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# Construction of Carbon-Heteroatom Bond Using C-H Functionalization and Cross Coupling Reactions

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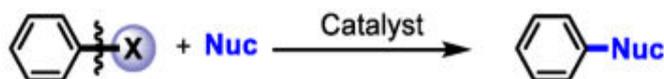
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**ABSTRACT:** The present review provides an overview of visible light-mediated environment- friendly approaches over the past decade for the formation of carbon-carbon and carbon-heteroatom framework. This area has recently emerged as a versatile, environmentally benign and green platform for the development of a highly sustainable synthetic methodology. According to the recent advancements, visible light has come to the forefront in synthetic organic chemistry as a powerful green strategy for the activation of small molecules. Photochemistry enables new synthetic means to form carbon-heteroatom bonds. Photocatalysts can catalyze carbon-heteroatom cross-couplings by electron or energy transfer either alone or in combination with a second catalyst. Photocatalyst-free methods are possible using photolabile substrates or by generating photoactive electron donor-acceptor complexes. This review summarizes and discusses the strategies used in light-mediated carbon-heteroatom bond formations based on the proposed mechanisms. Light induces carbon-heteroatom bond formations through different modes of action. Photochemical strategies to activate inert substrates or intermediates either with or without photocatalysts are discussed. The term visible light mediated, has recently emerged as versatile, environmentally benign and green platform for the development of a highly enabling synthetic methodology. According to the recent advancements, the visible light has come to the forefront in the synthetic organic chemistry as a powerful green strategy for the activation of small molecules. This present review highlights an overview in the field of the visible light mediated environment friendly approaches over the past decade for the formation of Carbon-Carbon and Carbon-Heteroatom framework.

**KEYWORDS:** carbon, heteroatom, C-H, functionalization, cross, coupling, reactions, construction

## I. INTRODUCTION

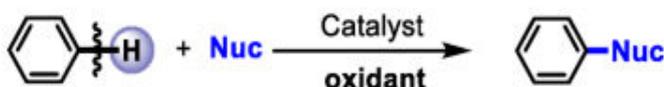
The construction of carbon-carbon and carbon-heteroatom bonds is a key objective for synthetic chemists to build up complex organic molecules. Such bonds are prevalent in many materials, medicinally and biologically active compounds. In the most recent decades, these linkages have been forged through transition metal catalyzed cross coupling between aryl/alkyl halides or pseudo halides and nucleophiles. However, such an approach requires prefunctionalized substrates and coupling partners, often prepared in a multistep reaction sequence, which is time-consuming and inefficient.[1]

**a Classic Cross-coupling Chemistry****Advantage**

- mature transformation

**Challenges**

- functional group required
- expensive substrates

**C–H Functionalization Chemistry****Advantages**

- no functional group required
- atom-efficient
- inexpensive substrates
- versatile transformation

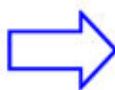
**Challenges**

- harsh reaction conditions
- high catalyst loadings
- long reaction times

*Rare in flow* → *Opportunity!*

**b C–H Functionalization Chemistry in Flow - Anticipated Advantages****Flow advantages**

- Increased mass transfer
- Improved heat transfer
- Excellent irradiation
- Easy handling of multiphase reactions
- High reproducibility
- Multistep Flow Sequences
- Safety
- Scalability
- Automation

