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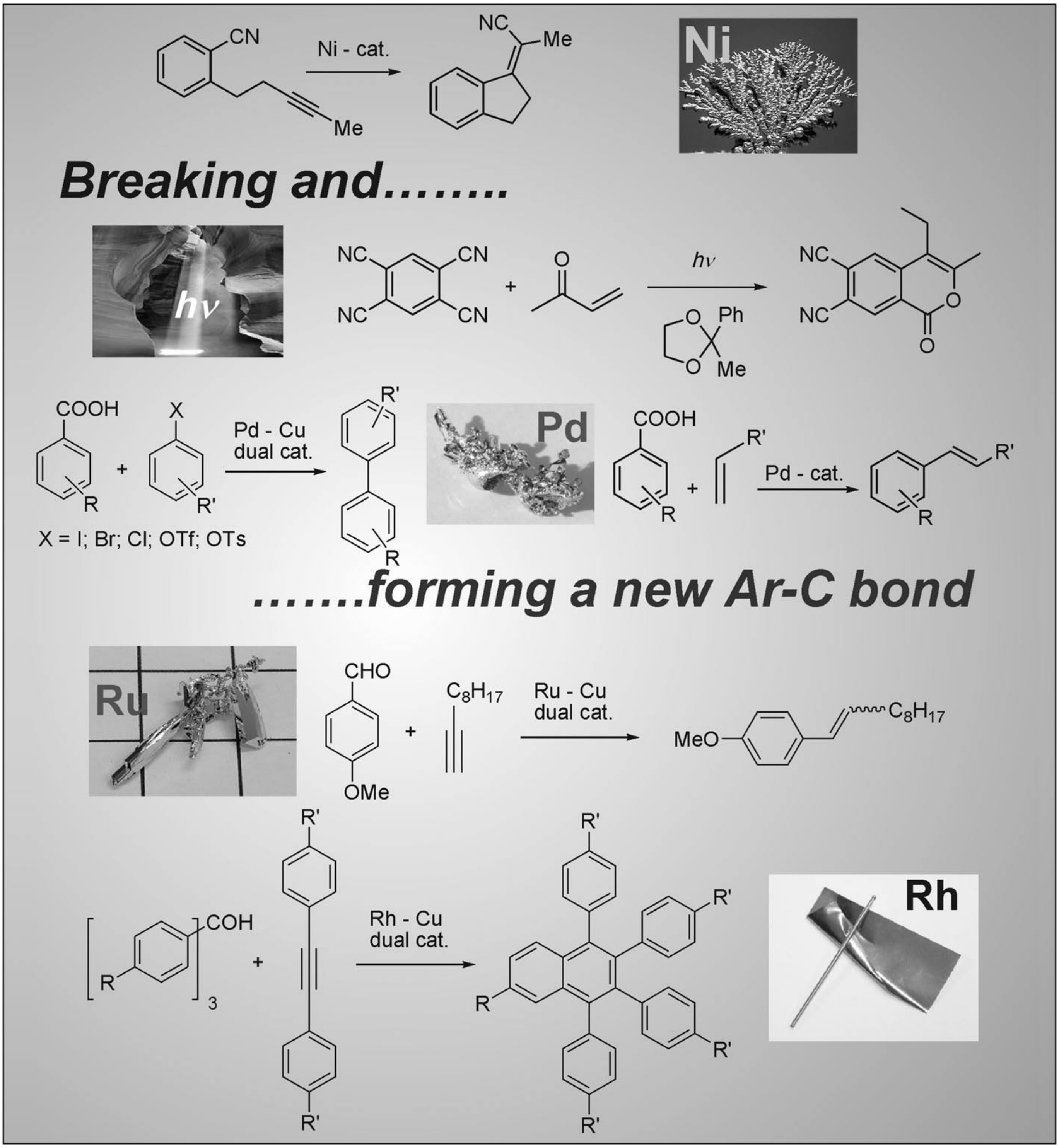
The Aromatic Carbon–Carbon *ipso*-Substitution Reaction

Sergio M. Bonesi[b] and Maurizio Fagnoni*[a]

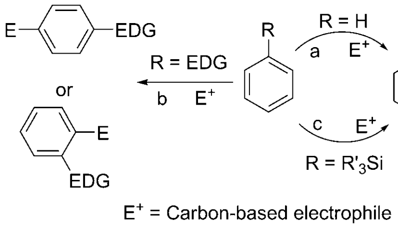


Abstract: The aim of this review is to illustrate what we have dubbed an aromatic carbon–carbon *ipso*-substitution reaction in which a new Ar−C bond is formed at the expense of another Ar−C bond. The potentiality of several C-based leaving groups including alkyl, carbinol, CN, COOH, and carbonyl groups in arylation reactions will be illustrated accordingly for the preparation of biphenyl-, vinyl-, alkynyl-, and alkyl-substituted aromatics.

Keywords: Ar–C bonds • aromatic substitution • arylation • C-based leaving groups • cleavage reactions

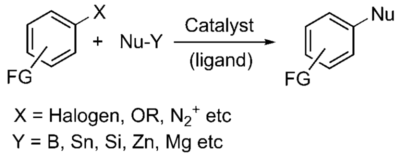
Introduction

The formation of Ar−C bonds is a key topic in organic chemistry. Electrophilic aromatic substitution (EAS) by using Friedel–Crafts alkylations and acylations was one of the first approaches to achieve this target[1] by which a hydrogen atom was replaced by a carbon electrophile (Scheme 1, path a). Although useful, EAS reactions cannot be applied to electron-poor aromatics, and in the case of aromatics that bear electron-donating groups (EDG), the reaction can give rise to *o*/*p* mixtures of regioisomers (Scheme 1, path b) or when a clean reaction occurs the electrophile may enter in an undesired position. To avoid these drawbacks, a substituent can be purposely tethered to the aromatic ring as a suitable leaving group (different from hydrogen) of the reaction. This process is a particular case of the EAS reaction and it is known as an *ipso*-substitution reaction. A typical example is the selective replacement of an R_3Si group by a carbon electrophile (E^+) in aryltrialkylsilanes (Scheme 1, path c).[2]



Scheme 1.

Nowadays, *ipso*-substitution reactions also include all of those reactions in which an Ar−C bond is formed at the expense of an Ar−X bond (X≠H) almost independently of the mechanism that occurs. In this sense, metal-mediated reactions are actually the most widely used *ipso*-substitution reactions (Scheme 2).[3]



Scheme 2.

An important merit of these reactions was their ability to enlarge the number and type of possible leaving groups in aromatic substitution reactions. Actually, several Ar−X bonds can be cleaved for this purpose, including the Ar–halogen bond (mainly Ar−Br or Ar−I),[3] the Ar−O bond in sulfonate[3] or carboxylate esters[4] or even in alkyl ether groups,[5] and the Ar−N bond in diazonium salts.[6] In addition, if a biaryl was formed (Nu = Ar) a large variety of Ar−Y bonds (mainly from organometallic compounds) have to be cleaved (see Scheme 2).[3]

At this point, an intriguing question might arise, namely, if a new Ar−C bond could be formed at the expense of another Ar−C bond or, in other words, if C-based leaving groups could be used in *ipso*-substitution reactions. Recently we highlighted that various metal-mediated reactions that belong to this class have been developed.[7] This has prompted us to collect most of these processes we have now defined as aromatic carbon–carbon *ipso*-substitution reactions. These reactions are classified according to the C-based leaving group as detailed below.

Alkyl as the Leaving Group (Activation of Alkylaromatics)

Since the Ar−alkyl bond is quite strong (103.9 kcal mol^{-1} in toluene[8] and 97.4 kcal mol^{-1} in *tert*-butylbenzene[8]), the alkyl group can be detached from the aromatic ring only when positively charged. Thus, an alkyl group (a tertiary alkyl group is preferred) can be *ipso*-substituted under common Friedel–Crafts acylation or alkylation conditions. In fact, when either isopropylbenzene or 2- or 3-phenylpentane were acetylated by using an acetyl chloride/$AlCl_3$ mixture in CS_2 heated to reflux, variable amounts of acetophenone were formed.[9] It was not clear, however, if a dealkylation followed the acylation rather than an actual *ipso*-substi-

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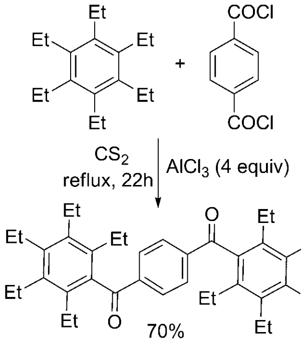
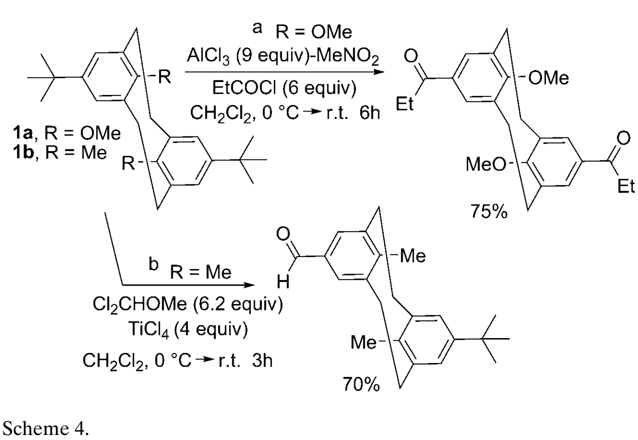
tution reaction taking place. An unsubstituted alkyl group is not prone to replacement in an *ipso*-substitution reaction due to the low stability of the carbocation liberated in the reaction. Nevertheless, the acylation of hexaethylbenzene by terephthaloyl chloride occurred quite efficiently as illustrated in Scheme 3.[10]



Scheme 3.

