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Reusable directing groups [8-aminoquinoline, picolinamide, sulfoximine] in C(sp^3)–H bond activation: present and future

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ABSTRACT

This report briefly discusses the reusable directing group assisted functionalization of unactivated remote alkyl C–H bonds and their synthetic potential in organic chemistry. The challenges involved for the functionalization of inert alkyl C–H bonds is highlighted. With the strong impact of C–H activation, we believe this report would boost researchers unraveling novel methods for the chemo-, regio-, and stereoselective activation of unbiased C(sp^3)–H bonds and their potential utility for the rapid synthesis of complex molecular entities.

1. Introduction

Direct functionalization of an unactivated C–H bond has versatile potentiality in synthetic chemistry, as this process uses ubiquitous C–H bond for the fabrication of novel molecules in an economically efficient manner.[1] The C–H activation strategy did not require the pre-functionalized materials, thus access to a wide spectrum of scope of substrates for functionalization and broadens the synthetic utility of the methods.[2] As this method offers opportunities for late-stage functionalization of C–H bond, consequently it promotes the efficient synthesis of complex molecules.[3,4] At the outset, this method is complimentary to the cross-couplings and the well-established *C*-heteroatom bond forming processes.

The functionalization of C(sp^2)–H of arenes and olefins has extensively been investigated in the last two decades and witnessed impressive applications in organic synthesis.[1,3] In contrast, the direct activation and functionalization of 'inert' C(sp^3)–H bonds of alkyl groups is poorly investigated. High bond dissociation energy (BDE), the 'inert' nature of C–H HOMO or LUMO, and the lack of π-assistance (compared to sp^2 C–H bond) and the difficulties in the reductive elimination are the specific challenges that prevent the effective functionalization of remote unactivated sp^3 C–H bonds.[5] The directing group-oriented strategy provides solutions to the challenges connected with the C(sp^3)–H activation. For example, the directing group promotes reactivity by enhancing the catalyst concentration as well as selectivity.[2,6] Among the transition-metal catalysts used in the C–H activation, the Pd(II)-catalyst showed outstanding reactivity and controllable selectivity in C(sp^3)–H activation.

Directing group is a motif with one or more heteroatom or with rich of π-electron cloud; it has the ability to bind the metal reversibly and dictate the regioselective activation of C–H bond; most often they are σ donor in nature.[6] Thus, the reversible binding ability of directing groups (DGs) to metal consequently kept the catalytic cycle active. Accordingly, a variety of DGs, e.g. pyridine, oxazole, pyrazole, pyrimidine, acetanilide, oxime, ester, carbamate, imines, amide, sulfonamide, sulfoxide, and so on have been developed and successfully deployed for the C–H activation reactions.[6,7] The DGs are generally non-modifiable, modifiable/transformable, and/or reusable. The non-modifiable DGs are robust, for example, pyridyl, pyrimidine etc.; it is difficult to modify or transformed them to other functional group, limiting the broad synthetic applications of the method. Whereas the modifiable/transformable DGs can easily be transformed to different functional groups or readily removed from the molecule after the functionalizations; this process inducts new functional groups in a molecule with particular importance.[7a] This strategy therefore found appreciable synthetic applications.

A reusable directing group (DG) can easily be introduced to the substrate and readily recovered from the C–H functionalized products. These DGs act as catalytic mimic in C–H functionalizations. Therefore, the reusable DG assisted C–H functionalization are atom-economical and synthetically viable (Scheme 1).

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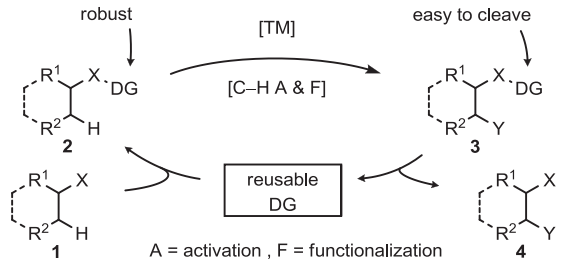


Scheme 1. Reusable directing group assisted C(sp^3)–H bond functionalizations.

This review provides a brief overview on the importance and utility of reusable DGs for the activation and functionalization of the remote unactivated C(sp^3)–H bond.

