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Pd-Catalyzed C(sp²)-H Aminocarbonylation Using Langlois Reagent as Carbonyl Source

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A Pd-catalyzed C(sp²)-H aminocarbonylation of aryl carboxamides assisted by *N*, *S*-bidentate directing group was developed, in which the cheap and stable sodium trifluoromethanesulfinate was firstly utilized as carbonyl source. The reaction can be applicable to a wide range of carboxamides with good functional group tolerance and afford isoindole-1,3-diones in moderate to good yields.

Introduction

In the past decades, great breakthroughs have been achieved in transition-metal-catalyzed C-H carbonylation, which provides a versatile synthetic method for carbonylated molecules.^[1] Among them, the direct Pd-catalyzed C-H carbonylation using carbon monoxide (CO) as carbonyl source attracted considerable attention.^[2] However, CO gas is difficult to handle, transport and highly toxic, which restricts its usage. Recently, formic acid and its esters,^[3] metal carbonyls,^[4] aldehydes,^[5] acyl chloride,^[6] azodicarboxylates,^[7] 2,2-azobisisobutyronitrile (AIBN),^[8] and some solvents^[9] including DMF, nitromethane or CHCl₃ were reported to act as CO sources to construct various carbonyl compounds. Nevertheless, the development of new CO surrogates by generating CO *in-situ* for the carbonylation is still desirable.

For numerous Pd-catalyzed C-H carbonylation reactions, directing groups are usually required to realize selectivity of these transformations. Various functional groups, such as amides,^[10] amines,^[11] *N*-containing heterocycles,^[12] amidines,^[13] hydroxyl including the phenolic hydroxyl groups,^[14] carboxylic acids,^[15] and phosphonic/phosphinic acids^[16] have been utilized as directing groups to realize the C-H carbonylation. However, the 2-methylthioaniline auxiliary was seldom used as the directing-group to construct structurally diverse molecules,^[17] presumably due to catalyst poisoning by the mercapto group.^[18] As part of our continuing interest in synthesis of sulfur compounds,^[19] we herein wish to report a Pd-catalyzed C(sp²)-H aminocarbonylation of aryl carboxamides assisted by an *N*, *S*-bidentate directing group. The readily available sodium trifluoromethanesulfinate (CF₃SO₂Na) was firstly used as CO surrogate. The unexpected reaction provided a

novel approach to isoindole-1,3-dione derivatives bearing methylthio group.

Results and discussion

Table 1. Screening Conditions^a

Entry	Catalyst	Oxidant (equiv)	Solvent	Yield (%)
1	Pd(OAc) ₂	Cu(OTf) ₂ (1.0)	Dioxane	5
2	Pd(OAc) ₂	Cu(OTf) ₂ (1.0)	DMSO	0
3	Pd(OAc) ₂	Cu(OTf) ₂ (1.0)	DCE	18
4	Pd(OAc) ₂	Cu(OTf) ₂ (1.0)	PhCl	21
5	PdCl ₂	Cu(OTf) ₂ (1.0)	PhCl	8
6	Pd(MeCN) ₂ Cl ₂	Cu(OTf) ₂ (1.0)	PhCl	32
7	Pd(TFA) ₂	Cu(OTf) ₂ (1.0)	PhCl	50
8	-	Cu(OTf) ₂ (1.0)	PhCl	NR
9	Pd(TFA) ₂	CuCl ₂ (1.0)	PhCl	12
10	Pd(TFA) ₂	Cu(BF ₄) ₂ (1.0)	PhCl	33
11	Pd(TFA) ₂	Cu(NO ₃) ₂ (1.0)	PhCl	6
12	Pd(TFA) ₂	-	PhCl	NR
13	Pd(TFA) ₂	Cu(OTf) ₂ (1.2)	PhCl	55
14 ^b	Pd(TFA) ₂	Cu(OTf) ₂ (1.2)	PhCl	66
15 ^c	Pd(TFA) ₂	Cu(OTf) ₂ (1.2)	PhCl	77
16 ^d	Pd(TFA) ₂	Cu(OTf) ₂ (1.2)	PhCl	NR

