Digest paper

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Indole synthesis through transition metal-catalyzed C-H activation

Tenglong Guo,[a] Fei Huang,[a] Likun Yu,[b] Zhengkun Yu[a]*

[a] *Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian, Liaoning 116023, China;* [b] *Fertilizer Analysis Station of Technology Center, SINOPEC Baling Petrochemical Company, Qilishan, Yueyang Tower Region, Yueyang, Hunan 414003, China*

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ABSTRACT

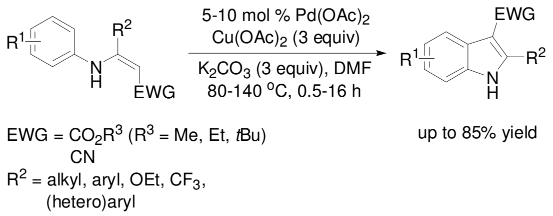
Indole synthesis is among one of the most important tasks in *N*-heterocyclic chemistry. Versatile synthetic methods have been developed for the establishment of an indole backbone, but concise and straightforward routes to access indole derivatives have been strongly desired. This digest paper summarizes the major advances in catalytic synthesis of indoles through transition-metal-catalyzed C-H activation during the last five years. Brief discussions are given for possible applications of these synthetic protocols.

Introduction

Indole functionality exists in many natural products and pharmaceuticals. A lot of efforts have been devoted to develop synthetic methods to access diverse indoles[1] since Fisher indoles were prepared in 1883.[2] Although indole derivatives can be obtained by functionalizing simple indoles,[3] specific methodologies have to be established to synthesize various indoles. Transition-metal-catalyzed cross-couplings involving C-H activation have recently been paid considerable attention for the construction of C-C[4] and C-N[5] bonds. For the synthesis of indole derivatives, C-H activation has been considered as an alternative strategy to supplement the relevant traditional synthetic protocols.[1] Åkermark and Knölker reported the first examples of palladium-catalyzed oxidative intramolecular C-H/C-H cross-coupling of ArXAr' (X = O, NY) to synthesize carbazoles and dibenzofurans, respectively,[6] which initiated the investigation on transition-metal-catalyzed cross-dehydrogenative coupling (CDC) to prepare heterocyclic compounds.[7] To date, the CDC strategy has become a promising strategy for the construction of an indole backbone. Herein, the major advances during the last five years in transition-metal-catalyzed indole synthesis through C-H activation, usually under oxidative conditions, are summarized with brief discussion of their possible applications. This digest is presented by the classifications of reaction types.

Intramolecular C-H/C-H cross-couplings

The intramolecular CDC reactions have been applied as a powerful tool to access functionalized indoles. Glorius et al. reported palladium(II)-catalyzed, copper(II)-mediated cyclization of enamine methyl (*Z*)-3-phenyl(amino)but-2-enoate and its analogues to form indoles (Scheme 1).[8] A proposed mechanism suggests that the reaction begins with an electrophilic palladation of the nuclephilic enamine at α-C atom, followed by deprotonation, resulting in a palladium complex intermediate suitable for intramolecular C-H activation. Subsequent reductive elimination generates the indole product and a Pd(0) species which can be reoxidized



Scheme 1.

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* Corresponding author.
E-mail address: zkyu@dicp.ac.cn (Z. K. Yu).