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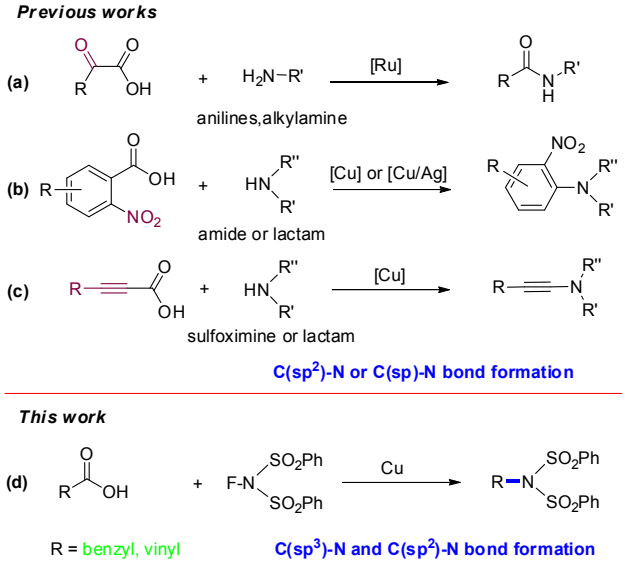
An efficient copper-catalyzed radical decarboxylative imidation reaction is presented. This strategy is carried out through the copper(I)-catalyzed decarboxylative C(sp^3)–N and C(sp^2)–N coupling of carboxylic acids with *N*-fluoroarylsulfonimides. The reaction shows well functional group tolerance and it provides a new approach for decarboxylative imidation. Preliminary mechanistic studies of this transformation suggest an involvment of N-centrered radical species.

Amines are featured prominently in active pharmaceutical ingredients, fine chemicals, agrochemicals, polymers and plasticizing agents. They can also serve as versatile building blocks in organic synthesis.[1] Consequently, the introduction of an amino group into a target molecule, in particular C-amination,[2] has attracted considerable attention. Especially, enormous efforts have been devoted to Schmidt reactions of carboxylic acids,[3] which provide a convenient entry to C–N bond formation through the decarboxylative amination. Nevertheless, traditional methods for the synthesis of amines via decarboxylative amination were rather limited in practical application due to the utilization of explosive azides as the nitrogen source,[4] strong sulfonic acids[5] and toxic reagents[6]. Therefore, the development of efficient synthetic routes for the synthesis of amines is very highly desirable.

In recent years, a rapidly growing number of catalytic coupling reactions with carboxylic acids as substrates have been reported.[7] Among these, the transition-metal-catalyzed decarboxylative reactions for C–N bond formation offer a new synthetic strategy for the introduction of an amino group into a molecule. Recently, Lei and co-workers revealed the first example of radical decarboxylation C(sp^2)–N coupling of α-keto acids with arylamines in a photoredox mediated system (Scheme 1a).[8] The groups of Mainolfi[9] and Jia[10] successfully developed the decarboxylative C(sp^2)–N coupling of aryl carboxylic acids and *N*–nucleophiles, respectively (Scheme 1b). Jiao[11] and Bolm[12] groups independently discovered oxidative decarboxylative C(sp)–N coupling of aryl propionic acids with amines under copper catalysis (Scheme 1c). However, these methods often require carboxylic acids bearing strong electron-withdrawing group adjacent to the carboxyl group. Meanwhile, transition-metal-catalyzed decarboxylative amidation with simultaneous formation of C(sp^3)–N and C(sp^2)–N bonds has rarely been investigated. Herein, we describe a novel route for in situ radical decarboxylative C(sp^3)–N and C(sp^2)–N couplings of alkyl/vinyl-substituted carboxylic acids with *N*–fluorobenzenesulfonimide (NFSI) as the nitrogen source. The reaction exhibits high chemo- and regioselectivity in forming various *N*-alkyl imides and *N*-vinyl imides products (Scheme 1d), which have shown great potential in medicinal chemistry and materials applications.[13]



