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RESEARCH ARTICLE

Ni-Catalyzed Reductive Acyl Cross-Coupling: Straightforward Synthesis of α-Trifluoromethylthiolated Ketones

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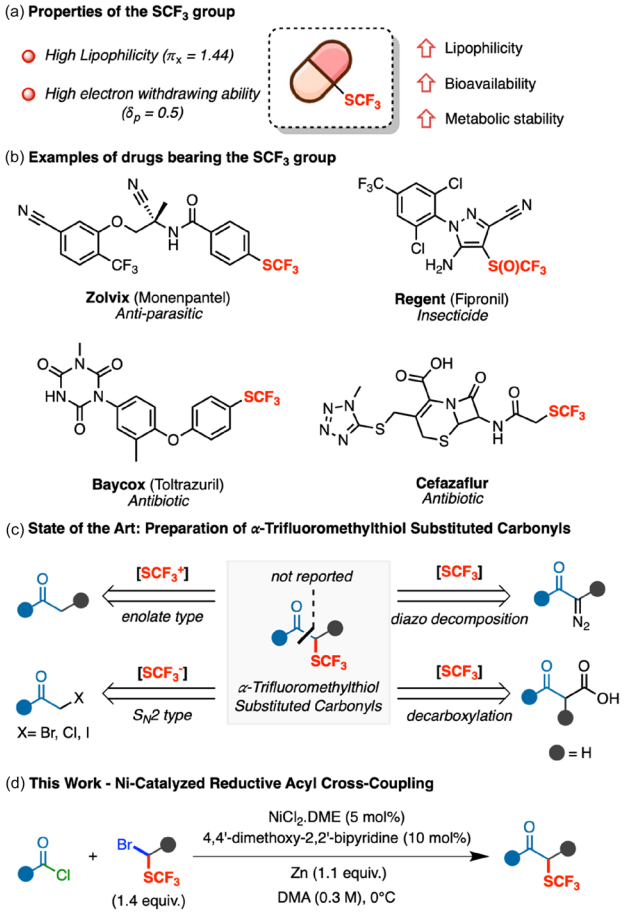
ABSTRACT

The trifluoromethylthiol group (-SCF_3) has attracted considerable attention due to its high lipophilicity and strong electron-withdrawing ability. Over the past decades, numerous methodologies have been developed for the construction of C(sp^2)–SCF_3 bonds through the selective introduction of the SCF_3 group into arenes or vinyl derivatives. In contrast, the synthesis of tertiary C(sp^3)-SCF_3 compounds remains more restricted. Herein, we present a Ni-catalyzed reductive acyl cross-coupling that enables the direct construction of α-trifluoromethylthiolated ketones in a single step utilizing a recently developed SCF_3-containing electrophiles. Moreover, mechanistic investigations have demonstrated the presence of an unusual pathway for reductive coupling and the essential role of zinc.

1 | Introduction

Fluorinated compounds have garnered increasing attention owing to their broad utility in the pharmaceutical, [1, 2] agrochemical [3–5], and materials sciences [6]. Incorporation of a fluorinated group into a biologically active molecule can markedly enhance its pharmacokinetic profile. [7, 8] Among these substituents, the trifluoromethylthiol group (-SCF_3) stands out for its high lipophilicity (Hansch parameter $\pi = 1.44$) and strong electron-withdrawing character (Hammett parameter $\sigma_p = 0.5$) (Scheme 1A) [9–11]. These features are known to improve cell membrane permeability, thereby increasing bioavailability and contributing to the enhanced metabolic stability of bioactive compounds (Scheme 1B).

Over the past decades, numerous methodologies have been developed for the construction of C(sp^2)–SCF_3 bonds through the selective introduction of the SCF_3 group into arenes and vinyl derivatives (For selected trifluoromethylthiolation of arene: [12–22]), (For selected trifluoromethylthiolation of vinyl derivatives [23–30]). In contrast, the synthesis of tertiary C(sp^3)-SCF_3 compounds remains considerably more limited. Although the radical approach have been reported to access C(sp^3)-SCF_3 derivatives via C–H functionalization or decarboxylation, the reliance on strong oxidants or photosensitizers often restricts their practical utility [31–36]. The most direct approach involves the α-functionalization of carbonyl compounds. With the advent of electrophilic SCF_3 reagents, enolate-based transformations were among the earliest to emerge (Scheme 1C), though their dependence on strong bases imposed notable constraints [37–47]. More recently, methods employing weak bases in catalytic amounts have broadened the scope and applicability of these reactions. Complementing these advances, nucleophilic approaches have also been developed using SCF_3 sources such as silver trifluoromethanethiolate ($AgSCF_3$) and copper-trifluoromethanethiolate complexes. (e.g., (bpy)Cu(SCF_3)). These reagents can react with α-haloketones or α-haloamides via an S_N2 pathway to give the corresponding α-trifluoromethylthiolated ketones or amides [48–50]. Alternatively, the SCF_3^- anion can be generated in situ from the Ruppert–Prakash reagent ($TMSCF_3$), elemental sulfur, and a fluoride source; however, a key limitation of this method is the requirement for a stoichiometric amount of copper [51, 52]. Subsequently, two strategies based on prefunctionalized