For a successful *ipso*-substitution reaction in less substituted aromatics, however, a tertiary alkyl group such as a *tert*-butyl group has to be replaced. What was interesting was the case of *tert*-butylated azulenes. Thus, when 1,3-di-*tert*-butylazulene was formylated by a Vilsmeier procedure, an excellent yield of 1-*tert*-butyl-3-formylazulene (as the exclusive product) was isolated.[11] More recently, the electrophilic *ipso*-substitution of 1,3,6-tri-*tert*-butylazulene took place by using an excess amount (5 equiv) of either acetyl or benzoyl chloride to give 1-acylated azulene in more than 70% yield.[12] *ipso*-Acylation of substituted [*n*.2]metacyclophanes (e.g., **1**) likewise occurred smoothly and two *tert*-butyl groups were substituted in one step by using $AlCl_3$–$MeNO_2$ as the catalyst (Scheme 4, path a).[13] Suitable conditions were found, however, for a monosubstitution of cyclophane **1b** in which a selective monoformylation has been achieved when using $TiCl_4$ as the catalyst (Scheme 4, path b).[14]

Milder reaction conditions have been used for the regioselective formylation of *p*-*tert*-butylcalix[4]arenes. As a result, the treatment of these substrates that have four *tert*-butyl groups with hexamethylenetetramine (HMTA) and trifluoroacetic acid (TFA) allowed the easy formation of the bisformylated adduct.[15]



Scheme 4.

In rare instances, an alkyl has been introduced in place of other alkyl substituents as in the $ZnCl_2$-mediated reaction of pentamethyldiphenylmethane with 4-nitrobenzyl chloride in which the benzylated derivative was obtained in 69% yield.[16]

Although the above reactions in some cases gave a satisfying yield of arylated products, the large amount of the catalyst employed (up to 9 equiv) and the requirement of the introduction of an alkyl group as the leaving group strongly limit their wide application.

Carbinol (R_3COH) as the Leaving Group (Activation of α,α-Disubstituted Arylmethanols)

Among alkyl-substituted aromatics, α,α-disubstituted arylmethanols are a particular case. In this case, the activation of the Ar–C bond requires a metal catalyst. α,α-Disubstituted (hetero)arylmethanols are interesting nucleophiles that can be used in palladium-catalyzed coupling reactions with

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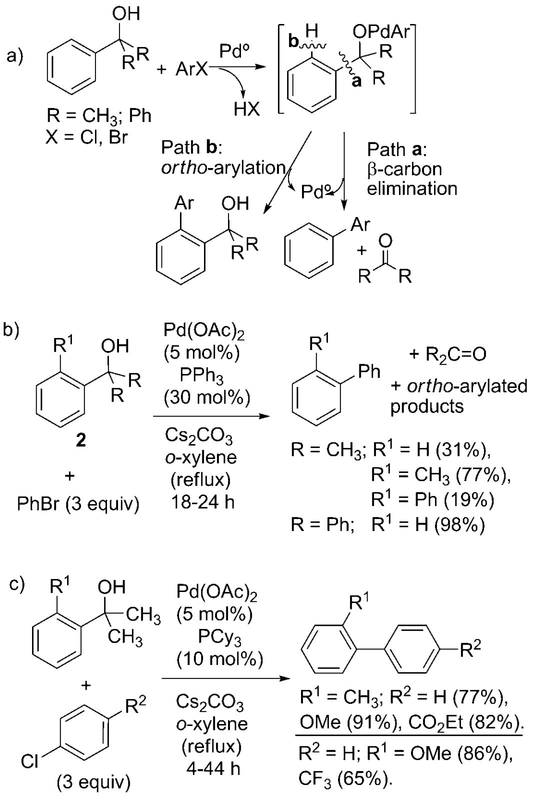
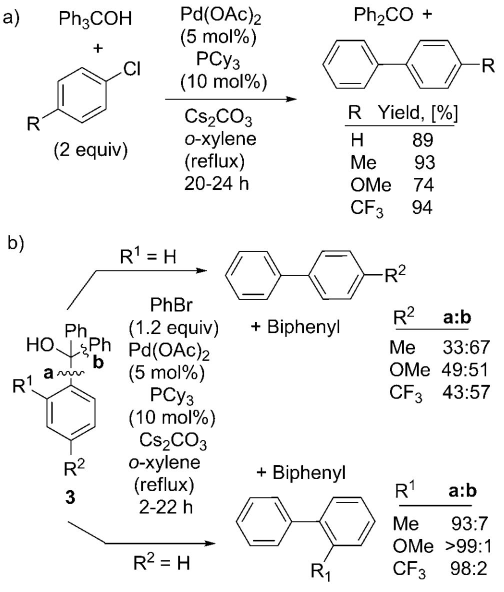
aryl halides to afford *ipso*-substituted products. Miura et al.[17] suggested that the reaction took place through the initial formation of an arylpalladium(II) alcoholate species (actually the key intermediate) followed by β cleavage and reductive elimination of a ketone (whether benzophenone or acetone, Scheme 5a, path a) Unfortunately, a C–H cleavage that led to *ortho*-arylated products (path b) competed to some extent. Selective examples that show the Pd-mediated cross-coupling reactions between bromobenzene with substituted arylmethanols (**2**) are shown in Scheme 5b. When the *ortho* position in the starting 2-aryl-2-propanol was blocked with an appropriate substituent different from a phenyl group, the β-carbon elimination process was selectively induced and the reaction became synthetically advantageous (Scheme 5c).



Scheme 5.

Besides, 2-(1-naphthyl)-, 2-(2-methoxy-1-naphthyl)-, 2-(9-anthranyl)-, and 2-(9-phenanthryl)-2-propanol reacted smoothly with several *ortho*- and *para*-substituted chloro- and bromobenzenes providing the expected biaryls with yields that ranged between 65 and 100 %.

In the reactions of triphenylcarbinol with substituted aryl chlorides, bulky and electron-rich phosphines (e.g., PCy_3) selectively induced β-carbon elimination to allow the preparation of biaryls in good yields (74–98 %, Scheme 6a) When the reaction was applied to triarylmethanols of general formula **3** (Scheme 6b) the reaction was clean (regioselectivity up to 88–99 %) only when $R^1 \neq H$, whereas a larger amount of the byproduct biphenyl was obtained in *ortho*-unsubstituted derivatives.[17]



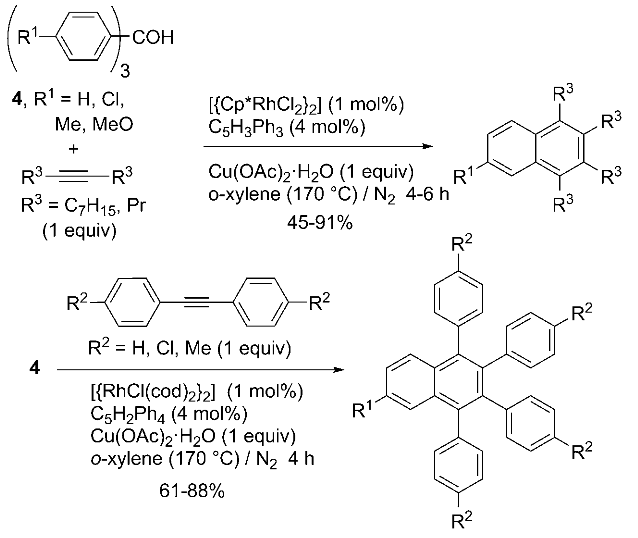
Scheme 6.

The low selectivity observed in the latter case suggested that each of the three sp^2–sp^3 C–C bonds was cleaved statistically, whereas steric and electronic effects of the substituents during the elimination process accounted for the high selectivity observed.[18]

Selective β-carbon elimination has been found in the reaction of 9-phenylxanthen-9-ol with 4-bromo- and 4-chlorotoluenes that cleanly proceeded to give 4-methylbiphenyl quantitatively along with xanthone. 2-Thienyl- and 2-furyl-(diphenyl)methanols were found to be similarly reactive, and the coupling with chlorobenzene was completed within 2 h to form 2-phenylthiophene and 2-phenylfuran in 89 and 87 % yields, respectively.[19] The high reactivity observed for the heteroaryl(diphenyl)methanols was ascribed to the coordination ability of the internal heteroatoms. This *ipso*-substitution reaction was also extended to bithiophene systems such as (2,2′-bithiophene-5-yl)diphenylmethanol.

Next, Miura et al.[20] studied the selective 2,3-diarylation reaction of 2-(thienyl-3-yl)-2-propanol, α,α-diphenyl(thienyl-3-yl)methanol, and 2-(benzo[*b*]thienyl-3-yl)-2-propanol by means of cleavage of the C–H and C–C bonds in the 2- and 3-positions, respectively. This reaction provided a useful route to the synthesis of 2,3-diarylthiophenes and 2,3-diarylbenzo[*b*]thiophenes by treatment of the carbinol (0.5 mmol) with an aryl bromide (2 mmol) in the presence of $Pd(OAc)_2$ (10 mol %), P(biphenyl-2-yl)(*t*Bu)$_2$ (20 mol %), Cs_2CO_3 (2 mmol) in toluene heated at reflux or *o*-xylene under N_2 for 10 h. Kotschy and co-workers,[21] however, reported a less clear-cut reaction when applying the procedure of Miura's group on the reaction between α,α-diphenyl-(thienyl-3-yl)methanol and bromobenzene.

It is noteworthy that, when shifting to the Rh/Cu-based catalysts, triarylmethanols acted as the electrophilic partner of the reaction and thus were able to react with internal alkynes. As a result, highly substituted naphthalenes were synthesized in good yields by means of consecutive Ar–H and Ar–C bond cleavages.[22] Triarylmethanols that bear substituents in the *para* position (e.g., MeO, Me, Cl) reacted similarly efficiently with diphenylacetylene to give 6-methoxy-, 6-methyl-, and 6-chloro-1,2,3,4-tetraphenylnaphthalenes in 61–88 % yield (see Scheme 7). Scheme 7 shows the reaction of a triphenylmethanol (e.g., **4**) with 8-hexadecyne in which the overall yields have been improved by using $[(Cp^*RhCl_2)_2]$ in combination with $C_5H_3Ph_3$ as the catalyst to form 1,2,3,4-tetraheptylnaphthalene in excellent yield.

