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Recent advances in the Heck–Matsuda reaction in heterocyclic chemistry

François-Xavier Felpin *, Luma Nassar-Hardy, François Le Callonnec, Eric Fouquet

Université de Bordeaux, UMR CNRS 5255, Institut des Sciences Moléculaires, 351 Cours de la Libération, Talence 33405, France

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1. Introduction

Palladium-catalyzed reactions for carbon–carbon bonds formation are now recognized as essential in the tool box of every synthetic chemist.[1] Of the many coupling reactions involving palladium catalysis, the Heck–Mizoroki reaction emerged as one of the most widely used transformations from both academic and

* Corresponding author. E-mail address: fx.felpin@ism.u-bordeaux1.fr (F.-X. Felpin).

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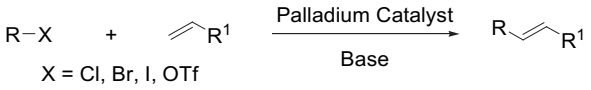
industrial laboratories.[2] The simultaneous discovery, in the laboratories of Mizoroki[3] and Heck,[4] that aryl iodides could be reacted with olefins in the presence of a palladium catalyst, was the starting point for 40 years of intense efforts directed at the development of this synthetic strategy.[5] On October 2010, the Nobel Prize in chemistry was awarded to Heck in recognition of his discovery.[6]

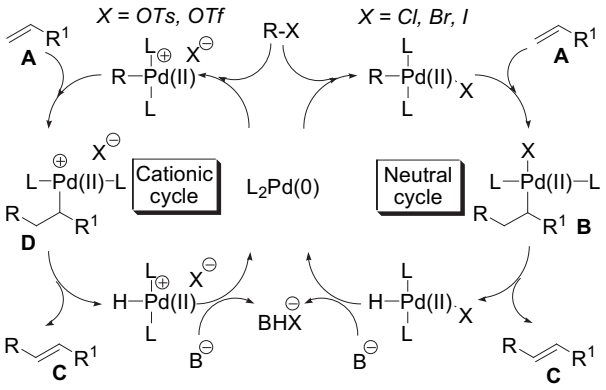
Under its usual form, the Heck reaction involves the coupling of aryl, vinyl, benzyl, or allyl halides with olefins in the presence of a homogeneous or heterogeneous source of palladium as catalyst (Scheme 1). However, many variants of this reaction entail the use of aryl triflates as aryl halide surrogates. The experimentally observed order of reactivity is usually I>OTf≥Br>Cl.



Scheme 1. General representation of the Heck–Mizoroki reaction.

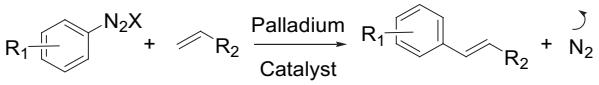
A number of palladium sources have been used in the Heck–Mizoroki reaction, however, Pd(II)-pre-catalysts, such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ or $PdCl_2CH_3CN$ are usually preferred in association with stabilising ligands, such as phosphines or carbenes. Quaternary ammonium salts have also been frequently used as stabilising agents especially under ligand-free conditions where palladium nanoparticles were the catalytic active species.[7] Continuous improvements of catalytic systems over the years have led to the design and the development of new ligands, including chiral ones for asymmetric Heck processes.[8]

From a mechanistic point of view, it is generally admitted that the palladium catalyst cycles between Pd(0) and Pd(II) oxidation states during the course of the reaction although Pd(II)–Pd(IV) cycles have also been proposed when using palladacycle pre-catalysts as palladium source.[9] The usually postulated mechanism of the Heck–Mizoroki reaction involves an oxidative addition of electron rich and nucleophilic Pd(0) species to the R–X electrophile, followed by a carbometallation of the olefin **A** (Scheme 2, right). Elimination of palladium hydride from intermediate **B** provides the olefin **C** and the $L_2Pd(II)HX$ complex. It is admitted that the base reduce $L_2Pd(II)HX$ to regenerate the active $Pd(0)L_2$ complex. It is admitted that the oxidative addition of aryl iodides[10] and activated aryl bromides[11] to palladium is not rate limiting. In contrast, the lower reactivity of aryl chlorides and electron rich aryl bromides tends to ascribe the oxidative addition as the rate limiting step, but other steps may also limit the reaction rate.[12] While this catalytic cycle involving neutral intermediates would be quite general with aryl or vinyl halides, it has been suggested that a cationic pathway could be involved with aryl and vinyl sulfonates (Scheme 2, left).[13] This feature could be explained by the easy dissociation of the Pd–X bond (X=OTs, OTf) after the oxidative addition step.