**Impact for C–H Functionalization**

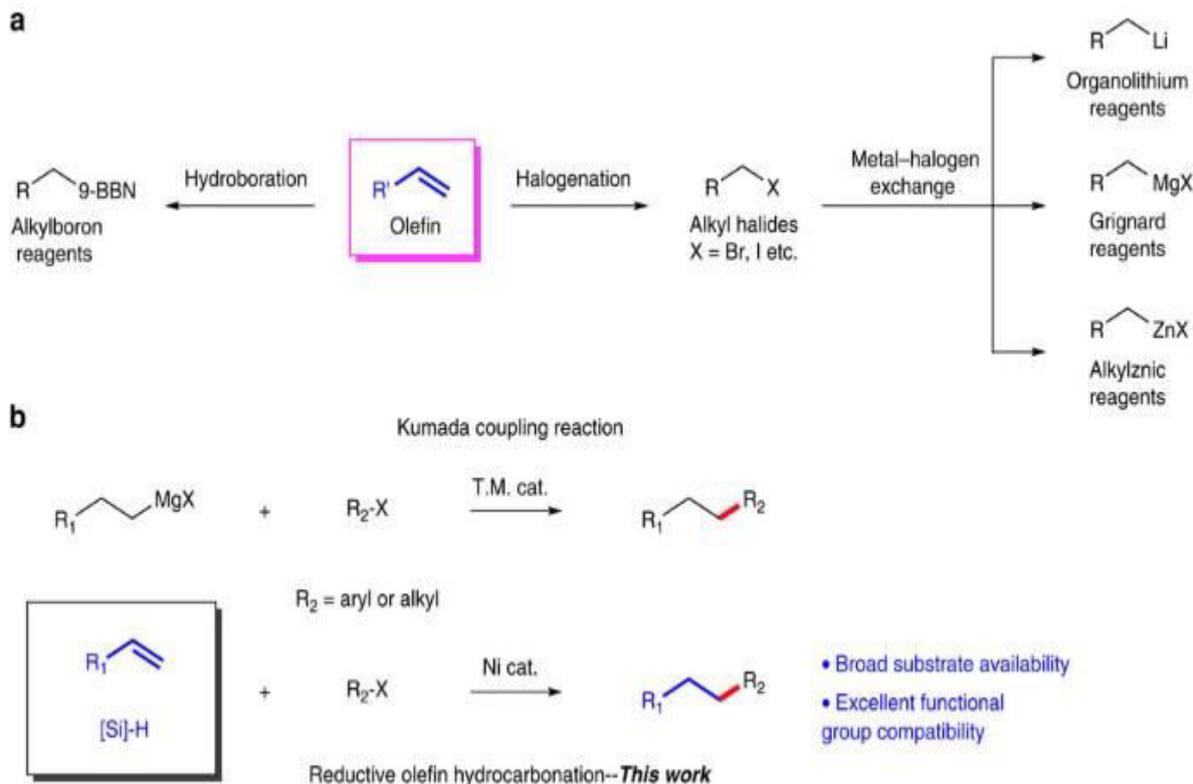
- Faster reactions, Less byproducts
- Handling of exothermic reactions
- Fast photochemical transformations
- Use of gaseous reagents
- Determination of reaction kinetics
- Time gain, Labor reduction,
- Handling of hazardous reagents
- From mg to g scale without reoptimization
- No human error

C–H bonds are the fundamental linkage in organic molecules and, consequently, C–H activation strategies would allow for very versatile transformations, even applicable in late-stage functionalizations enabling rapid diversification of hit molecules. This provides an atom-efficient and cost-effective alternative for the traditional cross-coupling strategies. In 2005, the ACS GCI Pharmaceutical Roundtable have ranked C–H activation as the top priority of the aspirational reactions, i.e. reactions which companies would like to use on the proviso that they are available [20, 21]. While C–H activation has indeed been hailed for its use of unfunctionalized starting materials, the applicability of C–H activation chemistry has been limited mainly by the inert nature of the carbon-hydrogen bond (bond dissociation energies of

aromatic C–H are around  $110 \text{ kcal mol}^{-1}$  and of aliphatic C–H around  $105 \text{ kcal mol}^{-1}$ ). Consequently, in order to cleave the C–H bond, harsh reaction conditions, long reaction times and high catalyst loadings are typically required. Also, stoichiometric amounts of toxic oxidants are often needed to close the catalytic cycle.[2,3]

## II. OBSERVATIONS

Carbon–carbon bonds formation from olefins.