Scheme 1 Transition-metal catalyzed decarboxylative amination of carboxylic acid

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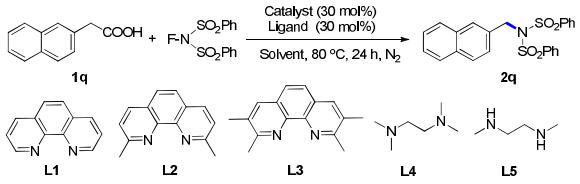
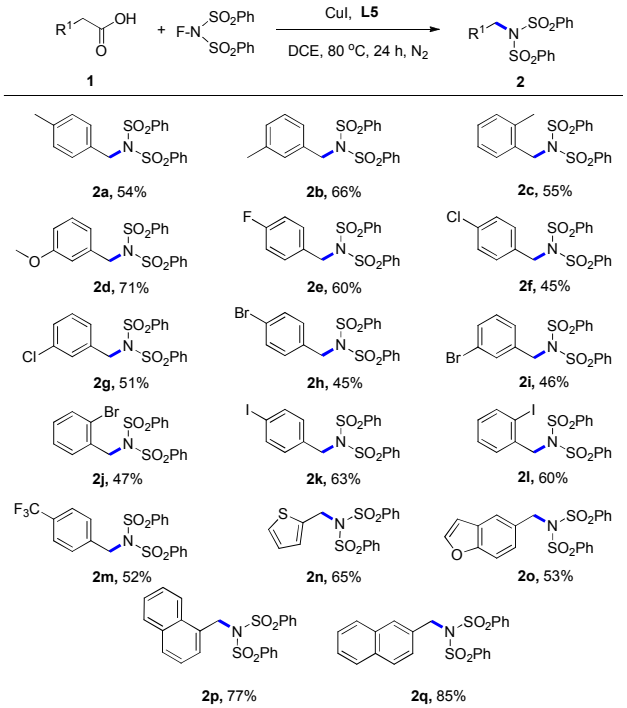
In order to optimize the reaction conditions for this decarboxylative imidation, a model reaction of 2-naphthylacetic acid (**1q**) and NFSI was carried out with various copper salts, ligands and solvents (Table 1). Preliminary experimental results displayed that Cu salts, such as CuCl, $CuCl_2$, CuI, and $Cu(OAc)_2$, were effective in the presence of 2,9-dimethyl-1,10-phenanthroline **L2** as ligand and 1,2-dichloroethane (DCE) as solvent at 80 °C for 24 h under nitrogen atmosphere (entries 1–4). Among the copper sources tested, CuI was the most effective catalyst, affording the target decarboxylative coupling product **2q** in 69% yield. After establishing CuI as the optimal catalyst, we focused on investigating other *N*-containing ligands (entries 5–8). Gratifyingly, the *N,N*-dimethyl-1,2-ethanediamine **L5** proved to be the most efficient and increased the yield of product **2q** to 93% (entry 7). In contrast, solvents such as CH_3CN, 1,2,3-trichloropropane(TCP), 1,4-dioxane, toluene and ethanol showed inferior reactivity in this reaction and gave the corresponding product with yields ranging from 30% to 77% (entries 9–13). Polar solvents *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) resulted in only trace amount of product **2q** (entries 14 and 15). The reaction did not occur without either CuI or ligand (entry 16 and 17). We therefore decided the utilization of CuI (30 mol %) and **L5** (30 mol %) in DCE at 80 °C under nitrogen atmosphere as the optimized reaction conditions for this protocol.