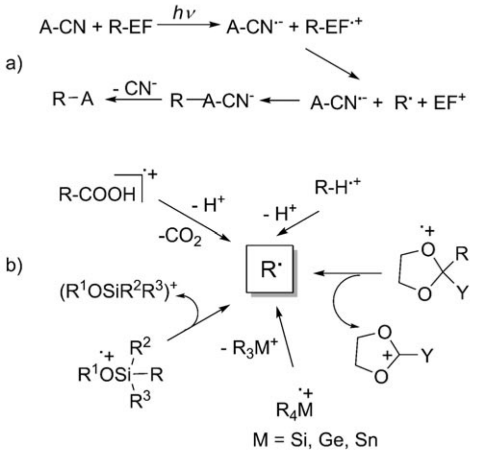


Scheme 7.

Thus, aryl carbinols are versatile reagents since they can act both as nucleophiles and as electrophiles in Ar–C bond-formation reactions. In most cases, these substrates can be valid substitutes of expensive and moisture-sensitive arylmetal reagents. In particular, the method appears promising for the synthesis of biaryls that have *ortho* substituents when starting from triphenylcarbinols and (hetero)aryl-α,α-diphenylcarbinols. Strong drawbacks, however, are the poor atom economy of the reaction (two aryl groups were lost in the reaction) and the high temperature required (≈170 °C). On the other hand, the preparation of highly substituted naphthalenes by means of an Rh-catalyzed reaction between aryl carbinols and alkynes is rather promising.

CN as the Leaving Group (Activation of Benzonitriles)

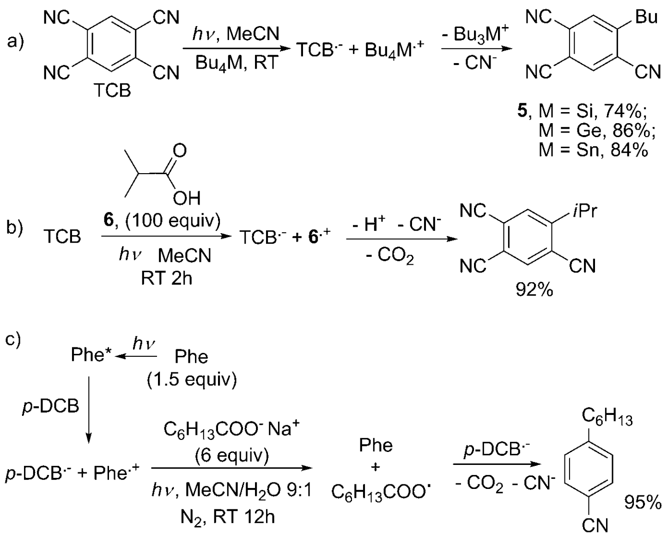
The activation and cleavage of the strong Ar–CN bond (ca. 133 kcal mol^{-1} for Ph–CN[8]) in aryl cyanides can be achieved both photochemically and by means of metal-catalyzed processes. The former reaction has been known for more than 30 years and involves the elimination of the cyanide anion as the last step of the reaction. The process is based on the marked increment of the reduction potential of aryl nitriles when in the excited state (e.g., 3.15 V vs. SCE in 1,2,4,5-tetracyanobenzene (TCB)[23]) to transform these aromatics in strong oxidants. As a result, they behave as exceptionally good electron acceptors able to undergo photoinduced electron transfer (PET) reactions even with poor electron donors.[23–26] In many cases, this process leads to an *ipso*-substitution reaction in which the cyano group is replaced by another C-based group (mostly an alkyl group) to form an alkylcyanobenzene. The general scheme of this metal-free reaction is depicted in Scheme 8a and involves an initial PET reaction between a cyanoarene (A-CN) and a donor (R-EF).



Scheme 8.

The success of this kind of reaction relies on the efficient fragmentation of the donor radical cation formed ($R\text{-}EF^{\cdot+}$), which in turn loses an electrofugal group (EF^+) to generate a radical ($R^{\cdot}$). Coupling of the resulting radical with the acceptor radical anion ($A\text{-}CN^{\cdot-}$), followed by cyanide elimination, gives the end *ipso*-substituted product.[24,25] Tetraalkyl silanes, germanes, and stannanes; 2-alkyl-2-aryl or 2-dialkyl-1,3-dioxolanes; silyl ethers, carboxylic acids, and even simple alkanes (e.g., adamantane) can be used as possible uncommon electron donors in the reaction depending on the reduction potential of the A-CN excited state (Scheme 8b).[23,27]

An example that is related to this approach is the photoinduced clean monobenzylation of *o*-dicyanobenzene to form *o*-benzylbenzonitrile in a high yield (75–81 %). In the latter case, benzyl radicals were formed from the fragmentation of either benzyltrimethylsilane or benzyltributylstannane radical cation.[28] TCB was selectively *ipso*-alkylated by using either group 14 metal–carbon σ donors[29] or carboxylic acids[30] as the radical source (Scheme 9a,b). It is quite interesting to note that the yield of the alkyltricyanobenzene **5** was quite independent of the Bu_4M used (74–86 %, Scheme 9a) and it was almost quantitative when using **6** as the donor. The use of carboxylate anion for the photoalkyla-



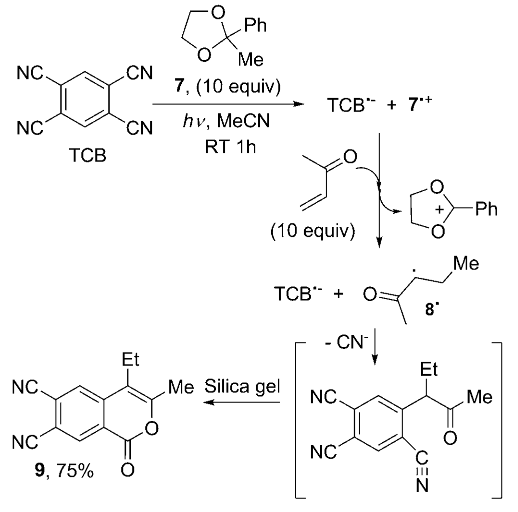
Scheme 9.

tion of cyanoarenes has been recently reconsidered and it was found that the presence of a cosensitizer (e.g., phenanthrene, Phe; Scheme 9c) improved the product yield.[31] The role of Phe was to accelerate the decarboxylative photosubstitution as evidenced in the photoreaction of a dicyanoarene (e.g., *p*-dicyanobenzene (*p*-DCB)) with sodium hexanoate (Scheme 9c). Since the carboxylate anion is a better donor than the corresponding acid, this allows its use in only a sixfold excess amount with respect to the cyanoarene. A similar photoalkylation occurred when using 2-dialkyl-1,3-dioxolanes as the donors.[32] Some dicyanobenzene isomers have been likewise allylated with recourse to allylsilanes, germanes, and stannanes as the donors.[33] Alkyl-substituted radicals can be obtained starting from better donors such as amines, thus allowing for an aminomethylation of aromatic nitriles, although the process was not clean in most cases.[34]

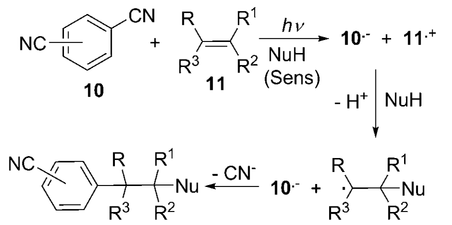
Substituted amides and lactams were used as electron donors in the photoalkylation of TCB.[35] This *ipso*-substitution reaction can be likewise extended to heteroarenes (e.g., cyanopyridines or cyanopyrazines).[36]

A variation of these photoinduced *ipso*-substitution reactions is the photo-ROCAS (radical olefin combination aromatic substitution) reaction, which allows the preparation of more elaborated cyanoarenes by adding an electron-poor olefin to the reaction mixture.[37] Scheme 10 illustrates a typical example of this interesting three-component reaction. Thus, the methyl radical formed in the cleavage of radical cation $\mathbf{7}^{\cdot+}$ added to an enone and the attack of the resulting radical adduct $\mathbf{8}^{\cdot}$ onto $TCB^{\cdot-}$ afforded a 3-aryl-substituted 2-pentanone that, upon purification on silica gel, cyclized to isocoumarine **9** (75 % yield).[37a] The peculiarity of such a reaction is that two C–C bonds (including an Ar–C) were formed at the expense of another two C–C bonds in a one-pot procedure.

A further variation is possible if the donor is not cleavable when photooxidized. This new *ipso*-substitution reaction is defined as the photo-NOCAS (nucleophile olefin combination aromatic substitution) process.[38] Typically, this reaction involves the addition of a nucleophile (mainly the reaction medium) to the donor radical cation. The neutral radical formed after deprotonation adds to the acceptor radical anion, whereas rearomatization by loss of the cyanide ion leads to an overall *ipso*-substitution reaction.[38] The reaction is another example of a three-component reaction that involves a cyanoarene (e.g., **10**), an alkene (**11**, the donor) and a nucleophile (NuH; Scheme 11). The reaction starts again by exploiting the good oxidizing properties of the singlet excited states of a cyanoarene, for example, a dicyanobenzene, 1,2,4,5-tetracyanobenzene, or naphthalene-1,4-dicarbonitrile. As mentioned before, the presence of a cosensitizer (Sens) is able to accelerate the photochemical reaction. Typically, these cosensitizers are biphenyl, 1,2,4-triphenylbenzene, phenanthrene, or 2,2′-methylenedioxy-1,1′-binaphthalene, since they have higher oxidation potentials than those of the alkenes (or alkadienes) used and they are quite unreactive towards the nucleophiles present in the reaction mixture.



Scheme 10.

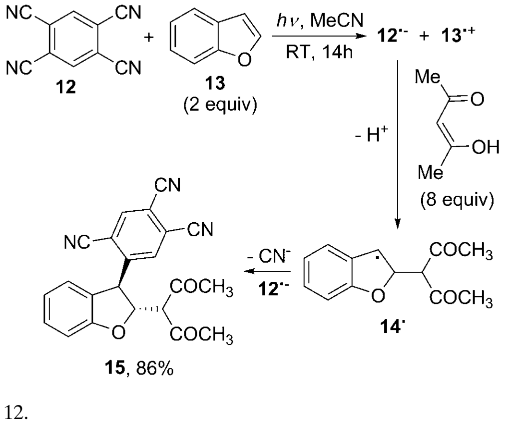


Scheme 11.