SCHEME 1 | State of the art trifluoromethylthiolated compounds. (a) Properties of the SCF_3 group (b) Examples of drugs bearing the SCF_3 group (c) Synthesis of α-trifluoromethylthiolated carbonyls compounds (d) This work - Ni-catalyzed reductive acyl cross-coupling.

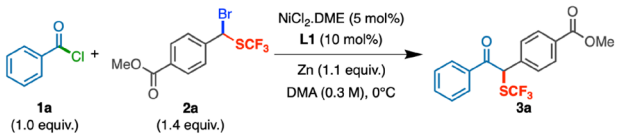
carbonyl compounds were developed. The first involves the decomposition of α-diazocarbonyl derivatives to introduce the SCF_3 group at the α-position, although the need for stoichiometric copper or costly rhodium catalysts significantly restricts its practicality [53–57]. The second strategy relies on the decarboxylation of β-ketocarboxylic acids, enabling installation of the SCF_3 group at the α-position; however, this approach remains relatively underexplored, with only a few reports to date [58, 59].

The emergence of reductive acyl cross-coupling, notably through the pioneering work of Prof. Sarah Reisman, introduced a powerful strategy for the construction of α-functionalized ketones (For selected examples: [60–66]). This approach circumvents the use of highly reactive organometallic reagents, thereby enhancing functional group tolerance. Moreover, the use of readily available, inexpensive, and air-stable reducing agents, such as Mn^0 or Zn^0, in presence of two distinct electrophiles enables the formation of diverse structural motifs under mild conditions. Based on this strategy, we envisioned a reductive acyl coupling involving a trifluoromethylthiolated benzylic bromide, a recently designed SCF_3-containing electrophile capable of generating tertiary $C(sp^3)$-SCF_3 frameworks (Scheme 1D) [67]. This powerful approach will enable the one-step synthesis of α-trifluoromethylthiolated ketones under mild conditions.

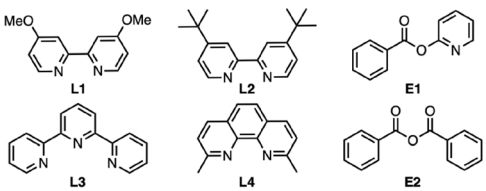
2 | Results and Discussion

Our investigations began with benzoyl chloride **1a** and SCF_3-substituted benzyl bromide **2a**, which was readily synthesized from the corresponding benzyl bromide derivative in two steps. Optimal conditions were identified following a comprehensive optimization study (see SI for additional details). Under these conditions, the desired product **3a** was obtained in 80% isolated yield using a low catalytic loading (Table 1, entry 1)). Notably, typical reductive cross-coupling reactions require a substantial excess of reductant (2.0–3.0 equiv.) to achieve high efficiency. In contrast, our system operates efficiently with only 1.1 equivalents of reductant (entry 1). In control experiments, we have observed that in the absence of either nickel or ligand, the desired product was still formed, albeit in moderate yield (entries 2–3). This observation could be rationalized based on mechanistic studies. In contrast, no product formation was observed in the absence of Zn, confirming its essential role as the reducing agent (entry 3). Terpyridine, phenanthroline, and bipyridine ligands were all found to be competent, although donor-substituted bipyridines provided improved yields (entries 5–7). The reaction also proceeded efficiently at very low catalytic loading (1 mol% Ni

TABLE 1 | Optimization of reaction conditions.