(a) Alkyl organometallic reagents used in cross-coupling reactions. Alkylboron reagents are usually made through alkene hydroboration. Grignard organolithium and alkylzinc reagents are generally obtained through insertion of metals into alkyl halides. However, an often ignored problem is that most terminal alkyl halides are converted from olefins (b) Comparison of reductive olefin hydrocarboxylation reaction with transition metal-catalyzed Kumada-coupling reaction. From a viewpoint of synthetic chemistry, the combination of olefins with silanes could be recognized as equivalent to alkyl organometallic reagents. 9-BBN=9-borabicyclo[3.3.1]nonane.

We have developed a practical and user-friendly method for the formation of carbon–carbon bonds through Ni-catalyzed intermolecular coupling of aryl or alkyl electrophiles with olefins under reductive conditions. This newly developed reductive olefin hydrocarboxylation reaction provides a useful and general approach for the construction of carbon–carbon bonds by directly using olefins as nucleophile precursors.[4,5] This reaction exhibited excellent compatibility with varieties of synthetically important functional groups and therefore, provided an efficient new approach for the modification of complex molecules. Our next challenge was the development of asymmetric version of this new carbon–carbon bond forming reaction and its extension to internal olefins.

## III. DISCUSSION

Carbon-carbon bond construction represents the basis of whole organic chemistry. Since the 1970s, transition-metal-catalyzed cross-coupling reactions have provided a straightforward route for the construction of carbon-carbon bonds and have been widely used in applications that range from complex natural product synthesis to drug discovery and manufacturing. Within the realm of transition-metal-catalyzed decarbonylative crosscoupling reactions, carbon-carbon bond formation with various aryl compounds has been at mostly explored.[6,7]



**Suzuki-Miyaura-Type Reaction** In 2004, an interesting rhodium-catalyzed Suzuki-type decarbonylative cross-coupling of aromatic carboxylic anhydrides with arylboroxines was achieved by Gooßen and coworkers. [8] This novel decarbonylative coupling process is distinguished by the use of  $[\text{Rh}(\text{ethylene})_2\text{Cl}]_2/\text{KF}$  catalytic system with a broad range of substrates (Scheme 4), potentially opening up new perspectives for the use of carboxylic acid derivatives in biaryl synthesis. Notably, the use of boroxines as coupling nucleophiles proved to give the best yields, whereas the use of boronic acids, esters or borates gave unfavorable results. Later, Sames and coworkers reported a ruthenium-catalyzed decarbonylative arylation reaction of cyclic 2-amino esters, which allows the replacement of ester groups at  $\text{sp}^3$ -carbon centers.

**Negishi-Type Reaction** Organozinc compounds have been considered as very useful and versatile reagents for a broad variety of transformations in organic synthesis owing to their straightforward preparation, high reactivity/selectivity and excellent functional group tolerance. In 2003, Rovis group presented a stoichiometric nickel-mediated decarbonylative cross-coupling of cyclic meso-anhydrides with diarylzinc compounds, which constitutes an extraordinary example of  $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^2)$  coupling that generates stereochemistry. [9,10]

**Mizoroki-Heck-Type Reaction** Mizoroki-Heck cross-coupling has found extensive application in transformations that do not require stoichiometric amounts of organometallic reagents for the desired carbon-carbon bond formation, which is a major advantage compared with other cross-coupling procedures. As early as in the late 1970s, chemists conducted investigations on the Ni- or Pd-catalyzed Mizoroki-Heck reaction of aryl chlorides with methyl acrylate, and observed the formation of decarbonylative coupling product [11,12]

**Sonogashira-Type Reaction** Alkynes are recurring structural motifs in a variety of natural products, bioactive molecules and functional materials. Among the established methods for the synthesis of substituted alkynes, the transition-metal-catalyzed Sonogashira coupling has proven to be one of the most popular and efficient procedures. In 2016, Itami and Yamaguchi group reported a palladium-catalyzed alkylation reaction of aromatic esters with terminal alkynes in a decarbonylative manner. [13]

**Decarbonylative C-H Coupling** In 2008, Yu and coworkers developed a ligand-free rhodium catalytic system for the decarbonylative C-H functionalization of benzo[h]quinolines or 2-aryl pyridines with acyl chlorides. [28] This protocol is distinguished by the use of 5 mol% of  $[\text{Rh}(\text{cod})_2\text{Cl}]_2$  and is applicable to a broad range of substrates (Scheme 19). Later on, new transformations using the same strategy were gradually developed and expanded to cinnamoyl chlorides, [29] anhydrides [30] and aldehydes