Scheme 2. Cationic versus neutral catalytic cycles of the Heck–Mizoroki reaction.

While the Heck–Mizoroki reaction has been intensively studied these last twenty years, a related approach, also called Heck–Matsuda reaction and involving the use of aryl diazonium salts as electrophiles instead of halides or sulfonates, has been much less explored despite significant interesting features (Scheme 3).



Scheme 3. General representation of the Heck–Matsuda reaction.

In this context, the present review will focus on the recent advances of the Heck–Matsuda reaction in heterocyclic chemistry and natural products synthesis (oxygen and nitrogen heterocycles). Heck–Matsuda couplings leading to acyclic olefins will not be considered since they have been already partially reviewed.[14] A discussion properties of aryl diazonium salts, on mechanistic considerations, as well as experimental conditions will introduce the general picture on the applications of the Heck–Matsuda reaction leading to a variety of useful heterocycles and natural products.

1.1. Diazonium salts: properties, preparation, and general reactivity

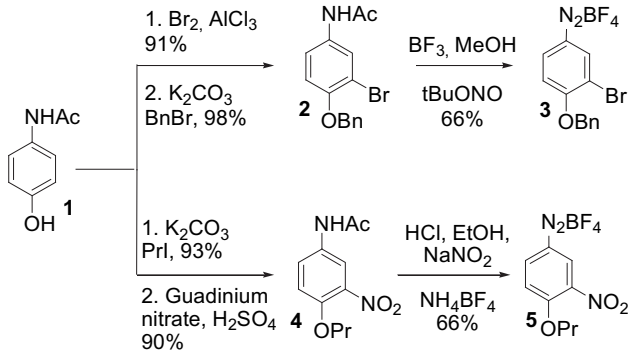
1.1.1. Properties. Aryl diazonium compounds have been discovered in 1858 by the German chemist Johann Peter Griess.[15] Diazonium salts are a class of compounds with the common structure of $R–N_2^+X^-$ where R is an aryl or alkyl fragment and X^- is a weak nucleophilic organic or inorganic anion. Although in theory a large variety of R/X combinations might be feasible, the nature of both the cation and the anion strongly influences the stability of diazonium salts and, thereby, limit their use for synthetic applications. For instance, alkyl diazonium salts are usually not isolable and rarely exploited in synthesis. By contrast, aryl diazonium salts are much more stable due to the electronic delocalization between the aromatic ring and the nitrogens. When associated with a proper stabilizing anion, they can be isolated as crystalline compounds. Although aryl diazonium salts are known for more than 150 years they have been underutilized in organic synthesis due to a reputation of unstable compounds. This, somewhat, usurped reputation origins from the fact that aryl diazonium salts were first mainly reported and used with a chloride as counterion. Unfortunately, aryl diazonium chlorides are usually highly unstable above 0 °C and even explosive. However, later developments showed that the stability of diazonium salts can be modulated by varying the counterion. In this prospect, tetrafluoroborates[16] became the most used salts but, disulfonimides,[17] carboxylates[18] as well as other salts have also been described for their good stability. From our own experience, we routinely use aryl diazonium tetrafluoroborates that have been stored at −20 °C for more than 3 years without noticeable decomposition as judged by ^1H NMR. Recently, Filimonov et al. determined by DSC analyses that aryl diazonium tosylates are not explosive compounds in the range of 0–600 °C.[19] The stabilization of the diazonium salt is attributed to the high affinity between the anion and the cation. The shorter the distance is between anion and cation, the more stable the diazonium salt is. For instance, X-ray crystal structures of aryl diazonium tosylates revealed that one independent cation is surrounded by three tosylate anions with a short inter-ionic distance (2.7 Å). By contrast, with less stable aryl diazonium chlorides, X-ray structure showed a N–Cl distance of 3.22–3.56 Å[20]

