Hybrid Reaction Systems for the Synthesis of Alkylated Compounds based upon Cu-catalyzed Coupling of Radical and Organometallic Species

Kentaro Takeuchi[a], Yumi Murata[a], Goki Hirata[a], Tom D. Sheppard*[b], Takashi Nishikata*[a]

Abstract: A transition metal catalyzed alkylation with an alkyl halide is one of the most difficult reactions to achieve, because of the difficult oxidative addition of an alkyl-halogen bond to a metal, and the strong tendency of the resulting alkylmetal intermediate to undergo a β-hydride elimination reaction to give an olefin. In this review, we discuss hybrid reaction systems involving Cu catalyzed combination of radical and organometallic species, which enable facile alkylation reactions to construct C-C and C-heteroatom bonds. This paper highlights recent arylation, alkenylation, alkynylation, cyclization, addition and introduction of heteroatoms via these hybrid reaction systems.

I. Introduction

Developing new reaction methodology to construct complex molecular structures is one of the central challenges of organic chemistry. Cross-coupling, C-H activation, organocatalyst systems, photoredox systems and other recent evolving methodologies have begun to change established synthetic strategies. In this short review, we will focus on a transition metal catalyzed radical and organometallic (or metallic species) hybrid (or combined/relay/crossover) reaction systems, which offer a new emerging synthetic approach. This concept makes use of two different active species (radicals and organometallics) in a single reaction system.

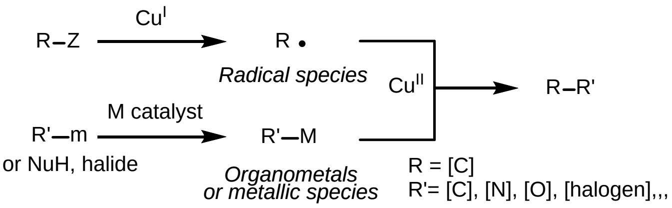
The idea to use different active species in a single reaction system has been recognized as a combined radical/ionic reaction.[1] In this paper, we only focus on Cu catalyzed radical/organometallic (or a species containing a metal-heteroatom bond) hybrid reaction systems. Asymmetric photoredox reactions are not included because their use in radical relay reactions has been recently summarized by Liu.[2] Although there are many reports of hybrid reaction systems, we have selected 20 recent examples covering C-C and C-heteroatom bond formation, cyclization reactions and addition reactions to illustrate the "hybrid reaction" concept within this short review. Proposed reaction mechanisms are included when they have been suggested by the original authors.

The concept of a hybrid reaction system:

A hybrid reaction system includes both a radical and an organometallic or metallic species as intermediates in the catalytic cycle. These two active species react together to produce newly formed carbon-carbon or hetero atom bond. The original Cu-catalyzed hybrid reaction system is known as Kharasch-Sosnovsky reaction, involving an allylic oxidation in the presence of a Cu catalyst and a peroxide-based oxidant.[3,4]

Under a hybrid reaction system, various chemical bonds can be formed as outlined in this review article. The hybrid reaction concept is shown in Scheme 1. The reaction of R-Z (radical precursor) and a radical initiator such as a Cu^{I} salt provides radical species R· via single-electron transfer (SET) along with a Cu^{II} species. On the other hand, a second reactant R'-m (organometallic e.g. an organoboron or organosilane) or NuH (nucleophile, e.g. amine alcohol, halide) reacts with catalyst M to produce an organometallic or metallic species (metal amide, alkoxide, halide, etc). After the generation of R· radical and R'-M, a coupling reaction occurs to produce R-R' as a product.

A transition metal catalyzed alkylation is potentially one of the most attractive approaches to construct aliphatic molecules but it is not easy to achieve because of the difficult oxidative addition of a metal catalyst to a C-X bond to generate an alkylmetal intermediate and the strong tendency of the resulting alkylmetal intermediate to undergo a β-hydride elimination reaction to give an olefin. However, by employing a hybrid reaction system the generation of a radical R· from an alkyl halide can enable an effective cross-coupling alkylation reaction to be achieved.



Scheme 1. Concept for hybrid reaction

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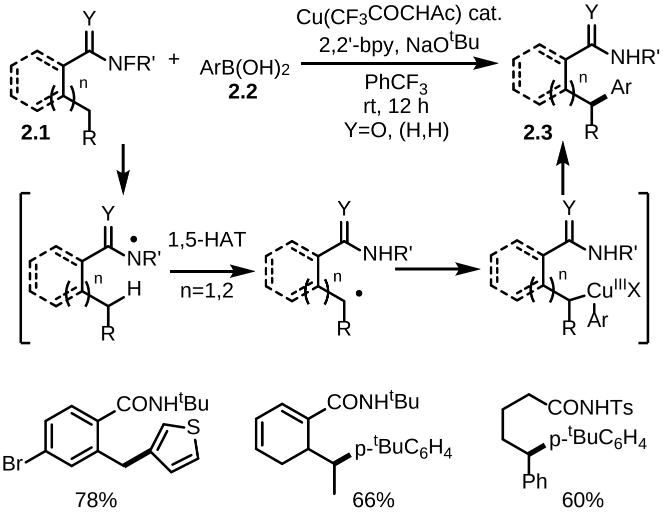
II. Couplings

IIA. C-C bond formations

Arylations

Friedel-Crafts alkylation is one of the most powerful methodologies to produce alkylated arenes but poor functional group compatibility under harsh conditions is sometimes problematic. An alternative method for alkylation of functionalized arenes has been accomplished via a hybrid reaction system by reaction of *N*-fluorocarboxamides or –sulfonamides (**2.1**) and arylboronic acids (**2.2**) (Scheme 2).[5,6] In the first step of this reaction, an amidyl radical is generated from the reaction of **2.1** and Cu^I via single electron transfer (SET) process. The amidyl radical gives a benzyl radical species via intramolecular 1,5-hydrogen atom transfer (HAT). This then couples with an arylcopper species, generated from transmetallation of the arylboronic acid, to produce the corresponding C-H arylation product (**2.3**). Under optimized conditions, alkylated arenes can be synthesized in good yields. A simple radical inhibitor test using TEMPO supported the intermediacy of radical species.

