SYNLETT
Spotlight 136

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Copper(I) Thiophene-2-carboxylate (CuTC)

Compiled by Anna Innitzer

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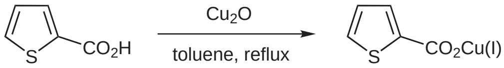
Introduction

In the early 1990s, the influence of co-catalytic copper(I) salts on Stille cross-coupling reactions was reported. The copper effect soon found application in numerous other palladium-catalyzed C–C bond forming reactions.[1] As it was suggested, that the cross coupling protocol could be mediated by simple copper salts alone,[1] various copper(I) carboxylates were screened and it was shown that copper(I) thiophene-2-carboxylate (CuTC) mediates most efficiently intermolecular cross-coupling reactions of aryl, heteroaryl and vinylstannanes with vinyl iodides at low temperature in high yields.[2]

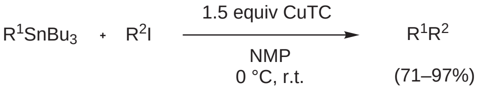
Soon, CuTC found application not only in a number of different types of cross-coupling reactions[4,6–8] but also in enantioselective allylation reactions[10] and very recently in asymmetric 1,4-additions.[11,12] CuTC can be easily prepared in multigram scale from thiophene-2-carboxylic acid and Cu_2O upon heating in toluene and azeotropic removal of water (Scheme 1). The obtained product is a tan, air-stable powder, which can be stored and handled at room temperature without any special precautions.[2]



Scheme 1 Preparation of CuTC

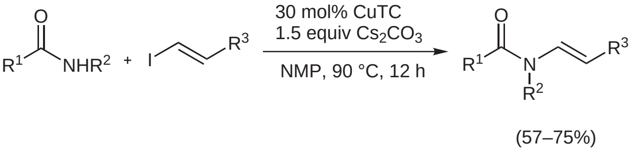
Abstracts

(A) Modified Stille Cross-Couplings
In the presence of CuTC aryl, heteroaryl and alkenylstannates can be cross-coupled with alkenyl iodides under mild conditions and in very good yields.[2] This protocol allows the cross-coupling of thermally sensitive substrates and is highly tolerable towards functional groups compared to palladium catalysts. The usefulness of this method was demonstrated in the coupling of two highly functionalized fragments in the endgame of the total synthesis of apoptolidin.[3]



$$R^1SnBu_3 + R^2I \xrightarrow[\text{NMP, 0 °C, r.t.}]{\text{1.5 equiv CuTC}} R^1R^2 \quad (71–97\%)$$

(B) Stereoselective Formation of Enamides
CuTC also promotes formation of enamides from amides and vinyl iodides. Best results were obtained using 30 mol% of CuTC and Cs_2CO_3 as base.[4] This method yields the enamides with complete *E*/*Z* olefin stereoselectivity and also found application in the total synthesis of complex natural products.[5]



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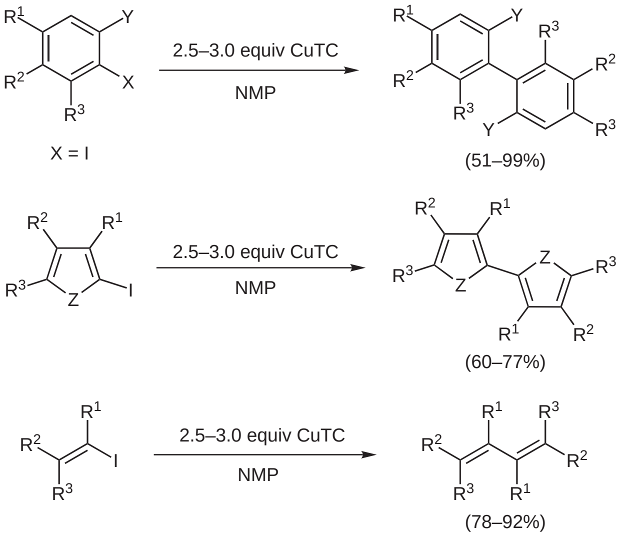
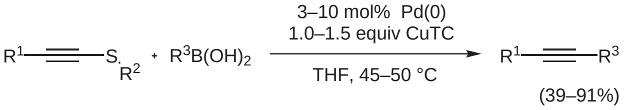
(C) Ullmann-Type Couplings

An Ullmann-like reductive coupling of aryl, heteroaryl and alkenyl iodides was recently reported.[6] Typically, the classical Ullmann coupling reactions are conducted above 200 °C, whereas the CuTC-mediated coupling may be performed at room temperature. Notable is the lack of reaction of aromatic substrates not bearing a coordinating *ortho* substituent. This is explained by the need for a precoordination of the substrate to copper prior to oxidative addition. The alkenyl substrates couple under retention of stereochemistry.



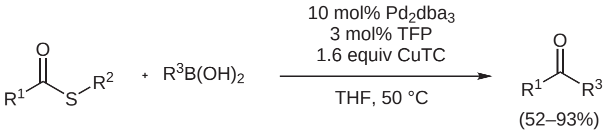
(D) Synthesis of Alkynes

An alternative to the Sonogashira protocol is the mild and non-basic palladium-catalyzed, copper carboxylate mediated coupling of thioalkynes and boronic acids.[7] The thioalkynes are reacted with the boronic acids in THF at 45–50 °C and furnish symmetrical as well as unsymmetrical alkynes in moderate to excellent yields.



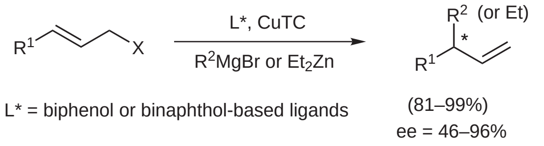
(E) Synthesis of Ketones

A general method leading to a variety of ketones is the CuTC-promoted, palladium-catalyzed coupling of thiol esters and boronic acids.[8] Both reaction partners are readily available and the reaction proceeds under non-basic and thus mild conditions to furnish ketones in good yields.



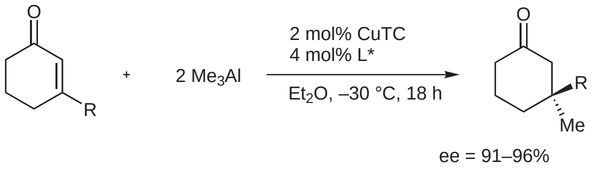
(F) Allylic Substitution

Asymmetric allylic substitution allows the creation of a chiral center in readily available starting materials. So far, there have been great efforts to control the chemo-, regio-, and enantioselectivities of the reaction product.[9] An enantioselective copper-catalyzed allylic alkylation with Grignard and organozinc reagents was recently reported.[10] The products are obtained in very good yields and usually in high enantiomeric excess.



(G) 1,4-Addition to Enones

CuTC also promotes the conjugate addition of trimethylaluminum to β-trisubstituted enones, which allows the formation of a quaternary all-carbon center.[12] The use of biphenol- and binaphthol-based ligands afforded very high enantioselectivities, yielding chiral building blocks for more elaborate natural products.



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