1.1.2. Preparation. Aryl diazonium salts have been prepared by a wide variety of methods. The oldest and commonly used method involves the diazotation of anilines with sodium nitrite in the

presence of an aqueous Brønsted acid.[16,21] The counterion (X^-), determined by the choice of the acid, has a crucial role for both stability and reactivity of the diazonium salt (vide infra). Numerous variants of this method relative to the acids and the solvents have been reported and usually give good yields of water insoluble diazonium salts. However, isolation of the dry aryl diazonium salts from an aqueous mixture can be tricky for stability and safety reasons. Anhydrous aryl diazonium salts with tetrafluoroborate as counterion can be prepared by reaction of anilines with an alkyl nitrite in the presence of boron trifluoride with THF or ether as solvent.[22] Anhydrous diazonium salts can also be obtained by acidic decomposition of triazenes.[23] Notably, this method has been elegantly exploited by Bräse et al. for the preparation of aryl diazonium salts from polymer-supported triazenes.[24]

Alternate methods for unreactive anilines have also been reported and involve the use of strong nitrosating agents, such as, from others, NOCl, $NOHSO_4$, $NOBF_4$, and $NOOCOCF_3$.[25] However, due to their high reactivity and dangerousness, these compounds must be handled with an extreme care.

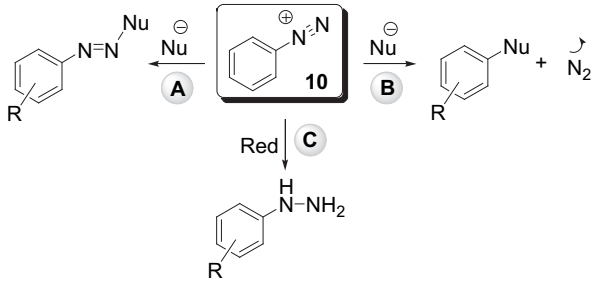
The preparation of substituted diazonium salts requires the functionalization of the corresponding anilines. Generally, the sensitivity of free anilines to various experimental conditions usually requires the use of protecting groups. In this context, Schmidt et al. reported the functionalization of hydroxyacetamides followed by a one-pot sequence of deacetylation, diazotation, and precipitation (Scheme 4).[26] To the credit of this protocol is the convenient one-flask transformation with consecutive addition of the reagents and the final isolation of the diazonium salt by simple filtration.



Scheme 4. Preparation of diazonium salts from hydroxyacetamides by Schmidt et al.[26]

1.1.3. General reactivity. The general reactivity of diazonium salts, represented in Scheme 5, can be divided into three classes of reactions: (A) addition over the diazonium function, (B) substitution of the nitrogens, and (C) reduction of the diazonium salts.

The addition of nucleophiles, such as tertiary anilines,[27] phenols,[28] and aryl zinc compounds[29] leads to the formation of aryl azo compounds that are of commercial interest as dyes and pigments[30] while the addition of free amines leads to the formation of triazenes.[31] The intramolecular reaction of alkenes with diazonium salts have been used for the Widman[32]–Stoermer[33] preparation of cinnoline heterocycles.



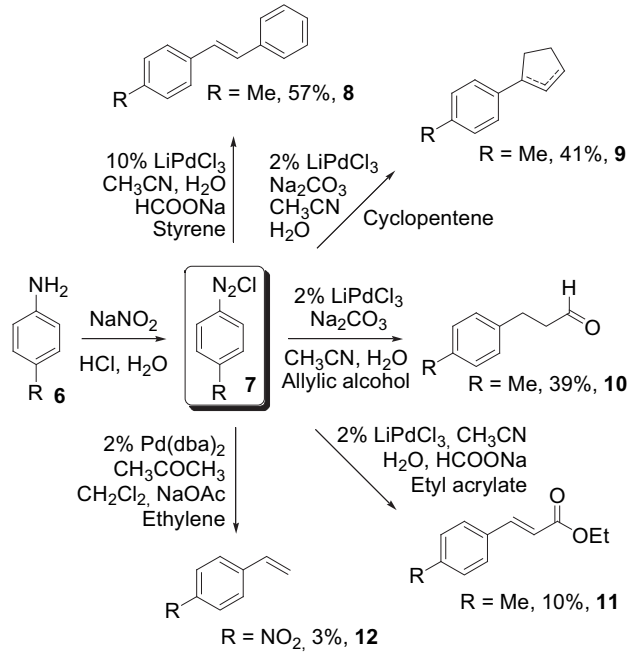
Scheme 5. General reactivity of diazonium salts.

