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Trifluoromethylative homo-coupling of carbonyl compounds

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ABSTRACT

Carbonyl compounds are abundant in nature and represent a substantial portion of biomass resources. Despite significant recent progress in homo-coupling of carbonyl compounds, achieving their deoxy-functionalization homo-coupling remains a highly intricate challenge. Herein, we report an entirely novel reaction paradigm: the trifluoromethylative homo-coupling of carbonyl compounds *via* hydrazones, which enables the formation of three $C(sp^3)$–$C(sp^3)$ bonds in a single step. This method provides a new pathway for synthesizing trifluoromethylative coupling product which has unique applications in both fields of medical and material sciences. Mechanistic investigations have unveiled that the formation of a trifluoromethyl-substituted benzyl radical plays a pivotal role as a key intermediate in this reaction.

In light of the continual depletion of fossil energy reserves, the matter of the energy crisis has attracted growing interest within the field of chemistry [1,2]. Biomass resources, a pivotal facet of renewable resources, present an ideal substitute for fossil fuels [3]. Unlike fossil resources, biomass resources possess a notably higher oxygen content, primarily in the form of carbonyl or hydroxyl groups [4–7]. Consequently, the efficient harnessing of the abundant carbonyl compounds within biomass resources has become increasingly imperative.

Carbonyl compounds are extensively employed in organic synthesis due to their abundance and chemical versatility. Over the course of extensive research, homo-coupling of carbonyl compounds has emerged as an efficient means of forging C–C bonds. The classic Pinacol coupling reaction (Scheme 1a) [8,9] is a well-established process in organic chemistry. Traditionally, stoichiometric quantities of metal reagents are utilized as reducing agents to convert carbonyl compounds into ketone radicals through a single electron transfer (SET) process. Subsequently, intermolecular radical coupling reactions yield pinacol products. With the advent of photochemical reactions catalyzed by metal photosensitizers, [Ir] photoredox catalysis for generating ketone radicals from carbonyl compounds through the SET process was reported by Rueping group in 2019 [10]. At the same time, our group reported Pinacol coupling of ketone compounds relying solely on N_2H_4 as a hydrogen atom transfer (HAT) reducing agent [11,12]. Furthermore, our group reported a Ni-catalyzed homo-coupling reaction of carbonyl compounds *via* hydrazones, successfully synthesizing bibenzyls [6]. In 2022, Yamaguchi reported the generation of diarylphosphinates from diarylketones and diphenylphosphine through the phospha-Brook rearrangement, and benzyls were also successfully generated using a palladium catalyst [13]. Another significant method for homo-coupling of carbonyl compounds is olefinative coupling (Scheme 1b) [14–18]. The McMurry reaction enables the reductive homo-coupling of aldehydes and ketones to form alkenes under the influence of low-valent titanium. In 2017, we successfully implemented the hydrazone as organo-metallic equivalent (HOME chemistry) [19–24] strategy to achieve olefinative coupling of carbonyl compounds catalyzed by ruthenium(II) [25]. Compared to the classic McMurry reaction, this process avoided the use of strong reducing agents under mild conditions and exhibited excellent functional group compatibility. In 2019, Konig *et al.* reported a photoredox catalytic reaction using $B_2(pin)_2$ as the terminal reducing agent, successfully achieving olefinative coupling of carbonyl compounds [26]. In 2022, Nagib *et al.* developed a novel olefinative coupling model that converted aldehydes into carbenes *via* zinc carbenoids, thereby accomplishing olefinic coupling of aldehydes through effective catalysis using cobalt salts [27]. Very recently, Nagib group reported cross-olefinative coupling reactions between different carbonyl compounds, producing *Z*- or *E*-olefins with Fe or Cr catalysis, respectively [28].

While there has been notable progress in the homo-coupling of carbonyl compounds in recent years, significant limitations continue to hinder their practical application in synthesis. Currently, carbonyl compounds tend to primarily yield either pinacols, as a result of the high bond energy of C–O bonds making deoxygenation difficult, or olefins through the elimination of hydroxyl groups

