SUMMARY OF THE DISSERTATION DONE

By

RAJIB DEBNATH

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COPPER CATALYSIS IN ORGANIC REACTIONS

FROM

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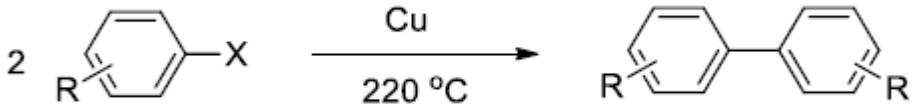
MURAGACHA, MEDGACHI

PURBA BARDHAMAN – 713405

Copper Catalysis in Organic Reactions

1. INTRODUCTION

Since the findings of the Ullmann reaction (Scheme 1), copper salts as catalysts have been known for more than one century and served well for C–N, C–S, C–O and other bond formation reactions.[1] After the discovery of palladium-catalyzed cross-coupling reactions, however, copper chemistry was somewhat neglected for an extended period of time. To date, aside from being capable of catalyzing the reactions for the synthesis of arylamines, palladium catalysts have been also employed in many other bond formations.[2,3]Despite many advantages of its use in organic synthesis, palladium chemistry itself has some drawbacks, including its cost, high toxicity and restrictions in scope. Therefore, chemists have started to reconsider other metal catalysts as an alternative for palladium. In the past years, copper has again received increasing attention for the construction of various bonds in organic synthesis.

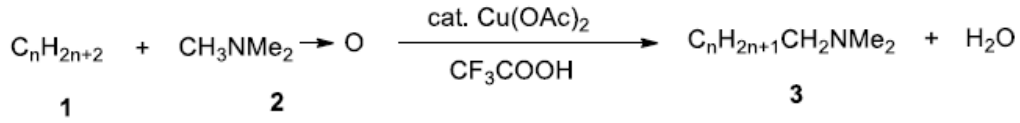


Scheme 1. Ulmann reaction.

Copper catalysts fascinate chemists for several reasons. First of all, copper is very cheap compared to palladium and the total amount of copper on earth is vast. Furthermore, copper salts generally present a low toxicity. More importantly, copper can take part in cross-coupling chemistry in a way strikingly similar to palladium and possesses unique chemoselectivity and reactivity. Although a number of reviews on copper-catalyzed reactions already exist, no specific summary on the type of reactions has been published yet.[4] In order to make it easier for the reader to find the respective synthetic applications, a detailed introduction to copper chemistry will be organized with respect to the type of reactions here.

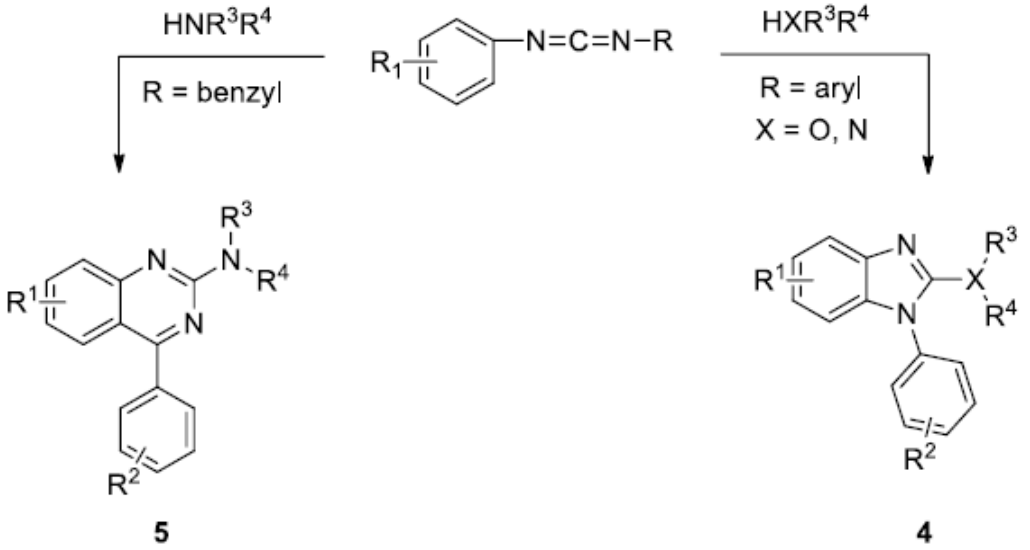
2. Copper-Catalyzed Direct Functionalization of C–H Bonds