The solvent was the first nucleophile considered and alcoholic media (e.g., MeOH, NuH in Scheme 11) were found to be suitable for the preparation of various alkoxylated derivatives.[39,40] In particular, when the reaction was carried out in an MeCN/MeOH 4:1 mixture by using furan as the "olefin," interesting 2,5-dihydro-2-methoxy-5-arylfurans were obtained.[41] Allenes could be used in place of simple alkenes, and irradiation of a 3:1 MeCN/MeOH solution that contained tetramethylallene and TCB gave a 1:1:1 arene–allene–methanol adduct in a regioselective fashion.[42] A partial aqueous medium was recently used in the *ipso*-substitution reaction between TCB and styrene derivatives for the preparation of isocoumarins, although in most cases the process led to a low product yield or to undesirable mixtures.[43] A further variation involved the presence of O-nucleophiles tethered to the alkene moiety as in ω-alkenols; as a result, a cyclization ensued the initial ET step to yield aryl-substituted tetrahydropyrans or tetrahydrofurans by means of a tandem Ar–C, C–O bond formation.[44] Despite their high electron-donor potentials, amines or ammonia can be used to some extent in place of alcohols.[45] To have a successful reaction, however, a cosensitizer (e.g., a triphenylbenzene) has to be used, and photoamination of alkadienes gave the corresponding 4-(4-aminobut-2-enyl)benzonitriles in a satisfying yield.[45c]

In some cases, the alkene itself can have the role both of the donor and of the nucleophile. α-Methylstyrene can be photochemically oxidized, and the resulting radical cation can add to the neutral alkene to form a distonic radical cation dimer; a 1,6-cyclization followed and after deprotonation and coupling with the cyanoaromatic radical anion an *ipso*-substituted adduct was formed in approximately 90% yield.[46]

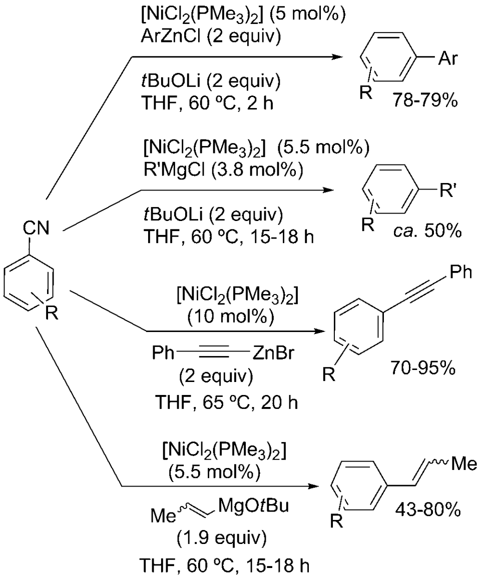
A more appealing three-component reaction has been reported when the carbon nucleophile is the malononitrile anion or easily enolized dicarbonyl compounds. In the first case, an aqueous acetonitrile mixture of a dicyanobenzene, a hexadiene, a cosensitizer (phenanthrene), and malononitrile in the presence of a mild base (carbonate) was irradiated to lead to a selective monoalkylation of the starting nitrile.[47] Another recent example is depicted in Scheme 12, in which benzofuran (**13**) was used as the donor and a 1,3-dicarbonyl as the nucleophile. The reaction took place with no need of a cosensitizer and a base to yield dihydrobenzofuran **15** as the *E* isomer by means of the radical intermediate **14**$^{\bullet}$ through the formation of new Ar–C and C–C bonds.[48]



Scheme 12.

The photochemical removal of the cyano group requires mild conditions since neither heating nor a metal catalyst are needed. Since the excited states of aromatic nitriles are shortlived species, the reaction requires in most cases a large excess amount of the donor. Polysubstitution reactions (e.g., when using TCB) or substitution of a hydrogen atom rather than a cyano group are quite common as concurrent processes. Moreover, the number of cyanoarenes studied so far is limited. Hence, to assess the importance of the method, purposely functionalized polycyanoarenes have yet to be tested, mainly in three-component reactions of synthetic values.

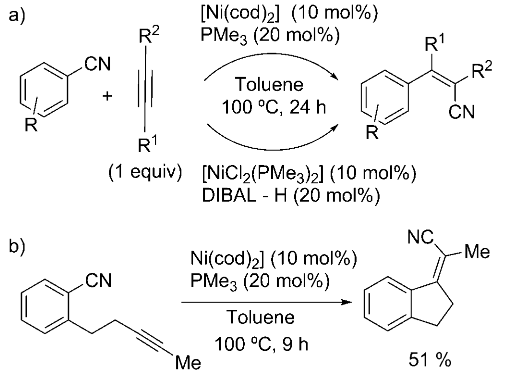
The second approach for an *ipso*-substitution reaction that involves aryl cyanides is the metal-catalyzed activation of the Ar–CN bond,[49] reported for the first time about ten years ago when Miller and co-workers discovered that both the Ar–Cl and Ar–CN bond were catalytically activated in 4-chlorobenzonitrile.[50a] Since the discovery of this process, efforts have been devoted to develop versatile synthetic applications. In particular, Miller et al. have developed an efficient, novel procedure to prepare unsymmetrical biaryls, styrenes, and alkylated benzene derivatives by means of Ni-catalyzed cross-coupling reactions starting from benzonitriles (see Scheme 13).[50] A survey of the catalysts indicated that $[NiCl_2(PMe_3)_2]$ was generally superior to other Ni- or Pd-based catalytic systems and it also had the advantage of being commercially available.[50b] Organozinc and Grignard reagents were used as the nucleophiles. In the latter case, addition of either *t*BuOLi or PhSLi was required to prevent the nucleophilic addition of the organomagnesium reagent to the nitrile group during the cross-coupling event. Organozinc reagents (prepared in situ by the reaction of ArMgCl with $ZnCl_2$) can be likewise used in the synthesis of biphenyls. The reaction readily proceeded when the benzonitrile



Scheme 13.

was both substituted with electron-withdrawing or -donating groups. Furthermore, heterocyclic nitriles such as 2-pyridine carbonitrile, 2-furane carbonitrile, and 2-thiophene carbonitrile were also suitable substrates for the reaction. The alkynylation reaction of benzonitriles showed a superior cross-coupling performance with alkynylzinc if compared to the corresponding organomagnesium reagents and can thus be applied to a broad variety of substrates (Scheme 13).[50d]

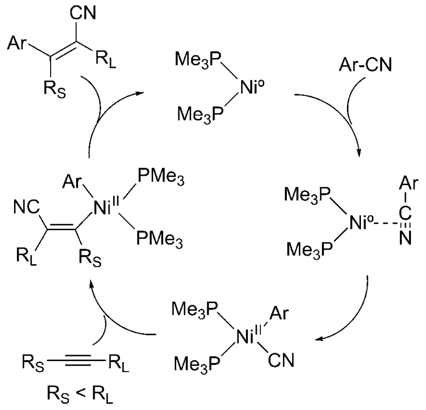
In some cases, mild nucleophiles (e.g., alkynes or alkenes) have been used where the CN group was incorporated into the end products.[51] Nakao and Hiyama thus developed a new catalyst for the arylcyanation of alkynes[52] in which the insertion of alkynes into an aromatic C–CN bond took place and various β-aryl-substituted alkenenitriles were thus accessible (Scheme 14a).



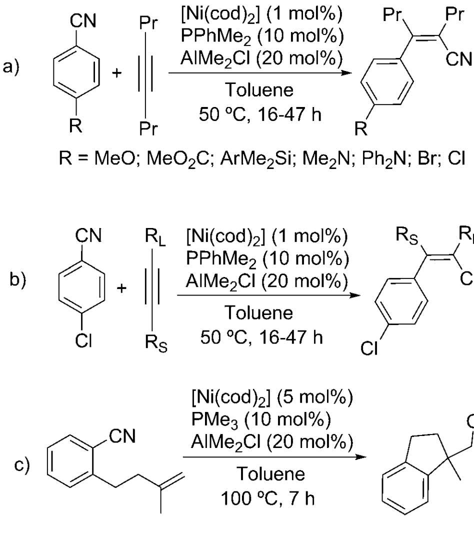
Scheme 14.

The arylcyanation of alkynes took place with a combination of $[Ni(cod)_2]$ (10 mol%; cod = cyclooctadiene) and PMe_3 (20 mol%) in toluene at 100°C or, alternatively, with a catalyst prepared in situ from air-stable $[NiCl_2(PMe_3)_2]$ (10 mol%) and diisobutylaluminum hydride (DIBAL-H; 20 mol%).[52] Generally, benzonitriles that have an electron-withdrawing substituent in the 4-position reacted effectively in good to excellent yields and a wide variety of functional groups including fluoro, keto, ester, and formyl were tolerated under these experimental conditions. Symmetrical alkynes gave the corresponding adducts in good to excellent yields, whereas unsymmetrical alkynes gave a mixture of regioisomers. However, when utilizing the unsymmetrical alkyne 4,4-dimethyl-2-pentyne, (R_S = Me, R_L = *t*Bu in Scheme 15) the regioisomer with the cyano group at the carbon that bore the larger substituent (R_L) was exclusively formed. This noticeable regioselectivity was attributed to steric effects since the nickel center was located far from the bulky *tert*-butyl group (Scheme 15). Intramolecular arylcyanation of alkynes was examined next, and cyclization in a 5-*exo*-dig fashion occurred (see Scheme 14b).

A dramatic effect of Lewis acids (LA) on the nickel-catalyzed arylcyanation of symmetrical and unsymmetrical alkynes has been reported, particularly to surmount the lack of reactivity of electron-rich aryl cyanides.[52b] Thus, the addition of a LA (e.g., an Al-based derivative) accelerated the rate of the oxidative addition and the arylcyanated products were obtained in more than 90% yields in an exclusive *cis* fashion (see Scheme 16). Under suitable conditions, unsymmetrical alkynes underwent the reaction with 4-chlorobenzonitrile to give the corresponding adducts with the larger substituent at the cyano-substituted carbon as major products (Scheme 16b).