A number of reactions advantageously exploit the diazonium function as an excellent leaving group. From others, the most representative ones are the Sandmeyer,[34] the Balz–Schiemann,[35] the Meerwein,[36] the Pschorr,[37] and the Gomberg–Bachmann[38] reactions. More recently, aryl diazonium salts have also been used as aryl halides surrogates in a variety of palladium-catalyzed reactions[14] including the Heck–Matsuda coupling. It should be noted that the Meerwein reaction is synthetically related to the Heck–Matsuda coupling although it involves free radical intermediates and has a more limited scope.[36]

Last, the reduction of the diazonium function by sodium sulfite leads to the corresponding hydrazine.[39]

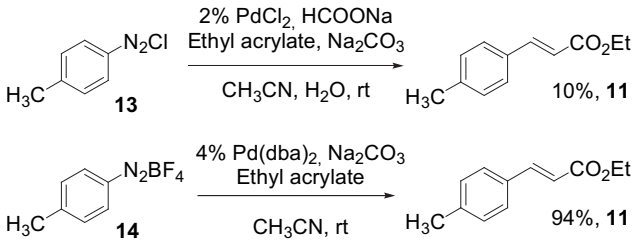
1.2. Early developments of the Heck–Matsuda reaction

Although the Heck–Matsuda reaction has been mostly overlooked until the end of the nineties, it has been first described in the laboratory of Kikukawa and Matsuda as early as 1977.[40–42] In this remarkable seminal work, the group reported that styrene, cyclopentene, allylic alcohols, ethyl acrylate, *n*-butyl vinyl ether, and ethylene were arylated with aryl diazonium chlorides in the presence of a catalytic amount of palladium(0) complexes in buffered (pH ~4.5) aqueous acetonitrile solution (Scheme 6). Interestingly, the authors also pointed out the complementary nature of this method with the well known copper-catalyzed Meerwein arylation reaction that involves free radical intermediates.[43] Although the exact nature of the mechanism was unknown at that time, the authors noticed that the reaction was completed in 1 h at only 40–50 °C. However, they also pointed out the instability of aryl diazonium chlorides at room temperature leading to safety issues and modest yields of coupled products.



Scheme 6. Selected examples from Matsuda et al.[40–42]

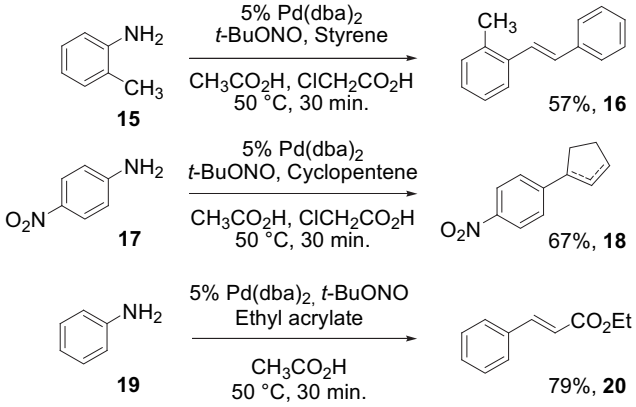
They also noticed that aryl diazonium tetrafluoroborates were more stable and could be handled at room temperature as crystalline salts.[44] As a consequence, improved yields were usually observed and sometimes in a significant extent as shown in the following example (Scheme 7).



Scheme 7. Influence of the diazonium salt coutnerion.[44]

To avoid the manipulation of potentially unstable diazonium salts, they subsequently developed a protocol where the aryl diazonium salt was in situ prepared by reaction of the corresponding aniline with *tert*-butyl nitrite.[45,46] To succeed in such a purpose, they opted for an acidic medium (CH_3CO_2H–$ClCH_2CO_2H$) playing the role of solvent, Brønsted acid, and counterion (RCO_2^-). With this protocol in hands, Matsuda et al. reported much improved yields of coupling products for the reaction of aryl diazonium salts with styrenes, acrylates and cyclic olefins (Scheme 8). It is interesting to note that under these conditions a base was not required.

Although not fully satisfactory due to large variations of the yields according to the substitution of anilines; in the context of the end of seventies and beginning of the eighties, this work already represented an excellent preamble that appealed to further developments.