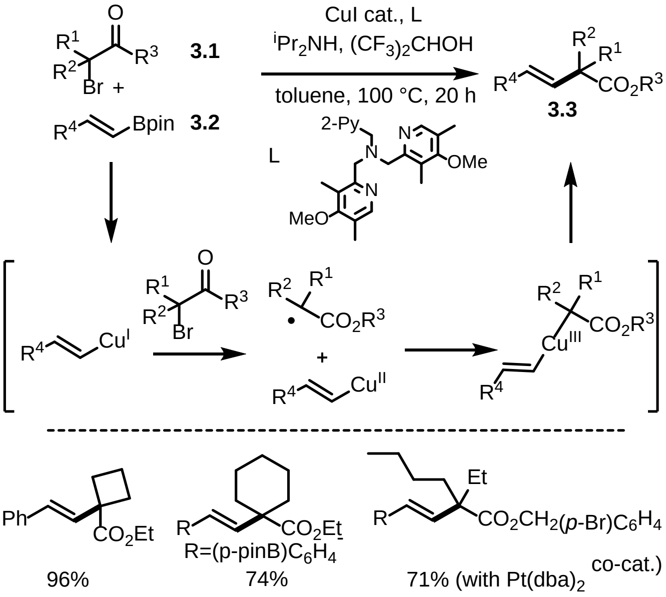


Scheme 2. Arylation at benzylic C-H bond

Alkenylations

Addition of a functionalized alkyl group (especially a tertiary alkyl group) onto a terminal alkene is very difficult to achieve, as traditional Mizoroki-Heck and related cross-couplings cannot usually be applied to the synthesis of alkylated alkenes due to the difficulties involved in oxidative addition and potential β-hydrogen elimination as outlined above.[7,8]

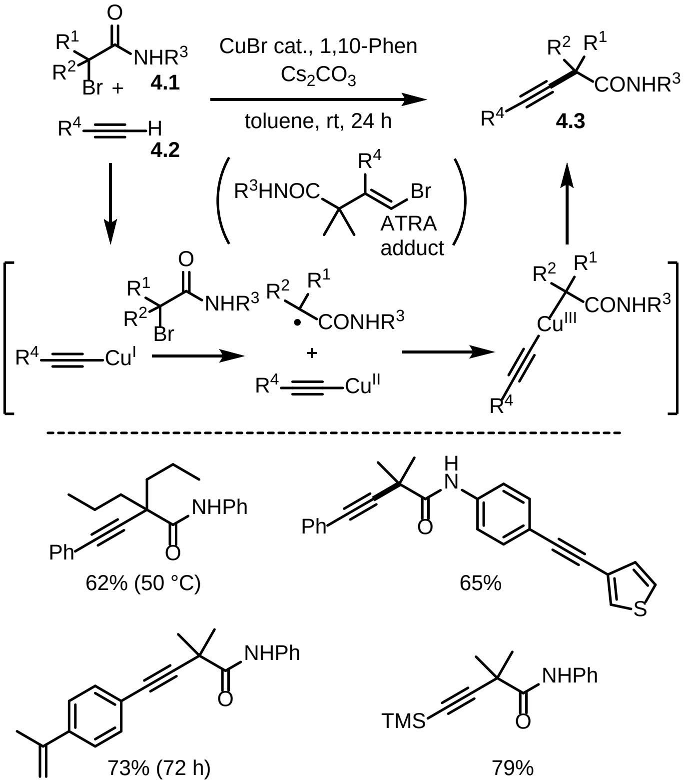
The "hybrid reaction system" concept can be exploited to accomplish Suzuki-Miyaura couplings of tertiary alkyl groups (Scheme 3).[9] The reaction of an alkenylboronic ester and a 2-bromoester as a *tert*-alkyl source gives the corresponding cross-coupled product in the presence of a copper catalyst. In this reaction, two active species are generated, a radical and an organometallic. A tertiary alkyl radical is generated from reaction of the Cu salt and the 2-bromoester (**3.1**) via a SET process and an alkenylcopper species is generated from transmetalation of the boronic ester (**3.2**). These two active species are coupled to generate **3.3**. The key to the success of this reaction is to avoid both oxidative addition and β-hydrogen elimination in the catalytic cycle. Indeed, an isolated alkenylcopper species smoothly reacts with **3.1** to produce **3.3**. Another possible mechanism could involve an addition/elimination pathway but the addition of tertiary alkyl radicals to internal olefins is generally difficult. The reaction scope is very broad but a Pt co-catalyst is required in some cases, although it's role is unknown. Overall, highly hindered tert-alkyl groups derived from **3.1** can be smoothly coupled to boronic esters **3.2**.