^a Reaction conditions: **1a** (0.2 mmol), CF₃SO₂Na (0.4 mmol), Pd catalyst (10 mol %), oxidant (1.0 equiv), H₂O (4.0 equiv) in

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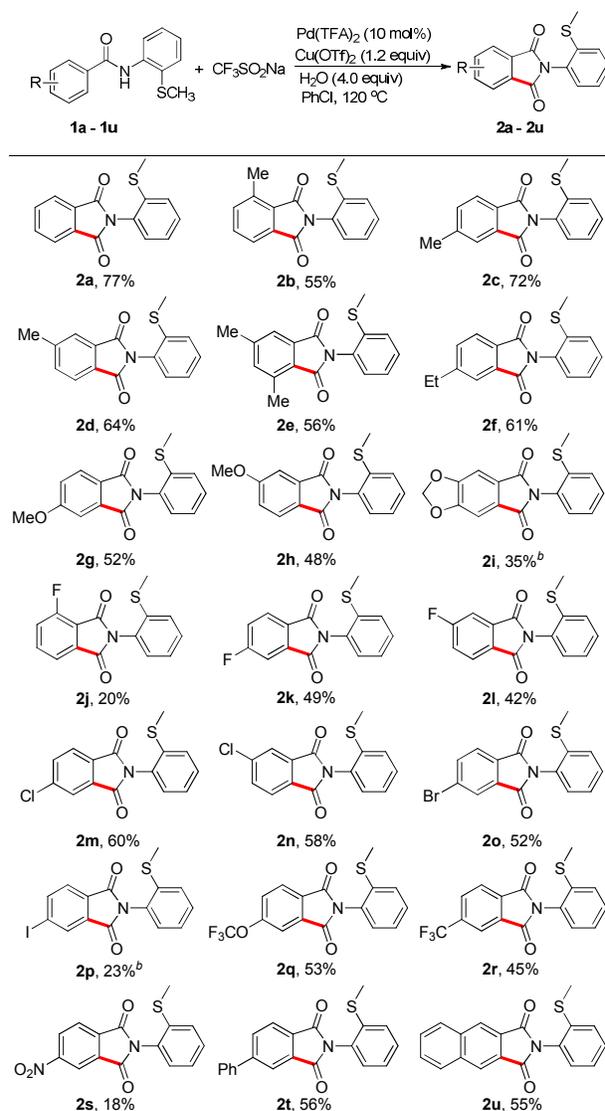
solvent (2 mL) at 120°C under air atmosphere for 24 h; Isolated yield; ^b CF₃SO₂Na (2.5 equiv); ^c CF₃SO₂Na (2.7 equiv); ^d Without CF₃SO₂Na; NR = no reaction.

The reaction of *N*-(2-(methylthio)phenyl)benzamide **1a** with sodium trifluoromethanesulfonate (CF₃SO₂Na) was chosen as the model reaction to optimize the reaction conditions, and the results were listed in Table 1. Initially, the reaction was conducted in the presence of 10 mol % Pd(OAc)₂, 1 equiv of Cu(OTf)₂ and 4.0 equiv H₂O in dioxane at 120 °C for 24 h, but product **2a** was isolated only in 5% yield (entry 1). Moreover, the structure of product **2a** was confirmed by X-ray crystallography. Other solvents including DMSO, DCE and PhCl were also examined, and 21 % yield of product **2a** was obtained in PhCl (entry 4). Encouraged by these results, different catalysts such as PdCl₂, Pd(MeCN)₂Cl₂ and Pd(TFA)₂ were further screened (entries 5-7). It was found that Pd(TFA)₂ was the most suitable catalyst for the aminocarbonylation and a 50% yield was obtained (entry 7), the reaction did not work in the absence of palladium catalyst (entry 8). Subsequently, various oxidants including CuCl₂, Cu(BF₄)₂ and Cu(NO₃)₂ were tested, but all gave worse results than Cu(OTf)₂ (entries 9-11). However, the reaction could not proceed without copper salts (entry 12). The yield was slightly enhanced to 55 % when the loading of Cu(OTf)₂ was increased to 1.2 equiv (entry 13). Then, various equivalents of CF₃SO₂Na were screened (entries 14-16). We were pleased to find that a 77 % yield was obtained when 2.7 equiv CF₃SO₂Na was used (entry 15). Moreover, no carbonylated product was generated in the absence of CF₃SO₂Na, which suggested CF₃SO₂Na actually acted as the carbonyl source (entry 16).