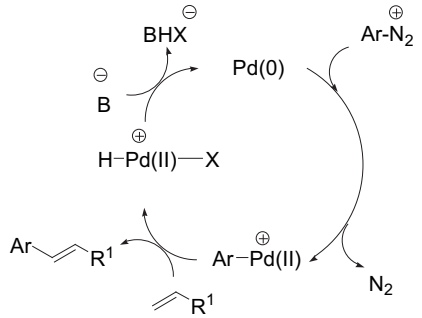


Scheme 8. Heck–Matsuda reactions using in situ generated diazonium salts.[45,46]

1.3. Mechanistic investigations

The catalytic cycle was first proposed by Matsuda et al.[44] on the basis of the postulated Heck–Mizoroki mechanism. However, significant differences were assumed by the authors due to the distinctive nature of the diazonium salts. Indeed, the observation of nitrogen evolution during the oxidative addition step led the authors to postulate the formation of highly active cationic palladium intermediates as showed in the following Scheme 9.

This mechanism has been accepted for almost 25 years without experimental evidence to confirm the hypothesis of Matsuda et al. It is much later, in 2004, that Eberlin et al. studied the Heck–Matsuda reaction by electrospray mass and tandem mass spectrometry.[47] This interesting study unambiguously confirmed the catalytic cycle proposed by Matsuda et al. Indeed, they were able to detect and characterize several cationic intermediates corresponding to the elementary steps of the catalytic cycle. They also showed that cationic palladium species were stabilized by solvent molecules (CH_3CN) and dba ligands.

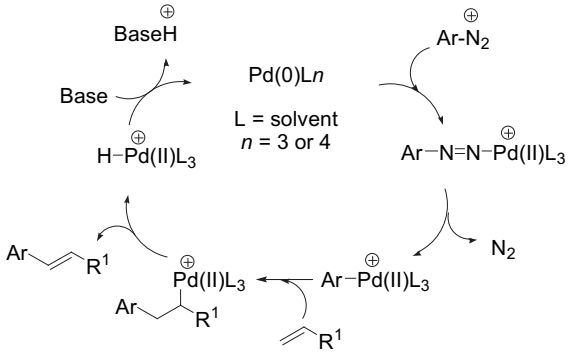


Scheme 9. Proposed mechanism by Matsuda et al.[44]

In order to understand the role of the solvent in stabilizing cationic palladium intermediates, we recently performed DFT calculations.[48] We compared the η2-coordination energy of $PhPd^+$ with various solvents (CH_3OH, THF, CH_3CN) and methyl 2-(2-nitrophenyl)acrylate. Theoretical results showed that the $PhPd^+$–acrylate complex is exoergic in CH_3OH, isoenergetic in THF and endoergic in CH_3CN. These calculations were in good agreement with experimental observations on the Heck–Matsuda reaction since we observed the higher kinetics in CH_3OH compared to THF and CH_3CN. Thereby, the $PhPd^+(CH_3OH)_n$ complex can easily dissociate in favour of the formation of the $PhPd^+$–acrylate complex. Solvents with higher coordination energy (i.e., CH_3CN) retard the olefin insertion step and slow down the reaction rate.

The presence of a cationic palladium intermediate was also confirmed by Roglans and Pla-Quintana with the aid of electrospray ionization mass spectrometry analyses.[49] However in this work, the cationic palladium species were stabilized with a triolefinic macrocyclic ligand having a strong affinity for the palladium and not with solvent molecules.

Based on these recent mechanistic studies, a general catalytic cycle can be drawn in Scheme 10 in which cationic palladium intermediates are stabilized with solvent molecules or a proper ligand. It should be noted that trivalent phosphorus compounds (phosphines and phosphites) are usually not considered as ligands of choice for the Heck–Matsuda reactions. Indeed, it has been reported that they give rise to de-diazonization pathway through formation of aryl free radicals.[50] As a consequence, Heck–Matsuda reactions are frequently carried out under ligand-free conditions.



Scheme 10. General catalytic cycle of the Heck–Matsuda reaction.

1.4. Influence of the counterion on the Heck–Matsuda reaction

Aryl diazonium salts are very reactive electrophiles when involved in Pd-catalyzed reactions, including the Heck–Matsuda coupling, due to an excellent nucleofugic property of nitrogen.