2. Reusable directing group in C(sp^3)–C bond formation

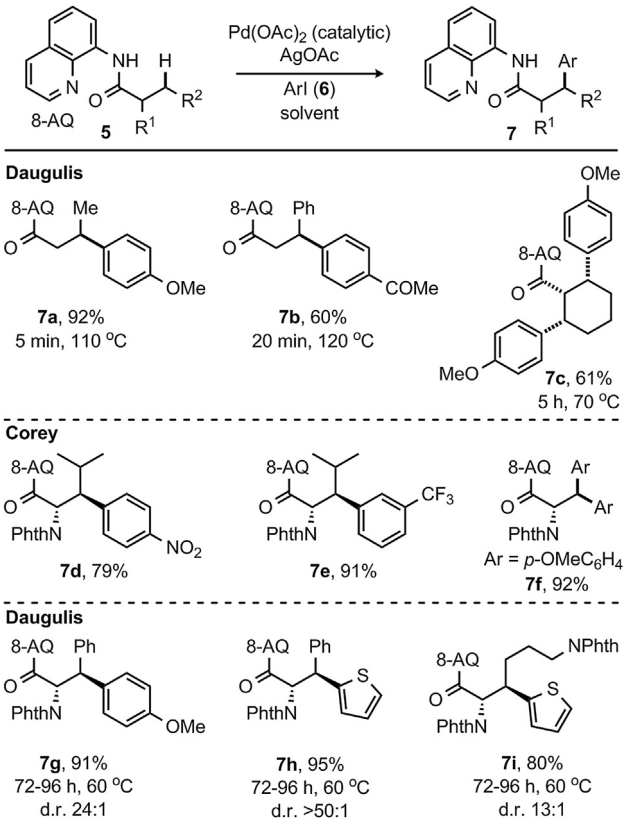
The C–C bond formation is the most fundamental reaction to synthetic chemists, as these methods connect two independent species for the construction of new molecular scaffolds.[2e] The direct activation of an unbiased C(sp^3)–H bonds delivers non-regioselective products. While a directing group can assist the regioselective activation of C(sp^3)–H bond for the construction of highly-selective C(sp^3)–C bonds, widening the synthetic utility of the method. Over the last few years, a handful number of C(sp^3)–H activation methods have been developed and applied for the synthesis of molecules relevant to biological, material, and pharmaceutical importance.

2.1. C(sp^3)–H arylation

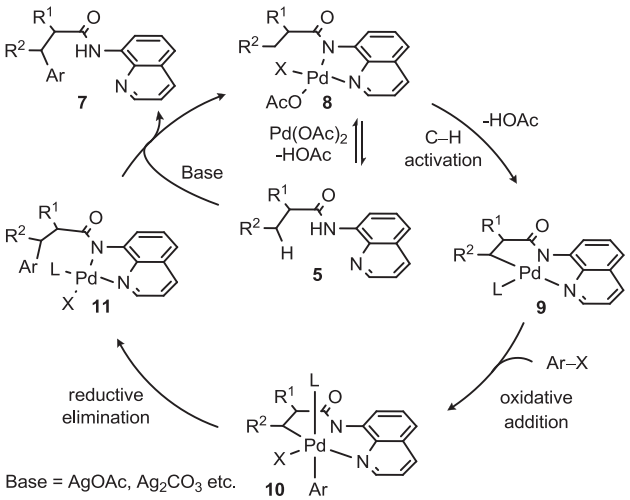
The bidentate directing group (BDG), 8-aminoquinoline (8-AQ), has extensively been used for the regioselective C–C bond formations. Daugulis and Corey groups have independently developed a Pd(II) catalyzed 8-AQ directed arylation of β-C(sp^3)–H bond in amide derivative **5** (Scheme 2); the reaction has broad scope.[8,9] Interestingly, the cyclohexanecarboxylic acid derivative underwent diarylation by activating two adjacent methylene C–H bonds to produce the syn-product **7c**. Finally, the acid mediated cleavage of amide bond produced the desired product with decent recovery of 8-AQ. This method is successfully employed for the synthesis of non-natural amino acid derivatives; for instance, diastereoselective mono-arylated products **7d**–**i** are accessed through mono-arylation of *N*-phthaloylamino acid derivatives.

A general well-accepted mechanism for $Pd(OAc)_2$ catalyzed arylation of C(sp^3)–H bonds of carboxamide is shown in Scheme 3.[8,10] At first, the coordination of DG-heteroatom with $Pd(OAc)_2$ forms **8**. Next, the insertion of metal to the C–H bond through agostic interaction and the concurrent elimination of AcOH deliver the activated complex **9**. The oxidative insertion of aryl halide to Pd(II) complex then generates the highly reactive Pd(IV)-complex **10**, which subsequently undergoes facile reductive elimination to form arylation product bound Pd(II)-complex **11**. Finally, proto-demetalation yields the desired product with the generation of active catalyst for the next cycle. The silver salts present in reaction medium act as base as well as halide scavenger.[10b]

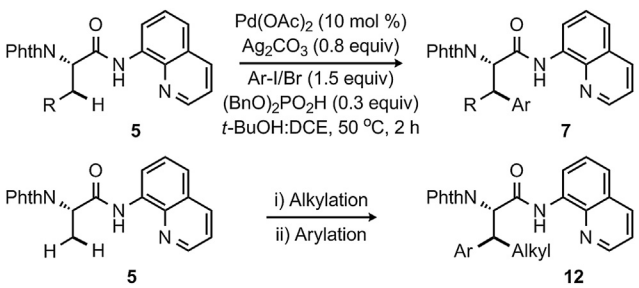
A seminal work by Shi group describes 8-AQ directed β-arylation of α-amino acid derivatives with aryliodide or bromide in presence of Pd(II)-catalyst (Scheme 4).[11] The chirality is preserved during the reaction, offering a decent pathway for the synthesis of unnatural α-amino acids. This method has wide substrate scope and scalable. Furthermore, a sequential arylation and alkylation of β-methyl group led to highly β-functionalized amino acid derivatives.



Scheme 2. 8-AQ directed Pd-catalyzed β-C–H arylation of amide derivatives.



Scheme 3. General mechanism for the Pd-catalyzed arylation of amide derivatives.



Scheme 4. β-Arylation of amino acid derivatives; synthesis of non-natural amino acids.