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Angewandte International Edition

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201810502
Angew. Chem. 10.1002/ange.201810502

Link to VoR: http://dx.doi.org/10.1002/anie.201810502
http://dx.doi.org/10.1002/ange.201810502

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10.1002/anie.201810502

Angewandte Communications

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DOI: 10.1002/anie.201((will be filled in by the editorial staff))

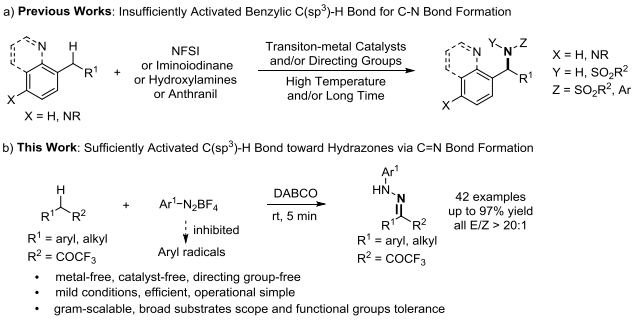
Intermolecular C(sp^3)-H Amination Promoted by Internal Oxidants: Synthesis of Trifluoroacetylated Hydrazones**

Chuanle Zhu, Hao Zeng, Fulin Chen, Zhiyi Yang, Yingying Cai, and Huanfeng Jiang**

Abstract: *An internal oxidants-promoted intermolecular C(sp^3)-H amination reaction via C=N bond formation is reported. This intermolecular C(sp^3)-H amination reaction of trifluoromethyl ketones and aryldiazonium tetrafluoroborates affords various valuable trifluoroacetylated hydrazones in high yields with excellent E/Z selectivities. The salient features of this reaction were metal-free, catalyst-free, directing group-free, azides-free, mild conditions, operational-simple, efficient, gram-scalable, and valuable functional group tolerance. Remarkably, an ectoparasites-controlling agent was smoothly synthesized on gram-scale with our protocol. Aryldiazonium tetrafluoroborates served as the aminating reagents as well as an internal oxidant.*

Due to the ubiquity of nitrogen-containing molecules in many natural and bioactive synthetic compounds, the development of efficient methods to construct carbon-nitrogen bonds plays a central role in chemical synthesis.[1] The installment of carbon-nitrogen bonds by direct C(sp^3)-H functionalization represents one of the most attractive and yet challenging strategies.[2-4, 6-7] In this context, great efforts have been devoted to develop new and efficient methods for intra-[3] and intermolecular[4] C(sp^3)-H amination. Generally, these reactions need stoichiometric amounts of strong external oxidants such as toxic transition-metal salts, BQ (benzoquinone), hypervalent iodine derivatives, or employ potential explosive organic azides as the aminating reagents. Internal oxidant is an idea oxidant, which serves as both a substrate and an oxidant in reactions.[5] Thus, internal oxidants-promoted C(sp^3)-H amination is quite attractive but still underdeveloped.[6]

Recently, internal oxidants such as *N*-fluorobenzenesulfonimide (NFSI), iminoiodinane, hydroxylamine derivatives, and anthranil promoted intermolecular C(sp^3)-H bond amination were investigated by different groups,[6] especially for the attractive intermolecular benzylic C(sp^3)-H bond amination.[6b-h, 7] However, owing to the insufficiently activated benzylic C(sp^3)-H bond, these amination reactions usually need transition-metal catalysts, directing groups, high temperature, and/or long reaction time to ensure the reactivity and selectivity, and led to the formation of C-N single bond (Scheme 1, a). Despite this progress, we envisioned that if the C(sp^3)-H bond was sufficiently activated by an valuable group, novel internal oxidants-promoted intermolecular C(sp^3)-H amination reactions might be efficiently realized under metal-free, catalyst-free, directing group-free, and mild conditions.



Scheme 1. Internal Oxidants-Promoted Intermolecular Amination of Activated C(sp^3)-H Bond.

