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Digest paper

Copper-catalyzed oxidative molecular transformation of amidines for synthesis of nitrogen heterocycles

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ABSTRACT

Copper (Cu) species show versatile chemical reactivity enabling functionalization of rather simple molecules in a variety of the reaction modes. The research on development of Cu-catalyzed oxidative molecular transformation has now a momentum in the community of synthetic organic chemistry, resulting in discovery of many kinds of molecular transformations for synthesis of complex molecules of medicinal and materials importance. To make catalytic turnover in Cu-catalyzed oxidative processes, use of stoichiometric oxidants is indispensable. These stoichiometric oxidants could uniquely change the reaction mechanism in the catalytic cycle to result in different outcomes (i.e., structure of the products and selectivity) from the same kinds of starting materials. This digest focuses on the role of the stoichiometric oxidants in several copper catalyzed oxidative molecular transformations of amidine derivatives (reported since 2008) primarily for the synthesis of nitrogen heterocycles.

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Introduction

Copper (Cu) species show versatile chemical reactivity enabling functionalization of rather simple molecules in a variety of the reaction modes owing to a broad range of oxidation states (typically from Cu^0 to Cu^{III}) available in their catalytic processes. Among a variety of chemical reactions that are catalyzed/mediated by Cu complexes, the research on development of Cu-catalyzed oxidative molecular transformation has now a momentum in the community of synthetic organic chemistry, resulting in discovery of many kinds of oxidative processes for synthesis of complex molecules of medicinal and materials importance.[1,2] In these processes, apparently, the choice and use of stoichiometric oxidants is indispensable to realize catalytic turnover in the oxidative processes with Cu catalysis. These stoichiometric oxidants could uniquely change the reaction course and reaction mechanism of the Cu catalysis to result in different outcomes (i.e., structure of the products and selectivity) from the same kinds of starting materials. This digest focuses on the role of the stoichiometric oxidants in several copper catalyzed oxidative molecular transformations of amidine derivatives (reported since 2008) primarily for the synthesis of nitrogen heterocycles through amino-functionalization of alkenes and alkynes as well as C–H amination.

Preparation methods of amidines and their reactivity

Amidine derivatives could be easily prepared by nucleophilic addition of amines to the corresponding carbonitriles or imidates.[3,4] As represented by DBU, amidines are electron rich

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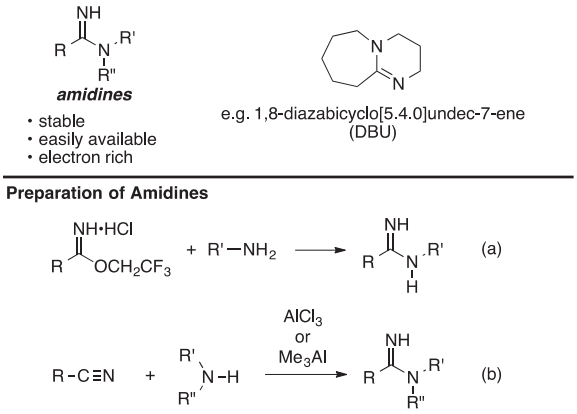


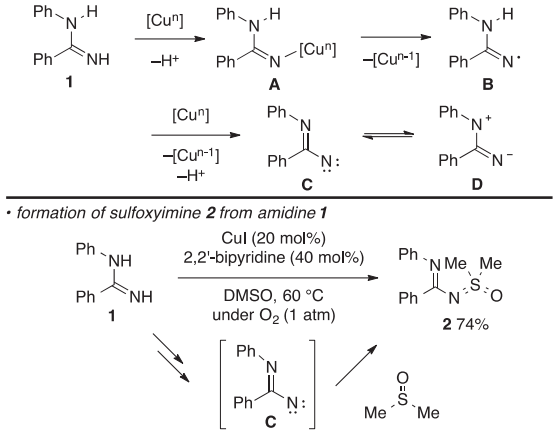
Scheme 1. Preparation methods of amidines.

molecules showing strong basicity and thus should exhibit unique reactivity under oxidative reaction conditions (Scheme 1).