Scheme 3. Suzuki-Miyaura type coupling

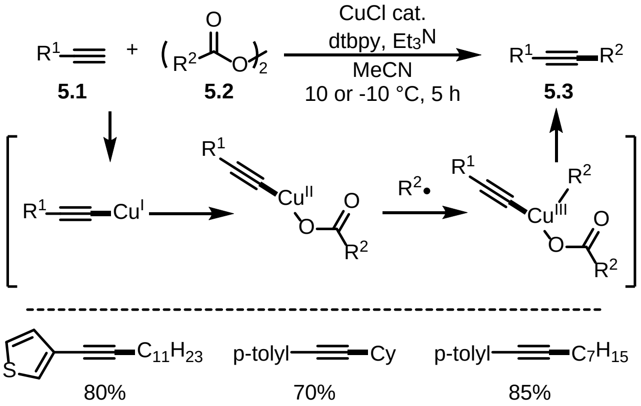
Alkynylations

Alkynylation reactions including Sonogashira type couplings, decarboxylative couplings, and C-H couplings have been reported using hybrid reaction system. Sonogashira couplings are mainly used for coupling an sp^2 carbon fragment to a terminal alkyne. Metal catalyzed Sonogashira coupling of alkyl groups remains a challenge to be overcome.[10] Again, tertiary alkylative couplings are one of the most difficult challenges because of steric effects (Scheme 4).[11] The reaction of a 2-bromoamide (**4.1**) as a tert-alkyl source with an alkyne (**4.2**) gives the corresponding tert-alkylated alkyne (**4.3**) in the presence of a copper catalyst at room temperature. In this catalytic cycle, a copper(I) acetylide is generated from the reaction of copper salt and **4.1**. Next, the reaction of this copper(I) acetylide with **4.1** generates an α-carbonylradical and a Cu(II) acetylide. Finally, this radical reacts with the copper(II) acetylide to produce **4.3**. When an isolated copper(I) acetylide reacts with **4.1**, **4.2** is produced. This result shows that a copper(I) acetylide is a plausible intermediate in this reaction. Interestingly, the atom transfer radical adduct of **4.2** (ATRA adduct) is predominantly obtained when tris(2-pyridylmethyl)amine (TPMA), or N, N, N', N" , N"-pentamethyldiethylenetriamine (PMDETA) is used as ligand instead of 1,10-phenanthroline (1,10-Phen). The generation of an α-carbonylradical is very fast in the presence of TPMA or PMDETA, which rapidly adds to alkyne **4.2** to yield ATRA adduct. Rapid generation of the copper(I) acetylide is therefore very important to obtain **4.3** in good yields. Under the optimized conditions, bulky *tert*-alkyl groups and functionalized alkynes can be used for the couplings.



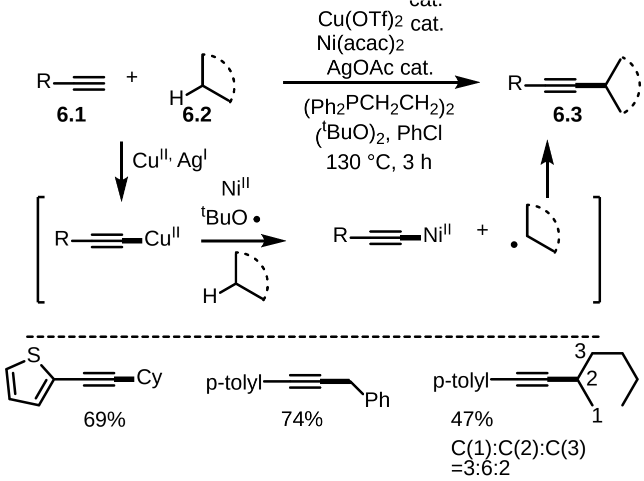
Scheme 4. Sonogashira type coupling

Alkylative Sonogashira couplings generally employ organic halides as a coupling partner, but the coupling of alkynes **5.1** and alkyl diacyl peroxides **5.2** in the presence of a copper catalyst has also been reported (Scheme 5).[12] The catalyst system (Cu/dtbpy) is very active and the decarboxylative couplings occur at low temperatures. The generation of a copper(I) acetylide is important at the first step of the catalytic cycle, followed by the generation of an alkyl radical species probably via single electron transfer from the copper(I) acetylide. Finally, the radical and organometallic hybrid reaction system enables alkylative Songashira coupling. The existence of a free radical was supported by a radical clock experiment and a radical inhibitor test using TEMPO. Under these conditions, primary- and secondary-alkyl groups can be loaded onto terminal alkynes in good yields.



Scheme 5. Decarboxylative Sonogashira type coupling

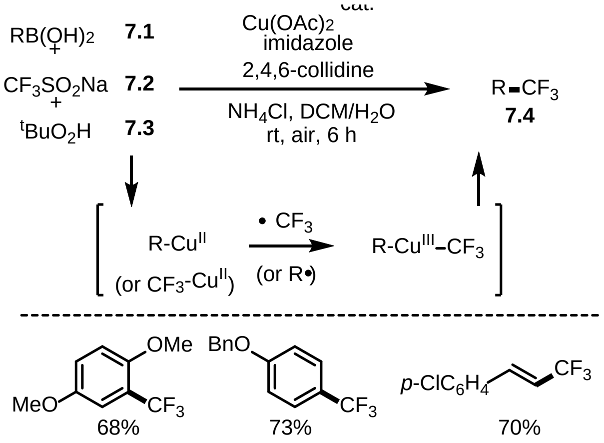
Sonogashira-type couplings with alkanes **6.2** are also possible (Scheme 6),[13] involving a dehydrogenative reaction of alkyne **6.1** and alkyne **6.2** using a multimetallic catalyst system. In the examples above, a Cu(I) salt is employed to generate a copper(I) acetylide, but in this reaction a combination of a Cu(II) salt and an Ag(I) salt generates a Cu(II) acetylide as a key intermediate. Alkyl radicals are generated from the reaction of alkane **6.2** and peroxide, and the resulting radical reacts with the Cu(II) acetylide to generate **6.3**. The resulting Cu(II) acetylide is immediately converted to Ni(II) acetylide. The addition of TEMPO into the reaction mixture results in no product, which indicates the existence of radical species in this catalytic cycle. In this reaction, cycloalkane or toluene give a single product (**6.3**) but acyclic alkanes afford a mixture of regioisomers.



Scheme 6. Dehydrogenative Sonogashira type coupling

Trifluoromethylations

Fluorinated carbon groups represent an important fragment in pharmaceuticals and agrochemicals, and trifluoromethylation via a radical and organometallic hybrid reaction system has been reported. Aryl- and vinyl boronic acids **7.1** smoothly react with Langlois reagent **7.2** to produce trifluoromethylated product **7.4** in good yields (Scheme 7).[14] One possible reaction pathway is shown in Scheme 7. The reaction starts with trasmetallation of the organoboronic acid to generate an organocopper species. After generation of a trifluoromethyl radical from the reaction of **7.2** and **7.3**, the organocopper species reacts with the radical to produce **7.4** via reductive elimination from a copper(III) species. Alternatively, generation of a trifluoromethyl copper species at the first stage of the catalytic cycle is also possible.[15]