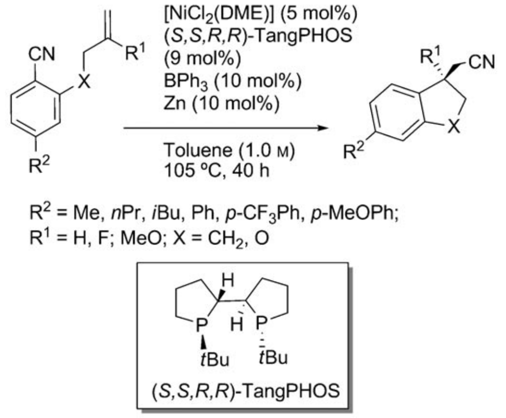


Scheme 15.



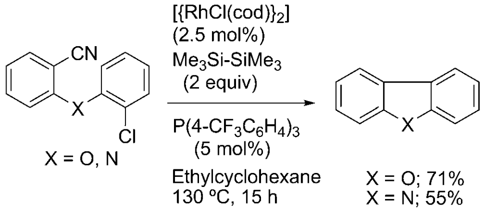
Scheme 16.

Recently, Nakao et al.[53] extended the reaction to the intramolecular arylcyanation of alkenes that require $[Ni(cod)_2]$ (5 mol%), PMe_3 (10 mol%), and $AlMe_2Cl$ (20 mol%) as the catalytic system in toluene at 100°C (Scheme 16c). This transformation afforded nitriles with up to two newly formed sp^3-carbon stereocenters in good to excellent yields. The cyclic adduct arose from the insertion of the olefin moiety into the Ar–CN bond in a 5-*exo*-trig fashion and it was formed in a trace amount in the absence of the Lewis acid cocatalyst. Larger ring systems including six- and seven-membered rings were successfully prepared, whereas no four-membered ring was formed from 2-allylbenzonitrile. The asymmetric version of the latter intramolecular reaction has been disclosed[53,54] with recourse to chiral ligands (e.g., (*R,R*)-*i*Pr-FOXAP ((*R,R*)-[2-(4'-isopropyloxazolin-2'-yl)ferrocenyl]diphenyl phosphine) or (*S,S,R,R*)-TangPHOS (1*S*,1*S*',2*R*,2*R*')-1,1'-di-*tert*-butyl-(2,2')-diphospholane); Scheme 17).



Scheme 17.

An interesting variation was introduced by the Chatani group in which aryl nitriles were also activated by an Rh catalyst. Aryl chlorides were used as electrophiles and dibenzofurans, carbazoles, and fluorene derivatives were prepared in good yields (53–78%) by an intramolecular biaryl coupling reaction and adopting the conditions described in Scheme 18.[55]



Scheme 18.

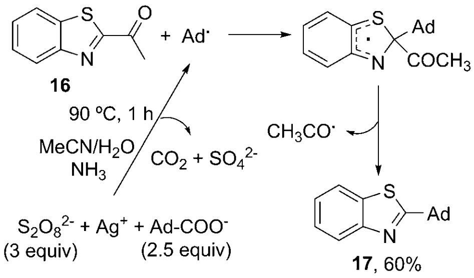
An attempt to apply this methodology to pyridine-containing systems failed, but the addition of catalytic amounts of $InCl_3$ (0.10 mmol) in place of the phosphine ligand was sufficient to induce the intramolecular arylations successfully.[55] The same reaction conditions used in Scheme 18 were later applied to the cross-coupling reaction between aryl nitriles and vinylsilanes.[56] Thus, an alternative procedure for the synthesis of alkenylsilanes by using a variant of the Mizoroki–Heck process resulted.

Summing up, the role of the nitrile group as pseudohalide in the cross-coupling reactions with strong nucleophiles is of scarce importance. In fact, though unsymmetrical biaryls, aryl alkynes, styrenes, and so forth were prepared in moderate to good yields, the protocol requires the use of moisture-sensitive organometallic nucleophiles (organozinc and Grignard reagents). However, the efficient $[NiCl_2(PMe_3)_2]$ catalysis allows the alkynylation reaction of aryl nitriles, which is an alternative route to the Negishi or Sonogashira alkynylation protocols in which aryl halides are commonly employed. Outstanding reactions, however, are those in which the cyano group is incorporated into the end products, namely, in intramolecular processes in which the use of chiral ligands enables the simultaneous construction of benzylic quaternary carbons in a one-pot procedure with high atom economy.

CO−R as the Leaving Group

Among the C-based leaving groups, the CO−R substituents are very versatile for an *ipso*-substitution process, since aromatic ketones, acids, anhydrides, and peroxides can be used as a partner of the reaction as summarized below.

Acyl or formyl as the leaving group (activation of aromatic ketones and aldehydes): The best way to make an acyl group a C-leaving group is by means of an acyl radical intermediate that is eliminated upon addition of either a different acyl or an alkyl radical. Heteroaromatics are the elective substrates for this reaction. Scheme 19 illustrates a typical example in which an adamantyl radical generated by Ag^{2+} oxidation of an adamantane carboxylate salt added to 2-acylbenzothiazole **16** affords the adamantyl derivative **17** in 60% yield.[57]

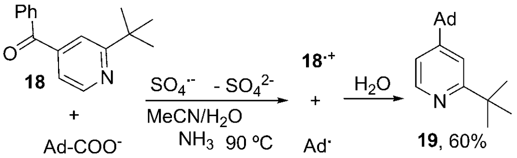

16

17, 60%

Scheme 19.

Substitution of an acyl group in 2-propanoylbenzothiazole upon addition of $MeCO^{\bullet}$ likewise took place in more than 70% yield.[58] The acetyl radical was generated in this case by treatment of MeCHO with a large excess amount of *t*BuOOH and $FeSO_4$.

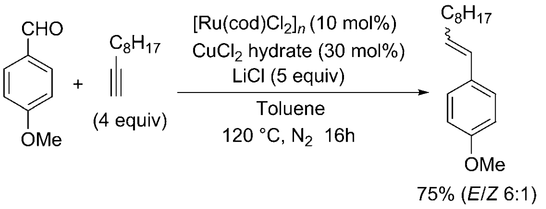
The reaction can be applied to a 4-acylpyridine such as **18**. The free heteroaromatic base was initially oxidized by $SO_4^{\bullet-}$ to the corresponding radical cation that in turn underwent radical addition and ultimately led to adamantyl pyridine **19** (Scheme 20).[59] On the contrary, when the acyl group was placed in the 2-position, a complex mixture resulted.



Scheme 20.

An alkyl radical can also add to formyl-substituted thiophenes to cause a partial replacement of the CHO group.[60]

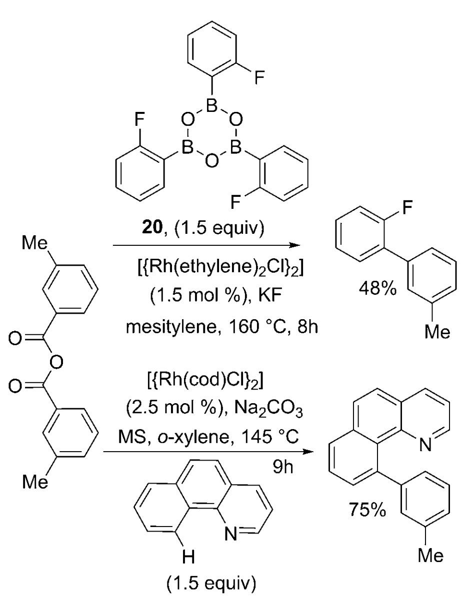
The aldehyde group, however, can be completely lost in the Rh-catalyzed decarbonylative coupling of aromatic aldehydes with alkynes (Scheme 21).[61] This new intriguing olefination reaction was very chemoselective since aliphatic aldehydes were virtually untouched by the catalytic system used as demonstrated by competitive experiments. The presence of a complex hydrate ($CuCl_2 \cdot 2H_2O$) and LiCl were beneficial for the process in which electron-rich aromatic aldehydes gave better yields with respect to those that bear electron-withdrawing groups.[61]



Scheme 21.

It is difficult to say if a simple carbonyl group has the potential to be a leaving group in an *ipso*-substitution reaction. Radical deacylation was in fact applied only to heteroaromatics by the addition of radicals generated by oxidation of aliphatic carboxylates about 30 years ago. On the other hand, the metal-mediated elimination of the CHO group is also rather too new a reaction to say if it can compete with the well-known Wittig reaction even if a milder nucleophile (an alkyne) is used.

Acyloyl as the leaving group (activation of aromatic anhydrides): The use of anhydrides for the occurrence of an *ipso*-substitution reaction in catalytic cross-coupling reaction is quite recent. Quite unexpectedly, the RCO-O-CO group can be an important leaving group since aromatic anhydrides are more sensitive to palladium(0) oxidative addition than aryl triflates or aryl bromides.[62] Nevertheless, the activation of the Ar−O bond in such compounds is demanding. One of the first reported reactions involved the arylation of electron-poor olefins by using $PdCl_2$ as the catalyst at 160 °C.[63] Later, the preparation of biaryls was devised[64] but the main drawback of the reaction was the formation of a significant amount of diarylketones as byproducts due to the lack of the decarbonylation step. However, it was found that when using arylboroxines (e.g., **20**) as the nucleophilic partner of the reaction in the presence of a rhodium catalyst, a biaryl was formed through CO extrusion (Scheme 22, top).[64] The addition of KF was proven to improve the catalyst activity. Nevertheless, the reaction appeared poor from the atom economy (three aryl groups were lost in the reaction), it required high temperatures (160 °C), and in some cases non-negligible amounts of biarylketones were formed.



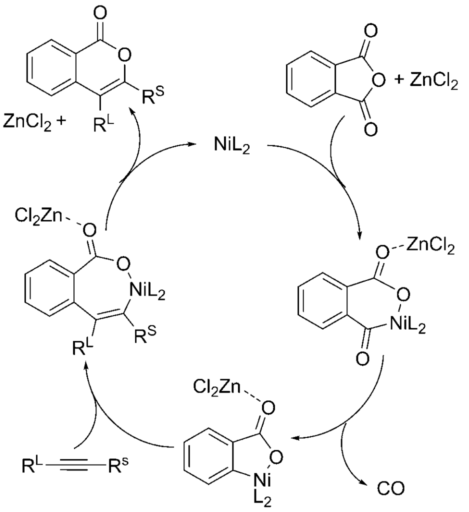
Scheme 22.

