the reaction (**3s**−**t**).

Scheme 3. Transformations of the Acetamino Moiety through Existing Methods



Furthermore, starting from the *ortho*-trifluoromethyl product **3a**, the acetamino moiety could be easily

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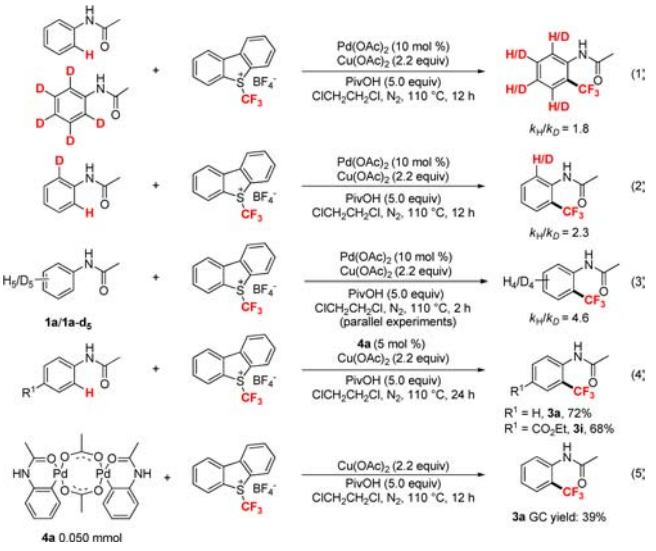
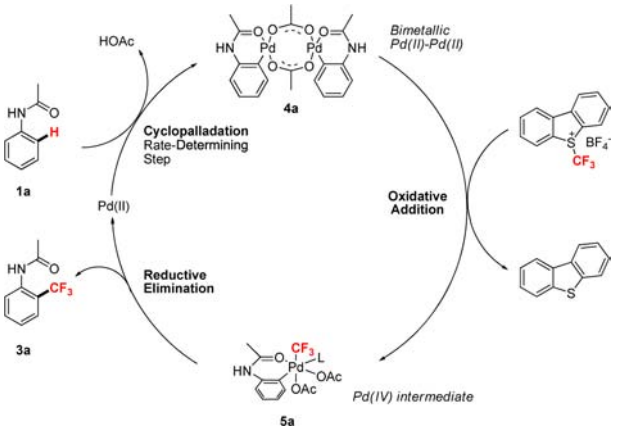
transformed into an amino group which could be transformed into different functional groups through existing methods successfully (Scheme 3).[17,21]

Scheme 4. Experiments for Mechanism Research



To unveil the catalytic mechanism, a series of experiments were conducted (Scheme 4).[18,19] The KIE for intermolecular, intramolecular, and parallel experiments[22] (1.8, 2.3, and 4.6, respectively) suggested that the C−H cleavage was involved in the rate-determining step (rds) at the catalytic cycle (eqs 1−3). To obtain more details about the reaction mechanism, we performed the reaction by using the palladacycle complex **4a**, which was prepared according to ref 20. To our delight, the desired product **3a** or **3i** was obtained in a comparable yield of 72% and 68%, respectively, when **4a** was used as the catalyst (eq 4). The stoichiometric reaction from **4a** under the same conditions also afforded the desired product **3a**, albeit in a GC yield of 39% (eq 5). Based on these studies, a plausible mechanism is proposed in Scheme 5.

Scheme 5. A Plausible Mechanism



First, directed by the acetamino group, the reaction was initiated by the palladation of acetanilide **1a** to afford the palladacycle **4a**. In the presence of $Cu(OAc)_2$ and Umemoto's reagent **2**, a Pd(IV) intermediate **5a** was supposedly generated in the system. Finally, the desired product of trifluoromethylation was afforded after reductive elimination. Alternatively, the electrophilic attack from CF_3^+ to the Pd−C bond[16] or the formation of the *bis*-Pd(III) complex as a key intermediate[18a] could not be excluded at this stage. Since the coordination ability of the amide carbonyl group was not strong enough, the addition of a stoichiometric amount of a Cu salt could coordinate with dibenzothiophene generated by Umemoto's reagent to maintain the activity of the Pd species.[8b] Other functions of a Cu salt in this system are still unclear, requiring further study.

In summary, we have developed an efficient Pd(II)-catalyzed trifluoromethylation of the aromatic C−H bond directed by an acetamino group. The broad substrate scope makes this method potentially useful for the synthesis of many biologically active molecules. The downstream experiments from the product highly explored the application of this method. Furthermore, a series of experiments were performed to support the proposed catalytic cycle. Further application of this method is underway.

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Supporting Information Available. Experimental procedures and spectral data for products and mechanistic study experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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