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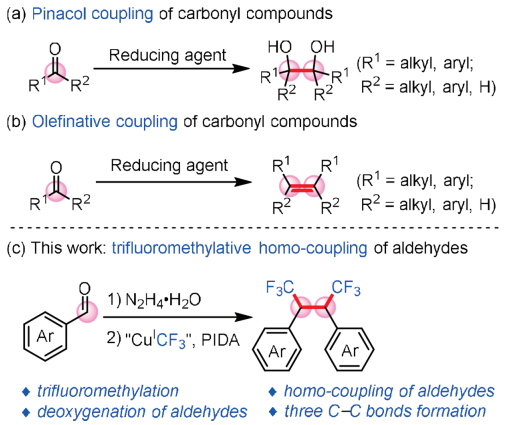


Scheme 1. Homo-coupling of carbonyl compounds.

in homo-coupling reactions. This limitation restricts our ability to fully harness the synthetic potential inherent in C=O bonds [29]. Consequently, substantial challenges persist in achieving deoxy-functionalization homo-coupling of carbonyl compounds.

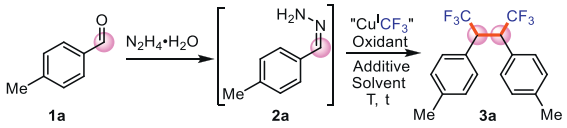
Trifluoromethyl groups are known for their strong electron-withdrawing and the strongest lipophilicity properties. Their introduction into organic molecules can greatly alter electron distribution and enhance lipophilicity [30,31]. Meanwhile, owing to the high stability of the C–F bond, the introduction of trifluoromethyl significantly enhances the metabolic stability of organic molecules in organisms [31]. Therefore, trifluoromethylation reactions are a hot topic in organic chemistry, attracting substantial interest from researchers.

Building on our earlier success in homo-coupling carbonyl compounds, we present a new advancement: the trifluoromethylative homo-coupling of carbonyl compounds [32] *via* hydrazones (Scheme 1c). Significantly, this protocol not only introduces the CF_3 group conveniently into natural and abundant aldehydes but also accomplishes the deoxygenative homo-coupling of aromatic aldehydes. This process leads to the creation of three C–C bonds in a single step, establishing a novel pathway for homo-coupling reactions of carbonyl compounds.

At the onset of our investigation, *p*-methylbenzaldehyde hydrazone (**2a**) was used as the model substrate, and "Cu^ICF_3" (prepared *in situ* from CuI, $TMSCF_3$ and CsF in 1.0 mL DMF solvent) [33] as trifluoromethyl source, to optimize the reaction conditions. When $K_2S_2O_8$ was used as an oxidant, trifluoromethylative homo-coupling product **3a** was detected in 5% ^{19}F NMR yield (Table 1, entry 1). Considering the importance of oxidants for this transformation, various types of oxidants were tested (Table 1, entries 2–7). (Diacetoxyiodo)benzene (PIDA) gave the best yield (52%) of the homo-coupling product **3a** among these oxidants (entry 7). Adjusting the amount of PIDA or reaction temperature did not significantly improve the yield of **3a** (entries 8–11). Exploring various bases did not improve the yield of the target product **3a** (entries 12–18). When 4 Å molecular sieve (MS 4 Å) was added to the reaction system, the yield of the target product **3a** was increased to 55% (entry 19). Then, we investigated the influence of the amounts of 4 Å molecular sieve and CuI (entries 20–22), neither of which increased the yield of target product **3a**. Extending the reaction duration or conducting the reaction in an argon atmosphere did not enhance the production of **3a** either (entries 23 and 24). Finally, we obtained the optimal conditions for trifluoromethylative coupling of aldehydes *via* hydrazones (entry 19).