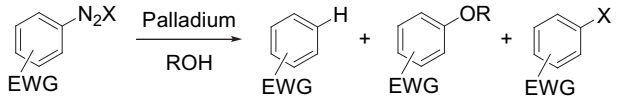
Although a systematic study of an anion–activity relationship has not been realized yet, the compilation of several independent works allows a first look. Aryl diazonium tetrafluoroborates,[16] sulfonates,[19] and disulfonimides[51] appear to be the most stable compounds that can be usually isolated as crystalline salts under safe conditions. It is thus not surprising to see excellent results when these salts are involved in the Heck–Matsuda reaction.[52] By contrast, aryl diazonium chlorides and acetates are much less stable and can usually not be isolated under pure form. Not surprisingly, these salts are inappropriate electrophiles for the Heck–Matsuda coupling. In an interesting work, Sengupta et al. studied the anion-activity relationship by treating triazenes with mineral and organic acids.[53] Thus, the in situ generated diazonium salts were reacted with ethyl acrylate in EtOH. This study revealed that diazonium salts with BF_4^-, ClO_4^-, $CF_3CO_2^-$, F^-, and $CH_3SO_3^-$ as counterion were effective partners for the Heck–Matsuda reactions while $CH_3CO_2^-$ and Dowex 50W-X8 ($P\text{-}SO_3^-$) gave low yields of the coupled product.

In summary, it should be noted that a systematic study with a large variety of counterions has to be done in order to evaluate their reactivity in the Heck–Matsuda reaction. However, based on the work of Sengupta and others it appears that yields depend, at least in part, of the diazonium salt stability. Other factors such as the interaction of the counterion with cationic palladium species during the catalytic cycle have not been studied and would provide useful information toward the establishment of an optimal catalytic system.

1.5. General considerations on experimental conditions

Heck–Matsuda reaction has been mainly described in alcoholic solvents, such as EtOH,[54] and MeOH,[55] under dry or aqueous conditions.[56] Alternatively, CH_3CN has also been widely used for various applications. Other solvents, such as THF,[57,58] ionic liquids,[59] PhCN[60] have also been considered with success for specific applications but usually led to lower catalytic activities.

It has been frequently observed that alcoholic solvents and especially MeOH, contrary to CH_3CN, considerably increase the reactivity of the diazonium salts under palladium catalysis. However, electron poor diazonium salts bearing, for instance, ester or nitro functions are so reactive in protic solvents that de-diazonization pathways compete with the desired coupling reaction (Scheme 11).



Scheme 11. Main side-products usually observed in protic solvents.

In contrast, in CH_3CN, diazonium salts are usually much more stable, and sensitive substrates may be cleanly reacted. As a consequence, kinetics of coupling reactions are higher in protic solvents, leading frequently to a complete conversion in a couple of minutes at moderately elevated temperatures (40–60 °C).

The use of a base also depends on the choice of solvent. While in CH_3CN, the use of a base such as NaOAc or Na_2CO_3 seems to be mandatory for the success of the coupling, it proved to be useless in MeOH and EtOH. However, to avoid any transesterification products with reagents bearing ester functions, the use of $CaCO_3$ has been reported to neutralize the liberated HBF_4.[61]

Many studies on the 'traditional' Heck–Mizoroki coupling have focused on the improvement of the catalytic system for lowering palladium loadings. Surprisingly, until recently, the palladium loading has rarely been the preoccupation of chemists using the Heck–Matsuda reaction. As a consequence, it has been reported that high loadings 5–10 mol % are required for optimal results. However, we recently reported that aryl diazonium salts can be efficiently coupled with various substituted olefins in MeOH at 25 °C with palladium loadings as low as 0.005 mol % under ligand-free and base-free conditions.[48] Interestingly, we also showed that under such mild conditions, nitro-substituted benzene diazonium salts remained stable and can be reacted with excellent efficiency.

In palladium chemistry, the use of stabilizing ligands represents the classical strategy for reducing palladium loadings. As already mentioned, trivalent phosphorous ligands cannot be used in the Heck–Matsuda reaction since they give rise to the de-diazonization pathways through the formation of aryl free radicals. On the other hand, it has been reported that aryl diazonium salts are compatible with molecular palladium complexes stabilized with *N*-heterocyclic carbenes **21**–**23**[58,62] (Fig. 1), thiourea **24**[63] (Fig. 2), as well as triolefinic macrocyle **25**[64] (Fig. 2). However, palladium loadings ranging between 0.5 and 5 mol % Pd demonstrated the weak influence of these ligands as stabilizing agents and, in some extent, the real impact of these ligands on the catalytic system efficiency may be questionable.