The activation of C–H bonds by transition metal complexes represents one of the most important and challenging problems in modern chemistry.[5] Transition metal-catalyzed reactions by C–H bond activation normally offer straightforward pathways for the synthesis of target molecules because the preactivation by halogenation and/or metalation is not needed. In the past years, copper salts have been broadly employed as catalysts in C–H bond activation reactions.[4] As early as 1995, Fujiwara and co-workers reported an aminomethylation of gaseous alkanes **1** with trimethylamine *N*-oxides **2** through C–H bond activation (Scheme 2).[6] *N*,*N*-dimethylisobutylamines or *N*,*N*-dimethylpropylamines **3** were synthesized from propane and ethane using a $Cu(OAc)_2/CF_3COOH$ system in good yields, respectively.



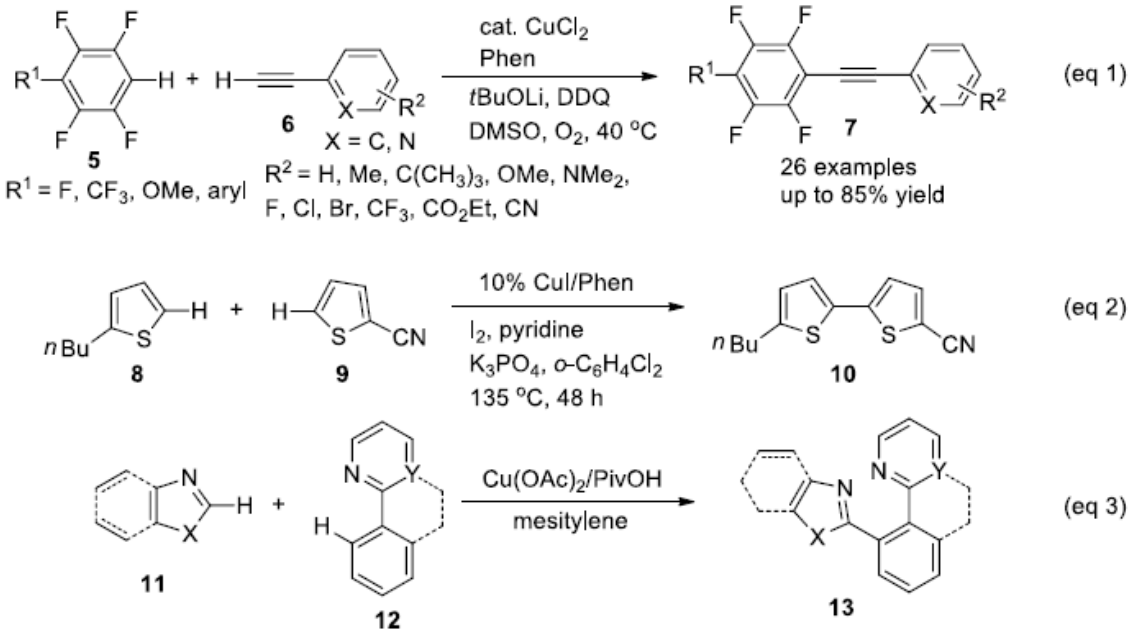
Scheme 2. Copper-catalyzed aminomethylation of gaseous alkanes through C–H bond activation.[6]

In 2010, the Bao group showed that 1,2-disubstituted benzimidazoles **4** and 1,2-disustituted quinazolines **5** could be prepared from diarylcarbodiimides and benzylphenylcarbodiimides through addition/intramolecular C–H bond activation (Scheme 3).[7] The reactions were performed using $Cu(OAc)_2/O_2$ as oxidants at 100°C in one-pot cascade procedure.



Scheme 3. Copper(II) acetate/oxygen-mediated nucleophilic addition and intramolecular C–H activation.[7]

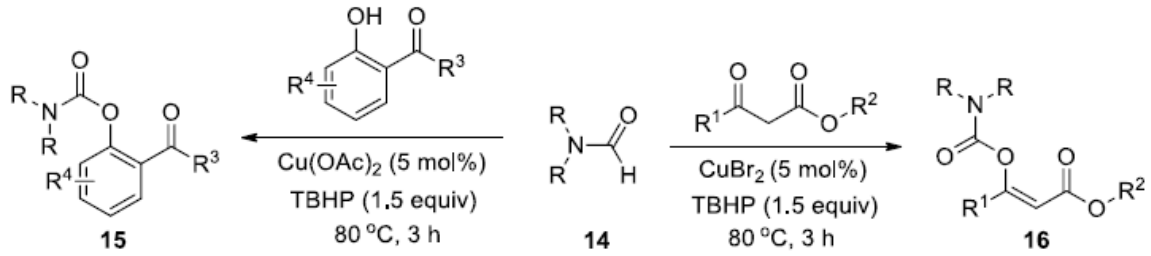
A copper-catalyzed Sonogashira-type reaction was developed by Su and co-workers in 2010. They used $CuCl_2$ as a catalyst for the direct alkynylation of electron-deficient polyfluoroarenes **5** with terminal alkynes **6** under mild conditions (Scheme 4, eq 1).[8] The procedure tolerated a number of functional groups using dioxygen as an oxidant.