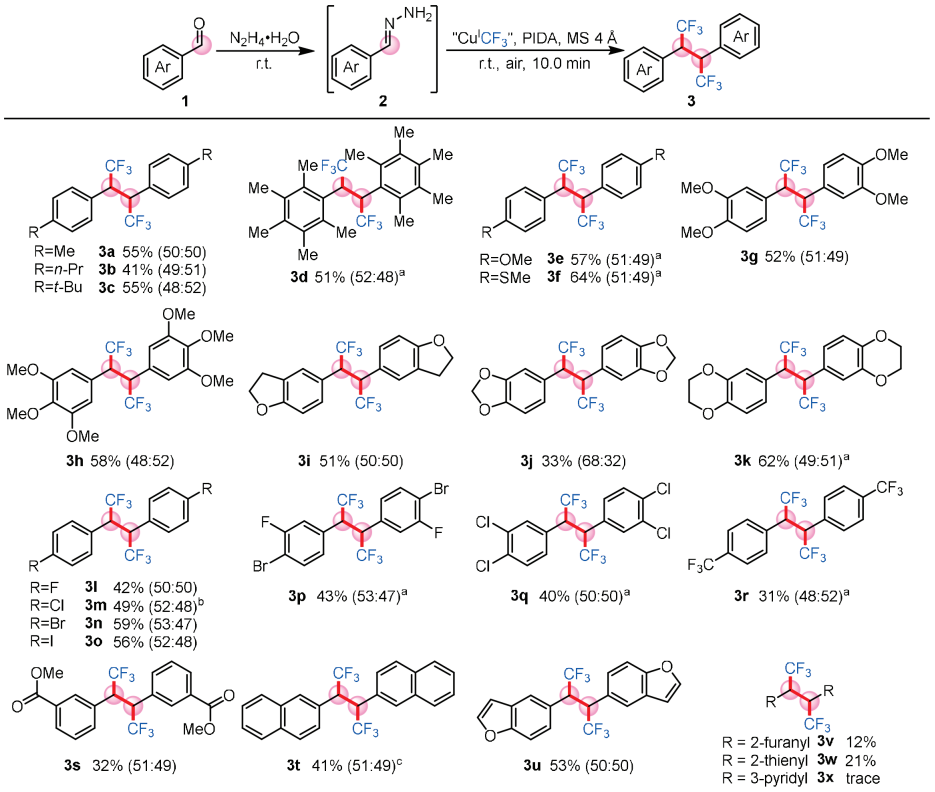
With the optimized reaction conditions in hand, the substrate scope for the aromatic aldehydes was explored (Scheme 2). Alkyl substituted benzaldehydes (*R* = Me, *n*-Pr, *t*-Bu) underwent the reaction smoothly and provided the target compounds in moderate yields (**3a**–**3c**). Even sterically hindered substrate, such as pentamethylbenzaldehyde (**1d**), yielded the desired product **3d** in 51% yield, indicating that the steric effect did not significantly impact the reaction. Strong electron-donating groups, such as methoxy and thiomethyl on the arene ring, led to trifluoromethylative homo-coupling products in moderate to good yields (**3e**-**3h**). It is worth noting that this transformation is also applicable with heterocyclic structures (**3i**–**3k**). Weakly electron-withdrawing halogen substituents (*X* = F, Cl, Br and I) proved compatible (**3l**–**3o**); in particular, polyhalogen substituted benzaldehydes also successfully produced the corresponding products in medium yields (**3p**, **3q**). For aromatic aldehyde hydrazones with strong electron-withdrawing substituents, we observed the partial generation of hydrotrifluoromethylation products [23], resulting in lower yields of trifluoromethylative homo-coupling products (**3r**, **3s**). Polycyclic hydrazones, like 2-naphthalene formaldehyde **1t**, also successfully achieved this transformation in 41% yield (**3t**). Moreover, when a hetero-aromatic aldehyde was subjected to the standard conditions, 53% yield was obtained with benzofuran-5-carbaldehyde **1u**. The reactivities of 2-furancarbaldehyde **1v**, 2-thiophenecarbaldehyde **1w**, and 3-pyridinecarbaldehyde **1x**, which were aldehydes containing heterocyclic aromatic rings, were less than satisfactory. The following reasons may affect the overall yield

Table 1
Evaluation of various conditions.[a]