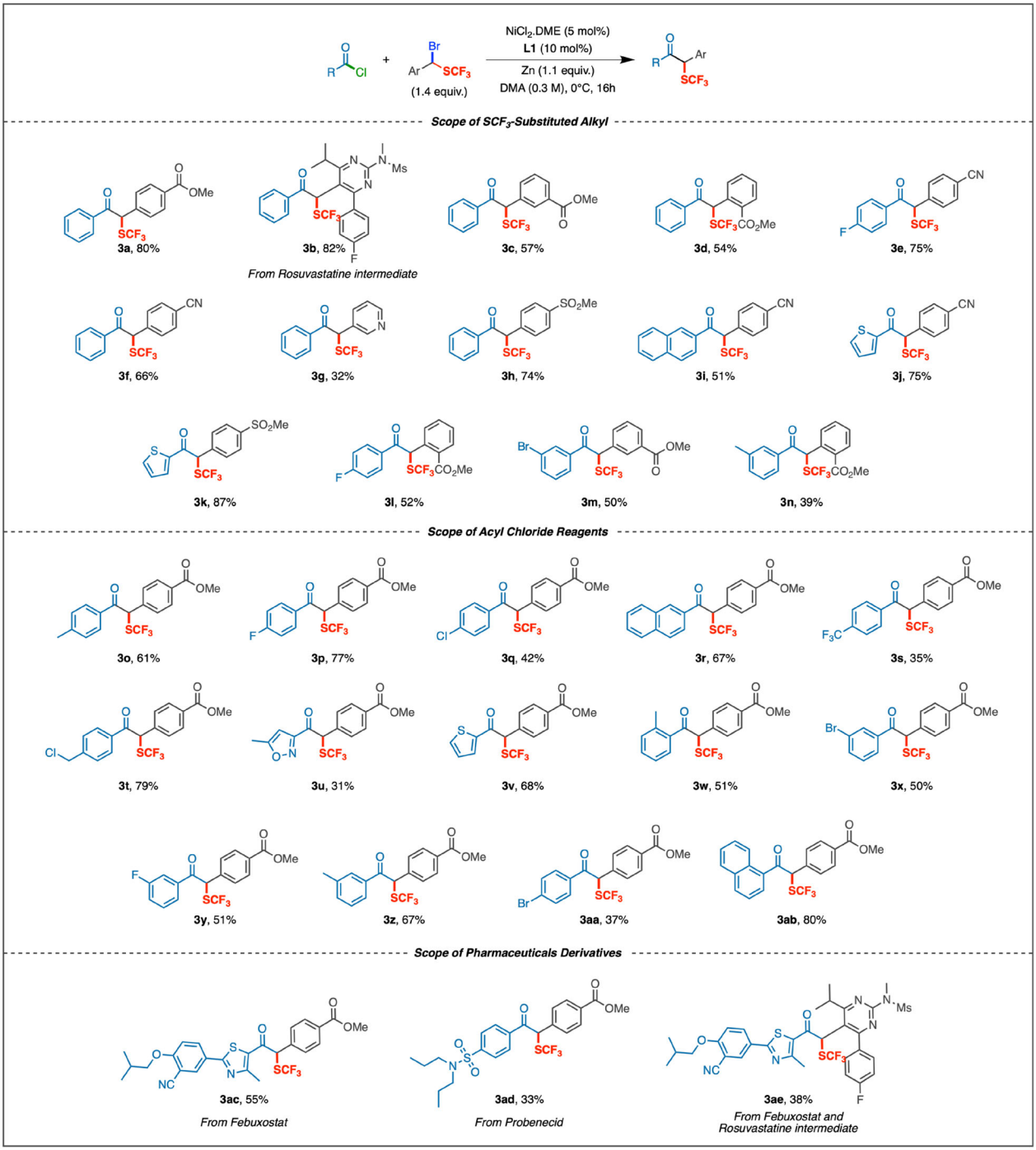


Entry[a]	Variations	Yield, %[b]
1	none	84 (80)[c]
2	w/o Ni	51
3	w/o L	52
4	w/o Zn	–
5	**L2**	60
6	**L3**	61
7	**L4**	71
8	1 mol% Ni/2 mol% L	73
9	TDAE or Mn	35–47
10	THF, DMP or NMP	5%–41%
11	**2a** (1.0 equiv)	64
12	r.t.	71
13	**E1**	4
14	**E2**	20