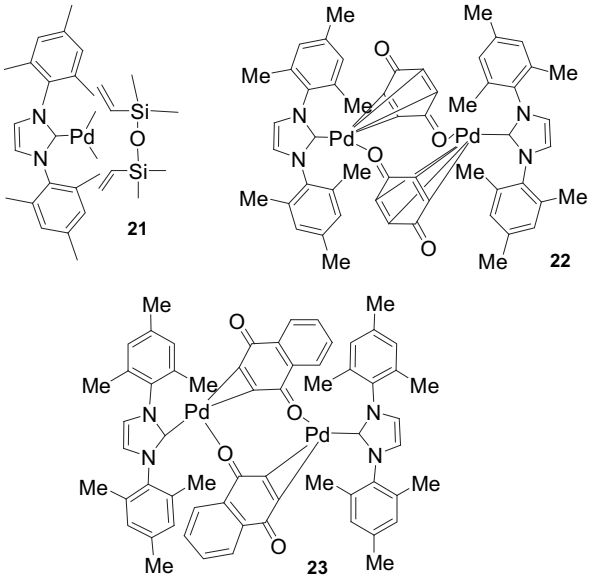


Fig. 1. Structure of *N*-heterocyclic carbene palladium complexes.

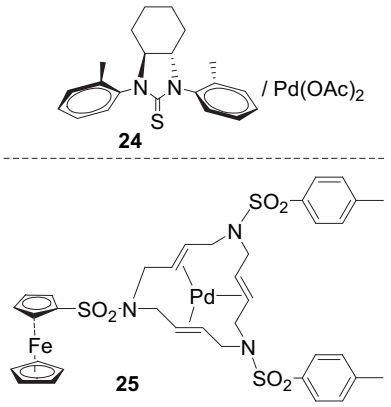
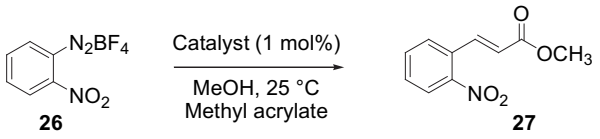


Fig. 2. Structure of thiourea ligand and palladium triolefinic macrocyclic catalyst.

While most arylation studies have been reported under homogeneous catalysis, essentially with $Pd(OAc)_2$ and Pd_2dba_3 as molecular complexes, the use of Pd/C as heterogeneous catalyst was less studied and gave good results for the arylation of ethyl acrylate,[65] and methyl vinyl ketone.[66] In our laboratory, we conducted

a property–activity relationship study of various Pd/C catalysts for the arylation of acrylates with aryl diazonium salts.[67] The optimized protocol showed that a Pd(II) on charcoal with an eggshell distribution was required for optimal results (Scheme 12). Other combinations of oxidation degree and distribution of palladium gave a significantly decreased activity. Although the catalyst could not be recycled, low palladium leaching measured by ICP-MS renders the method safer to the environment compare to homogeneous conditions.



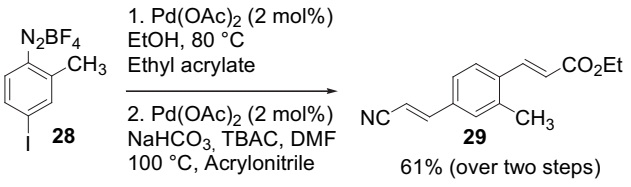
Catalyst	Yield [%]
Pd(0)/C Eggshell	42
Pd(0)/C Uniform	29
Pd(II)/C Eggshell	78
Pd(II)/C Uniform	53

Scheme 12. Property–activity relationship of various Pd/C catalysts by Felpin et al.[68]

The heterogeneous $Pd/CaCO_3$ catalyst has also been proposed by the group of Genêt et al.; $CaCO_3$ playing the role of support and base.[68] However, we observed for Suzuki–Miyaura reactions that $CaCO_3$ (and $BaCO_3$) reacts with HBF_4 leading to a significant leaching of palladium species into the solution which then may limit the accuracy of such system in terms of environmental concerns.[69]

The safety issue linked with the manipulation of diazonium salts as crystalline compounds has been addressed with a protocol allowing their in situ preparation. Indeed, prior to the coupling reaction with the olefin under palladium catalysis, aniline can be in situ diazoted with *t*-BuONO and BF_3/Et_2O[58] or $NaNO_2$ and HBF_4.[56a] However, it seems that the observed yields were slightly inferiors compared to protocols employing crystalline salts. Clearly, a general and efficient procedure addressing the safety issue remains to be established.