With the optimal reaction conditions in hand, the substrate scope of various carboxamides was next investigated. As shown in Table 2, carboxamides with both electron-donating and electron-withdrawing groups underwent the aminocarbonylation smoothly, affording the products **2b** – **2u** in moderate to good yields. Generally, aromatic amides with electron-donating groups gave the products in higher yields than those bearing electron-withdrawing groups. For example, methyl, ethyl and methoxyl carboxamides provided isoindole-1,3-diones **2b** – **2h** in 48-72 % yields, while fluoro, chloro, bromo, trifluoromethoxy and trifluoromethyl substituents (**2j** – **2r**) were isolated in 20-60 % yields. 4-Iodide isoindole-1,3-dione **2p** was also obtained, albeit in a low yield (23%), which could provide potential handles for further modification. A low yield was observed in the case of 4-nitro-substituted benzamide (18%), possibly resulting from the poor solubility of both reactant and product **2s**. It was noteworthy that aminocarbonylation of aromatic amides bearing *ortho*-methyl and fluoro group proceeded well and the corresponding products **2b** and **2j** were obtained in 55% and 20 %, respectively. For *meta*-substituted amides, such as 3-methyl, 3-methoxy and 3-fluoro benzamides, the aminocarbonylation occurred at the less hindered *ortho*-position, giving the same products (**2d**, **2h** and **2l**) as those *para*-substituted substrates. Gratifyingly, 4-phenyl and 2-naphthyl carboxamides also underwent the reaction smoothly and provided products **2t** and **2u** in moderated yields. Unfortunately, many heterocyclic carboxamides including furan, thiophene, and indole

carboxamides were tested, but no desired products can be obtained.

Table 2. Scope with respect to the aryl carboxamides ^a

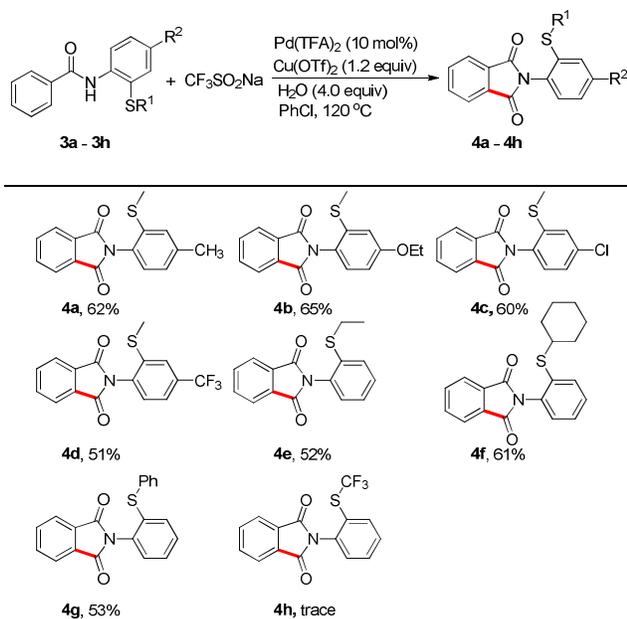


^a Reaction conditions: **1** (0.2 mmol), CF₃SO₂Na (5.4 mmol), Pd(TFA)₂ (10 mol%), Cu(OTf)₂ (1.2 equiv) and H₂O (4.0 equiv) in dry PhCl (2 mL) at 120°C under air atmosphere for 24 h; Isolated yield. ^b 20 mol % of Pd(TFA)₂ was used.

