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Digest Paper

Catalytic C—C bond forming transformations via direct β-C—H functionalization of carbonyl compounds

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ABSTRACT

Strategies have emerged over the past decade to enable the direct functionalization of the remote and inert β-C—H bonds of carbonyl compounds. Based on these strategies, a wide collection of novel β-C—C bond formation transformations have been developed, including arylation, alkylation, alkenylation, alkynylation, and carbonylation. This review summarizes these recent methods for C—C bond formations via direct β-C—H functionalization of carbonyl compounds. The scope and limitation of each strategy are also discussed.

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Introduction

Functionalization of carbonyl compounds represents a cornerstone of organic chemistry. The inherent electrophilicity of the carbonyl group and acidity of the α-C—H bond provide convenient handles for the installation of various functional groups at the *ipso* and α-position of carbonyl compounds, respectively. However, the β-C—H bond is usually considered inert and thus less facile to functionalize directly. On the other hand, such β-substituted motifs are frequently found in a wide array of bioactive compounds, including pesticides, anti-oxidants, and drug candidates.[1] Traditionally, functionalization of the β-position is often accomplished with conjugate addition of nucleophiles to the corresponding α,β-unsaturated carbonyl compounds (Scheme 1).[2] However, α,β-unsaturated carbonyl compounds are often prepared from their saturated derivatives using stoichiometric oxidants.[3] Thus, direct

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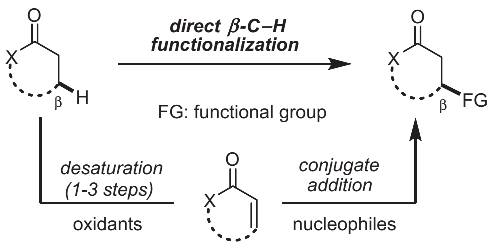


Scheme 1. β-C—H functionalization of carbonyl compounds.

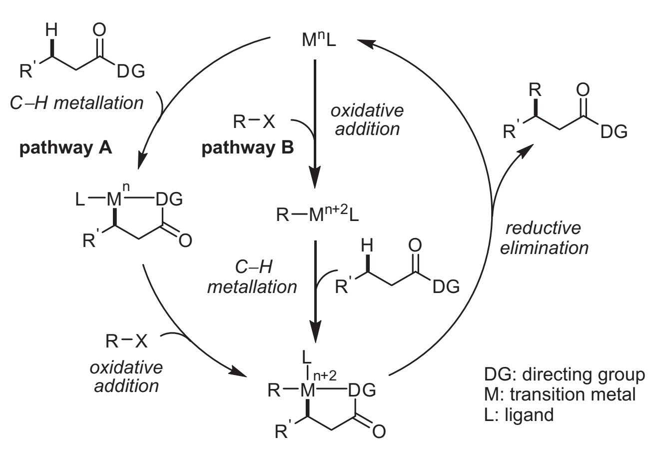
methods to convert the β-C—H bond to the desired functional group would considerably increase the efficiency of preparing β-substituted carbonyl compounds. During the last decade, significant efforts have been devoted toward direct β-C—H functionalization of carbonyl compounds. In this digest, we primarily focus on discussing the transformations that directly replace a β-C—H bond of carbonyl compounds with a C—C bond. While not intended to comprehensively cover all literature references, it rather offers a perspective on strategy design and discovery through selected examples to highlight representative reaction types.

