Short Articles

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Copper(I) Thiophene-2-carboxylate (CuTC): A Versatile Non-Nitrogen Ligand-Based Catalyst for Direct *N*-Arylation of Imidazole and Pyrazole Using Aryl Iodides, Aryl Bromides, and Aryl Chlorides

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A new protocol to prepare *N*-aryl heterocyclic adducts in excellent yields via cross-coupling of H*N*-heterocycles with aryl halides is reported using commercially available and easy-to-prepare copper(I) thiophene-2-carboxylate (CuTC) as catalyst.

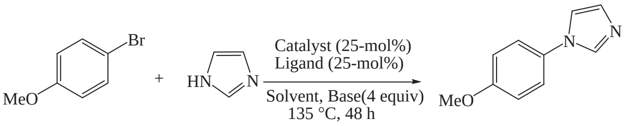
Copper(I) carboxylates have emerged as one of the most effective systems gaining wide applicability as antifungal agents,[1] enzyme models,[2] in molecular magnetism,[3] and very notably, in molecular catalysis for the synthesis of organic molecules.[4] One of the most interesting aspects of copper(I) carboxylates is the exhibition of rate enhancement in chemical reactions.[5] For example, such rate enhancements were observed for "living" radical polymerization reactions.[5] In copper(I)-catalyzed Ulmann-type cross-coupling reactions, similar positive rate enhancement with respect to unfunctionalized substrates has been demonstrated using coupling partners that contain a copper-chelating carboxylic group, such as 2-halogenobenzoic acids, α-amino acids, and β-amino acids in the reactions.[6] This can be attributed to the formation of copper(I) carboxylates during reaction, which enables Ulmann-type reactions to proceed with rate enhancement.[6e,6f]

Pioneering work by Liebeskind and Allred have shown, copper(I) thiophene-2-carboxylate (CuTC) mediates cross coupling of organostannanes and organic iodides at room temperature.[7] Since this report, the impact of CuTC in effecting various cross-coupling reactions in organic synthesis has been incredible.[8] Among the various advantages of CuTC, the most important one is that it can be easily prepared in multigram scale from thiophene-2-carboxylic acid, and thus, is cost effective and readily available from commercial vendors. Furthermore, CuTC is a tan, air-stable powder, which can be stored and handled at room temperature without any special precautions. These characteristics of CuTC makes its use very attractive in organic synthesis, particularly, for the construction of C–N bonds involving modified Ulmann conditions.[9] This reaction is industrially very important because it enables direct formation of C–N bonds between various aryl halides and nitrogen-containing compounds.

In particular, such cross couplings with nitrogen heterocycles, such as imidazole, pyrazole, and benzimidazole have found extensive use in the construction of a vast range of natural products, bioactive molecules, and functional materials.[10] Substantial progress has been made in this area using copper(I)-catalyzed C–N coupling reactions.[6e,6f,11] This is evident from the pioneering work of Buchwald, Taillefer, and others.[12] The key to success in this area is the in situ utilization of special nitrogen ligand additives along with copper(I) precursor salts as catalysts. In this communication, we present our studies in this dynamic field using CuTC as catalyst for *N*-arylation reaction of nitrogen heterocycles with aryl halides. This protocol does not require additional nitrogen ligand additives to the reaction mixture to promote direct *N*-arylation of H*N*-heterocycles with aryl halides.

First, CuTC was screened for its activity in the coupling reaction of 4-bromoanisole with imidazole as standard substrates in a number of solvents and with metal carbonates or phosphates as base (Table 1). For these screening studies 25 mol % of CuTC (relative to the substrate) was used as catalyst. At 110 °C, this reaction even after 48 h gave the corresponding product in poor yield (45%, Entry 1). However, at higher tem-

Table 1. Screening of Reaction Parameters for CuTC-Catalyzed *N*-Arylation of Imidazole with *p*-Bromoanisole[a)]



Entry	Catalyst	Ligand	Solvent	Base	Yield[b)]/%
1	CuTC	–	DMSO	K_2CO_3	45[c)]
2	CuTC	–	DMSO	K_2CO_3	89
3	Cu_2O	I	DMSO	K_2CO_3	84
4	CuI	I	DMSO	K_2CO_3	45
5	CuCl	I	DMSO	K_2CO_3	20
6	$Cu(OAc)_2$	I	DMSO	K_2CO_3	15
7	CuTC	–	NMP	K_2CO_3	55
8	CuTC	–	DMF	K_2CO_3	45
9	CuTC	–	DMSO	Cs_2CO_3	65
10	CuTC	–	DMSO	K_3PO_4	35
11	Cu_2O	II	DMSO	K_2CO_3	NR
12	Cu_2O	III	DMSO	K_2CO_3	5
13	Cu_2O	IV	DMSO	K_2CO_3	18
14	Cu_2O	V	DMSO	K_2CO_3	15
15	Cu_2O	VI	DMSO	K_2CO_3	24
16	Cu_2O	VII	DMSO	K_2CO_3	30
17	CuTC	VIII	DMSO	K_2CO_3	10[d)]
18	Cu_2O	VIII	DMSO	K_2CO_3	4