Scheme 4. Copper-catalyzed cross-coupling reactions through dual C–H cleavages.[8,9,10]

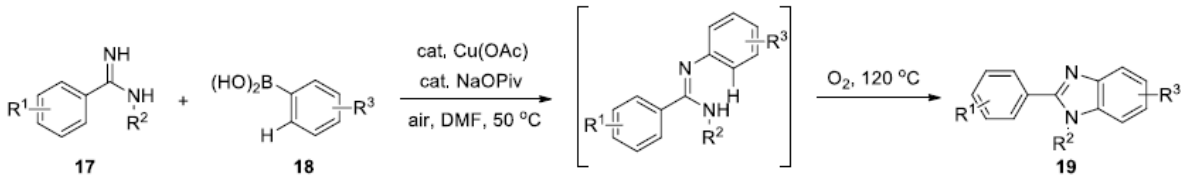
Do and Daugulis reported a general method for copper-catalyzed arene cross-dimerization, which provided a highly regioselective cross-coupling of two aromatic compounds using iodine as an oxidant (Scheme 4, eq 2).[9] This procedure involved the initial iodination of one arene **8** followed by arylation of the most acidic C–H bond of the other coupling component **9**. Electron-rich/poor arenes and five/six-membered heterocycles were employed in the reactions and various substitutes like esters, ketones, aldehydes, nitro- and amine-groups were well tolerated. Later, Miura and co-workers reported a copper-mediated intermolecular direct biaryl coupling between **11** and **12** (Scheme 4, eq 3).[10] This work showed the high potential of copper salts in direct C–H arylation chemistry and offered a new approach to biaryl compounds **13**.

Reddy and co-workers demonstrated a formamide C–H bond activation under oxidative conditions (Scheme 5).[11] They synthesized *Z*-enol carbamates **15** and 2-carbonyl-substituted phenol carbamates **16** using a copper catalyst and TBHP as the external oxidant in high yields.



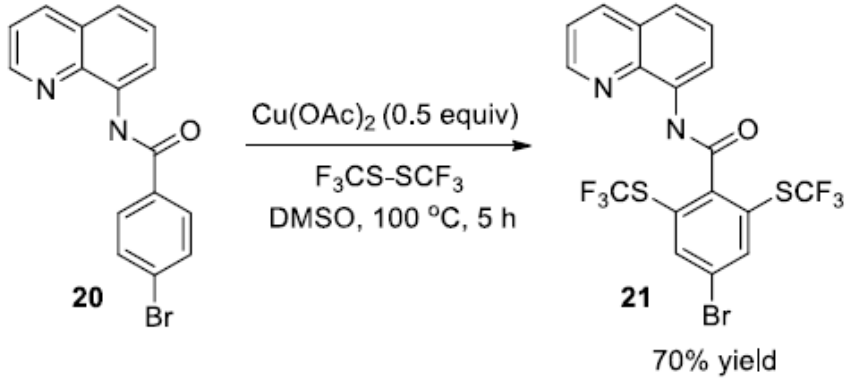
Scheme 5. Copper-catalyzed C–O coupling by direct C–H bond activation of formamides.[11]

In 2012, Neuville and co-workers showed that mono-*N*-arylation of benzamidines **17** with aryl boronic acids **18** could be effectively performed in the presence of a catalytic amount of $Cu(OAc)_2$ and NaOPiv under mild aerobic conditions. Combining this step with an intramolecular direct C–H bond functionalization, benzimidazoles **19** were synthesized using the same catalytic system but under dioxygen at 120°C in good to excellent yields (Scheme 6).[12]



Scheme 6. One-pot synthesis of benzimidazoles through a copper catalyzed C–H activation/C–N bond forming process.[12]

Recently, the transition metal-catalyzed direct C–H bond functionalization through bidentate-chelation assistance such as a quinolinamide bidentate system has attracted much attention. These include arylation,[13] alkylation,[14] ethynylation,[15] sulfenylation,[16] and alkoxylation.[17] Among them, a copper-promoted sulfenylation of C_{sp}^2–H bonds was developed by Daugulis and co-workers in 2012 (Scheme 7).[16] The reaction was performed using disulfide reagents and $Cu(OAc)_2$ in DMSO with the assistance of an auxiliary at 90–130°C.



