1713

A Ligand-Free Copper-Catalyzed Decarboxylative Trifluoromethylation of Aryliodides with Sodium Trifluoroacetate Using Ag₂O as a Promoter

Yaming Li,* Tao Chen, Huifeng Wang, Rong Zhang, Kun Jin, Xiuna Wang, Chunying Duan*

State Key Laboratory of Fine Chemicals, School of Chemical Engineering, Dalian University of Technology, Dalian 116024, P. R. of China Fax +86(411)84986295; E-mail: ymli@dlut.edu.cn; E-mail: cyduan@dlut.edu.cn Received 26 February 2011

Abstract: A practical and ligand-free Cu-catalyzed decarboxylative trifluoromethylation of aryl iodides with sodium trifluoroacetate using Ag_2O as a promoter was reported. A variety of trifluoromethyl-substituted aromatics are synthesized in moderate to excellent yields and with wide functional-group tolerance under relatively mild reaction conditions.

Key words: copper-catalyzed, trifluoromethylation, decarboxylative, silver oxide, cross-coupling

Trifluoromethyl-substituted arenes possess a number of useful properties, particularly in the synthesis of pharmaceuticals, agrochemicals, and functional materials.¹ Obviously, availability of synthetic tools for selective aromatic trifluoromethylation is of considerable importance.² Transition-metal-mediated cross-coupling of haloarenes with CF₃-transferring nucleophilic reagents for the preparation of trifluoromethylate aromatic compounds is yet a major challenge.^{3–5}

Recently, Yu⁶ reported the first Pd-catalyzed oxidative trifluoromethylation via C–H activation with electrophilic CF_3^+ source. Buchwald and co-workers⁷ has detailed the classical Pd⁰/Pd^{II} trifluoromethylation cycle of aryl chlorides assisted by the use of bulky ligands. At the same time, Sanford⁸ demonstrated the feasibility of fast Ar–CF₃ bond formation from Pd^{IV} complexes under mild conditions. The copper-catalyzed trifluoromethylation encountered a key problem as the intermediate CuCF₃ was unstable even at room temperature.^{9–11} In order to obtain

Previous work

This work



Scheme 1 Transition-metal-mediated trifluoromethylation

SYNLETT 2011, No. 12, pp 1713–1716 Advanced online publication: 05.07.2011 DOI: 10.1055/s-0030-1260930; Art ID: W05711ST © Georg Thieme Verlag Stuttgart · New York maximum yield, stoichiometric amounts of copper complex, such as Cu salt^{12–16} and SIMes Cu–CF₃ complexes,¹⁷ were required. Amii¹⁸ has developed the copper-catalyzed nucleophilic trifluoromethylation of highly reactive iodoarenes containing electron-withdrawing groups on the ring and some iodoheterocycles. Qing¹⁹ proposed that trifluoromethylated aromatic compounds could be prepared through copper-mediated oxidative trifluoromethylation of acetylenes and boronic acids with TMSCF₃ (Scheme 1).

However, many developed efforts are limited to the trifluoromethylation reagents.²⁰ Trifluoroacetate perhaps is

Table 1Trifluoromethylation of p-Chloroiodobezene with SodiumTrifluoroacetate



Entry	Cu (mol%)	Additive (mol%)	Yield (%) ^a
1	CuI (20)	_	17
2 ^b	CuI (20)	_	n.r.
3	CuI (20)	Ag ₂ O (10)	54 (3)
4	CuI (20)	Ag ₂ CO ₃ (10)	52 (4)
5	CuI (20)	AgOAc (20)	48 (2)
6	CuI (20)	AgI (20)	32 (2)
7	_	Ag ₂ O (10)	n.r.
8	CuI (20)	Ag ₂ O (10)	54 (3)
9	$Cu(acac)_2$ (20)	Ag ₂ O (10)	31 (15)
10	CuO (20)	Ag ₂ O (10)	31 (2)
11	Cu (20)	Ag ₂ O (20)	75
12	Cu (20)	Ag ₂ O (10)	64 (4)
13	Cu (30)	Ag ₂ O (30)	90 (3)
14 ^b	Cu (20)	Ag ₂ O (20)	66 (8)

^a Reaction conditions: *p*-chloroiodobenzene (0.5 mmol), CF₃COONa (2 mmol), and DMF (2 mL) under argon reacted at 130 $^{\circ}$ C for 15 h. Yield was determined by GC-MS.

^b 20 mol% ligand (phen) was added.

LETTER

the most convenient, inexpensive, and readily available source of the trifluoromethylation for both industrial and medicinal purposes. Moreover, decarboxylation by heating copper salts with sodium trifluoroacetate form a trifluoromethyl source that can be trapped with various organic substrates.¹⁶ However, these protocols still had the drawback of requiring high reaction temperatures and use of stoichiometric amounts of copper. Most recently, Cu- and Ag-catalyzed decarboxylative C–C bond forming reactions have been investigated largely through the efforts of Goossen²¹ and others.²²

The goal of this work is to use copper and silver salts as catalysts for developing decarboxylative trifluoromethylation of organic halides with sodium trifluoroacetate under mild conditions.