Changing the Rh^I catalyst (e.g., $[Rh(COD)Cl]_2$), however, allowed one to carry out the reaction at a lower temperature (in *o*-xylene heated at reflux) and by using simple N-heteroaromatics as the nucleophiles. Scheme 22 shows a representative example in which the direct arylation of benzo[*h*]quinoline takes place in a regioselective fashion under phosphine-free conditions.[65]

To increase the atom economy of the process, cyclic anhydrides were employed in such a way that only CO can be lost upon Ni-mediated reaction.[66] In fact, the nickel-catalyzed decarbonylative addition of anhydrides to alkynes by means of insertion of an unsaturated C−C bond into a C−O bond of an oxacyclic compound took place in a single step. Matsubara et al.[66] have performed the reaction of phthalic anhydride with alkynes using nickel(0) catalyst (e.g., $[Ni(cod)_2]$ 10 mol %) in MeCN at 80 °C for 12–24 h to form isocoumarins in good to excellent yields. A plausible reaction pathway is outlined in Scheme 23.

When unsymmetrical aliphatic alkynes were tested, two regioisomers (1:1 ratio) were formed; alternatively, when bulky and electron-rich trimethylsilyl-substituted alkynes (R^L = TMS, R^S = Me, Ph in Scheme 23) were used, a complete regiocontrol with yields > 86 % were reported.

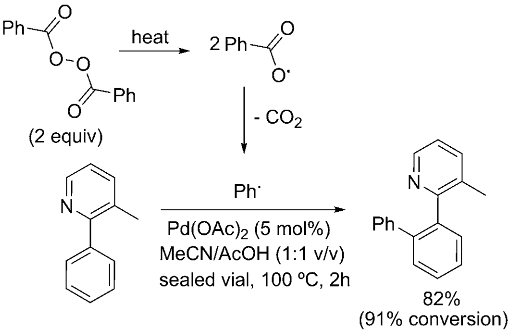
As for the above, we can conclude that the acyloyl group is not presently suitable as the leaving group for cross-coupling reactions (poor atom economy of the process, high



Scheme 23.

temperatures required, and so on). On the contrary, aromatic anhydrides are interesting substrates for isocoumarine synthesis under Ni-based catalysis.

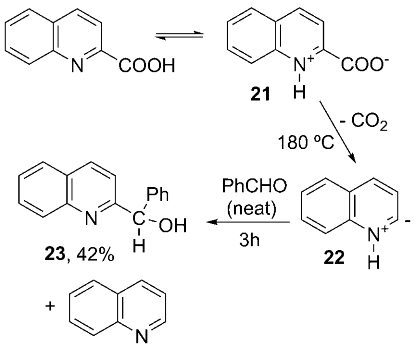
PhCOO$_2$CO as the leaving group (activation of aryl acylperoxides): In rare instances, an aryl acylperoxide can be an alternative source of an aryl group for an *ipso*-substitution reaction.[67] The reaction started with the thermal decomposition of the peroxide (easily prepared from the corresponding acid) that generated an aryl radical by means of carbon dioxide loss. This radical in turn reacted with a palladacyclic complex generated upon Pd(OAc)$_2$-catalyzed addition onto substrates that contained pyridyl, oxime, and oxazoline groups in which the heteroatom directed an *ortho*-selective C–H activation. As a result, a biaryl was formed as depicted in Scheme 24.



Scheme 24.

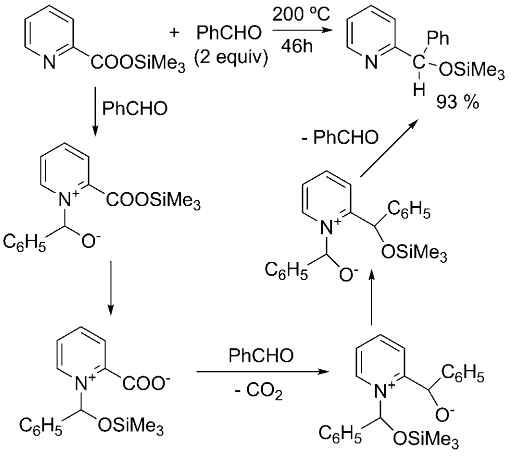
Despite the promising performance of the reaction, this required in some cases heating in a sealed tube up to 160 °C to complete the process. Moreover, due to the explosive behavior of the peroxides, these have to be utilized in small amounts.[67]

COOH (COOR) as the leaving group (activation of aromatic carboxylic acids or esters): One of the most appealing carbon-based leaving groups is the carboxylic group. In fact, a large number of benzoic (or heteroaromatic) acid derivatives are easily commercially available. The decarboxylation step, however, is not straightforward since the bond-dissociation energy (BDE) of the Ar–COOR′ bond (at least in pyrethroid model esters) is about 113.8 kcal mol^{-1}.[68] Nevertheless, about 70 years ago, an *ipso*-substitution reaction was reported in which a quinaldinic or an isoquinaldinic acid were heated to reflux in neat high-boiling carbonyl compounds (e.g., benzaldehyde, acetophenone) up to approximately 250 °C to give the corresponding quinolidylarylcarbinols in a modest yield (Scheme 25).[69] The process known as the Hammick reaction[70] was initiated by the decarboxylation of the zwitterionic form (**21**) to give a further reactive zwitterion (**22**) in which the aryl anion moiety ultimately added to the electrophilic partner of the reaction. A concurrent formation of decarboxylated heteroaromatic, the large excess amount of the ketone or aldehyde used, and the high temperature that was required strongly limited the application of this reaction. However, the use of *p*-cymene as the cosolvent (in place of the carbonyl derivative) improved the atom economy of the process and some pyridyl-based antihistaminic agents were prepared by using this protocol.[71] The reaction was then extended to 2-pyridylacetic acid[72] and methoxypyridine-2-carboxylic acids[73] (up to 53 % of the product in the latter case) or to lactones (e.g., 1,4-benzodioxin-2[3*h*]-one)[74] in place of ketones.



Scheme 25.

A protocol improvement was later proposed in which the acidic hydrogen was protected with a trialkylsilyl group as illustrated in Scheme 26.[75] Although the reaction conditions were similarly prohibitive ($T > 180$ °C was required to induce the CO$_2$ loss; the reaction took place in the absence of a cosolvent) the yield of the end diarylcarbinols was decent in most cases (> 60 % starting from 2-pyridinecarboxylates, > 40 % from 2-pyrazine- 3-pyridazine-, and 4-pyrimidinecarboxylates). The proposed mechanism is depicted in Scheme 26 and involves an initial addition of the aromatic aldehyde onto the pyridine nitrogen. On the contrary, vari-



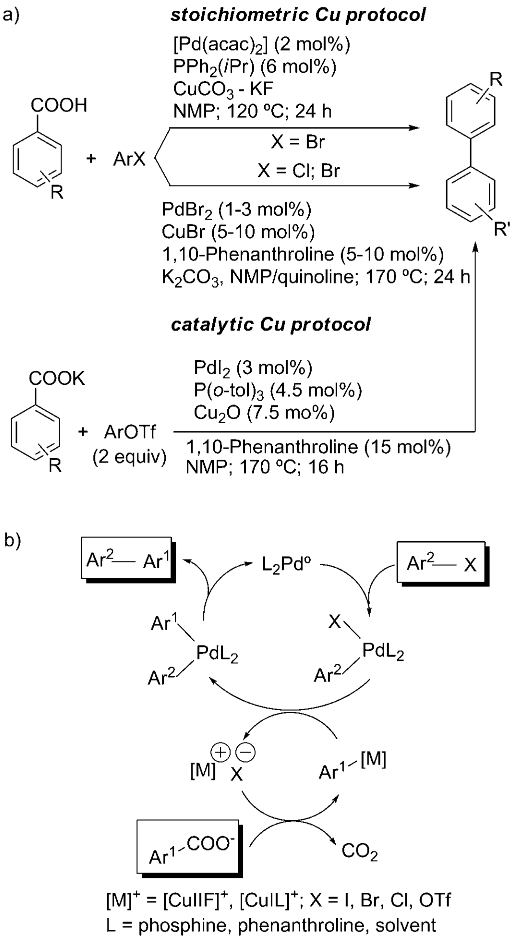
Scheme 26.

ous attempts for carrying out the intramolecular version of the Hammick reaction were rather disappointing.[76]

A more straightforward and catalytic metal-mediated decarboxylative cross-coupling reaction starting from (hetero)-aromatic carboxylic acids has been recently reported in the literature. This process was mainly applied for the preparation of a series of unsymmetrical biaryls and arylated heterocycles in good to excellent yields. In the latter case, the carboxylic acid is a valid substitute for sensitive and costly organometallic reagents (organoboron, -tin, -zinc, -copper, -silicon, or -magnesium) that are usually employed for this purpose.[3]

Most of the merit can be attributed to the group of Goossen,[77–85] which has introduced an advantageous decarboxylative cross-coupling methodology in which a carboxylic acid or its alkaline salt were converted into carbon nucleophiles by extrusion of CO_2 followed by coupling with haloarenes (Ar–X; X = I, Br, or Cl) or aryl triflates as electrophilic substrates. The original Pd-mediated decarboxylative cross-coupling reaction was accomplished by using stoichiometric amounts of a copper catalyst.[77] However, the addition of copper-chelating ligands allowed the cross-coupling reaction to be substoichiometric for both metal catalysts (see Scheme 27a).[78] This methodology has successfully been applied to a growing number of aromatic carboxylic acids, including *ortho*-substituted benzoic acids, heteroarene carboxylic acids, and cinnamic acids in the reaction with various aryl halides.[79] Typical experimental conditions and the postulated mechanism of the decarboxylative metal-mediated biaryl synthesis are depicted in Scheme 27b.

However, the above-mentioned protocols failed when nonactivated aryl chlorides were used. To overcome this drawback, Goossen and co-workers[81] developed a second-generation catalyst (formed in situ from CuI, 1,10-phenanthroline, PdI_2, and di(*tert*-butyl)biphenylphosphane) that enabled the use of nonactivated aryl chlorides as electrophiles and widely available, stable, and inexpensive carboxylic acid salts as carbon nucleophile. Both electron-rich and electron-poor aryl chlorides underwent smooth conversion when common functionalities (ester, ether, cyano, formyl, and so on) were present as substituents on the aromatic ring.