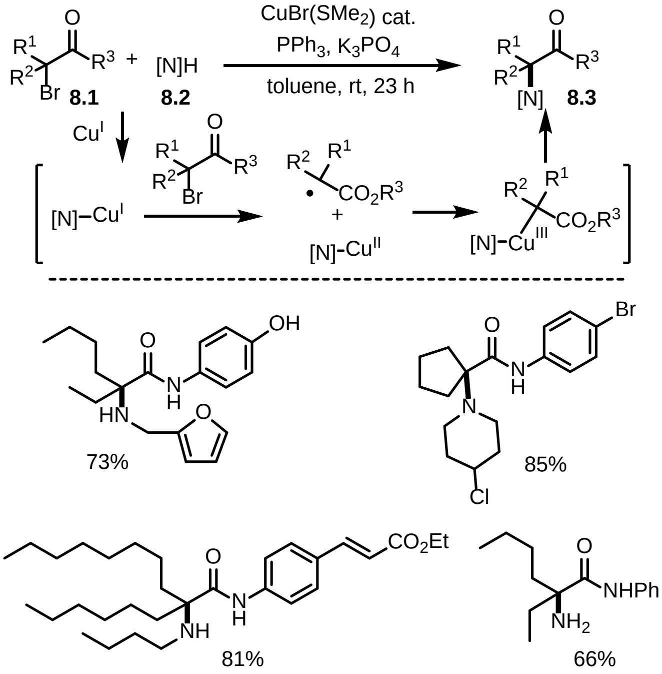


Scheme 7. Trifluoromethylation with arylboronic acid

IIB. C-heteroatom bond formations

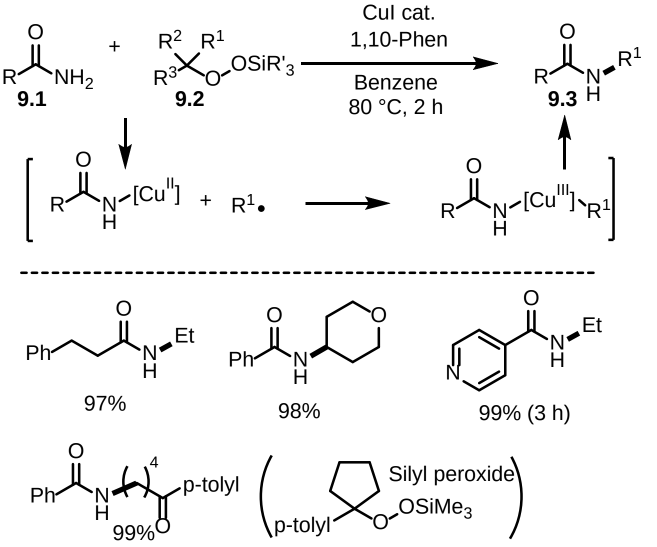
C-N bond formations

Alkylamines can be synthesized by nucleophilic substitution via S_N2 or S_N1 reactions. However, these reactions are often unsuitable for the synthesis of functionalized and congested amines possessing a tertiary alkyl group. A hybrid reaction system is suitable for the reaction of amines **8.2** including ammonia, primary and secondary alkylamines and amides with an α-bromocarbonyl compound **8.1** as a tertiary alkyl source to construct congested C(sp^3)–N bonds (**8.3**) (Scheme 8).[16] In the catalytic cycle, a copper amide species is generated from the reaction of the copper salt and the amine. The resulting copper amide generates a tertiary alkyl radical species via SET. The amine coupling product **8.3** is potentially generated after a reductive elimination process. Indeed, an isolated copper amide, generated from the reaction of copper salt and amine **8.2**, reacts with **8.1** to give **8.3**. A copper amide can also act as a catalyst for this reaction. Under optimized conditions, the reaction of various congested **8.1** and amine nucleophiles **8.2** including ammonia occur to produce highly congested amine couplings **8.3** in good yields.



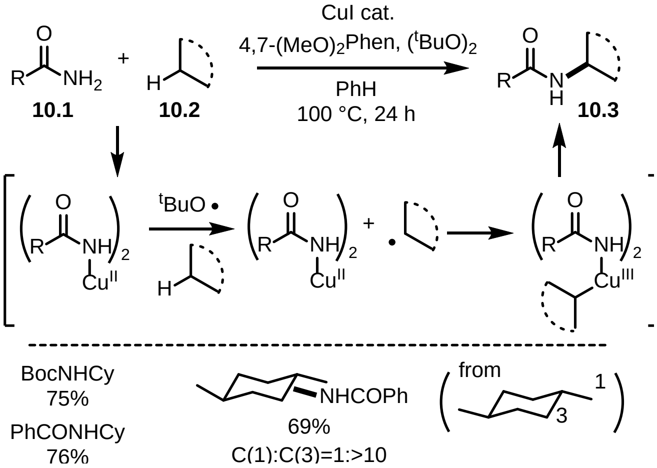
Scheme 8. Tertiary alkylative amination

Alkyl silylated peroxides **9.2**, which can be synthesized from alcohols and are bench stable, can also react with nitrogen nucleophiles **9.1** to give a coupling product **9.3** (Scheme 9).[17] In the presence of a copper(I) salt, an alkyl radical can be generated from **9.2**. The resulting copper(II) salt reacts with amide 9.1 to produce a copper(II) amidate. The desired product **9.3** can be formed via reductive elimination from a copper(III) species. This reaction is suitable for the synthesis of simple secondary amides **9.3**. Moreover, a ring opening product **9.3** is obtained in 99% yield when a cyclic peroxide is used.



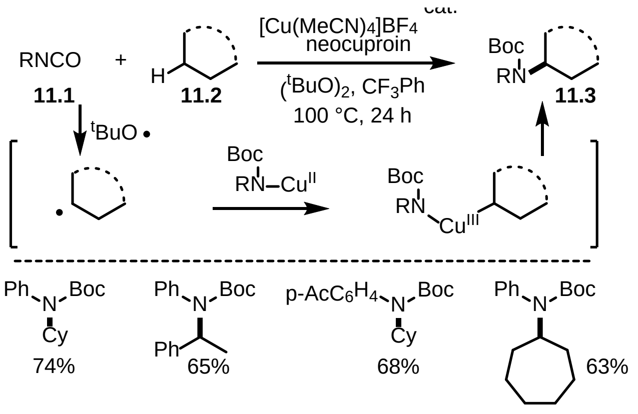
Scheme 9. *N*-Alkylation with silyl peroxide

An alkane C-H bond (**10.2**) is also a good coupling partner for a nitrogen nucleophile **10.1** via a copper catalyzed hybrid reaction system, in which alkylated amide **10.3** is produced (Scheme 10).[18] In this reaction, the formation of a copper(II) amidate from the reaction of 10.1 and a copper salt in the presence of organic peroxide is very important. The resulting alkyl radical reacts smoothly with the copper(II) amidate to produce **10.3** in good yield. In this reaction, symmetric unsubstituted cycloalkanes give a single product but acyclic and cyclic alkanes containing both primary and secondary fragments afford a mixture of regioisomers.