Scheme 7. Copper-promoted sulfenylation of C_{sp}^2–H bonds.[16]

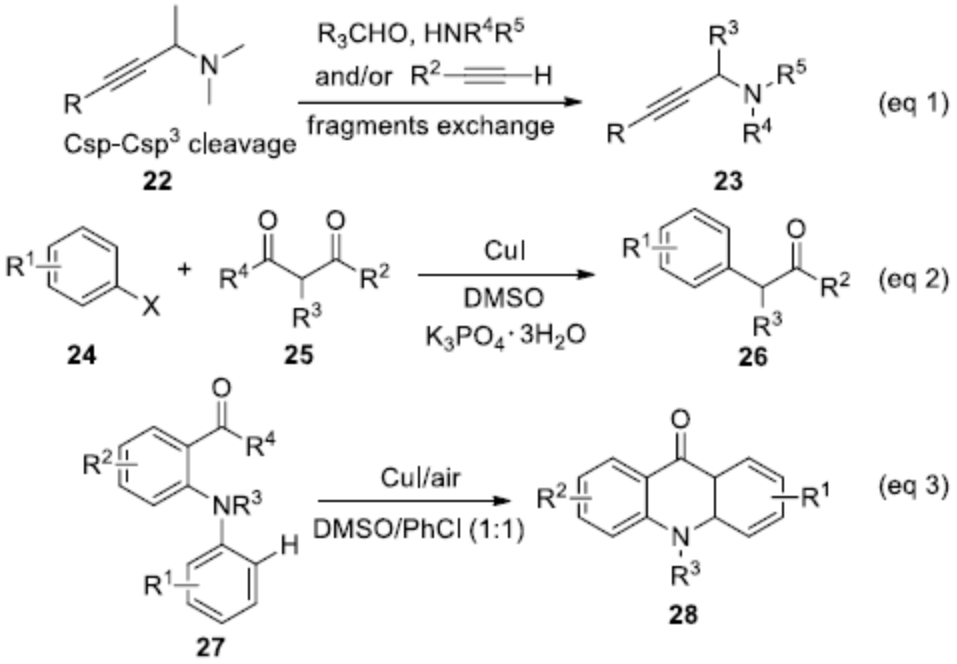
3. Copper-Catalyzed Reactions Through C–C Bond Cleavage

Typically, C–C σ-bonds are considered to be relatively inert bonds. Doubtlessly, transition metal-catalyzed reactions through C–C bond cleavage fascinate chemists due to their high selectivity and diversity. In the past years, a variety of selective C–C cleavages have been reported.[18]

Recently, Nakamura and co-workers discovered that substitution reactions of propargylic amines **22** could proceed in the presence of copper(I) catalysts (Scheme 8, eq 1).[19] Mechanistic studies showed that C_{sp}–C_{sp}^3 bond cleavage assisted by nitrogen lone-pair electrons was essential for the reaction and the resulting iminium intermediates underwent amine exchange, aldehyde exchange and alkyne addition reactions. Furthermore, aside from

reconstructing propargylic amines, this transformation was also effective for asymmetric induction of racemic compounds in the presence of chiral catalysts.

In 2010, He et al. discovered an efficient arylation/C–C bond activation process, in which the reaction of β-diketones **25** with aryl iodides or aryl bromides **24** reacted readily in the presence of Cu(I) or Cu(II) salts in DMSO (Scheme 8, eq 2).[20] Trace amounts of H_2O were critical for the activation of the C–C bond. Under the optimized reaction conditions, various α-aryl ketones **26** could be efficiently synthesized. A copper-catalyzed approach for the synthesis of acridones **28** through C–C bond cleavage and intramolecular cyclization of **27** was very recently reported by Zhou and co-workers using air as the oxidant under neutral conditions (Scheme 8, eq 3).[21]