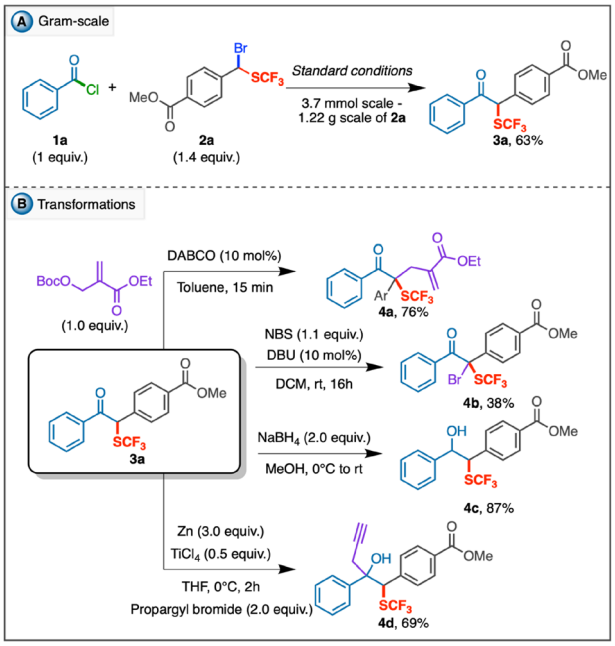


[a]Reaction condition: **1a** (0.1 mmol), **2a** (0.14 mmol), Ni cat. (5 mol%), **L1** (10 mol%), Zn dust (0.11 mmol), DMA (0.33 mL), 0°C, 16h.
[b]^{19}F NMR yield using 3,3′-bis(trifluoromethyl)benzophenone as an internal standard.
[c]Yield of the isolated product. See Supporting Information for additional details.

and 2 mol% ligand), with only a slight decrease in yield (entry 8). Traditional reductants commonly employed in reductive couplings, such as Mn or tetrakis(dimethylamino)ethylene (TDAE), gave the desired product in only low to moderate yields, highlighting the crucial role of Zn as the reductant (entry 9). Among the solvents examined, DMA proved uniquely effective, whereas other amide or ether solvents resulted in a substantial reduction in yield (entry 10). The loading of SCF_3-substituted benzyl bromide **2a** was also found to be a critical for the success of the reaction, using 1.0 equivalents led to a significant decrease in yield (entry 11). The reaction performed at 0°C afforded the highest yield, whereas run at ambient temperature still delivered the product with only a minor loss in yield (entry 12). Finally, other activated carboxylic acid derivatives such as pyridyl ester **E1** and anhydride **E2** were evaluated, confirming that the presence of an acyl chloride was essential for the transformation (entries 13–14). With the optimized reaction conditions in hand, we next explored the generality of the substrate scope (Scheme 2). First, we investigated various SCF_3-substituted benzyl bromide and were pleased to find that a broad range of functional groups was well tolerated. Substrates bearing ester (**3a, 3c-3d, 3l-3n**), cyano (**3e-3f, 3i-j**) or sulfone (**3hr, 3k**) furnished the