We chose the model coupling between *p*-chloroiodobezene and sodium trifluoroacetate to optimize the reaction condition. We started our experiment with and without ligand (Table 1, entries 1, 2). The addition of ligand did not enhance the yield of trifluoromethylation product as compared to the ligand-free conditions. We speculated that co-ordinating ligand might inhibit decarboxylation of sodium trifluoroacetate or quenched the intermediate CuCF₃ at high temperature. To our delight, in the presence of 10 mol% Ag_2O as an additive, the yield of *p*-chlorotrifluorobezene was enhanced to 57% (Table 1, entry 3); 3% byproduct of the reduction was detected by GC-MS. Other silver salt such as Ag_2CO_3 and AgOAc showed similar effect (Table 1, entries 4, 5), while AgI was less effective (Table 1, entry 6). The experimental results indicated that Ag_2O was crucial for the success of Ar–CF₃ bond forming. We supposed that the activation energy of decarboxylation of sodium trifluoroacetate to generate AgCF₃ in situ is lower than that of CuCF₃. In addition, the formation of AgI precipitation accelerated the process of reductive elimination.

Different copper catalysts were investigated, and either CuI or Cu powder is effective in this procedure. After considering the cost and atom economical, we choose copper powder as the main catalyst. If only silver oxide was used as the catalyst, no product was detected in the absence of copper (Table 1, entry 7).

To achieve maximum yield, various amount of Ag_2O and Cu was used to probe the optimal conditions. It was found that when 30 mol% copper and 30 mol% Ag_2O were used as catalysts, the highest yield (90%) was obtained (Table 1, entry 13). Therefore, the optimized conditions were as following: copper (30 mol%) and silver oxide (30 mol%) in DMF at 130 °C for 15 hours.



Scheme 2 Cu(0)/Ag₂O-catalyzed trifluoromethylation of aromatic halides with sodium trifluoroacetate.²³⁻²⁵ *Reagents and conditions*: ^a Cu (30 mol%), Ag₂O (30 mol%); ^b Cu (40 mol%), Ag₂O (40 mol%); ^c NMR yield measured by ¹⁹F NMR relative to the 2,2,2-trifluoroethanol internal standard; ^d Isolated yields.

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With the optimal reaction conditions, we turned our attention to the scope of this transformation (Scheme 2). Both electron-rich and electron-deficient aryl iodides could give the expected trifluoromethylation products in good to excellent yields, such as the isolated yields of trifluoromethyl bisphenyl (**2p**), diaryl ether (**2q**), and aryl sulfides (**2r**) were 90%, 93%, and 95%, respectively. The procedure tolerated a range of functional groups, such as chloro, nitril, ester, nitro, alkyl, alkoxy, and dialkylamine groups.

However, substrates with nitro substituent and electrondeficient iodoheterocycles did not give good results. We supposed that the Ullmann homocoupling reaction was also activated especially for electron-deficient aryl iodides under these conditions. Dehalogenation and the biphenyl byproducts were observed as well. For the substrates with electron-donating groups, 40 mol% copper source and 40 mol% Ag₂O were required to achieve full conversion. The steric hindrance at the phenyl ring had little effect on this reaction. For example, **2d**, **2f**, and **2h** gave the corresponding products in 70%, 90%, and 87% yields, respectively, showing that this catalytic system was not sensitive to the steric effect for trifluoromethylation reaction.

In conclusion, we have discovered a general and efficient method of Cu/Ag_2O -catalyzed decarboxylative trifluoromethylation reaction of aryl iodides. The functionalgroup tolerance and broad substrate scope are the advantages of this process. Our future efforts will be directed to systematically explore the effects of additives, ligand modifications, and substrate scope on the reaction.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(23) General Procedure for the Preparation of Aryl Trifluoromethylation Derivatives Method A for the Electron-Deficient Aryl Iodides (Compounds 1a-e,l-n,p-r) A flame-dried Schlenk test tube with a magnetic stirring bar was charged with Cu (9.6 mg, 0.15 mmol), Ag₂O (34.8 mg, 0.15 mmol), aromatic halides (0.5 mmol), sodium trifluoroacetate (272 mg, 2.0 mmol), and DMF (2 mL) under argon. Method B for Electron-Rich Aryl Iodides (Compounds 1f-k,o)

A flame-dried Schlenk test tube with a magnetic stirring bar was charged with Cu (12.8 mg, 0.2 mmol), Ag_2O (46.4 mg, 0.2 mmol), aromatic halides (0.5 mmol), sodium trifluoroacetate (272 mg, 2.0 mmol), and DMF (2 mL) under argon. After reacting at 130 °C for 15 h, the reaction mixture was cooled to ambient temperature, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhyd Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel with an eluent of PE and EtOAc.

(24) After the reaction mixture was cooled to r.t., the yields of compounds 2a–f,h,i,l were determined by ¹⁹F NMR with CF₃CH₂OH (0.5 mmol, 36 μL) as internal standard due to their low bp; compounds 2a,d,h are also commercial available.

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- (25) **1,3-Dimethoxy-5-(trifluoromethyl)benzene (2g)** Following the general procedure (method **B**) NMR yield: 82%. ¹H NMR (400 MHz, CDCl₃): $\delta = 6.74$ (2 H, d, J = 1.6Hz), 6.59 (1 H, t, J = 2.0 Hz), 3.81 (6 H, s). ¹³C NMR (100
- MHz, CDCl₃): δ = 161.2, 132.6 (q, *J* = 30 Hz), 124.1 (q, *J* = 270 Hz), 103.8, 103.4, 55.7. ¹⁹F NMR (376 MHz, CDCl₃): δ = -63.4 (3 F, s). HRMS (GC-TOF MS, EI): *m*/*z* calcd for C₉H₉O₂F₃: 206.0555; found: 206.0546.

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