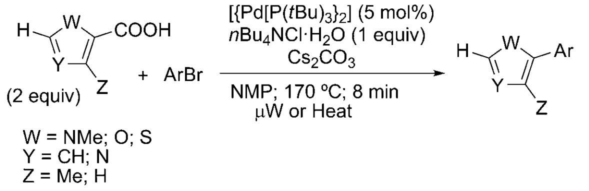
Scheme 27.

Also, basic nitrogen heterocycles were compatible with this transformation. Aryl triflates have been used in place of aryl halides, even if a modification of the Pd/Cu-based catalytic system was required (Scheme 27a, bottom).[82,83] Inexpensive and more robust aryl *p*-toluenesulfonates (tosylates) have been recently introduced as efficient electrophiles in place of aryl halides and moisture-sensitive aryl triflates in the Ar–Ar bond formation starting from (hetero)aryl carboxylates.[84]

The use of silver salts in place of copper salts seemed not to be advantageous in the Pd-mediated decarboxylative biaryl synthesis[77,78] in which biaryls were formed in somewhat lower yields. Furthermore, a large amount of Ag_2CO_3 (3 equiv) and high loadings of Pd and As were used as was recently demonstrated by Becht et al.[86] In some cases, this protocol had some limitations when using inactivated aryl bromides and aryl chlorides.[87] However, Crabtree and co-workers[88] found that the Ag/Pd-catalyzed cross-coupling reaction between carboxylic acids and aryl iodides took place under microwave heating in the presence of $P\textit{t}Bu_2(o\text{-}C_6H_4Ar)$ (10 mol%) and *t*Bu-XPHOS (20 mol%) along with Ag_2O or Ag_2CO_3 (1 equiv) and crushed MS4A over

5 min (200 °C) in DMF/DMSO (9:1). A new dual Pd–Ag catalyst has been similarly developed that allowed the decarboxylative cross-coupling reaction between potassium arenecarboxylates and aryl triflates at only 120–130 °C.[85] The reaction has been tested with potassium 2-nitrobenzoate and *p*-chlorophenyl triflate, and the best results were obtained with $PdCl_2$ (3 mol %) in the presence of catalytic amounts of Ag_2CO_3 (10 mol %) and 2,6-lutidine (20 mol %) to give the desired biaryl in 85 % yield. A benefit of the lower reaction temperature was that transesterification between the aryl triflates and nucleophilic carboxylates was avoided. Furthermore, microwave irradiation (130 °C, max 150 W, 5 min) was likewise advantageous for performing the reaction (80 % yield of the biaryl formed).

Recently, Forgione et al. succeeded in extending the C–C coupling reaction on a series of five-membered heteroaromatic (e.g., furans, pyrroles, thiophenes, oxazoles, and thiazoles) carboxylic acids with different bromoarenes (Scheme 28).[89]



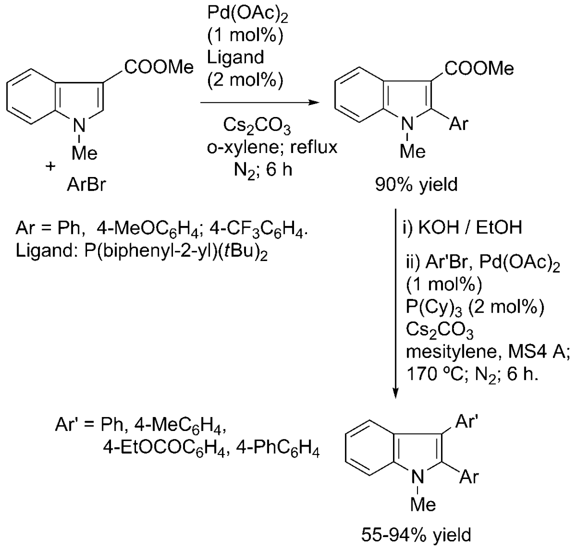
Scheme 28.

The use of microwave irradiation allowed the copper-free Pd-catalyzed synthesis of biaryls in only 8 min with $[Pd\{(P(tBu)_3)\}_2]$ as the catalyst.[90]

Very recently, the Pd-catalyzed decarboxylative cross-coupling of potassium pentafluorobenzoate with aryl bromides, chlorides, and triflates to achieve pentafluorobiaryls (useful compounds in material and medicinal sciences) in good to excellent yields was reported.[91] The best results for this reaction were obtained by using $Pd(OAc)_2$ (2 mol %) and $P(Cy)_3$ (4 mol %) as catalyst and phosphine ligand, respectively, in diglyme at 130 °C for 24 h; no co-oxidant was required for the reaction outcome.[91] The same reactions can be also carried out under Pd-free conditions by using CuI–1,10-phenanthroline (20 mol %) as the catalyst.[92]

The highly desirable direct cross-coupling of benzoic acids with simple arenes in place of aryl halides or esters have been disclosed.[88,93] In fact, the efficient Pd-catalyzed inter- and intramolecular direct arylation of benzoic acids by tandem decarboxylation/C–H activation was found to be highly chemo- and regioselective. Copper and silver salts assisted the decarbonylation step and behaved as oxidants for the C–H activation pathway.[88,93] A variety of dibenzofuran derivatives can be synthesized in good yields (55–85 %) with recourse to this protocol.[93] A decarboxylative C–H cross-coupling of heteroaromatic acids with azoles has been recently developed in which $Pd(OAc)_2$ was employed as the catalyst in the presence of either stoichiometric amounts of silver or copper carbonates and biphosphine (bis(dicyclohexylphosphino)ethane) as the ligand.[94]

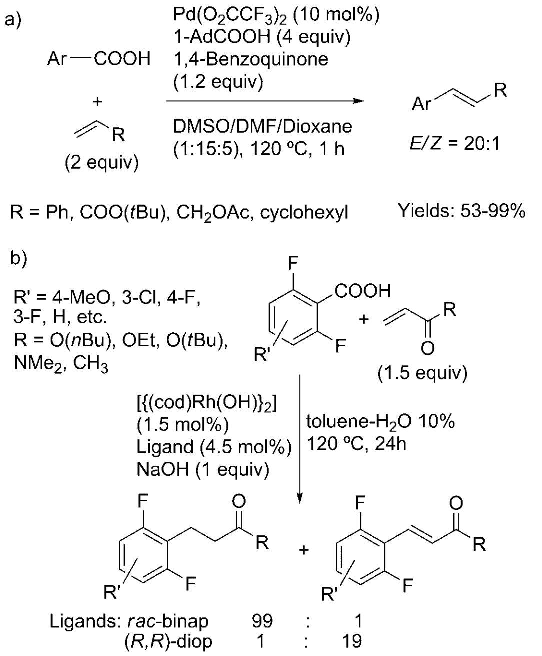
Miura et al. have recently reported the synthesis of 2,3-diarylindoles by Pd-catalyzed reaction starting from carboxyindoles.[95] This synthetic approach involved sequential *ortho-* and *ipso*-arylations and the desired 2,3-diarylindole was obtained in 90 % yield, as depicted in Scheme 29, in which the free carboxylic acid was liberated from the corresponding ester under basic conditions.



Scheme 29.

Another interesting *ipso*-substitution reaction that involved benzoic acid derivatives is the Heck reaction by means of palladium-catalyzed cross-coupling reaction with alkenes. Myers and co-workers[96] in their pioneering work disclosed an efficient method for the palladium-mediated decarboxylative Heck-type reaction. Nevertheless, the original optimal procedure involved the use of high loadings of $Pd(OTf)_2$ (20 mol %) as a catalyst and Ag_2CO_3 (3 equiv) as an oxidant, and the protocol was applied to a limited number of olefins. The replacement of expensive silver carbonate by accessible 1,4-benzoquinone, in the presence of aliphatic acids as additives, allowed the Heck-type cross-coupling reaction to occur successfully (Scheme 30a).[97] This reaction proceeded efficiently with electron-rich benzoic and heteroaromatic acids and inactivated alkyl-substituted olefins, and electron-deficient olefins and styrenes in good to excellent yields with noticeable *E*/*Z* selectivity (20:1).

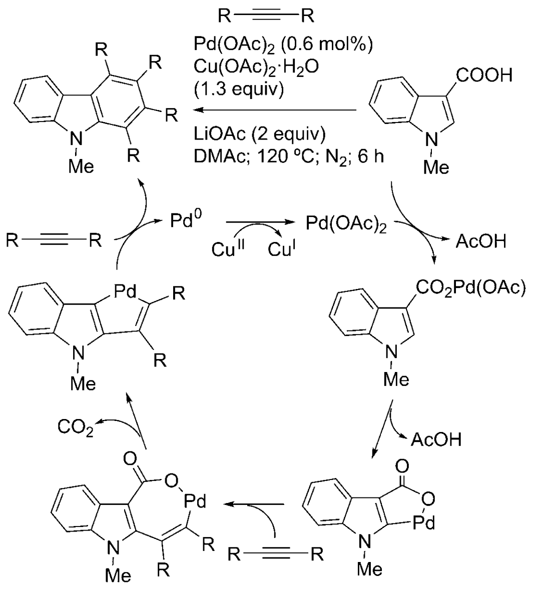
Alternatively, rhodium-catalyzed decarboxylative conjugate addition of fluorinated benzoic acids to the β position of acrylate esters afforded either Michael-type or Heck–Mizoroki-type adducts in good yields depending on the phosphine ligand used (Scheme 30b).[98] The highest reactivity was observed when adopting $[\{(cod)Rh(OH)\}_2]$ as the metal catalyst.



Scheme 30. Binap: 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; (*R*,*R*)-diop: (4*R*,5*R*)-(−)-4,5-bis(diphenylphosphanylmethyl)-2,2-dimethyl-1,3-dioxolane.

