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Review

Catalytic C–C coupling through C–H arylation of arenes or heteroarenes

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Dedicated to Fausto Calderazzo, a scientist of exceptional level and an old good friend.

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ABSTRACT

The present review refers to catalytic methods to arylate arene or heteroarene compounds. The resulting compounds are ubiquitous in biology and in pharmaceuticals or fine chemicals production. Until a few decades ago they were prepared according to laborious procedures often involving a series of steps all requiring product isolation. Catalytic methods are much simpler and convenient and often consist of one-pot procedures leading to highly selective reactions. The reaction types described here encompass intermolecular as well as intramolecular reactions. Assistance by chelating groups, heteroatoms and metallacycles are considered for metal-catalyzed reactions not involving the use of oxygen or stoichiometric oxidants.

1. Introduction

Catalytic formation of biaryl compounds has been the object of a variety of methods which successfully compete with the more laborious conventional ones. It is essentially based on the replacement of an aryl-bonded leaving group such as a halide with a suitable nucleophile under the catalytic action of a transition metal. The latter must be able to undergo oxidative addition of the aryl halide to afford an arylmetal halide (or other leaving group) complex, where substitution with an aryl group can take place. This latter group generally is another organometallic species such as Grignard, Stille and Negishi reagents or an arylboronic acid [1–4].

Direct C–H arylation of arene compounds overcomes the need for a functional group in one of the aryl moieties undergoing C–C coupling [5]. As we shall see, however, to obtain a selective reaction some type of assistance is usually necessary. For recent reviews on aryl–aryl coupling by metal catalyzed direct arylation see Refs. [6–12]. For the use of oxygen or stoichiometric oxidants, which are not considered here, see Ref. [13,14].

We shall deal with catalytic non-oxidative: (i) intermolecular C–H arylation of unactivated arenes; (ii) intramolecular arylation; (iii) assisted intermolecular arene C–H activation.

2. Intermolecular C–H arylation of unactivated arenes

Unactivated arenes such as benzene react efficiently with aryl iodides [15], in general according to an arene electrophilic substitution operated by an arylmetal complex formed by oxidative addition of an aryl halide to a low valent metal. Using

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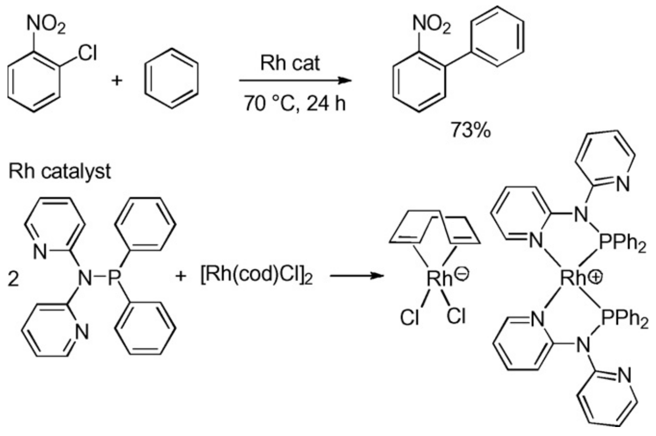


Scheme 1.

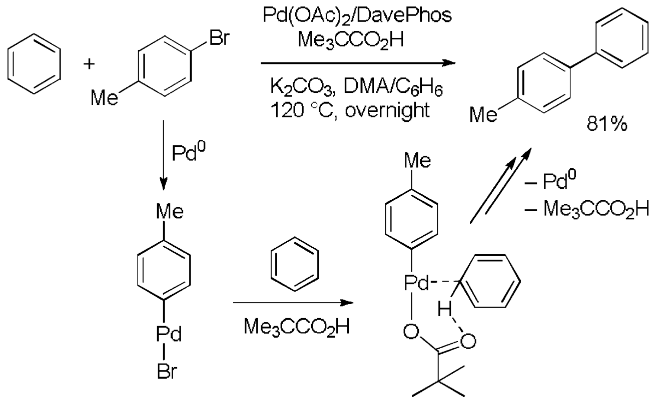
[C_p^*Ir(H)Cl]$_2$ ($C_p^* = C_5Me_5$) in the presence of *t*-BuOK as a base at 80 °C the cross-coupling reaction of 4-iodoanisole and benzene led to a 66% yield of 4-methoxybiphenyl. A new bimetallic Rh catalyst which tolerates functional groups was used to couple aryl bromides and chlorides with benzene at 70 °C with satisfactory yields and high turnover numbers. As shown in Scheme 1 the catalyst is formed in situ by reaction of [bis(2-pyridyl)amino]diphenylphosphine with half an equivalent of [Rh(cod)Cl]$_2$ (cod = cyclooctadiene). Both the anionic and cationic Rh species are needed for catalysis [16].