Scheme 10. Dehydrogenative amidation

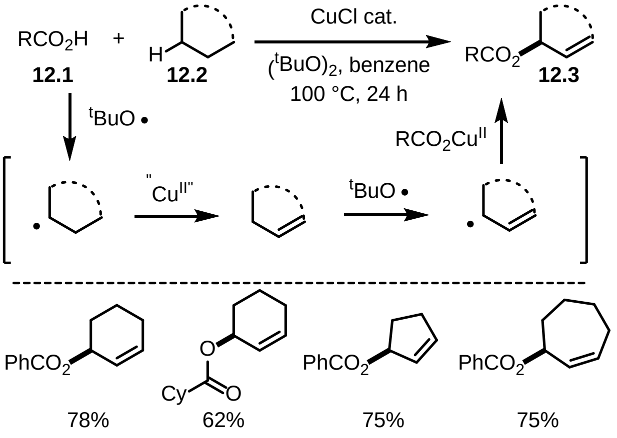
A hybrid reaction system enables the addition of alkane **11.2** to isocyanate **11.1** to produce an alkyl carbamate adduct **11.3** (Scheme 11).[19] A Copper(II) carbamate species and an alkyl radical species are generated *in situ* and combine to produce an alkyl carbamate copper(III) species. After reductive elimination, the desired adduct **11.3** is produced. Secondary alkylations occur smoothly with good yields of the product. This reaction suffers from regioselectivities when alkanes having primary, secondary and tertiary alkyl groups are used.



Scheme 11. Addition of alkane C-H bond to isocyanate

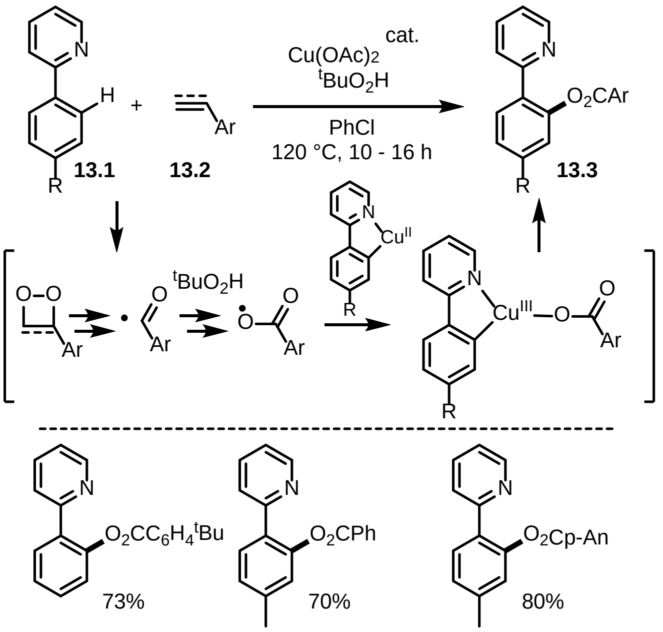
C-O bond formations

Copper catalyzed dehydrogenative caroboxylation of C-H bonds is a useful approach for the synthesis of esters. Although oxidative addition of a transition metal catalyst into an alkane C-H bond is very difficult due to the strong bond energy, hydrogen abstraction of an alkane C-H with a radical source to generate an alkyl radical species offers a promising approach to load a carboxyl group. For example, unactivated alkane **12.2** reacts with carboxylic acid **12.1** in the presence of a copper catalyst and $(tBuO)_2$ to produce allylic ester **12.3**, in which oxidative dehydrogenative carboxylation occurs (Scheme 12).[20] Interestingly, this reaction is not a simple C-H acetoxylation. The reaction starts with generation of a *tert*-butoxy radical and then an alkyl radical species. The alkyl radical species is oxidized by the resulting copper species to generate an alkene. An allylic radical is next generated from reaction of the alkene with another *tert*-butoxy radical. Finally, a copper(II) carboxylate reacts with the allylic radical to produce **12.3**. Under the conditions, cyclic alkanes give the product in good yields, but acyclic alkanes show low reactivity.



Scheme 12. Dehydrogenative caroboxylation of alkyl C-H bond

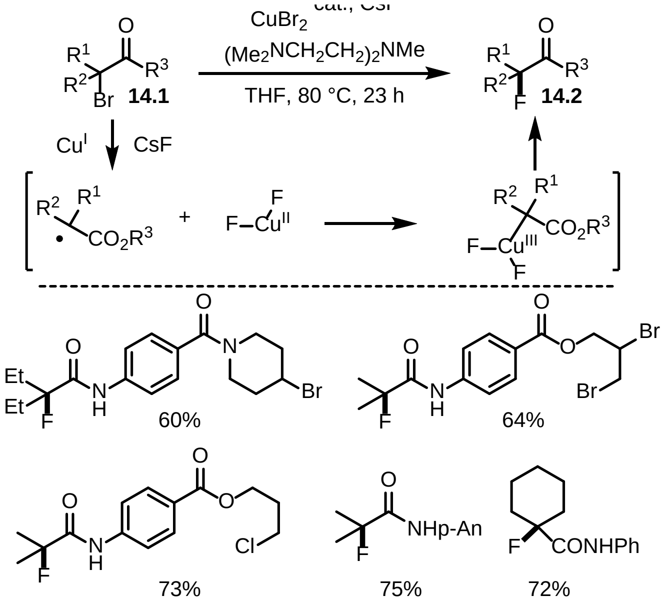
C-H acetoxylation of arene compounds can also be achieved, but using a different carboxylate source. The reaction of 2-pyridyl arene **13.1** and an alkene or alkyne **13.2** in the presence of a copper catalyst and $tBuO_2H$ (TBHP) provides acetoxylated arene **13.3**. In this reaction, **13.2** acts as a carboxyl source via oxidative C-C bond cleavage (Scheme 13).[21] At the first stage of this reaction, a carboxy radial is generated from the oxidation of **13.2** in the presence of copper and TBHP via the formation of phenylglyoxal. The loss of CO from phenylglyoxal is a key process and CO is detected. The resulting carboxy radical reacts with arylated copper, which is generated from copper acetate and **13.1** probably via concerted metalation deprotonation (CMD) pathway, to generate **13.3** via reductive elimination from a Cu(III) species. This reaction requires a 2-pyridyl directing group but various aryl substituents on both the arene and the alkene/alkyne can be used in the reaction.