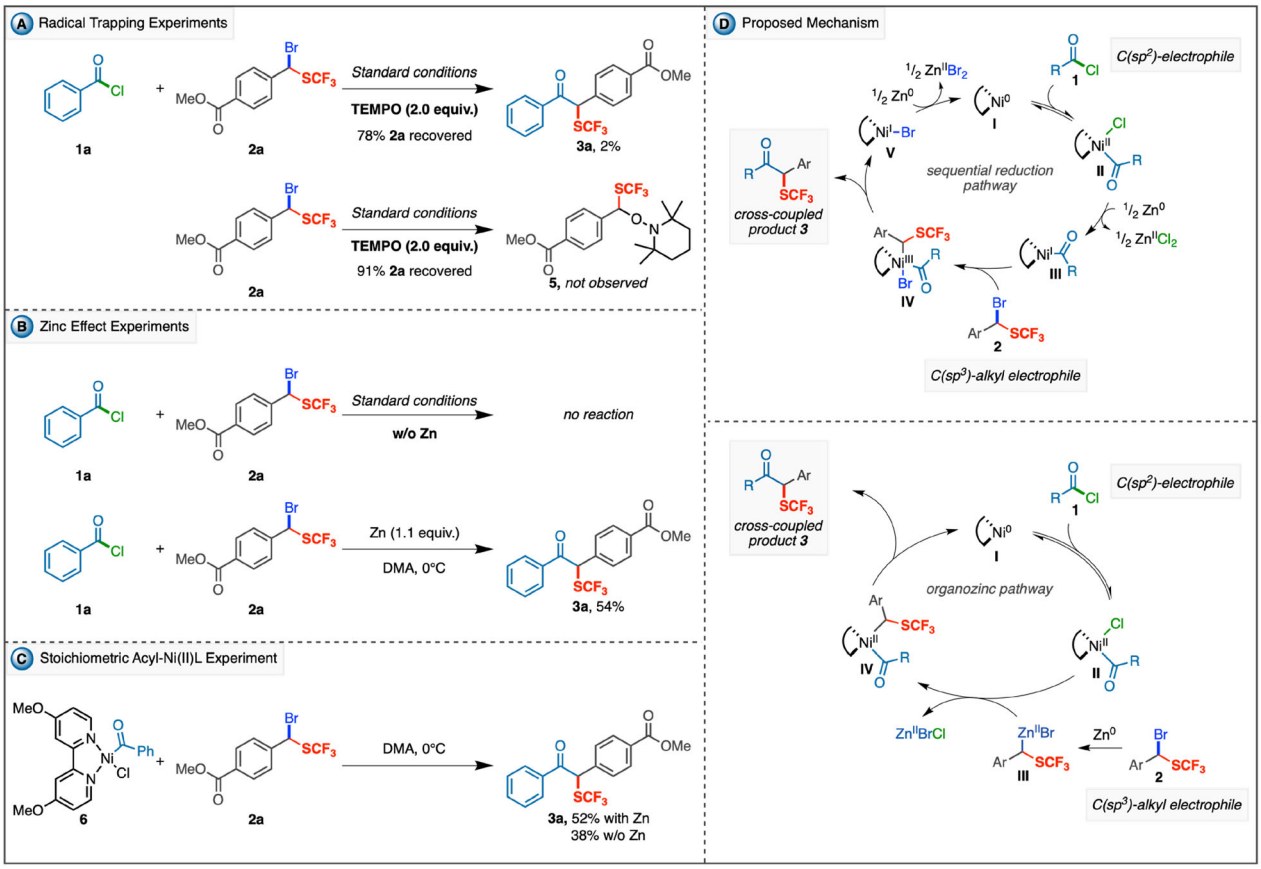


SCHEME 2 | Substrate scope α-trifluoromethylthiolated ketones. Reaction condition: **1a** (0.2 mmol), **2a** (0.28 mmol), Ni cat. (5 mol%), **L1** (10 mol%), Zn dust (0.22 mmol), DMA (0.67 mL), 0°C, 16 h.



SCHEME 3 | Synthetic applicability. (a) Gram-scale reaction (b) Further transformations.

corresponding products in moderate to excellent yields (39%–87%). Electron-deficient heteroaromatic were also well tolerated. A pyrimidine (**3b**) derivative originating from a *Rosuvastatine* intermediate provided the product in excellent yield (82%) and a pyridine-containing substrate (**3g**) gave a fair yield. Ester substituents at the *meta* (**3c**) or *ortho* (**3d**) position gave comparable, moderate yield, whereas the *para*-substituted analog afforded the product in the highest yield (**3a**, 80%). These results highlight that the transformation proceeds efficiently even in the presence of sterically demanding groups on the SCF_3-substituted benzyl bromide. A range of acyl chlorides was subsequently examined, revealing a broad and synthetically useful substrate scope (31%–80%). Halogenated substrates bearing *para* (**3q, 3s, 3aa**) or *meta* (**3x-y**) substitution provided the desired product in moderate yields, while fluorinated analog (**3p**) performed better (77%). Both electron-rich or electron-poor heterocycles were competent coupling partners. The thiophene derivative (**3v**) delivered a satisfactory yield (68%), whereas the isoxazole derivative (**3u**) gave a modest yield (31%). Methyl substitution position on the aromatic ring had negligible influence on the reaction outcome, underscoring the operational flexibility of the method. However, some limitations may be encountered depending on the nature of the acyl chloride used (See SI for additional details). To showcase the synthetic utility of the protocol, several pharmaceutical agents were successfully derivatized. A *Febuxostat* analog (**3ac**) containing a thiazole moiety was obtained in good yield (55%), while the corresponding *Probenecid* derivative (**3ad**) was delivered in moderate yield. A final combination of the *Febuxostat* and *Rosuvastatine* fragments (**3ae**) provided a highly complex target molecule in fair yield (38%). The practicality of the method was further demonstrated through a series of transformation



SCHEME 4 | Mechanistic investigation. (a) Radical trapping experiments (b) Zinc effect experiments (c) Stoichiometric acyl-Ni(II) experiment (d) Proposed mechanism.