Radical mechanisms have been proposed both for Ir- [15] and Rh- [16] catalyzed reactions.

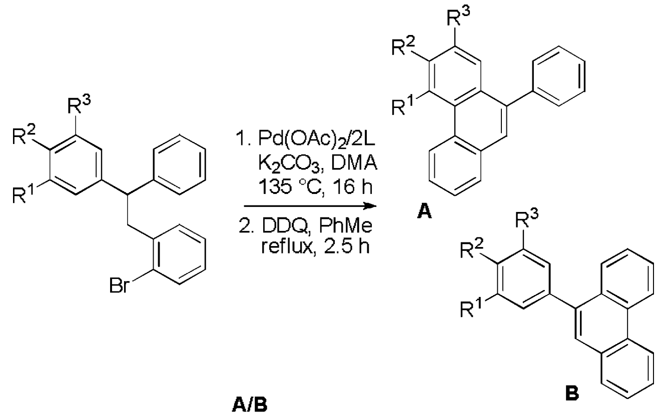
Pd catalysis has been successfully used to arylate the polar hydrocarbon azulene regioselectively at the electron-rich 1-position [17].

A recent achievement consists of the use of pivalic acid in the reaction of Pd(0) (from Pd(OAc)$_2$) with bromoarenes and benzene in the presence of K_2CO_3 at 120 °C (Scheme 2). 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos) was the ligand of choice for Pd [18]. The addition of 30 mol.% Me_3CCO_2H led to 4-methylbiphenyl in 81% yield from *p*-bromotoluene and benzene.

An intermediate in which the pivalate anion helps to abstract hydrogen from benzene has been postulated as first proposed by Echavarren [19]. Theoretical studies on aryl–aryl intramolecular coupling have shown that in many cases of intramolecular arene arylation substituent effect and kinetic isotopic effect are not compatible with the traditional electrophilic substitution mechanism and are best interpreted by a mechanism involving hydrogen abstraction by a base or by an appropriate ligand [19,20]. Experiments and theoretical calculations by Fagnou and coworkers have lent support to this interpretation [21], which appears to be valid for any type of intra and intermolecular arylation of arenes.



Scheme 2.



	A/B
R^1, R^2, R^3 = F	25:1
R^1, R^3 = H; R^2 = F	1.6:1
R^2 = H; R^1, R^3 = F	19:1
R^1, R^3 = H; R^2 = *t*-Bu	1:1.5

L = 2-(diphenylphosphino)-2′-(*N*, *N*-dimethylamino)biphenyl

Scheme 3.

Selectivity in the arene position to be arylated is a problem in these reactions and orienting groups such as the chelating ones (Section 4.1) or heteroatoms (Section 4.2) or bridges between the aryl coupling moieties [22a] can help to obtain acceptable results. Using *o*-bromobenzyldiarylmethane systems where one ring contained substituents while the other was unsubstituted, arylation occurred preferentially on the ring bearing electron-withdrawing substituents, including those like the methoxy one that behave electronegatively by inductive effect. Electron-releasing substituents such as the trimetylsilyl and the *tert*-butyl drove the reaction towards the unsubstituted ring. Selectivity depends on substituent position, the *ortho* position close to the C–H bond being the most sensitive (Scheme 3) [19b].

Pentafluorobenzene and other electron-poor perfluoroaromatics can be cross-coupled with aryl halides using as catalyst precursor Pd(OAc)$_2$ and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos) in isopropyl acetate [22b]. As in the pivalate case a base assisted C–H substitution mechanism has been postulated [22c]. According to theoretical calculations this mechanism also accounts for reactions of electron-rich arenes. DFT calculations by Fagnou's group have in fact confirmed the metalation–deprotonation mechanism and have led to predict the site of attack in a number of arylations, especially heteroatom assisted arylations. The similar outcome for very different structures has been explained as resulting from the balance between the expense of energy required for bringing the arene and the catalyst to the transition state (distortion energy) and the gain in electronic interaction energy due to bringing the two partners together [21].

The reader will be referred to the mechanistic results of these studies throughout the present review because of their general significance.

C–H arylation of arenes substituted by electron-withdrawing groups, has also been obtained extending the Cu-phenanthroline-based method cited in Section 4.2.

3. Intramolecular arene C–H arylation

In contrast with the intermolecular arene C–H arylation seen above the intramolecular arylation readily occurs selectively. The field is dominated by Pd catalysis.