Scheme 13. Acetoxylation of aryl C-H bond

C-F bond formations

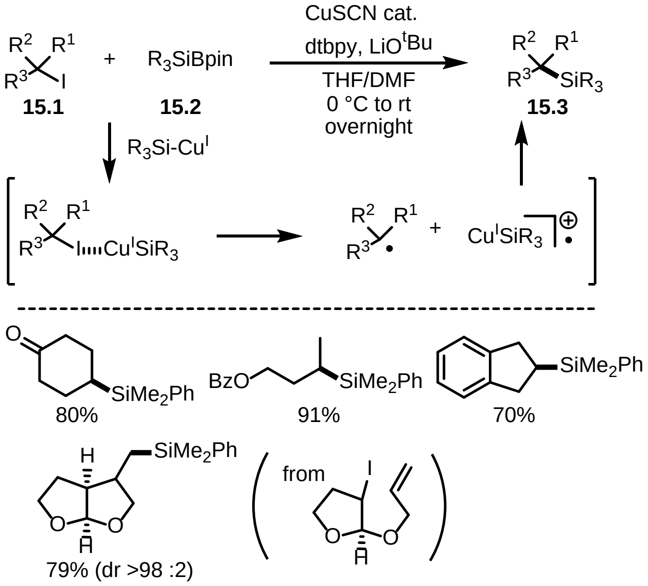
The formation of alkyl-fluorine bonds is one of the most important reactions in organic synthesis. The Finkelstein reaction is the conventional choice for synthesizing 1° and 2° alkyl fluorides via S_N2 reaction with a fluoride anion. However, complex fluorinating reagents, such as Selectfluor, NFSI, DAST, PyFluor, Phenofluor, Deoxo-Fluor, XtalFluor, and Fluolead, are required to synthesize 3° alkyl fluorides.[22] Previous reports have described very successful fluorinations of substrates with single reaction sites by using special fluorinating reagents, whereas fluorinations of substrates possessing multiple reaction sites (1°, 2° and 3° C-X), that is, site-selective fluorinations, remain a challenge. A hybrid reaction system is one of the most promising methodologies to achieve a 3° alkyl–selective fluorination reaction. For example, α-bromoamides **14.1** possessing multiple reaction sites, such as 1°, 2° and 3° C–halogen bonds, underwent 3° alkyl–selective fluorinations to produce **14.2** in the presence of a copper catalyst and CsF as a fluorinating reagent (Scheme 14).[23] In this reaction, CuF_2 generated in situ from the reaction of $CuBr_2$ and CsF is a key fluorinating reagent and reacts with 3° alkyl radicals generated from the reaction of an α-bromoamide and a Cu(I) salt. In the first step of this catalytic cycle, the reaction of the copper salt with the α-bromoamide **14.1** gives an alkyl radical species. The alkyl radical reacts with Cu(II)F_2, which is generated from the reaction of Cu(II)XBr and CsF, with the aid of an amide group, to form the desired product **14.2** with concomitant formation of a Cu(I) species to complete the catalytic cycle. Similarly, a chlorination reaction is possible in the presence of a copper catalyst and dichloromethane as a chlorine source.



Scheme 15. Site-selective fluorination

C-Si bond formations

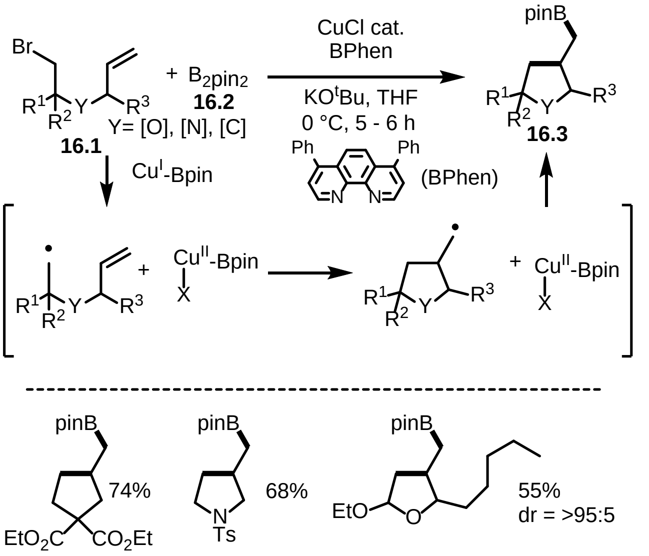
Silylated compounds are one of the most important and widely used reagents in organic synthesis. 1° alkyl silanes can be synthesized by nucleophilic displacements, whereas 2° alkyl silanes are difficult to synthesize via simple substitution reactions. To synthesize 2° alkyl silanes or complex 1° alkyl silanes, a hybrid catalyst system is useful. In the presence of a copper catalyst, an alkyl iodide **15.1** reacts with silaborane **15.2** to produce an alkyl silane **15.3** in good yield (Scheme 15).[24] Adamantyl iodide as a 3° alkyl source is also reactive but other 3° alkyl groups are not applicable in the reaction. 1° alkyl silanes can be also synthesized from cascade cyclization reactions under these conditions. The reaction starts with the generation of a silylcopper species, then an alkyl radical species is generated via SET from the silylcopper species to the alkyl iodide. The product **15.3** was proposed to be formed via a transient intermediate and not from the reductive elimination of an alkyl silylcopper(III) intermediate on the basis of DFT calculations.