(Scheme 3). A gram-scale synthesis (1.22 g of **2a**) proceeded smoothly to deliver the product in good yield. The ketone functionality (**3a**) enabled diverse transformations: a allylic alkylation reaction furnished the adduct (**4a**) in high yield (76%), whereas α-bromination proceeded in modest yield (38%). Reduction with sodium borohydride afforded the corresponding alcohol (**4c**) in excellent yield (87%). Additionally, a Barbier-type propargylation of the ketone delivered the propargylated product (**4d**) in good yield (69%) without compromising the ester group.

To differentiate between a sequential reduction process and a radical-chain pathway, we conducted a more detailed mechanistic study (for selected reductive cross-coupling mechanistic studies: [68–72]). A radical-trapping experiment using TEMPO was first performed (Scheme 4A).

Under the standard conditions, only traces of the desired product (**3a**) were obtained. However, this inhibition likely results from competitive reaction of TEMPO with the acyl chloride (**1a**), rather than interception of a radical intermediate. To test this hypothesis, the reaction was repeated in the absence of acyl chloride. no TEMPO-adduct (**5**) was detected by High Resolution Mass Spectrometry (HRMS), supporting a mechanism that does not involve radical intermediates. Next, the role of Zn was evaluated. In the absence of Zn, no reaction occurred, and all starting materials were recovered (Scheme 4B). In contrast, the use of 1.1 equiv of Zn yielded the product in moderate yield. This is consistent with the behavior expected in a sequential reduction pathway, wherein the reductant is essential for productive turnover [62, 73, 74]. We then examined a stoichiometric reaction employing an isolated acyl–Ni(II)L1 complex (**6**) (Scheme 4C). This complex successfully furnished the product, supporting its involvement as an intermediate in the catalytic cycle. Under these conditions, disproportionation of two acyl–Ni(II)L1 species is proposed to generate a low-valent acyl–Ni(I)L1 complex capable of undergoing oxidative addition with **2a**. Notably, addition of Zn markedly increased the yield of the stoichiometric reaction, indicating that reduction of acyl–Ni(II)L1 to the catalytically active acyl–Ni(I)L1 species is a key step in the sequential reduction mechanism. Taken together, these experiments indicate that (i) radical pathways are unlikely to be operative, (ii) Zn is required for productive turnover, and (iii) the acyl-Ni(II)L1 complex functions as a key reaction intermediate, with Zn promoting its reduction to the catalytically active low-valent acyl–Ni(I)L1 species. Based on precedent literature and our mechanistic investigations, two competing pathways are proposed (Scheme 4D) [69–71]. In the first, a sequential reduction mechanism operates: the Ni complex **I** undergoes oxidative addition to the acyl chloride, forming the acyl–Ni(II) intermediate **II**. Subsequent reduction by Zn generates the active acyl–Ni(I) species **III**, which then engages in a second oxidative addition with the SCF_3-substituted alkyl bromide (**2**). Reductive elimination from the resulting high-valent intermediate furnishes the cross-coupled product (**3**). In the competing pathway, an organozinc species is generated through oxidative addition of Zn into the SCF_3-substituted alkyl bromide (**2**). Transmetalation between this organozinc reagent and the acyl–Ni(II) complex is followed by reductive elimination to deliver the product (**3**) [75–79]. Finally, to account for product formation in the absence of Ni or ligand, the nucleophilic organozinc reagent may directly react with the electrophilic acyl chloride via an S_N2-type process. However, even if an uncatalyzed reaction pathway occurs, optimum yields require the use of the nickel-based catalyst (see SI for more experiments).

3 | Conclusion

In summary, we have developed a Ni-catalyzed reductive acyl cross-coupling that enables direct access to a wide array of α-trifluoromethylthiolated ketones from SCF_3-substituted benzyl bromides in a single step, representing a significant advance in their synthesis. The method features a broad substrate scope (>30 examples), mild reaction conditions, readily available feedstock reagents, and low catalyst, ligand, and reductant loadings. Mechanistic studies suggest an unusual pathway within the context of reductive coupling. We anticipate that this methodology will facilitate further transformations involving SCF_3-containing building blocks and offer valuable opportunities for the streamlined preparation of structurally diverse SCF_3-functionalized molecules.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.