Trifluoromethyl group served as privileged moieties in the field of medicinal chemistry because of its impressive impact on the enhancement of the metabolic stability, bioavailability, and lipophilicity of potential drugs.[8] Consequently, the synthesis and application of novel trifluoromethyl group decorated compounds have been extensively investigated in library design and drug discovery.[9] Recently, we have reported a C(sp^3)-H activation reaction of trifluoromethyl ketones by internal oxidative oxime acetates.[10a] As part of our continuous effort in internal oxidants-promoted C(sp^3)-H activations,[5] as well as recent interest in trifluoromethyl decorated compounds,[10] herein, we report the internal oxidants-promoted intermolecular C(sp^3)-H amination reaction of trifluoromethyl ketones and aryldiazonium tetrafluoroborates, delivering various useful trifluoroacetylated hydrazones in high yields and excellent E/Z selectivities via C=N bond formation (Scheme 1, b). Remarkably, aryldiazonium tetrafluoroborates served as the aminating reagents as well as an internal oxidant, and their C-N_2 bond cleavage pathway is completely inhibited in our process.[11]

On the basis of our previous works, the initial experiment of this internal oxidants-promoted intermolecular C(sp^3)-H amination reaction was carried out with aryldiazonium tetrafluoroborate **1a** and trifluoromethyl ketone **2a** in the presence of Cs_2CO_3 in toluene at room temperature under N_2 (Table 1, entry 1). We were pleased to find that the desired trifluoroacetylated hydrazone **3a** via C=N Bond formation was isolated in 61% yield with excellent E/Z isomer selectivity (E/Z > 20:1) in 5 minutes. To optimize the reaction conditions, different types of inorganic bases such as K_2CO_3, Na_2CO_3, Li_2CO_3, *t*-BuOLi, *t*-BuOK, and MeONa and organic bases such as DBU, DABCO, and Et_3N were examined (Table 1, entries

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[**] This work was supported by the National Program on Key Research Project (2016YFA0602900), the National Natural Science Foundation of China (21472051, 21420102003, and 21702064), the Pearl River S&T Nova Program of Guangzhou (201806010138), and the Guangdong Natural Science Foundation (2016A030310460).

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10.1002/anie.201810502

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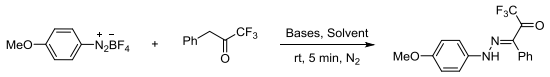
Table 1. Optimization of the reaction conditions.[a]