Scheme 15. Alkylative silylation

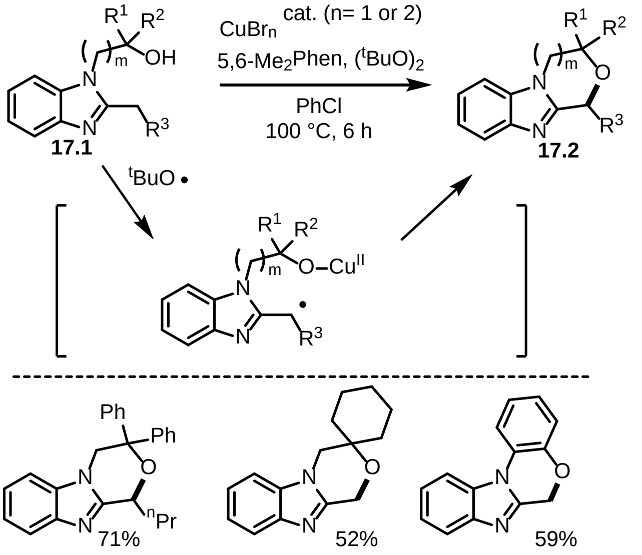
III. Cyclizations

Radical reactions are very useful for the construction of cyclic compounds. The introduction of a boron group under radical cyclization conditions could give useful borylated cyclic compounds. The synthesis of boron compounds having various carbon structures is highly valuable, because those compounds can easily be transformed into useful molecules by means of Suzuki-Miyaura and other related couplings. The reaction of alkenylated alkyl bromide **16.1** and diboron **16.2** provides a borylated cyclic compound **16.3** in the presence of a copper catalyst (Scheme 16).[25] This borylative radical cyclization is highly stereoselective and shows good functional group compatibility. In the catalytic cycle, borylated copper (I) species is generated and reacts with **16.1** to produce alkyl radical species via SET. The resulting alkyl radical reacts with borylated Cu(II) species to produce **16.3**.



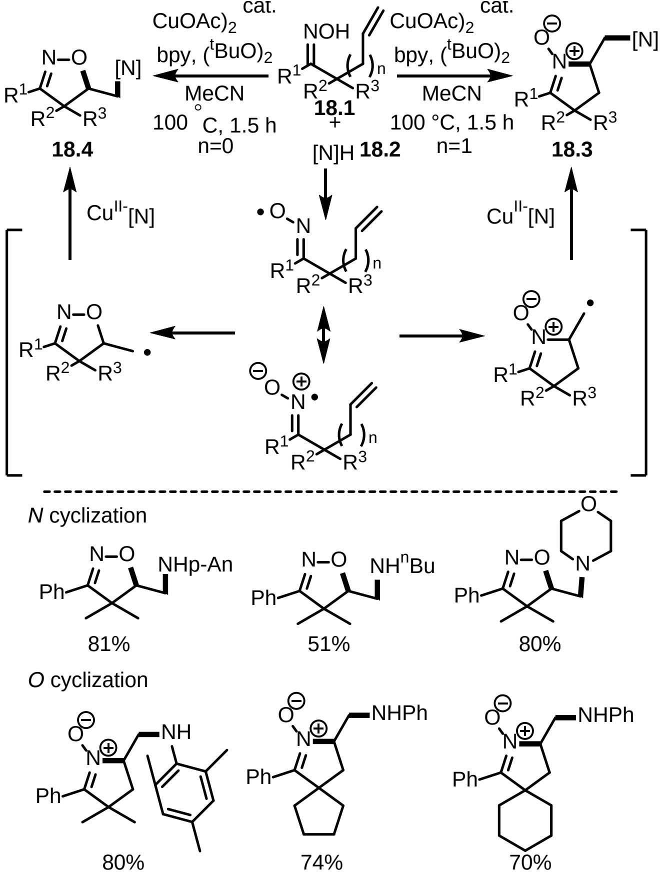
Scheme 16. Borylative cyclization

Intramolecular reaction of **17.1** to synthesize heterocyclic ring **17.2** containing a new ether bond is possible via a hybrid reaction system (Scheme 17).[26] The generation of a benzylic radical is key to accomplishing the intramolecular etherification reaction. Therefore, formation of tertiary butoxy radical from Cu(I) and $(tBuO)_2$ is the first step of this reaction. The resulting Cu(II) reacts with alcohol moiety of **17.1** to generate a copper alkoxide bearing a benzylic radical. The reaction of the copper alkoxide and the benzylic radical results in the formation of ether bond. The cyclization is inhibited by radical inhibitors such as TEMPO, and a TEMPO adduct was also detected in 45% yield. Benzimidazole derivatives smoothly undergo this cyclization reaction to produce a variety of heteroaromatic rings in moderate to good yields.



Scheme 17. Intramolecular etherification with C-H bond

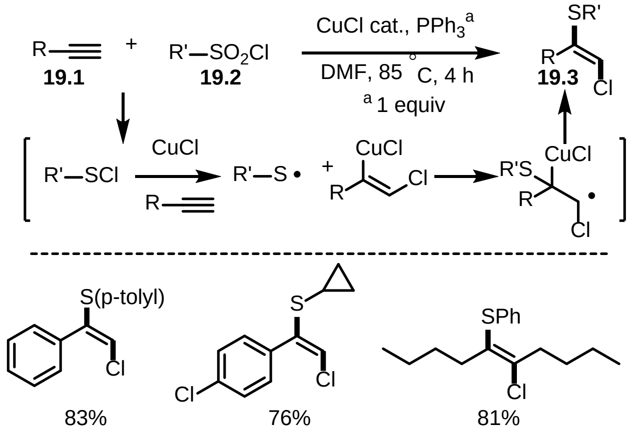
Controlled reaction of alkyl radical and copper amide species enables the vicinal oxyamination and diamination of alkenes. Reaction of ketoxime **18.1** and amine **18.2** in the presence of a copper catalyst leads to two different oxidative cyclizations to give nitrones **18.3** and oxazoles **18.4**, which can be controlled by substrate structure (Scheme 18).[27] In both reactions, the reaction of Cu(II) and **18.1** via SET is the first step to give an iminoxyl radical. Homoallylic substituted ketoxime (**18.1** where n=1) undergoes intramolecular *N*-cyclization, whereas allylic substituted ketoxime (**18.1** where n=0) provides *O*-cyclized intermediate. The final product nitrone **18.3** containing a five-membered ring structure is produced from the reaction of *N*-cyclized intermediate and copper(II) amide. On the other hand, oxazole **18.4** is from the reaction of *O*-cyclized intermediate and copper(II) amide. Under the optimized conditions, various heterocycles including spirocycles are synthesized in moderate to good yields.