Notably, the C-H aminocarbonylation was also compatible with some substituted 2-thioaniline derivatives with *para*-methyl, ethoxyl, chloro and trifluoromethyl moieties, and the targeted products **4a-4d** were isolated in 51-65 % yields (Table 3). In addition, various 2-alkylthioanilines, such as 2-ethyl and 2-cyclohexylthioaniline were tolerated well, giving their corresponding products **4e** and **4f** in 52% and 61 % yields, respectively. To our delight, when the *N*-(2-(phenylthio)phenyl)benzamide **3g** was reacted with CF₃SO₂Na under standard conditions, the product **4g** was isolated in 53 % yield.

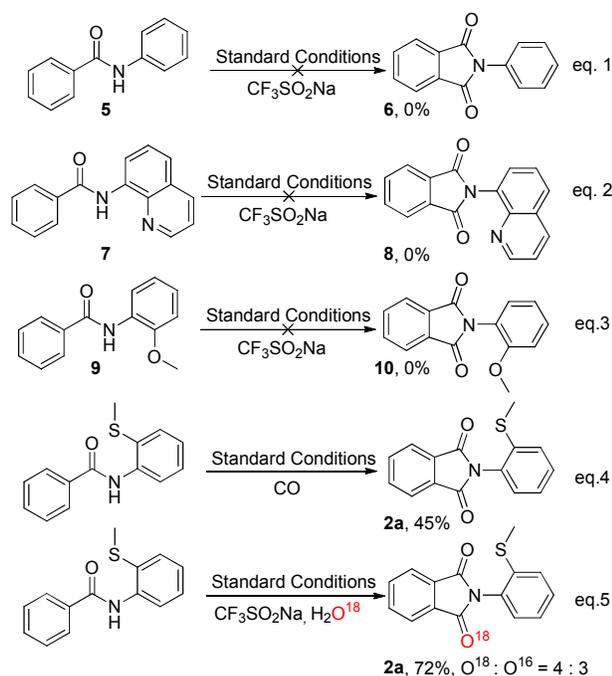
However, the reaction was totally restrained when methylthio group (SCH₃) was changed to trifluoromethylthio (SCF₃, **3h**), which suggested that the electronic property of thio group affected the aminocarbonylation dramatically.

Table 3. Scope with respect to the 2-alkyl(aryl)thioanilines^a



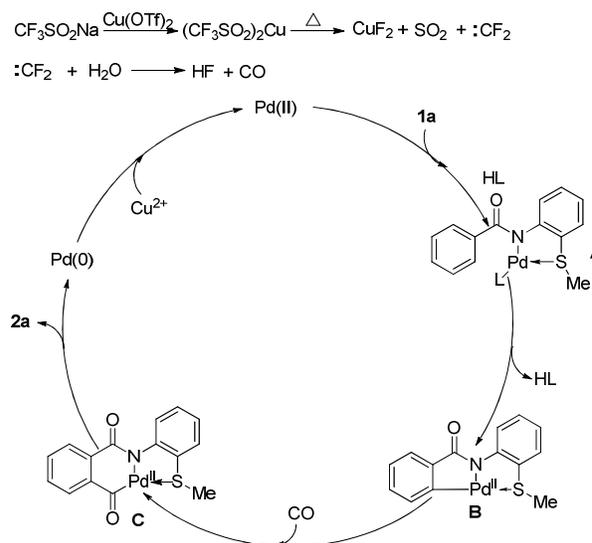
^a Reaction conditions: **1** (0.2 mmol), CF₃SO₂Na (5.4 mmol), Pd(TFA)₂ (10 mol%), Cu(OTf)₂ (1.2 equiv) and H₂O (4.0 equiv) in dry PhCl (2 mL) at 120°C under air atmosphere for 24 h; Isolated yield.