**Cyanation Reaction** A new palladium-catalyzed decarbonylative cyanation reaction of carboxylic amides was recently developed by Szostak and coworkers. [33] A key challenge in the cyanation protocols is the risk of hazardous hydrogen cyanide gas generation. To circumvent this, the authors applied zinc cyanide, which is commonly recognized as a cheap and harmless cyanating agent. The new amide to nitrile interconversion is characterized by its high efficiency and excellent functional group tolerance, providing a practical and versatile approach to a wide range of aryl, heteroaryl, and alkenyl nitriles [14]

**Intramolecular Decarbonylation of Ketones** While the synthetic methods presented so far have involved transition-metal-catalyzed acyl carbon-heteroatom bond cleavage prior to decarbonylation, new transformations via decarbonylative carbon-carbon bond cleavage of ketones would be of interest. [4d] In 1994, Murakami reported a pioneering work on rhodium-catalyzed decarbonylation of cyclic ketones via selective C-C bond cleavage. [35] With the utilization of a high loading of a  $\text{Cp}^*$  rhodium complex, Brookhart observed a unique decarbonylation process of simple biaryl ketones to achieve the corresponding biaryls

**Ring-Opening and Alkyne/Alkene Insertion** In 2008, Kurahashi and Matsubara reported a nickel-catalyzed decarbonylative ring-opening/alkyne insertion reaction of cyclic anhydrides. [41] This coupling reaction, accomplished with a  $\text{Ni}(0)/\text{PMe}_3$  catalyst as well as a Lewis acid ( $\text{ZnCl}_2$ ), exhibits high reactivity and broad substrate scope with respect to both cyclic anhydrides and alkynes. Diverse isocoumarins and  $\alpha$ -pyrones could be synthesized in good yields and regioselectivities under the reaction conditions [15]

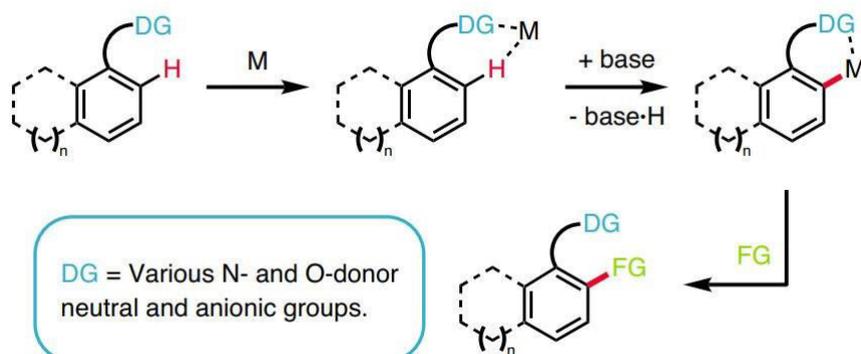
#### IV. RESULTS

Pd-Catalyzed C-H functionalization of acyldiazomethanes with aryl iodides has been developed. This reaction is featured by the retention of the diazo functionality in the transformation, thus constituting a novel method for the introduction of diazo functionality to organic molecules. Consistent with the experimental results, the DFT calculation

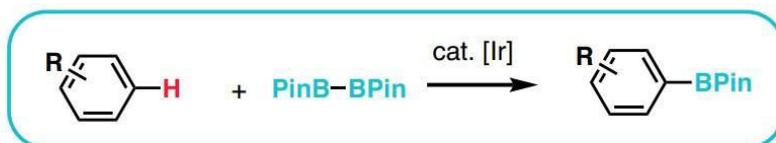
indicates that the formation of Pd carbene species in the catalytic cycle through dinitrogen extrusion from the palladium-EDA complex is less favorable. The reaction instead proceeds through  $\text{Ag}_2\text{CO}_3$ -assisted deprotonation and subsequently reductive elimination to afford the products with diazo functionality remained. This C-H functionalization transformation can be further combined with the recently developed Pd-catalyzed cross-coupling reaction of diazo compounds with aryl iodides to develop a tandem coupling process for the synthesis of  $\alpha,\alpha$ -diaryl esters. DFT calculation supports the involvement of Pd carbene as reactive intermediate in the catalytic cycle, which goes through facile carbene migratory insertion with a low energy barrier (4.3 kcal/mol).