Table 1 Decarboxylative coupling of 2-naphthylacetic acid with NFSI over different conditions[a]

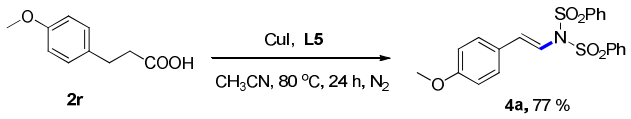


entry	catalyst	ligand	solvent	yield[b] (%)
1	CuCl	**L2**	DCE	58
2	$CuCl_2$	**L2**	DCE	48
3	CuI	**L2**	DCE	69
4	$Cu(OAc)_2$	**L2**	DCE	46
5	CuI	**L1**	DCE	87
6	CuI	**L3**	DCE	80
7	CuI	**L5**	DCE	93
8	CuI	**L4**	DCE	80
9	CuI	**L5**	CH_3CN	54
10	CuI	**L5**	TCP	77
11	CuI	**L5**	1,4-dioxane	52
12	CuI	**L5**	Toluene	30
13	CuI	**L5**	Ethanol	62
14	CuI	**L5**	DMF	trace
15	CuI	**L5**	DMSO	trace
16	CuI	-	DCE	None detected
17	-	**L5**	DCE	None detected

[a] Reaction condition: 2-naphthylacetic acid (0.3 mmol), NFSI (0.42 mmol), catalyst (30 mol %). ligand (30 mol %) and solvent (2.0 mL). [b]Yield by LC.



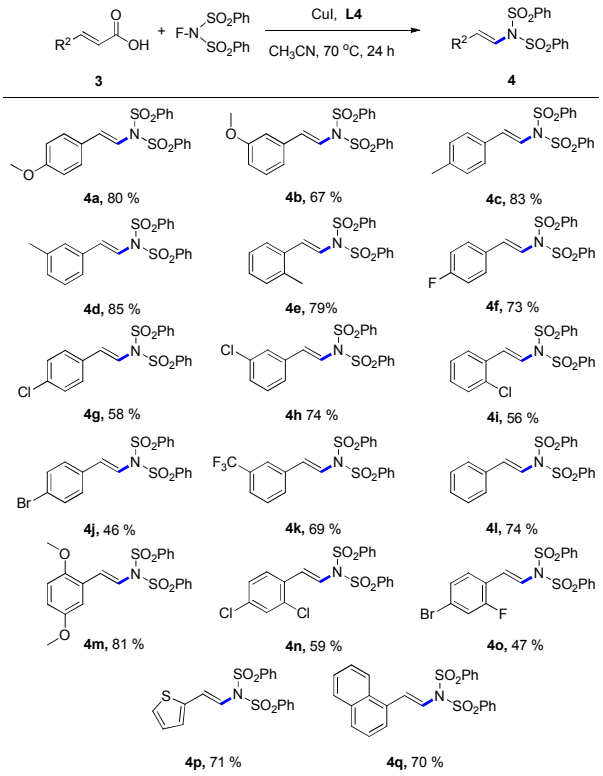
Scheme 2 Reaction scope. Conditions: arylacetic acids (0.3 mmol), NFSI (0.42 mmol), CuI (30 mol %), **L5** (30 mol %) and DCE (2.0 mL), isolated yield.



Scheme 3 Decarboxylative coupling with 3-(4-Methoxyphenyl) propanoic acid. The reaction was carried out under the optimal reaction conditions reported above.

To examine the reaction scope of this decarboxylative imidation reaction, various aliphatic carboxyl acids were reacted with NFSI under the optimized reaction conditions, and the results were summarized in Scheme 2. First, phenylacetic acids with electron-donating substituents, such as methoxy, methyl group were tolerated for this transformation, leading to the target products **2a**-**2d** in moderate to good yields. Meanwhile, halo-substituted phenylacetic acid was tolerated in the aminofluorination reaction, thus affording the corresponding products (**2e**-**2l**) in good yields. The electron-withdrawing 4-trifluoromethyl phenylacetic acid afforded **2m** in 52% yield. Moreover, Similarly with phenylacetic acids, acids with polycyclic and heterocyclic group, i.e. naphthalenes, benzofurans and thiophenes were also compatible, and providing the corresponding products **2n**-**2q** in 53–85% isolated yields. Interestingly, the utilization of the 3-(4-methoxyphenyl)propionic acid **2r** as the substrate was preferred the formation of the vinyl imide **4a** in 77% yield.