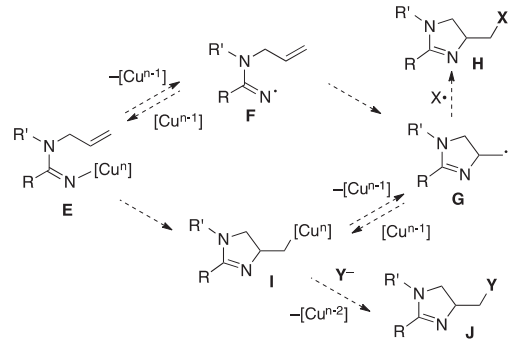
The reactions of amidine **1** with higher valent Cu complexes (oxidation) could generate a series of reactive nitrogen species (Scheme 2). At first, ligand exchange could provide amidine–Cu complex **A**, that can undergo N–Cu bond homolysis to afford amidinyl radical **B**. Further single-electron-oxidation of amidinyl radical **B** by higher valent Cu species might be possible, providing nitrene species **C**, which should be an equivalent with 1,3-diazadipole **D**.[5] Actually, it was reported that Cu-catalyzed aerobic reaction of *N*-phenylamidine **1** in DMSO provides sulfoxyimine **2**.[6] The formation of sulfoxyimine **2** could support the presence of nitrene species **C**, which traps solvent DMSO to give sulfoxyimine **2**.[7] With proper substrate design and choice of stoichiometric oxidants, these nitrogen reactive species could be utilized for a variety of catalytic oxidative C–N bond forming reactions onto C–C unsaturated bonds or C–H bonds to construct nitrogen-containing heterocyclic frameworks.

Amino-functionalization of C–C unsaturated bonds

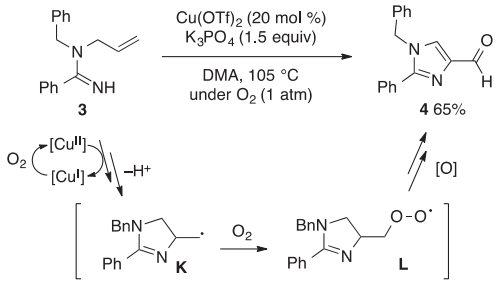
In the reactions of *N*-alkenylamidines with Cu^n species (where n = II or III) in oxidative reaction conditions, the resulting amidine–Cu species **E** induces N–Cu bond homolysis to generate amidinyl radical **F**, that undergoes radical cyclization to construct nitrogen-heterocyclic framework **G** having a C-radical moiety (Scheme 3). The resulting C-radical could be trapped with appropriate radical trapping reagent (**X**·) to give the final product **H**, while this C-radical species could undergo radical-recombination



Scheme 2. Cu-mediated oxidation of amidine **1**.



Scheme 3. Reaction modes of *N*-alkenyl amidine with Cu species.



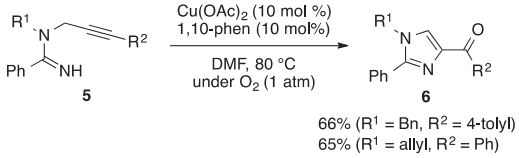
Scheme 4. Cu-catalyzed aerobic reactions of *N*-allylamidines **3**.

with the present Cu species to give organocopper intermediate **I**, which is presumably reversible. In turn, the organocopper **I** could also be formed directly from amidine–Cu species **E** via amino-cupration onto the pendant alkene (Scheme 3). The resulting organo-copper moiety in **I** could be further functionalized in double-electron-transfer events through substitution reactions with heteroatom nucleophiles ($\mathbf{Y}^-$) or reductive elimination of the C-heteroatom bond.

For example, the aerobic reactions of *N*-allylamidines **3** in the presence of 20 mol% of $Cu(OTf)_2$ and 1.5 equiv of K_3PO_4 deliver 4-formylimidazoles **4** via amino-oxygenation of the alkene (Scheme 4).[8] In this case, the resulting C-radical **K** formed either by radical cyclization or by amino-cupration and ensuing C–Cu homolysis (see Scheme 3) is captured by molecular oxygen to form peroxy radical **L**. Further fragmentation of the peroxy moiety and aromatization completes the process to afford formylimidazole **4**. The catalytic turnover is maintained by reoxidation of the lower valent Cu^I species by molecular oxygen.

The reactions of *N*-propargylamidines **5** undergo analogous amino-oxygenation under Cu-catalyzed aerobic reaction conditions, providing 4-benzoylimidazoles **6** in good yields (Scheme 5).[9,10] This Cu-catalyzed aerobic amino-oxygenation exhibits unique chemoselectivity toward alkyne over alkene in the reaction of *N*-allyl-*N*-propargylamidine.

TEMPO could also be utilized as an oxygen source in aminooxygenation of *N*-allylamidine **7** with $Cu(OAc)_2$ to form dihydroimidazole **8** with prevention of aromatization (Scheme 6), while the catalytic turnover was not attained.[11]



Scheme 5. Cu-catalyzed aerobic reactions of *N*-propargylamidines **5**.