C-H functionalization has been called the holy grail of synthetic organic chemistry. Recent efforts across organic chemistry, organometallics, and catalysis have made serious inroads in both understanding the reactivity of C-H bonds and developing robust reactions taking advantage of this insight, suggesting that the time is right to widely introduce these tactics to the retrosynthetic lexicon. The reliable and predictable conversion of a C-H into a C-C, C-N, C-O, or C-X bond in a selective and controlled way is beneficial in terms of step economy and waste reduction.[16]

Novel methods for C-H activation extend the number of sites that can be targeted in a given molecule, increasing the opportunity to elaborate it into a more complex product. In addition, it allows for completely different kinds of chemical bonds to be targeted in organic synthesis, particularly with high chemoselectivity. Combined with traditional functional-group chemistry, C-H functionalization considerably streamlines chemical synthesis for the construction of complex natural products and pharmaceutical compounds. While clearly there are advantages to the application of C-H functionalization logic, many curricula for organic chemistry have not yet been updated to reflect this approach and further information can be found in the C-H Functionalization Manual.



### General strategy for functionalization

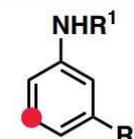
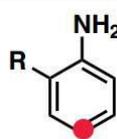


monoborylation selectivity

conditions a  
simple arenes

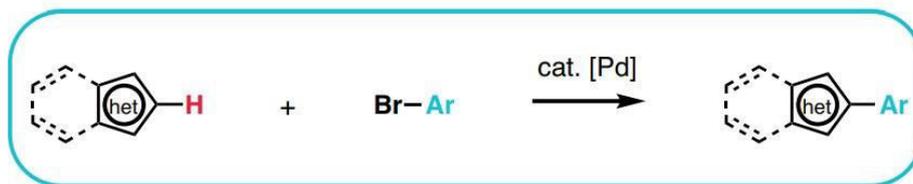


conditions b  
anilines

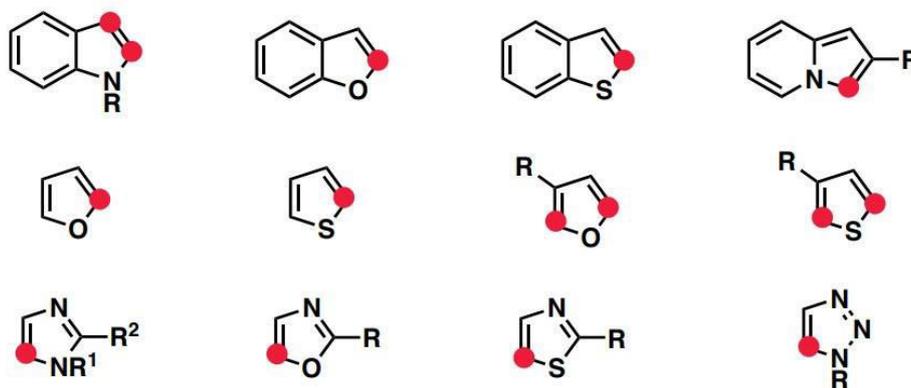


● = observed selectivity

### Undirected borylation

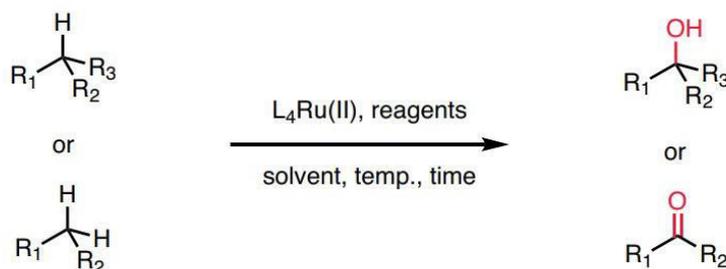


mono-arylation regioselectivity

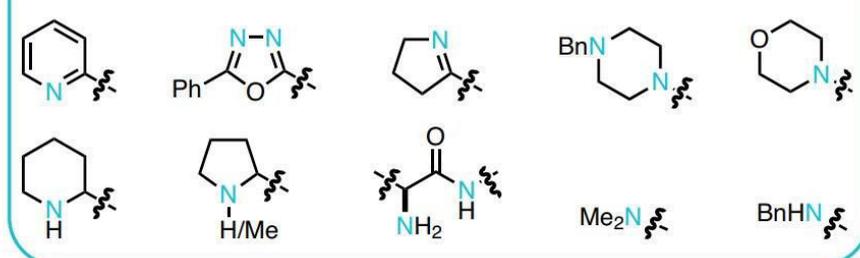


● = observed selectivity

### Undirected sp<sup>2</sup> direct arylation

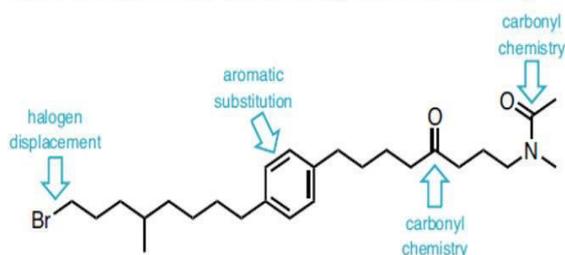


Nitrogen-Functional Groups Tolerated Include:

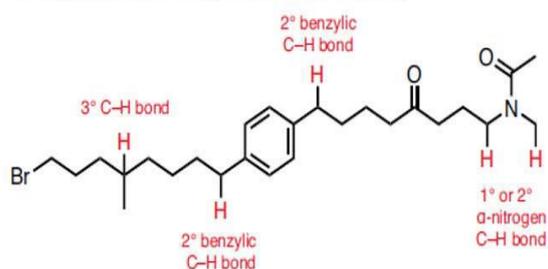


### Undirected C-H hydroxylation

## Conventional Functional-Group Based Reactivity



## C-H Functionalization Based Reactivity



## Based reactivity

## V. CONCLUSIONS

Recently, Lan and co-workers disclosed the Rh(III)-catalyzed oxidative C–H/C–H cross-coupling of [1,2,4]triazolo[1,5-a]pyrimidines with indoles and pyrroles to afford the ESIPT fluorophores (Scheme 40).<sup>51</sup> In this work, 7-(Pyrrol-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidines and 7-(indol-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidines were synthesized in moderate to excellent yields. A large library of ESIPT fluorophores could be obtained by removing the pyrimidyl directing group using sodium methoxide. These ESIPT fluorophores exhibited bright emission and high quantum yields in both solution and solid states. p-Conjugated polymers have been considered as promising fluorescent materials for the fabrication of optoelectronic devices. The transition-metal-catalyzed direct C–H/C–H polymerization of non-preactivated (hetero)arenes would be one of the most straightforward and effective approaches to construct p-conjugated polymers, which would eliminate the extra steps to prepare bifunctional monomers. In 2014, the You group disclosed the Cu-catalyzed oxidative C–H/C–H polymerization of benzodiiimidazoles to prepare polybenzodiiimidazoles with moderate number-average molecular weight in good yields (Schemes 42 and 43).<sup>52</sup> These polybenzodiiimidazoles exhibit strong blue fluorescence emissions in chloroform and PS film. In 2015, Li and co-workers reported Pd-catalyzed oxidative C–H/C–H homopolymerization of thiazole derivatives with thiophene to construct p-conjugated polymers 76a–76c (Scheme 44).<sup>53</sup> Emission maxima of 76a–76c were observed at 609, 626, and 645 nm in the film state, respectively. [15,16]

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