Scheme 1. Control Experiments



To probe the reaction mechanism, some control experiments were conducted as shown in Scheme 1. The reactions of *N*-phenylbenzamide **5**, *N*-(quinolin-8-yl)benzamide **7** (assisted by *N*,*N*-bidentate ligand) and *N*-(2-methoxyphenyl)benzamide **9** (assisted by *N*,*O*-bidentate ligand) with CF₃SO₂Na were conducted under standard conditions, no desired products were observed (eqs. 1, 2 and 3, Scheme 1), which demonstrated that sulfur atom in the *N*-phenyl group play an important role for the aminocarbonylation. When the reaction was conducted under CO atmosphere (CO balloon) in the absence of CF₃SO₂Na, 45% yield of the targeted product **2a** was obtained (eq. 4), suggesting the reagent CF₃SO₂Na acted as the CO source. Furthermore, 4 equiv of H₂O¹⁸ was added into the reaction using the anhydrous chlorobenzene (PhCl) as solvent, the product **2a** was isolated in 72 % yield with the ratio of O¹⁸-**2a** : O¹⁶-**2a** in 4 : 3 according to the GC analysis and HRMS results (eq. 5). These results proved that the oxygen atom of carbonyl group might be derived from the water.

Scheme 2. Possible Mechanism



On the basis of the obtained experimental results and previous report,^[11] a plausible mechanism is proposed for this aminocarbonylation (Scheme 2). Initially, (CF₃SO₂)₂Cu is formed in the reaction of CF₃SO₂Na with Cu(OTf)₂, which is decomposed to release carbene :CF₂ accompanied with CuF₂ and SO₂.^[20] Then, the obtained CF₂ carbene reacts with H₂O to produce HF and CO *in-situ*.^[21] In addition, Pd(II) coordinates with **1a** to form *N,S*-chelated intermediate **A**. Subsequently, the further C-H activation of benzene ring furnishes the arylpalladium complex **B** with loss of a HL. Next, the arylpalladium species **B** is converted into acylpalladium species **C** through a carbonyl insertion. Finally, the nucleophilic displacement of intermediates **C** gives the carbonylated product **2a** and Pd(0), which is oxidized by copper (II) salt to regenerate Pd (II) catalyst.

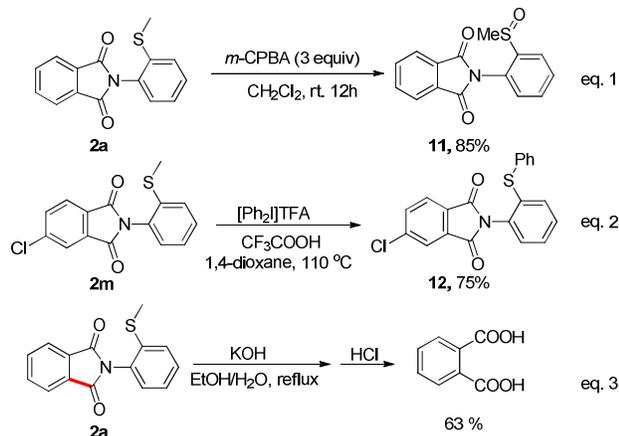
Many compounds with sulfoxide group moiety have been found to possess the biological activity.^[22] Thus, the oxidation of the obtained isoindole-1,3-dione **2a** was carried out with 3 equiv of *m*-CPBA in CH₂Cl₂ at room temperature (Scheme 3, eq. 1),^[23] the corresponding sulfoxide **11** was obtained in 85% yield. In addition, the methylthio group can be easily arylated using diaryliodonium salts under acidic conditions.^[24] When the chloride isoindole-1,3-dione **2m** reacted with diphenyl iodonium trifluoroacetate under

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CF₃COOH, the arylated product **12** was obtained in 75 % yield (Scheme 3, eq. 2). This reaction provided a versatile route to structurally diverse aryl thioether products. During the removal of the directing group, phthalic acid was generated in KOH solution owing to easy hydrolysis of **2a** (Scheme 3, eq. 3).^[25]

Scheme 3. Further Elaboration



Conclusions

In conclusion, we have developed an efficient Pd-catalyzed C(sp²)-H aminocarbonylation of aryl carboxamides bearing *N*, *S*-bidentate directing group. A range of carboxamides with various functional groups underwent this reaction smoothly to afford the corresponding isoindole-1,3-dione derivatives in moderate to good yields. Mechanism study revealed that carbonyl group was derived from the readily available sodium trifluoromethanesulfinate and water. The reaction represents the first utilization of Langlois reagent as carbonyl source.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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