Encouraged by these results of the decarboxylative C(sp^3)–N coupling reaction, we next extended the scope of the reaction to cinnamic acids under the optimized reaction conditions presented in Table S1. A range of cinnamic acids with various substituents at

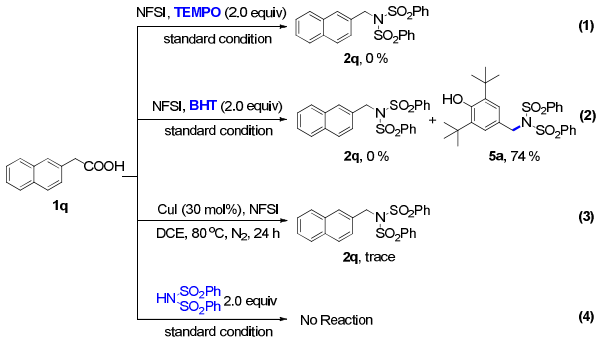


Scheme 4 Reaction scope. Conditions: cinnamic acid (0.3 mmol), NFSI (0.42 mmol), CuI (30 mol %), **L4** (30 mol %) and CH_3CN (2.0 mL), isolated yield

the phenyl ring were appreciated, and led to the formation of products in 46% to 85% yields (Scheme 4). Cinnamic acid resulted in the desired vinyl imides **4a**-**4e** in 67−85% yields, whereas cinnamic acid derivatives bearing halo-substituents at the phenyl ring provided the vinyl imides **4g**-**4j** in 46−74% yields. The electron-withdrawing 4-trifluoromethyl cinnamic acid afforded **2k** in 69% yield. Even polysubstituted cinnamic acids produced the target products **4m**-**4o** in 47−81% yields. Moreover, substrates bearing thiophene and naphthalene moiety resulted in the corresponding decarboxylative products **4p** and **4q** in 57% and 67% yields, respectively.

To gain insight into the mechanism of decarboxylative C(sp^3)–N and C(sp^2)–N couplings of carboxylic acids bearing alkyl or vinyl groups with NFSI, a series of mechanistic experiments were performed (Scheme 5 and S1). In the presence of 2.0 equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) as a radical scavenger (entry 7, Table 1), the reaction of 2-naphthylacetic acid **1q** failed to give the target product under the optimal reaction conditions [eq (1)]. Meanwhile, when 2.0 equivalent of 2,6-di-tert-butyl-4-methylphenol (BHT) were added instead of TEMPO, the decarboxylative amidation product **2q** was not observed, instead of forming the adduct **5a** of BHT and NFSI in 74% isolated yield [eq (2)].

It should be noted that in the absence of ligand **L5** only trace amount of product **2q** was detected with the prolonging reaction time after 24h [eq (3)]. The control experimental results indicated that the ligand is necessary for this



Scheme 5 Control experiments

transformation. In addition, when 2.0 equivalent of dibenzenesulfonimide was added instead of NFSI, the decarboxylative imidation product was not observed [eq (4)]. Therefore, the N-centered radical species was plausibly generated via N-F bond cleavage of NFSI. The parallel mechanistic experiments of cinnamic acids were shown in Scheme S1 in the Supporting Information, which also probably proceeded via a free radical process.[14]

In summary, we have developed a new facile copper-catalyzed intermolecular decarboxylative imidation of carboxylic acids by using commercially available NFSI as the nitrogen source, which provides an efficient, direct and practical access to form a new C(sp^3)–N or C(sp^2)–N bond. Meanwhile, the application of decarboxylative coupling reactions of carboxylic acids to construct new C–C, C–heteroatom bonds are ongoing in our laboratory.

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