a) Reactions were performed on a 1.0 mmol scale with CuX (0.25 mmol, 25 mol %), bromoanisole (1.0 mmol), ligand (0.25 mmol, 25 mol %), imidazole (1.5 mmol), K_2CO_3 (4 mmol), and 5 mL of DMSO at 135 °C. b) Values are isolated yields after chromatographic purification. c) Reaction was performed at 110 °C. d) Reaction performed at 105 °C.

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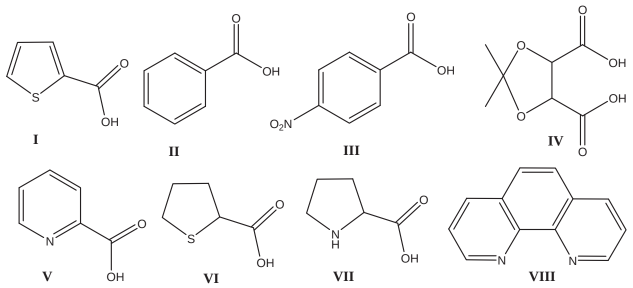
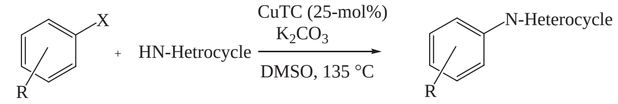


Figure 1. Representative carboxylic acid ligands that are screened for *N*-arylation reaction with copper precursor.

perature (135 °C), the reaction proceeded smoothly, and gave yields up to 89% for the *N*-arylated product (Entry 2). Copper(I) oxide in the presence of thiophene-2-carboxylic acid (TCA) ligand also promoted cross-coupling of 4-bromoanisole with imidazole in DMSO, and the yields are comparable to those obtained using CuTC (Entry 3). In contrast, copper salts such as CuI, CuCl, and $Cu(OAc)_2$ in the presence of TCA, gave comparably lower yields than those obtained using CuTC (Entries 4–6). Among various solvents and bases screened, DMSO and K_2CO_3 were found to be the best under our experimental conditions (Entries 2 and 7–10).

To investigate whether this reaction is unique to CuTC or rather to copper carboxylates in general, more relevant control experiments using additional carboxylic acid ligands (II–VII, Figure 1) were carried out under our experimental conditions. As can be seen in Entries 11–16, the reactions of imidazole with *p*-bromoanisole, in the presence of carboxylic acid ligands such as benzoic acid, *p*-nitrobenzoic acid, (+)-2,3-*O*-isopropylidinetartaric acid, pyrrolidine-2-carboxylic acid, pyridine-2-carboxylic acid, and thiazolidine-2-carboxylic acid proceed rather sluggishly, and gave low yields (0–29%) for the desired product. Thus, there does not appear to be any direct correlation between carboxylic acid groups in the structural motif of ligand and good catalytic activity for C–N coupling reactions. The observed efficacy with CuTC in our study is most likely due to the unique ability of CuTC to stabilize the oxidative addition product during the course of the reaction as was originally proposed by Liebeskind et al. for direct C–C cross-coupling reactions. Further, to see whether lower reaction temperatures could be achieved with the addition of a nitrogen ligand as an additive, 1,10-phenanthroline was added to CuTC-catalyzed reaction of 4-bromoanisole and imidazole at 105 °C. However, interestingly, the desired cross-coupled product was obtained in low yield (Entry 17). It is to be noted that we have obtained best results with CuTC in DMSO and K_2CO_3 at 135 °C (Entry 2).

Table 2. The Scope of CuTC-Catalyzed *N*-Arylation of H*N*-Heterocycles with Various Aryl Halides[a)]



