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Palladium-based innovative catalytic procedures: Designing new homogeneous and heterogeneous catalysts for the synthesis and functionalisation of N-containing heteroaromatic compounds

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ABSTRACT

N-containing heteroaromatics, particularly those owning an indole or quinolone substructure, are found in numerous natural or synthetic alkaloids of biological and pharmaceutical relevance. Therefore, various synthetic methodologies have been reported to access these backbones. The most advanced procedures use transition metal catalysts, usually as soluble (homogeneous) materials. In this short review article, we report our recent developments devoted to improving current catalytic pathways toward greener processes and to designing new heterogeneous Pd-based catalysts. The latter approach brings as main advantages low metal contamination and recyclability. The potential of these developments is demonstrated through the selective synthesis, as well as the functionalisation, of (NH)-indoles, quinolones, indoxyls or stilbenes.

1. Introduction

Condensed heteroaromatics are important (sub)structures present in numerous natural or synthetic alkaloids finding applications in pharmaceuticals, agrochemicals and cosmetics [1–5]. Among heterocycles belonging to this class of compounds, those containing at least one nitrogen atom, like indoles and quinolones, are undoubtedly the most important as they usually concern the human health. The diversity of the structures encountered, as well as their biological and pharmaceutical relevance, have motivated researches aimed at the development of economical, efficient and selective synthetic strategies [6–13]. These methodologies, while successful and commonly applied in the chemical industry, suffer from a low structural diversity and are thus not suitable for the selective synthesis of highly functionalised compounds. Therefore, transition metal-catalyzed procedures dedicated either to the construction or the transformation of such heterocycles have been developed. These methods provide generally an increased tolerance toward functional groups and higher chemical yields [14–31] and are currently applied in target- or diversity-oriented syntheses at the laboratory scale [26,27,32–37]. Comparatively, concerning indoxyls, only few transition metal catalyzed procedures have been reported [38–41].

Whatever the nucleus considered, these procedures suffer from several drawbacks, the main being unacceptable metal contamination of the product, generally over the accepted limits as expressed

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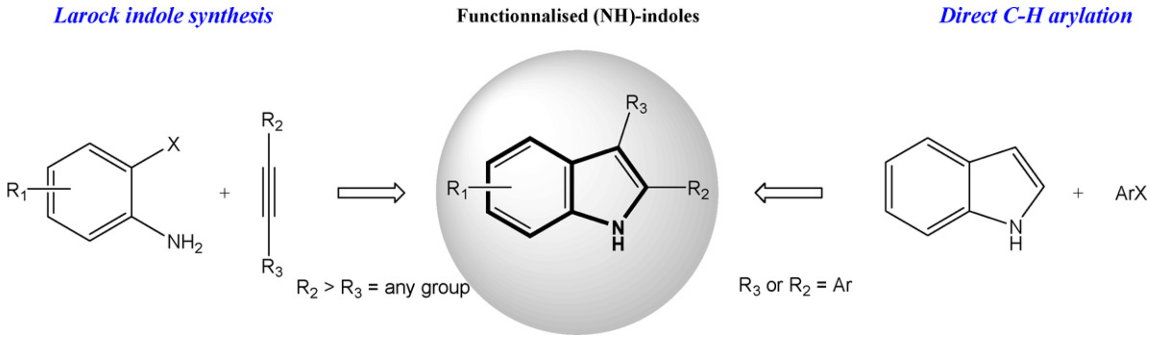

Fig. 1. Larock indole synthesis *versus* direct C-H arylation toward the synthesis of functionalised (NH)-indoles.

in the medicinal regulations that often prevented further industrial developments [42]. This situation encouraged us to develop alternative methodologies with respect to environment and economy in order to offer viable procedures for the preparation of such compounds at the industrial scale.

The aim of this review article is not to be exhaustive but rather to report our recent research progresses aiming at developing greener processes for the synthesis of N-containing heteroaromatics by using, for example water as solvent and one-pot multi-component reactions, or by replacing homogeneous Pd-catalysts commonly used by either commercially available or specifically designed heterogeneous Pd-catalysts. The powerful applications of these alternative approaches are demonstrated by the selective syntheses and functionalisations of (NH)-indoles, quinolones, indoxyls and stilbenes.