Cyclometallation via directing groups

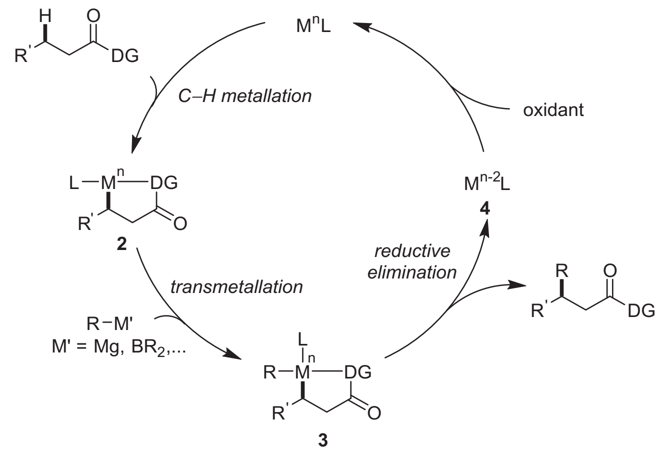
Directing-group strategies have been widely applied in transition-metal-mediated site-selective C—H activation, through which a significant number of catalytic transformations have been developed. Nevertheless, compared with sp^2 C—H bonds, the sp^3-hybridized β-C—H bond of carbonyl compounds is less prone to be cleaved by transition metals from both kinetic and thermodynamic prospectives,[4] which presents a significant challenge for design and development of new directing groups.

General mechanisms

Regarding the mechanism of these cyclometallation-type transformations, two general classes can be imagined based on the coupling partners employed. When an electrophile, such as an aryl halide, is involved, a typical reaction pathway proceeds through a selective metallation at the β-position assisted by the directing group, followed by oxidative addition of the electrophile to the metal giving intermediate **1** (Scheme 2, pathway A). It is also possible that the C—H metallation and oxidative addition occur in a reverse order (pathway B). Under either pathway, reductive elimination of intermediate **1** delivers the β-functionalization product and restores the active catalyst.



Scheme 2. Cyclometallation-type β-C—H functionalization via oxidative addition of electrophiles.



Scheme 3. Cyclometallation-type β-C—H functionalization via transmetallation of organometallic reagents.

When an organometallic reagent (i.e., arylboronic acids) is used, the coupling proceeds through a different mechanism (Scheme 3). After the C—H metallation step, transmetallation between the organometallic reagent and intermediate **2** installs the functional group on the metal center while the oxidation state of the metal remains unchanged. Subsequent reductive elimination affords the product, and oxidation of the reduced catalyst (**4**) by an external oxidant regenerates the catalyst.

According to the types of the directing groups employed, the β-functionalization through cyclometallation can be classified into two categories: type A is with strong bidentate directing groups; type B is with weaker coordinating directing groups.

Type A: Bidentate directing group

Arylation

In 2005, Daugulis and co-workers disclosed a palladium-catalyzed β-arylation of amides using 8-aminoquinoline (AQ) as a directing group (Scheme 4).[5] In their proposed intermediate, the 8-aminoquinoline auxiliary provides an L-type (quinoline) and an X-type (amide) ligand to chelate with palladium in a bidentate fashion. The 5–5 fused palladacycle **5** was formed after the selective palladation of the β-C—H bond. Methyl, methylene, and benzylic C—H bonds β to the carbonyl can be arylated selectively with aryl iodides as the aryl source under neat conditions. Silver salts are likely used as an iodide scavenger. When activating a methyl group, the arylation occurred twice to give diarylation products.

Soon after the seminal work by Daugulis, Corey and co-workers successfully applied this strategy to prepare non-natural amino acids (Scheme 5).[6] With the 8-aminoquinoline moiety as the directing group, *N*-phthaloyl valine and phenylalanine derivatives underwent diastereoselective β-arylation through coupling with a range of aryl iodides. The diastereoselectivity could be explained by the formation of a less sterically hindered *trans*-palladacycle (**7**). When alanine derivative **6** was submitted to the reaction conditions, a diarylation product was selectively formed, which is consistent with the observation by Daugulis.[5]

Daugulis and co-workers subsequently discovered that the use of silver salts and neat conditions can be avoided by using a combination of main-group inorganic salts and alcoholic solvents (Scheme 6).[7] In addition, while the diarylation product dominates when 8-aminoquinoline was used as the directing group, 2-methylthio aniline was found to afford selective monoarylation of primary β-C—H bonds. This new directing group also works for

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