Entry	R	X	HN-Het	Time/h	Yield[b)]/%
1	*p*-Me	I	Im	24	91
2	*p*-OMe	I	Im	24	88
3	*p*-OMe	I	Py	24	82
4	H	Br	Im	35	89
5	H	Br	BzIm	35	85
6	H	Br	Py	35	82
7	*p*-OMe	Br	Im	48	89
8	*p*-OMe	Br	BzIm	48	85
9	*p*-OMe	Br	Py	48	81
10	*p*-COMe	Br	Im	30	85
11	*p*-COMe	Br	BzIm	30	82
12	*p*-CHO	Br	Im	30	70
13	*p*-CHO	Br	Py	30	75
14	*p*-Me	Br	Im	48	89
15	*p*-NO_2	Br	Im	18	96
16	*o*-Me	I	Im	38	75
17	*o*-NO_2	Br	Im	18	90
18	*o*-Me	Br	Im	48	60
19	*p*-CF_3	Cl	Im	30	85
20	*p*-CN	Cl	BzIm	24	90
21	*p*-NO_2	Cl	Im	24	95
22	*p*-NO_2	Cl	BzIm	24	89
23	*p*-COMe	Cl	Im	40	81
24	*o*-NO_2	Cl	Im	24	90
25	*o*-CN	Cl	Im	24	84
26	H	Cl	Im	48	NR

a) Reactions were performed on a 1.0 mmol scale with CuTC (0.25 mmol, 25 mol %), bromoanisole (1.0 mmol), H*N*-heterocycle (1.5 mmol), K_2CO_3 (4 mmol), and 5 mL of DMSO at 135 °C. b) Values are isolated yields after chromatographic purification.

In an attempt to probe the generality of the CuTC method, a variety of structurally divergent aryl halide substrates were subjected to the cross-coupling reaction with H*N*-heterocycles such as benzimidazole, pyrazole, and imidazole, and the results are summarized in Table 2. Aryl iodides with strongly electron-donating groups like *p*-Me and *p*-OMe groups react smoothly with imidazole and pyrazole giving excellent yields of the coupling adducts within 24 h at 135 °C (Entries 1–3). Aryl bromides substrates, however, required longer reaction times (35–48 h) for the completion of the reaction (Entries 4–14). For example, bromobenzene reacts with imidazole, pyrazole, and benzimidazole providing the corresponding coupling products in excellent yields (Entries 4–6). Aryl bromides with strong electron-donating groups such as *p*-OMe and *p*-Me substituents also reacted with various H*N*-heterocycles yielding the corresponding *N*-arylated adducts in good yields (Entries 7–9 and 14). Interestingly, reactions of aryl bromides containing electron-withdrawing groups like *p*-COMe, *p*-CHO, and *p*-NO_2 proceeded much faster than those containing electron-donating groups (Entries 10–14). Finally, to our delight, we observe that the present methodology also enables direct cross-coupling reaction between various H*N*-heterocycles with difficult aryl chloride substrates, particularly when they contain electron-withdrawing groups. To date, only a few examples involving aryl chloride activation for copper-catalyzed C–N bond formation with azaheterocycles have been reported.[13] To verify whether unactivated aryl chlorides could also be used, the reaction of chlorobenzene with imidazole was first attempted. However, this reaction, even after 48 h, gave insignificant amounts of cross-coupled product (Entry 26).

Extension of CuTC based methodology to *ortho*-substituted or sterically hindered bromoarene substrates has yielded promising results. As can be seen in Table 2, *o*-bromonitrobenzene, *o*-bromotoluene, and *o*-iodotoluene react with imidazole yielding corresponding *N*-arylated adducts in moderate to excellent yields (Entries 16–18). It is important to note that *o*-bromonitrobenzene having a supplementary chelating nitro group reacted much faster (18 h) with imidazole than other hindered substrates. However, it is very unlikely this reaction proceeds through chelation of the nitro group to copper because *p*-bromonitrobenzene also took about 18 h for the completion under identical reaction conditions with imidazole (Entries 15 and 17). More importantly, with CuTC, we also observed sterically hindered *o*-substituted chloroarenes react with imidazole giving excellent yields in 24–40 h (Entries 19–25). Unlike Pd^0 mediated protocols,[14] tolerance to steric factors by copper is well known in C–N cross-coupling chemistry. This distinct feature could be related to mechanistic divergence in their chemistry as well as due to the different nature of intermediates that are formed in the catalytic cycle.[13c,15]

In conclusion, we have shown CuTC is a versatile catalyst for effecting direct *N*-arylation of aryl halides with various important nitrogen heterocycles. It is clear from the above discussion that the CuTC-based catalyst system for direct *N*-arylation demands slightly higher temperatures (135 °C), which is somewhat on the higher side when compared to copper-catalyzed *N*-arylation reaction promoted by basic nitrogen ligand additives (110–125 °C).[12] Nevertheless, CuTC-based methodology reported herein is a very important synthetic protocol because we have shown diverse aryl halides including activated chloroarenes undergo direct *N*-arylation smoothly in the presence of CuTC with no side-products being formed at the working temperature range (135 °C). Even though we could not find any direct correlation with ligand carboxylic acid ligand structures and C–N cross-coupling reaction (see Figure 1 and Table 1), we are currently investigating this aspect of chemistry in our laboratory.

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Supporting Information

General synthesis procedure for *N*-arylation and spectral data. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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