2. When indole met palladium: direct C-H arylation *versus* Larock heteroannulation

Among the amazing diversity of heteroaromatic compounds, indole can be considered as “the special one” with respect to its outstanding reactivity and the numerous biological activities [1,6] of natural alkaloids or synthetic derivatives. Since several decades, chemists have thus developed and improved new catalytic methodologies to access and/or functionalise this unique backbone [43]. In our opinion, two of the most advanced procedures, which avoid traditional cross-coupling reactions [44], have been brought through the well-known Larock heteroannulation and the direct C–H arylation of such heterocycles (Fig. 1) [8]. Therefore, we present in this chapter our recent progresses toward the development of innovative reaction conditions dedicated to these two special topics.

2.1. *“On water” direct and site-selective C-H arylation of (NH)-indoles*

Since the pioneering work of Ohta in the middle 1980s, considerable improvements have been achieved in the field of the indole direct C-H arylation [8,45]. Nevertheless, these methodologies suffer from several drawbacks which relay on the use of sophisticated catalytic systems (design of carbenes or phosphines, co-catalyst...), prior syntheses of arylating agents from commercially available aryl halides ($ArB(OH)_2$, $ArBF_3K$ or [Ar-I-Ar]OTf), the often required nitrogen protecting groups or the need of high-boiling, toxic and non environmentally friendly solvents. Furthermore, only few reports deal with site-selective arylation and the control of regioselectivity is closely linked to a specific nitrogen activation (respectively N-magnesium and N-acetyl indoles with respect to Sames [46] and Gaunt [47] work). Recently, our group was the first to report the use of a versatile catalytic system (i.e. metal/ligand) that allows either the C2- or the C3-arylation of (NH)-indoles and works “on water” [48], an alternative eco-friendly solvent which found some recent exciting applications in the field of direct C-H arylation [49–53].

Initially, we turned out our attention to the development of a selective C2-arylation protocol. Inspired by Sames work [54], we examined the performance of $Pd(OAc)_2$ (5 mol%) for the coupling of indole with iodobenzene. A base screening revealed that AcOK gave the highest selectivity toward the expected 2-phenylindole. Nevertheless, the poor yield obtained (20% after 24 h) prompted us to evaluate the role of phosphine ligands. While bulky, electron rich or hydrosoluble phosphines were found to be unsuitable for this transformation, mono- or bidentate arylphosphines resulted in improved yields (50–75%), the highest activity (i.e. 75% yield within 24 h; 20/1 C2/C3 selectivity) being achieved with the system $\{Pd(OAc)_2/dppm\}$ in a Pd/P ratio of 1/2. During these studies, a base-controlled regioselectivity was uncovered as mainly C3-arylation occurred while replacing AcOK by MOH (M = Li, Na or K) whether bromobenzene or iodobenzene is used; nevertheless, higher conversions and C3-selectivities were generally obtained with the cheaper aryl bromides and $LiOH{\cdot}H_2O$ as a base. Fig. 2 illustrates the broad scope of this versatile catalytic system applied either to the C2- or the C3-arylation of diversely substituted (NH)-indoles, with AcOK/Ar-I and $LiOH{\cdot}H_2O$/Ar-Br partners respectively.

From a mechanistic point of view, these results support an electrophilic palladation pathway at the C3-position of the indole nucleus and suggest that two kind of active palladium species are involved (Scheme 1). Indeed, the highly electrophilic cationic Pd-complex **A**, which formation would result from the higher dissociation behavior of iodides, is expected to easily undergo a C3-palladation. On the other hand, the activation of the neutral complex **B** requires the synergistic action of a stronger base than AcOK, probably through *in situ* deprotonation of the indole nitrogen. Therefore, the key intermediate **C** is expected to follow two pathways: (a) a C3 → C2 migration of the palladium center favored in the presence of the weak base AcOK, affording the complex **D** which leads to the C2-regioisomer; (b) a rearomatization privileged with stronger bases such as OH^- affording the σ–Pd complex **E**, precursor of the C3-regioisomer after reductive elimination of Pd(0). Notably, such a rearomatization could be elsewhere promoted by the presence of the more nucleophilic bromide anions compared to the iodide ones. However, we cannot rule out the co-existence of the so-called “concerted metallation-deprotonation” pathway when AcOK/ArI partners are used.

In summary, we have developed a unique catalytic system allowing an innovative “on water” direct and site-selective arylation of (NH)-indoles. This palladium-catalyzed C-H functionnalization reaction highlighted a [base/halide]-controlled regioselectivity, so that the arylation can be directed to either the 2- or the 3-position of (NH)-indoles. These procedures exhibit good to high regio- and chemoselectivities, displaying high structural versatility with regard to both indole and aryl moieties.