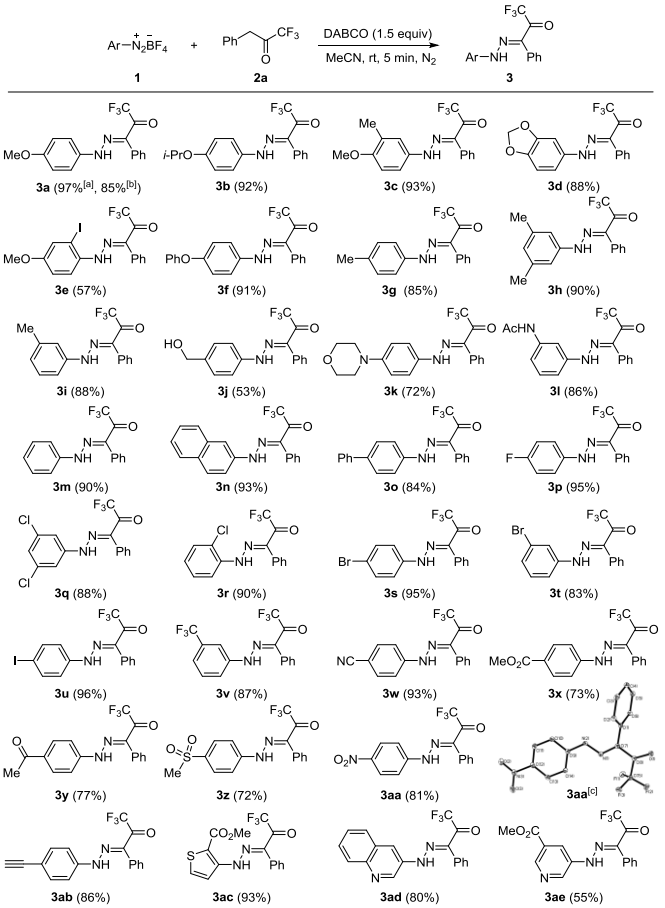
1a 2a 3a

Entry	Bases	Solvent	Yield (%)[b]
1	Cs_2CO_3	toluene	63 (61)
2	K_2CO_3	toluene	64
3	Na_2CO_3	toluene	44
4	Li_2CO_3	toluene	13
5	*t*-BuOLi	toluene	trace
6	*t*-BuOK	toluene	32
7	MeONa	toluene	44
8	DBU	toluene	34
9	DABCO	toluene	67
10	Et_3N	toluene	3
11	-	toluene	0
12	DABCO	DCE	90
13	DABCO	MeCN	99 (97)
14	DABCO	1.4-dioxane	83
15	DABCO	THF	74
16	DABCO	DMF	98
17	DABCO	DMSO	98
18	DABCO	EtOH	80
19[c]	DABCO	MeCN	65
20[d]	DABCO	MeCN	0

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), **2a** (1.5 equiv), bases (1.5 equiv) and solvent (2 mL) in a 25 mL Schlenk tube at room temperature for 5 min under N_2. [b] The yields were determined by ^{19}F NMR spectroscopy of the crude product with $PhCF_3$ as an internal standard, and all of the E/Z isomer ratios > 20:1. [c] 4-Methoxyphenyldiazonium hexafluorophosphate was used instead of **1a**. [d] 4-Methoxyphenyldiazonium 4-methylbenzenesulfonate was used instead of **1a**. The numbers in the parentheses were isolated yields.

2-10). To our delight, a base of DABCO gave **3a** in 67% ^{19}F-NMR yield with E/Z > 20:1. Without a base, no desired product **3a** was detected (Table 1, entry 11). Next, different types of solvent such as DCE (1,2-dichloroethane), MeCN, 1,4-dioxane, DMF, DMSO, and EtOH were screened (Table 1, entries 12-18). A solvent of MeCN further enhanced the isolated yield of **3a** to 97%. Additionally, other types of aryldiazonium salts with different counterions such as hexafluorophosphate and 4-methylbenzenesulfonate were also investigated (Table 1, entries 19-20). The obtained results indicated the suitable oxidative potential of aryldiazonium tetrafluoroborates is very important to this transformation.

Under the optimized reaction conditions, we then turned our attention to the generality of aryldiazonium tetrafluoroborates with trifluoromethyl ketone **2a** as the reaction partner in this internal oxidants-promoted intermolecular C(sp^3)-H amination reaction (Scheme 2). In general, aryldiazonium tetrafluoroborates with electron-donating, electron-neutral, and electron-withdrawing groups on the different positions of the aryl ring all could afford the desired trifluoroacetylated hydrazones smoothly with excellent E/Z isomer selectivity (**3a**-**3ab**). It is worth mentioning that this mild and efficient reaction system could tolerate diverse valuable functional groups on the aryl ring of the aryldiazonium tetrafluoroborates, such as alkoxyl, phenoxyl, alkyl, hydroxyl, morpholinyl, amino, aryl, halo, trifluoromethyl, cyano, ester, acetyl, sulfonyl, nitro, and ethynyl groups (products **3a**-**3ab**), providing ample potential for further synthetic applications. Significantly, product **3aa** was proved to be crystalline, then its structure and relative stereochemistry were confirmed by the means of X-ray crystallographic analysis.[12] Furthermore, different hetereo aromatic groups such as thienyl, quinolyl, and pydridyl-bearing aryldiazonium tetrafluoroborates were also found to be good substrates, and the corresponding products **3ac**-**3ae** were obtained in high yields.



Scheme 2. Substrate scope of aryldiazonium tetrafluoroborates. Unless otherwise noted, the reaction was run at 0.2 mmol scale under the standard reaction conditions, and all the E/Z isomer ratios > 20:1. [a] The average isolated yield of two parallel runs. [b] At 10 mmol scale, 0 °C to rt, 30 min, and E/Z isomer ratio > 20:1. [c] ORTEP representation with 50% probability thermal ellipsoids of a crystal structure of **3aa**.

To further define the limitation of our protocol, the substrate scope was extended to different trifluoromethyl ketones **2** (Scheme 3). Pleasingly, trifluoromethyl ketones with electron-donating group such as methoxyl, and methyl groups and withdrawing groups such as chloro, bromo, and iodo groups on the phenyl ring all could undergo this reaction smoothly, providing the corresponding trifluoroacetylated hydrazones in high yields with excellent E/Z isomer selectivity (**3af**-**3an**). Especially, product **3al** was obtained in 76% isolated yield, indicating that this reaction was not sensitive to the steric hindrance. Additionally, 1,1,1-trifluoropentan-2-one also gave the desired product **3ao** in 29% yield.