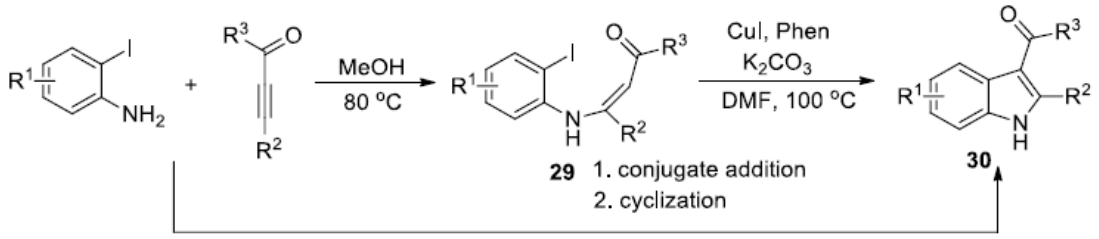
Scheme 8. Copper-catalyzed reactions through C–C bond cleavage.[19,20,21]

4. Copper-Catalyzed Cyclization Reactions

Transition metal-catalyzed cyclization reactions are very attractive to organic chemists due to their applications for the preparation of heteroatom-containing products. Heteroatom-containing ring cores are known for their biological activity in a number of compounds such as the potent vasodilator amauromine.[22] Here a short review on recent copper-catalyzed cyclization reactions is presented.

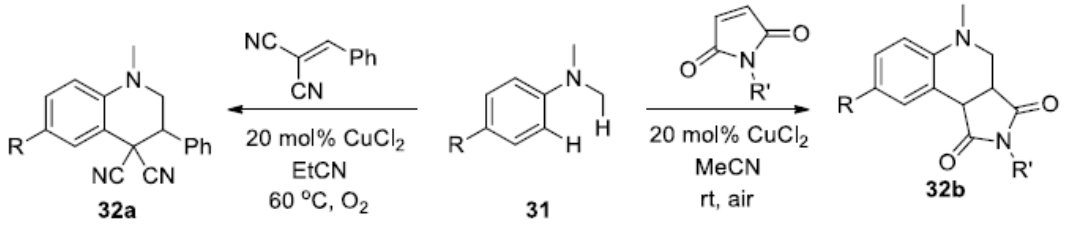
Through C–C Bond Formation

In 2009, Cacchi and co-workers[23] reported a copper-catalyzed cyclization of *N*-(2-iodoaryl)enamiones **29** for the synthesis of 3-aroylindoles **30** (Scheme 9). A variety of useful functionalities including ether-, keto-, cyano-, bromo-, and chlorosubstituents were well tolerated.



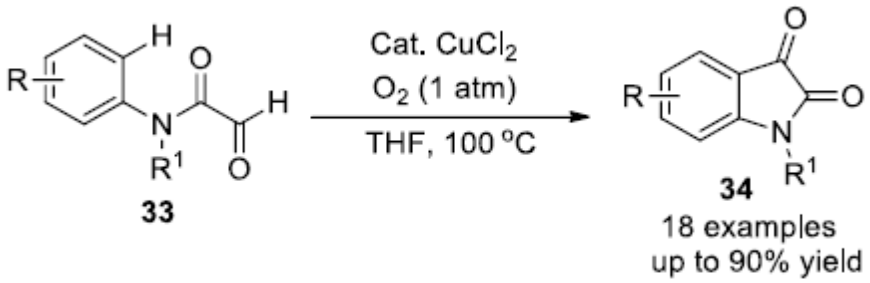
Scheme 9. Copper-catalyzed cyclization of *N*-(2-iodoaryl)enamiones.[23]

Later, Hirano, Miura and co-workers[24] developed a copper-catalyzed oxidative direct cyclization of *N*-methylanilines **31** with electron-deficient alkenes for the synthesis of corresponding tetrahydroquinolines **32a** and **32b** in good yields (Scheme 10). The procedure involved maleimides and benzylidene malononitriles through sp^3 and sp^2 C–H bond cleavage.



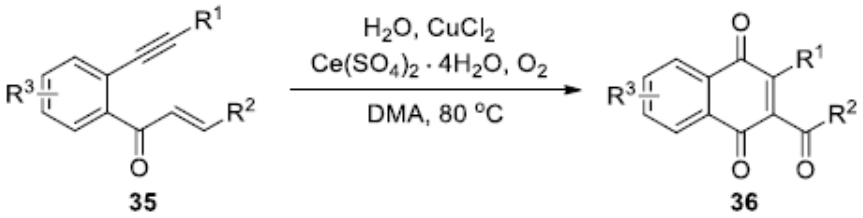
Scheme 10. Copper-catalyzed oxidative direct cyclization of *N*-methylanilines.[24]

A copper-catalyzed intramolecular C–H oxidation/acylation of starting material **33** was presented by Li and co-workers[25] for the synthesis of indoline-2,3-diones 34 (Scheme 11). A variety of functional groups were well tolerated under the optimized reaction conditions.