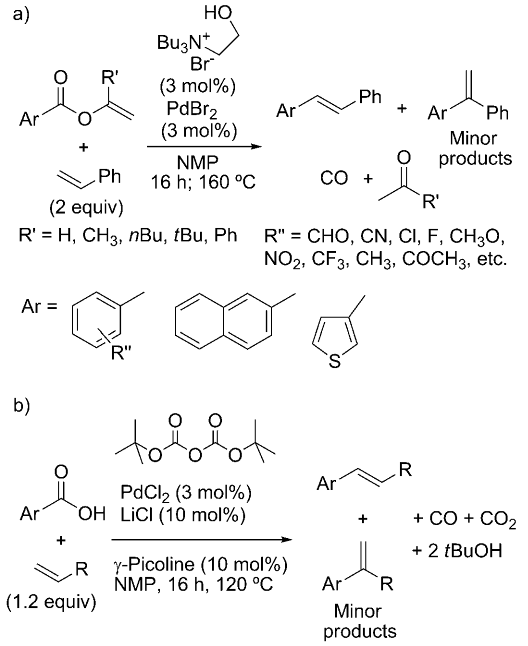
A dual Pd–Cu catalyst has been discovered for promoting the oxidative coupling of heteroarene carboxylic acids with two equivalents of alkynes accompanied by decarboxylation to prepare highly substituted indoles, benzofurans, dibenzofurans, and carbazoles in good to excellent yields.[99] Scheme 31 shows the reaction conditions and the plausible reaction mechanism.

The use of Ag_2CO_3 (30 mol %) in the presence of 2,6-dimethylbenzoic acid (8 mol %) instead of $Cu(OAc)_2$–LiOAc as oxidant and additive, respectively, likewise promoted the coupling reaction between indole carboxylic acids and diarylacetylenes for the synthesis of unsymmetrical substituted carbazole derivatives.[99b]



Scheme 31.

The esters of (hetero)aromatic carboxylic acids have been recently tested as an alternative to the corresponding acids for an *ipso*-substitution process. As an example, a novel strategy for the introduction of carbon chains to arenes was the decarbonylative Heck olefination of enol esters (e.g., isopropenyl esters; Scheme 32a).[100] This reaction led to the formation of vinyl arenes in good yields and with a high selectivity (a negligible amount of 1,1-diarylethene was also formed) by an environmentally friendly protocol with the easy elimination of volatile compounds (CO and acetone). $PdBr_2$ as the catalyst and ammonium salts as the ligand were suitable for the reaction, and higher selectivity was obtained when using activated olefins such as acrylates.



Scheme 32.

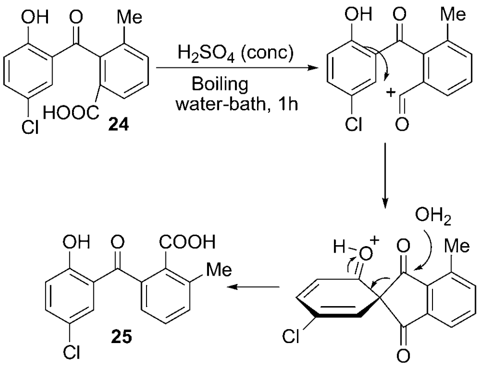
p-Nitrophenyl aryl carboxylates were similarly useful substrates in the decarbonylative Heck olefination in which only CO and water were produced as wastes and in which the released phenol could be efficiently recycled.[101]

The aromatic carboxylic acids could be derivatized in situ with di-*tert*-butyl dicarbonates to form the mixed anhydrides of carbonic and aromatic carboxylic acids as reactive intermediates for the Pd-mediated Heck cross-coupling (Scheme 32b).[102]

At this point, it is worth mentioning that carboxylic acids (or their alkaline salts) can be considered outstanding and valuable substrates in the metal-catalyzed mediated cross-coupling synthesis of (hetero)biaryls and styrenes. Since arene carboxylic acids are widely available, cheap, and easy to handle, they can be employed in place of arene boronic acids or organometallic compounds, which are too expensive, difficult to prepare, and have a limited functional-group tolerance. The protocol, mainly developed by Goossen and co-workers, is a valid alternative to traditional synthetic approaches that involve Stille, Kumada, Suzuki, and Negishi reactions. Moreover, the electrophilic partner of the reaction is not limited to aryl halides. Aryl triflates or aryl tosylates can be used in a like manner. Arene carboxylic acids are useful and versatile substrates for the synthesis of vinyl arenes with high *E*/*Z* selectivity by means of Pd-mediated Heck-olefination and Rh-mediated Heck–Mizoroki-olefination reactions. On the other hand, if a catalytic system will be devised for carrying out the cross-coupling reactions under milder conditions (a lower temperature is desirable), arene carboxylic acids (or their esters) will have a widespread use in successful arylation and olefination reactions.

Miscellaneous

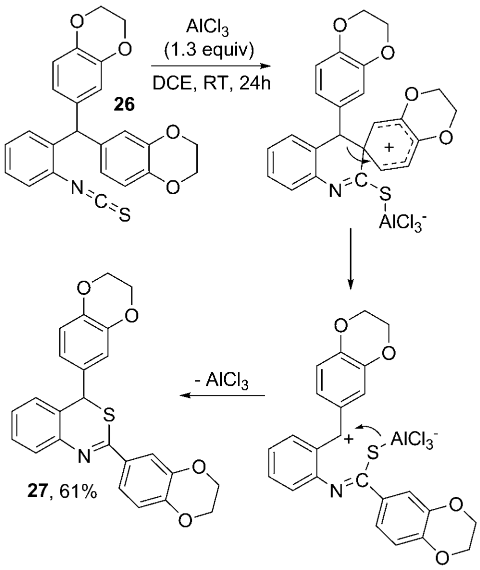
In the last part of this work, we mention other reactions that belong to rearrangement reactions that usually involve an intramolecular step. One dated example consists of the treatment of a chlorohydroxybenzoyltoluic acid (**24**) with sulfuric acid to lead to the toluic acid isomer (**25**). This process is known as the Hayashi rearrangement[103] and involves the intramolecular *ipso*-substitution of a benzoyl group with an acyl group (Scheme 33).



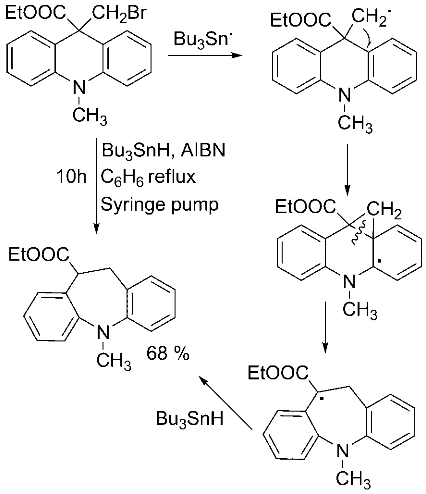
Scheme 33.

This rearrangement was found to occur on various substituted *o*-benzoyl[104,105] and *o*-aroylbenzoic acids[106] and it was one important step in the synthesis of benzophenanthridine alkaloid (±)-chelidonine[107] and of an isoquinoline-5,10-dione based DNA intercalator.[108] A similar process was recently developed and made use of isothiocyanatobenzene derivatives (e.g., **26**) for the $AlCl_3$-catalyzed synthesis of benzothiazines (e.g., **27**) in good yield as depicted in Scheme 34.[109]

A carbon radical rather than a carbocation could likewise initiate an intramolecular *ipso*-substitution reaction. A typical case is the neophylic rearrangement.[110] Thus, a ring enlargement of a 9,10-dihydroacridine system to form a dibenzazepine skeleton was described to have occurred by means of a Bu_3SnH-mediated carbon-centered radical formation (Scheme 35).[111] The process has some interest due to the biological importance of dibenzazepines for depressive illness.



Scheme 34.



Scheme 35.

A related ring enlargement was reported in the radical cyclization of *o*-ethenyltrichloroacetanilides induced again by Bu_3SnH.[112]

An uncommon amidomethyl leaving group was likewise successfully used in an *ipso*-substitution reaction. In this case an aryl–aryl bond was formed starting with an aryl radical addition. The reaction was successful both inter- and intramolecularly, and in the latter case gave access to *ortho*-

aryl benzaldehydes through the hydrolysis of a 1,3-oxazolidin-4-one group.[113] As the final example, we also mention the intramolecular *ipso* attack of an α,α-difluoroalkyl radical to an aromatic Schiff base that gave the end β,β-difluorocarboxylic acid ester by means of a benzonitrile elimination.[114]

Summary and Outlook

The examples described in this Review demonstrate that, although counterintuitive, a lot of processes belong to the class of the aromatic carbon–carbon *ipso*-substitution reactions. Actually, most of the carbon-based substituents (an alkyl, a cyano, a CO–R group, and so forth) of the aromatic ring can be replaced for the formation of new C–C bonds depending on the conditions used. Although some dated examples have been reported here, these processes represent an emerging and intriguing field for the synthesis of substituted aromatics (biphenyls, alkyl-, and vinylbenzenes) thanks to the strong development of the metal-mediated (mainly Ni, Pd, Rh, and Ru) cross-coupling processes.

It is thus possible to choose a suitable starting derivative in such a way that it can function either as the electrophilic or the nucleophilic partner of the reaction. It is noteworthy that in some cases the nature of the reaction partner could be tuned only by varying the reaction conditions adopted (e.g., by changing the catalytic system).

A lot of work, however, has to be performed on carbon-based leaving groups to compete with aryl halides or aryl sulfonate esters as the electrophilic partner of this reaction since the latter compounds require milder reaction conditions and have a wider applicability. In fact, apart from photochemical activations that are easily carried out at room temperature, in most of the cases described a lot of energy has to be supplied for the completion of the reaction and this is usually incompatible in multistep syntheses of lead compounds. An improvement in the catalytic systems is the actual breakthrough to avoid reducing these *ipso*-substitution reactions to a marginal role among other synthetic methods. The design of a new, more labile C-based leaving group is another challenge that has to be confronted.

Nevertheless, the substitution of strong basic and nucleophilic organometallic partners with noncharged aromatics that bear a carbon leaving group is worthy of serious consideration in the near future. In our opinion, apart from the metal-mediated cross-coupling reaction, other *ipso*-substitution reactions deserve more attention, such as the photochemical activation of aryl nitriles and the radical alkylation of (hetero)aromatic ketones.

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