Intrigued by this unique internal oxidants-promoted intermolecular C(sp^3)-H amination reaction, we further explored the synthetic applications of these useful trifluoroacetylated hydrazones (Scheme 4). Reduction the carbonyl group of **3a** easily gave the corresponding alcohol product **4** in 91% yield. N-protection of **3a** with propargyl bromide afforded trifluoroacetylated hydrazone **5** in 93% yield. On the other hand, diazo compound **6** was obtained in 67% yield via the selective O-protection of **3a** with benzoyl chloride. Next, various attractive but not easily accessible trifluoromethylated

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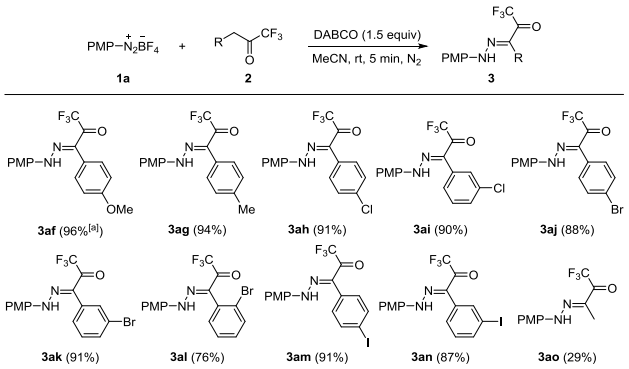
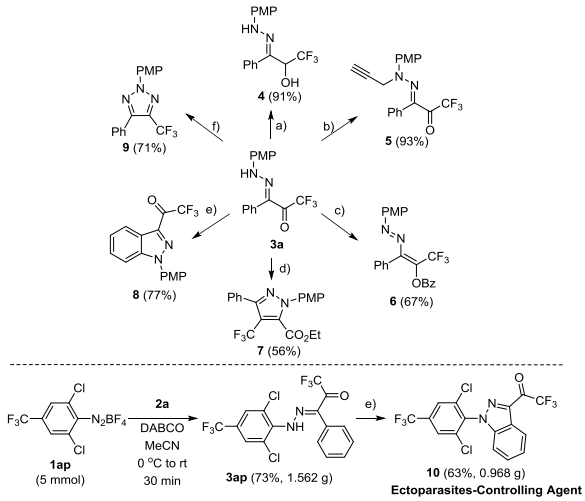


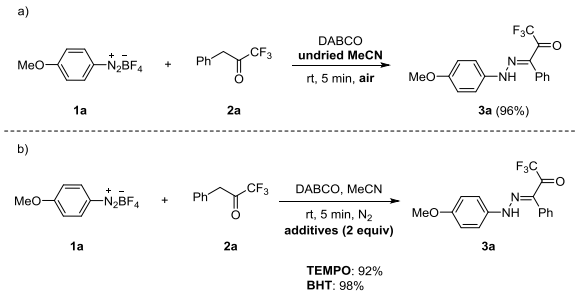
Scheme 3. Substrate scope of trifluoromethyl ketones. Unless otherwise noted, the reaction was run at 0.2 mmol scale under the standard reaction conditions, and E/Z isomer ratios > 20:1. [a] The average isolated yield of two parallel runs.

heterocycles in the field of medicinal chemistry, such as compounds with 4-(trifluoromethyl)-pyrazole (**7**), 3-trifluoroacetyl indazol (**8**), and 5-(trifluoromethyl)-2*H*-1,2,3-triazole (**9**) core skeletons, were smoothly synthesized from **3a**. Furthermore, a 5 mmol scale reaction of aryldiazonium tetrafluoroborate **1ap** and trifluoromethyl ketone **2a** was carried out in 30 minutes, providing the desired trifluoroacetylated hydrazone **3ap** in 73% yield (1.562 g). The subsequent intramolecular dehydrogenative coupling of **3ar** affords 3-trifluoroacetyl indazol derivative **10** in 63% yield (0.968 g). It is worth to note that 3-trifluoroacetyl indazol derivative **10** is an ectoparasites-controlling agent.[13]