Scheme 18. Divergent cyclization

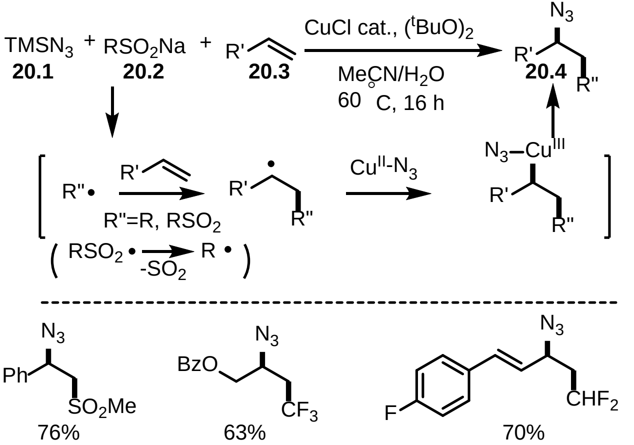
IV. Additions

Difunctionalization of unsaturated C-C bonds is a useful approach for the synthesis of complex functionalized aliphatic compounds in one step.[28] This difunctionalization system is similar to ATRA (atom-transfer radical addition) reactions catalyzed by a copper salt. For example, chloro-thiolation of alkyne **19.1** to give chlorothiolated alkene **19.3** is catalyzed by a copper catalyst in the presence of stoichiometric amounts of PPh_3 and sulfonyl chloride **19.2** (Scheme 19).[29] In the catalytic cycle, PPh_3 acts as a reductant for sulfonyl chloride **19.2** to give a sulfenyl chloride intermediate. Chlorocupration of alkyne **19.1** gives the corresponding vinylic copper which reacts with the sulfenyl radical via an addition-elimination process to yield the product. The reaction of vinylic copper and sulfenyl chloride gives **19.3** in good yield and with high *E*-selectivity.



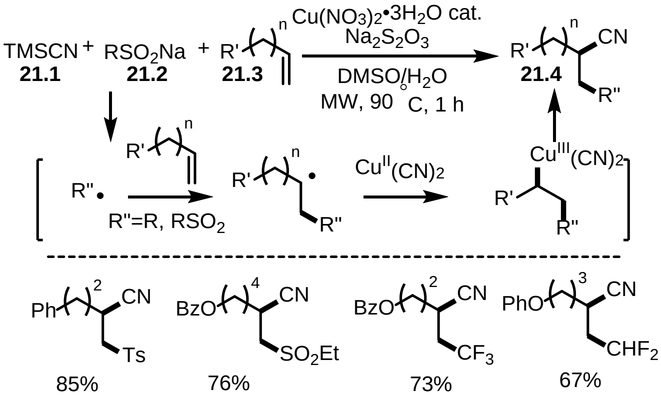
Scheme 19. Chloro-thiolation of alkyne

Olefins are good substrates for difunctionalization reaction. The reaction of silylated azide **20.1**, sodium sulfonate **20.2** and olefin **20.3** in the presence of copper catalyst and $(tBuO)_2$ proceeds via a radical oxidative sulfonylation-azidation reaction to give azidofunctionalized product **20.4** (Scheme 20).[30] At first, CuCl reduces $(tBuO)_2$ to produce a *tert*-butoxy radical which reacts with **20.2** to produce an R" radical. Sulfonyl radical is generated when R" is a simple alkyl group, whereas a CH_mF_n radical is generated via extrusion of SO_2 when R" is a fluorinated alkyl. After the addition of the R" radical to olefin **20.3**, followed by trapping of the Cu(II) azide species to give an alkyl azide copper(III) species, the product **20.4** is produced via reductive elimination. The substrate scope is broad and various unactivated C-C double bonds can be employed in this reaction.



Scheme 20. Fluoroalkylative Azidation of alkyne

Similar to the reaction in Scheme 20, a difunctionalization reaction involving introduction of a CN group is possible via reaction of cyanide **21.1**, sodium sulfonate **21.2** and olefin **21.3** under microwave irradiation (Scheme 21).[31] Intermolecular cyanosulfonylation and cyanotrifluoromethylation of unactivated alkenes occurs by using a hybrid catalyst system. In the reaction, a CF_3 or sulfonyl radical is generated from the reaction of **21.2** and oxidant. An alkyl copper species is generated after the addition of the resulting CF_3 or sulfonyl radical to **21.3** followed by coupling with copper(II) cyanide. Various cyano compounds can be synthesized with good functional group compatibility.



Scheme 21. Cyanation of alkyne

Summary

In this paper, we have summarized representative examples of the use of Cu-catalyzed hybrid reaction systems.[32] This reaction methodology is suitable for the formation of C-C, C-F, C-N, C-O, and C-Si bonds, cyclization reactions, and addition reactions. Radical reactions are typically not sensitive to steric hindrance but organometallic species typically are. In contrast, organometallic reactions usually show good selectivity but radical reactions are often less selective. The Cu-catalyzed hybrid reaction system offers a complementary methodology involving both radical and organometallic intermediates which can bring together the advantages of both classes of reaction.

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Keywords: copper • radical • alkylation • addition •coupling

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[32] The hybrid concept can also be seen in recent review. See Ref. [8]

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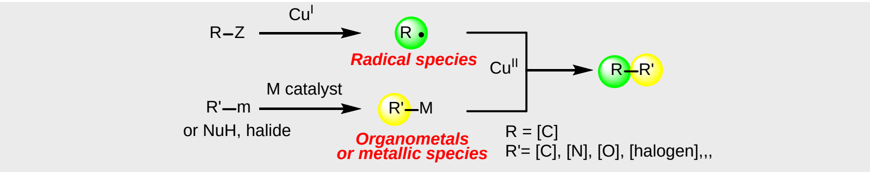

Controlling two different active species is very difficult. In this paper, we introduce recent copper catalysed radical and organometallic species combined reaction system, which is suitable for various alkylations or heteroatom loadings.

Kentaro Takeuchi, Yumi Murata, Goki Hirata, Tom D. Sheppard, Takashi Nishikata**

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Hybrid Reaction Systems for the Synthesis of Alkylated Compounds based upon Cu-catalyzed Coupling of Radical and Organometallic Species