Ambient Temperature, Ullmann-like Reductive Coupling of Aryl, Heteroaryl, and Alkenyl Halides

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The Ullmann synthesis of biaryls by the copperinduced reductive coupling of aromatic halides is of broad synthetic use.¹⁻⁷ Typically, the reaction is conducted above 200 °C, although certain specific substrates undergo Ullmann reductive coupling under much milder conditions.⁸ Cohen demonstrated that CuOSO₂CF₃ in acetone in the presence of ammonia could induce the reductive coupling of a few selective aryl and vinyl halides at much lower temperature,^{9,10} and Ziegler described an ambient-temperature cross-coupling of preformed arylcopper reagents with aryl iodides.¹¹ Although not a reductive coupling, Lipshutz has developed a synthesis of unsymmetrically-substituted biaryls by the oxidative degradation of kinetic higher-order cuprates generated at -125 °C from aryllithium reagents.¹² Zerovalent nickel-based protocols have also been described.^{13,14}

It was recently shown that copper(I) thiophene-2carboxylate (CuTC) promotes a very rapid Stille crosscoupling of aryl-, heteroaryl-, and alkenylstannanes with alkenyl iodides and some aryl iodides between 0 °C and room temperature,¹⁵ suggesting the possibility of a facile oxidative addition of CuTC to alkenyl iodides at ambient temperatures. That mechanistic possibility led to consideration of a CuTC-mediated Ullmann reductive coupling at or near room temperature, which if suitably general and versatile could be of significant synthetic utility. Herein, we report that copper(I) thiophene-2carboxylate induces the reductive coupling of substituted aromatic iodides and bromides, 2-iodoheteroaromatics, and the stereospecific reductive coupling of alkenyl iodides efficiently and in many cases rapidly at room temperature.

Depicted in Table 1 are representative examples of the CuTC-mediated reductive coupling of aryl iodides and bromides, heteroaryl iodides, and alkenyl iodides.¹⁶ The CuTC-mediated reaction is quite general and tolerant of functionality. Efficient reductive coupling of the aromatic substrates minimally requires the presence of an ortho-

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Figure 1.

ligating substituent, while 2-iodoheteroaromatic and alkenyl substrates do not. The latter substrates couple with retention of alkene stereochemistry. A synthetically versatile range of substrates participate in the reductive coupling, including aromatics bearing both electronwithdrawing and electron-donating ortho-substituents. The most noticeable limitation of the process is the lack of reaction of aromatic halide substrates not possessing a coordinating ortho-substituent. The reductive coupling requires a polar, coordinating solvent such as N-methylpyrrolidinone, perhaps to generate reactive Cu(I) monomers from the insoluble Cu(I) carboxylate polymer. The intramolecular reductive coupling example depicted in eq 1 suggests that CuTC might be useful in other intramolecular reductive-coupling reactions.



Although radical intermediates are possible in the classical high-temperature Ullmann coupling of aryl halides,¹⁷ they are not required. In the present ambienttemperature Ullmann-like reductive coupling, retention of stereochemistry for the alkenyl substrates precludes the presence of radical intermediates and strongly implicates the existence of organocopper intermediates formed by oxidative addition to the Cu(I) reagent, as first suggested by Cohen over 20 years ago.^{9,10,18}

What then is the unique attribute that Cu(I) thiophene-2-carboxylate brings to this Ullmann-like reductive coupling? It is probably not internal coordination as depicted in structure 7 (Figure 1), since certain other Cu(I) carboxylates also induce the reductive coupling reaction.¹⁹ If, as suggested,¹⁰ the oxidative addition of CuX reagents to aryl iodides is reversible (eq 2), the efficacy of CuTC may be due to an inherent ability of carboxylate as a

⁽¹⁶⁾ Representative Experimental Procedure. CuTC (1.14 g, 6.0 mmol, 3.00 equiv) was added in one portion to N-acetyl-2-iodo-3,4,5-trimethoxyaniline (0.70 g, 2.0 mmol, 1.00 equiv) in 8 mL of NMP under N₂. After being stirred at rt for 1 h, the mixture was diluted with 15 mL of EtOAc, and the resulting slurry was passed through a plug of SiO₂ using EtOAc as eluent (150 mL). Solvents were removed by rotary evaporation and then vacuum distillation. Residual NMP was removed under vacuum overnight at rt. The crude product was dissolved in 4 mL of CH_2Cl_2 and 10 mL of Et_2O , the volume of solvents was reduced by half, and then 2 mL of hexane was added. On standing in a freezer, *N*,*N*-diacetyl-6,6'-diamino-2,2',3,3',4,4'-hexamethoxybiphenyl was formed as an off-white solid (0.380 g, 0.85 mmol, 85%): mp 149–151 °C (Et₂O/hexane); IR (CH₂Cl₂, KCl, cm⁻¹) 3410 (br, m), 1691 (s), 1601 (s); ¹H NMR (CDCl₃) δ 7.49 (s, 2 H), 7.08 (s, 2 H), 3.88 (s, 6 H), 3.84 (s, 6 H), 3.62 (s, 6 H), 1.91 (s, 6 H); ¹³C NMR (CDCl₃) δ 168.8, 153.5, 151.2, 139.1, 132.4, 111.5, 103.2, 61.0, 60.9, 55.9, 24.2. Anal. Calcd for C22H28N2O8: C, 58.91; H, 6.29; N, 6.25. Found: C, 59.00; H, 6.29; N, 6.23

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⁽¹⁹⁾ Dramatic differences in the ease of synthesis, stability to air, and rate of reaction with aryl halides have been noted for a variety of Cu(I) carboxylates. The results of these studies will be reported in due course.



Table 1. Cu(I) Thiophene-2-carboxylate-Induced Reductive Coupling Reactions

^a yield based on 89% conversion. ^b yield based on 50% conversion ^c yield based on 62% conversion. ^d yield based on 82% conversion

ligand to stabilize the oxidative addition product, as implied by the position of the equilibrium depicted in eq 3.

$$\begin{array}{c} Cu-OCOR \\ + \\ Ar-I \end{array} \xrightarrow{Ar} \overbrace{Cu}_{O} \xrightarrow{biaryl} \qquad (3)$$

Control experiments demonstrated that both CuCl and CuBr, but not CuI, can induce the reductive coupling of methyl 2-iodobenzoate at room temperature in *N*-methylpyrrolidinone. However, the yields are low and compromised by halide exchange between the substrate and CuX, the latter observation a further indication of the reversible oxidative addition of aryl iodides to copper(I) halides. In order to probe the unique aspect of the carboxylate ligand in this chemistry, a survey of the reactivity of additional Cu(I) carboxylates is underway.¹⁹

The results collected here strongly implicate a necessary precoordination of the substrate to copper prior to oxidative addition and restrict the choice of copper reagent to one that is coordinatively unsaturated or one easily made so. The *ortho*-substituent on the aromatic halides, the heteroatom of the 2-iodoheteroaromatics, and the alkene of the alkenyl substrates all provide the necessary site for coordination to copper. The easy and economical preparation of CuTC, its handling in air, and the high yields of reductively coupled products achieved under mild reaction conditions could make CuTC or other Cu(I) carboxylates¹⁹ the reagents of choice for many Ullmann-like reductive coupling reactions. Further studies of copper-mediated reductive and cross-coupling reactions are in progress and will be reported in due course.

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Supporting Information Available: A complete description of the synthesis and characterization of all compounds in the manuscript (21 pages).

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