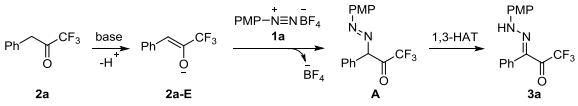
Scheme 4. Synthetic applications. a) $NaBH_4$, EtOH, rt, 2 h. b) NaH, DMF,30 min; propargyl bromide, rt, 12 h. c) Et_3N, benzoyl chloride, CH_2Cl_2, rt, 12 h. d) K_2CO_3, ethyl bromoacetate, DMF, rt, 12 h. e) Hexafluoroisopropanol (HFIP), $PhI(CF_3CO_2)_2$, rt, 12 h. f) $CuBr_2$, NH_4OAc, DMF/AcOH, 120 °C, O_2, 12 h.

To cast some light on the mechanism details of this internal oxidants-promoted intermolecular C(sp^3)-H amination reaction, some control experiments were performed. ^{19}F-NMR and ^{1}H-NMR analysis experiments were conducted to monitor the reaction. However, no signals of the possible intermediates were detected, owing to the highly efficiency of the reaction.[14] Performing the reaction under air and undried MeCN, **3a** was obtained in 96% NMR yield, indicating our reaction was not air and moisture sensitive (Scheme 5, a). Furthermore, the addition of radical scavenger such as TEMPO, *tert*-butylhydroxytoluene (BHT) under the standard reaction conditions almost has no influence on the yields of **3a**, indicating the reported C-N_2 bond cleavage pathway of aryldiazonium tetrafluoroborates is completely inhibited in our process and a radical process might not be involved in this transformation (Scheme 5, b)



Scheme 5. Control experiments

On the basis of these experimental results as well as previous works,[5, 10] we tentatively proposed the reaction mechanism illustrated in Scheme 6. Under the treatment of bases, **2a** is likely to deprotonating into its enolate anion **2a-E**. The nucleophilic attack of enolate intermediate **2a-E** at the terminal N atom of aryldiazonium tetrafluoroborate **1a** provided an trifluoroacetylated azo intermediate **A**,[15] which further converted to the desired trifluoroacetylated hydrazone **3a** via 1,3-hydragen atom transfer (1,3-HAT). Aryldiazonium tetrafluoroborates not only served as the aminating reagents but also as an internal oxidant in this transformation.



Scheme 6. Proposed mechanism.

In summary, we have reported an internal oxidants-promoted intermolecular C(sp^3)-H amination reaction via C=N bond formation. This intermolecular C(sp^3)-H amination reaction of trifluoromethyl ketones and aryldiazonium tetrafluoroborates affords various valuable trifluoroacetylated hydrazones in high yields with excellent E/Z selectivities. This reaction features metal-free, catalyst-free, directing group-free, azides-free, mild conditions, operational-simple, efficient, gram-scalable, and valuable functional group tolerance. Remarkably, an ectoparasites-controlling agent was smoothly synthesized on gram-scale with our protocol. Aryldiazonium tetrafluoroborates served as the aminating reagents as well as an internal oxidant. The preliminary mechanism studies indicated that a radical process might not be involved in this transformation and the C-N_2 bond cleavage pathway of aryldiazonium tetrafluoroborates is completely inhibited in our process. Efforts are currently underway in our laboratory to investigate the mechanistic details and explore the synthetic applications of our protocol, and the results of which will be reported in due course.

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Keywords: C(sp^3)-H amination • internal oxidants • fluorine • synthetic methods

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10.1002/anie.201810502

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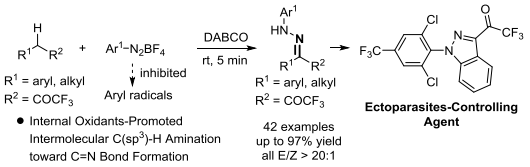

Intermolecular C(sp^3)-H Amination Promoted by Internal Oxidants: Synthesis of Trifluoroacetylated Hydrazones

An internal oxidants-promoted intermolecular C(sp^3)-H amination reaction is realized under mild conditions. The obtained trifluoroacetylated hydrazones via C=N bond formation were further transformed into various useful trifluoromethyl group decorated compounds.

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