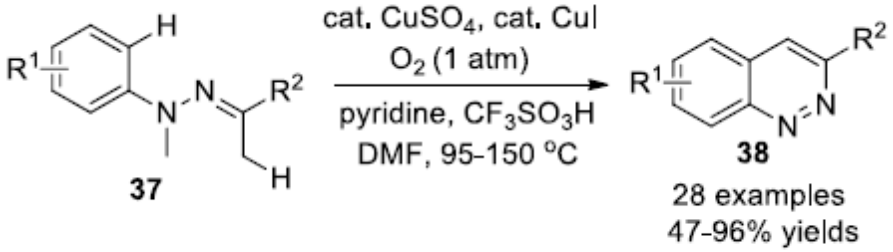
Scheme 11. Copper-catalyzed intramolecular C–H oxidation/acylation.[25]

In 2011, the Li group[26] demonstrated a copper-catalyzed intramolecular oxidative 6-*exo*-trig cyclization of 1,6-enynes **35** in the presence of H_2O and O_2 (Scheme 12). This was the first example of a copper-catalyzed enyne oxidative cyclization for constructing 1,4-naphthoquinones **36** by the incorporation of two oxygen atoms into the organic framework from molecular oxygen and water.



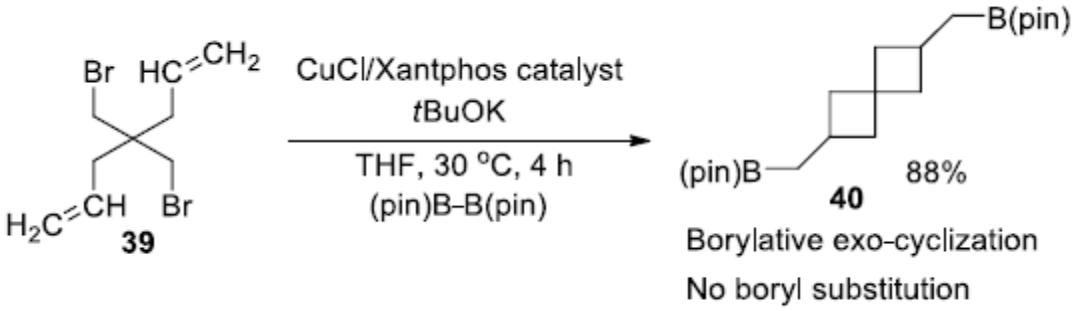
Scheme 12. Copper-catalyzed intramolecular oxidative 6-*exo*-trig cyclization of 1,6-enynes.[26]

Recently, Zhang *et al.*[27] presented a copper-catalyzed aerobic dehydrogenative cyclization of **37** for the synthesis of cinnolines 38 (Scheme 13). This transformation was the first example on copper-catalyzed coupling reactions of hydrazones through a $C_{sp}{}^3$–H bond functionalization pathway.



Scheme 13. Copper-catalyzed aerobic dehydrogenative cyclization leading to cinnolines.[27]

Ito and co-workers[28] reported a copper(I)-catalyzed borylative *exo*-cyclization of alkenyl halides **39** very recently (Scheme 14). The reaction involved the regioselective addition of a borylcopper(I) intermediate to unactivated terminal alkenes, followed by the intramolecular substitution of the resulting alkylcopper(I) moiety for the halide leaving groups. Various alkylboronates **40** containing strained cycloalkyl structures were synthesized from simple starting materials.



Scheme 14. Copper(I)-catalyzed borylative exo-cyclization of alkenyl halides.[28]

5. Conclusion

Copper is a very versatile transition metal that has been used as a building material by human civilizations for over 6000 years. Copper is also an essential element, responsible for important biological processes. The growth in copper-catalyzed organic reactions may be driven by a couple of factors. First, copper chemistry is incredibly diverse. Depending on its oxidation state, this metal can efficiently catalyze reactions involving both one and two-electron (radical and polar) mechanisms, or both. Copper coordinates easily to heteroatoms and to π-bonds and is well-known to activate terminal alkynes. The Ullman and Goldberg C–C and C–N cross-coupling reactions were discovered over a century ago and their development has really blossomed over the past twenty years. Second, copper is an earth-abundant metal, making its use more cost effective and more sustainable than precious transition metal catalysts.

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