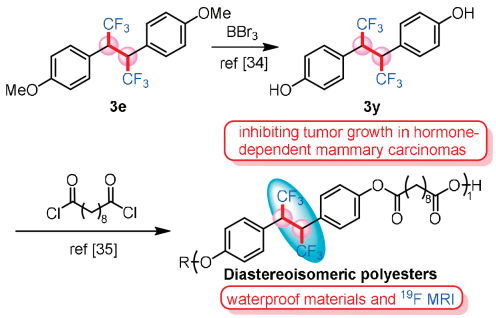


Entry	Oxidant (equiv.)	Additive (equiv.)	Yield (%)[b]
1	$K_2S_2O_8$ (1.5)	–	5
2	TBHP (1.5)	–	44
3	DTBP (1.5)	–	27
4	TBPB (1.5)	–	42
5	BPO (1.5)	–	41
6	NFSI (1.5)	–	n.p.
7	PIDA (1.5)	–	52
8	PIDA (1.2)	–	48
9	PIDA (1.8)	–	49
10[c]	PIDA (1.5)	–	41
11[d]	PIDA (1.5)	–	51
12	PIDA (1.5)	Na_2CO_3 (1.0)	50
13	PIDA (1.5)	NaOAc (1.0)	48
14	PIDA (1.5)	*i*-$PrCO_2Li$ (1.0)	49
15	PIDA (1.5)	NaOH (1.0)	50
16	PIDA (1.5)	DABCO (1.0)	43
17	PIDA (1.5)	DBU (1.0)	52
18	PIDA (1.5)	TMG (1.0)	41
19[e]	PIDA (1.5)	MS 4 Å	55
20[f]	PIDA (1.5)	MS 4 Å	49
21[e,g]	PIDA (1.5)	MS 4 Å	36
22[e,h]	PIDA (1.5)	MS 4 Å	45
23[e,i]	PIDA (1.5)	MS 4 Å	55
24[e,j]	PIDA (1.5)	MS 4 Å	54

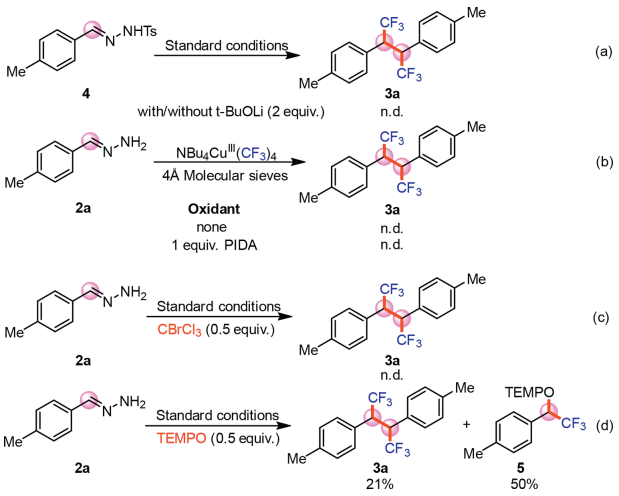
[a] **2a** (0.2 mmol), "Cu^ICF_3" (2.0 equiv., 1.0 mL DMF as solvent), and oxidant (x equiv.) were stirred in the 20.0 mL tube under air for 10.0 min at room temperature.
[b] Yields were determined by ^{19}F NMR using $PhOCF_3$ as an internal standard.
[c] 0 °C.
[d] 50 °C.
[e] 4 Å molecular sieve (50.0 mg).
[f] 4 Å molecular sieve (100.0 mg).
[g] CuI (1.5 equiv.).
[h] CuI (2.5 equiv.).
[i] 3.0 h.
[j] Under argon atmosphere.



Scheme 2. The scope of hydrazone substrates. General conditions: **2** (0.2 mmol), "$Cu^{I}CF_3$" (2.0 equiv., 1.0 mL DMF as solvent), PIDA (1.5 equiv.) and 4 Å molecular sieves (50.0 mg) were stirred for 10.0 min at r.t. in 20.0 mL tube under air. Unless otherwise indicated, the ^{19}F NMR yields were shown, diastereoselectivity (*syn*/*anti*) were determined by ^{19}F NMR given in parentheses. [a]Under Ar. [b]Isolated yield. [c]1.0 mL DMSO as solvent.



Scheme 3. Derivatization of **3e** in application in drug activity and materials.



Scheme 4. Mechanistic studies.

of products: (1) The benzyl radical underwent a radical substitution reaction with an aromatic ring to form by-products; (2) Deoxygenative hydrotrifluoromethylation products [23] can be detected as by-product.

Furthermore, the demethylation of trifluoromethylative homo-coupling product **3e** has unique applications in medicine and materials. It can significantly inhibit tumor growth in hormone- dependent mammary carcinomas [34], as well as has important applications in waterproof materials and ^{19}F MRI (Scheme 3) [35].

To elucidate the mechanism of this reaction, controlled experiments were carried out (Scheme 4). Firstly, *N*-tosylhydrazone **4** was used instead of hydrazone **2a** under standard conditions, and no target product **3a** was obtained, indicating that the reaction did not involve diazo compounds or metal carbene intermediates (Scheme 4a). Considering that PIDA might oxidize "$Cu^{I}CF_3$" to generate "$Cu^{III}(CF_3)_3$" species, which might be responsible for this reaction, we used $NBu_4Cu^{III}(CF_3)_4$ as the CF_3 source (Scheme 4b) and no target product **3a** was detected. The addition of $CBrCl_3$ (0.5 equiv.) as a radical inhibitor to the reaction system led to complete inhibition of target product generation, indicating that the reaction process might involve radical intermediates (Scheme 4c). When TEMPO was added as a radical capture agent to the reaction system, the trifluoromethylative homo-coupling product **3a** was inhibited, and the formation of compound **5** showed that the trifluoromethyl substituted benzyl radical might be an important intermediate (Scheme 4d).

