COPPER-CATALYZED HYDROAMINATION OF ALKENES AND ALKYNES

Reported by Alfredo Garcia September 29th, 2015

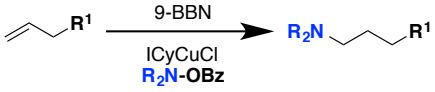
INTRODUCTION

Amines are found in a variety of biologically active natural products and medicines.[1] Synthesis of amines by direct addition alkenes and alkynes is an attractive area of research in view of the availability and ease of preparation of these starting materials.[2] Metal-catalyzed hydroamination reactions have been developed using, but not limited to, lanthanides, alkali and alkaline earth metals, and early and late transition metals. However, many of these catalysts are limited in substrate scope, are air and moisture sensitive, and are relatively expensive.[2] The search for efficient, selective, and environmentally benign hydroamination catalysts with broader substrate scope (particularly for unactivated substrates) are in high demand. Recent advances in copper-catalyzed hydroamination provide general and practical systems for the hydroamination of alkenes and alkynes. These catalysts display a broad substrate scope and high levels of regio- and enantioselectivity.[3]

COPPER-CATALYZED HYDROAMINATION

Alkenes

The first copper-catalyzed hydroamination developed was limited to the addition of aryl amines to activated olefins.[4] Later advances include an anti-Markovnikov hydroamination of unactivated, terminal alkenes via a hydroboration/electrophilic amination strategy (Scheme 1).[5] This work inspired the development of a novel method for highly enantioselective, copper-catalyzed hydroamination of styrenes to branched tertiary amines.[6,7] The hydroamination (Figure 1) commences with insertion of the styrene, ligand bound copper hydride **I** (formed from silane reduction of $Cu(OAc)_2$), producing alkyl copper species **II**. Oxidative addition of a benzoyloxyamine to form a Cu(III) species, followed by reductive elimination from **III**, regenerates **I** and the product amine. This electrophilic amination method has been extended to the enantioselective, copper-catalyzed hydroamination of a broad range of substrates, including unactivated, internal alkenes,[8] to generate tertiary and secondary amines.[9]



Scheme 1. Anti-Markovnikov hydroamination of terminal, unactivated alkenes

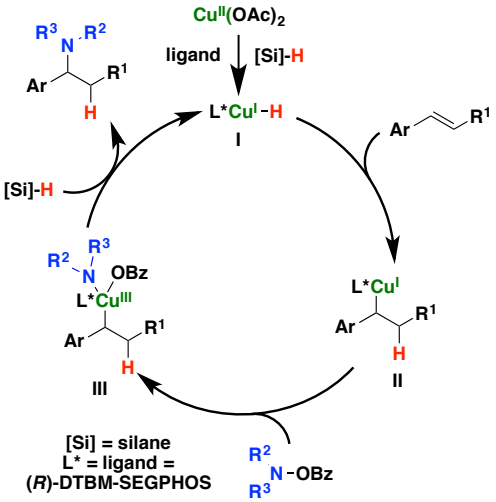
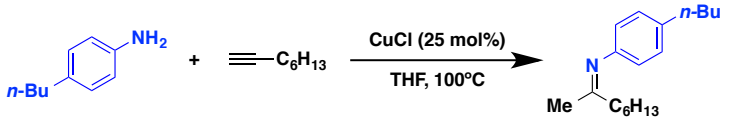


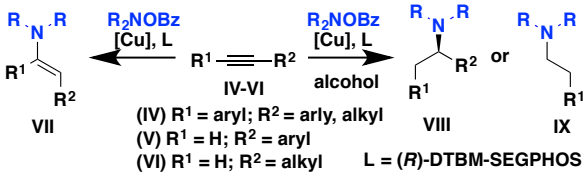
Figure 1. Proposed catalytic cycle for the Buchwald copper-catalyzed hydroamination of styrenes

Alkynes

Copper-catalyzed intramolecular hydroaminations of alkynes are common, whereas intermolecular reactions are relatively scarce.[2] Hartwig and co-workers have reported a homogeneous, intermolecular hydroamination of terminal alkynes to imines using CuCl as the catalyst (Scheme 2).[10] Buchwald and coworkers achieved the highly chemo-, regio- and stereoselective hydroamination of internal aryl alkynes (**IV**) to form enamines (**VII**), using the electrophilic amination strategy (Scheme 3).[11] This process can be further extended to the enantioselective, direct hydroamination of terminal aryl alkynes (**V**) and terminal aliphatic alkynes (**VI**) to α-branched amines (**VIII**) and linear alkyl amines (**IX**), respectively.[11] A one-pot alkyne semi-reduction and subsequent alkene hydroamination, with the desired selectivity, has not been reported, thus the direct hydroamination cascade mentioned above provides a powerful method for alkyne manipulation.[11]



Scheme 2. CuCl catalyzed hydroamination of terminal alkynes to imines



Scheme 3. Cu-catalyzed hydroamination of alkynes (IV-VI) to form enamines (VII), branched (VIII) and linear (IX) alkylamines

FUTURE DIRECTONS

The enantioselective copper-catalyzed hydroamination of unfunctionalized, internal olefins[8] represents a major advance. Development of a more enantioselective hydroamination of unactivated, terminal alkenes would be highly desirable.[12] In addition, application of modified amine transfer reagents to form secondary amines would be ideal for all of these processes.

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