Furthermore, the oxidation state of Cu was examined subsequent to the reaction (please see Section II in Supporting information for details), with the Ag $3d_{5/2}$ signal at 368.27 eV serving as the reference for charge calibration (Fig. 1a). X-ray photoelectron

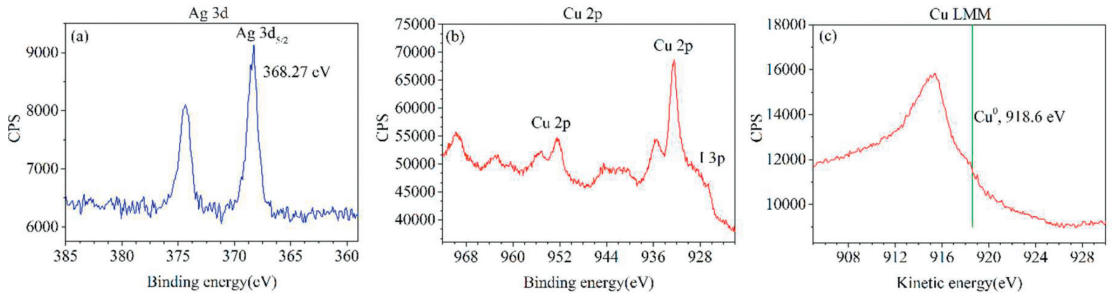
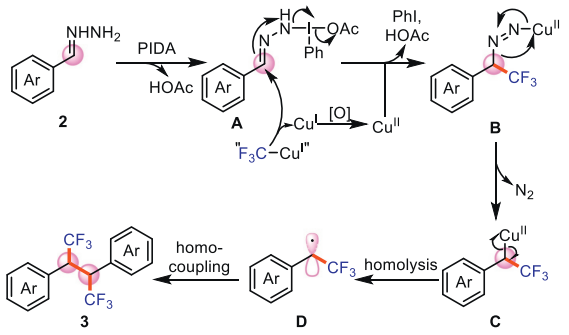


Fig. 1. X-ray photoelectron spectroscopy (XPS) and Auger electron spectroscopy (AES) of the Cu-containing mixture. (a-c) The remaining solids in the trifluoromethyl homo-coupling reaction system, respectively.



Scheme 5. Possible mechanism of trifluoromethylative coupling of carbonyl compounds *via* hydrazones.

spectroscopy (XPS) analysis of copper showed that the Cu^{II} signal was clearly detected under general condition (Fig. 1b). Auger electron spectroscopy (AES) analysis of copper showed that there was no obvious peak at the kinetic energy position of Cu^0 at 918.6 eV (Fig. 1c), which revealed that the reaction system did not contain Cu^0 (Fig. 1).

Based on the above experimental results, a possible reaction mechanism is proposed. As shown in Scheme 5, PIDA is attacked by terminal N atoms of hydrazone **2** to form intermediate **A** and loose acetic acid. Then, under the attack of the trifluoromethyl anion from "$Cu^{I}CF_3$", intermediate **A** releases iodobenzene and HOAc to form Cu^{II} coordinated intermediate **B**. Subsequently, the intermediate **B** releases nitrogen gas to generate organic copper(II) species **C**, which forms trifluoromethyl substituted benzyl radical **D** due to the homolysis of the C–Cu^{II} bond [36,37]. Finally, the benzyl radical **D** is homo-coupled to generate trifluoromethylative homo-coupling product **3**.

In conclusion, we have successfully pioneered the trifluoromethylative homo-coupling of aldehydes, which resulted in the formation of three C–C bonds in a single step. Mechanistic studies showed that the trifluoromethyl substituted benzyl radical was an important intermediate. This protocol introduces an innovative pathway for the deoxy-functionalization homo-coupling of aldehydes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Xinlong Han: Methodology, Writing – original draft. **Huiying Zeng:** Conceptualization, Project administration, Writing – review & editing. **Chao-Jun Li:** Conceptualization, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109817.

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