As in alcoholic solvents a base is not required and temperatures can be maintained under 80 °C, a high chemoselectivity at the diazonium group can be reached in the presence of bromine and iodine atoms on the aryl partner. Sengupta and Sadhukhan have exploited this interesting property for the development of sequential couplings using the aryl partner **28** having a dual reactivity (Scheme 13).[70]



Scheme 13. Sequential Heck–Matsuda and Heck–Mizoroki couplings.[70]

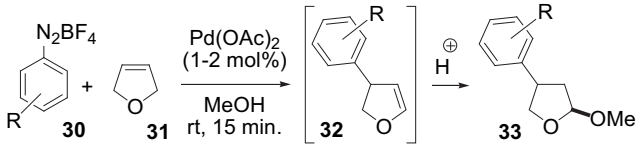
2. Heck–Matsuda reaction in heterocyclic chemistry

2.1. Oxygen heterocycles

Oxygen heterocycles of small to medium size are widely distributed in natural products and biologically active compounds.[71] They have attracted much attention from organic chemists due to the synthetic challenge posed by the extremely diversified structures found in nature.[72] The search for innovative, efficient, and environmentally friendly synthetic routes is still of actuality and the Heck–Matsuda arylation of heterocyclic olefins could certainly be a tool toward this end.

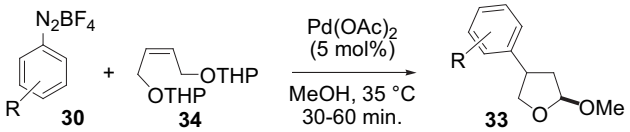
2.1.1. Five-membered oxygen heterocycles. Heterocyclic olefins have been successfully used in Heck–Matsuda reactions, giving synthetically relevant building blocks for natural products or biologically relevant targets synthesis. Sengupta et al. were pioneering in this area and reported the arylation of 2,5-dihydrofuran **31** with variously substituted aryl diazonium tetrafluoroborates (Scheme 14).[73] While *para*-substituted diazonium salts were efficient arylating agents whatever the electronic nature of the substituents, the more sterically hindered *o*-tolyl salt gave a disappointing low yield. As they worked under base-free conditions, the transient dihydrofuran intermediate **32** was in situ trapped as a γ-lactol ether **33** presumably due to the presence of HBF_4.

Interestingly Cacchi et al. described under similar conditions the preparation of similar γ-vinyl ethers starting from the THP derivative **34** of (*Z*)-2-butene-1,4-diol as a 2,5-dihydrofuran surrogate (Scheme 15).[74] Despite the good overall yields obtained, this approach does not appear to be particularly competitive over the procedure described by Sengupta et al. from an atom economy point of view.



R	Yield [%]	R	Yield [%]
H	80	4-Cl	86
4-OMe	86	4-CO_2Et	80
4-Me	77	2-Me	26

Scheme 14. Arylation of 2,5-dihydrofuran with diazonium salts by Sengupta et al.[73]

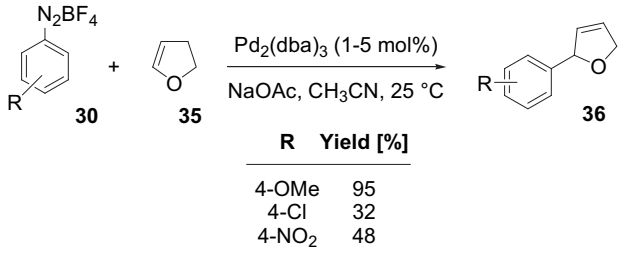


R	Yield [%]	R	Yield [%]
H	76	4-CN	74
4-OMe	72	4-COMe	72
4-Me	89	3-CF_3	67
4-F	72	2,4-Me_2	68
4-Cl	76	2-Me-4-F	90
4-I	34	2-OMe	76
4-CO_2Me	83	2-Cl	64
4-NO_2	72	2-Br	77

Scheme 15. Preparation of γ-lactol ether using the Heck–Matsuda arylation by Cacchi et al.[74]

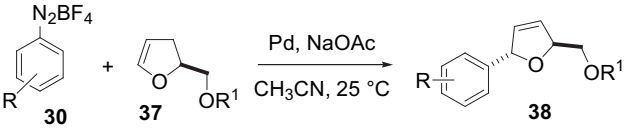
Under basic conditions in CH_3CN, γ-lactol ethers are not formed and the arylated dihydrofurans can be isolated. However, as reported by the team of Professor Correia the yields of isolated products are strongly dependant of the nature of the diazonium salt, electron rich ones giving better results than electron deficient ones (Scheme 16).[75]

Following the same strategy, Correia et al. reported the diastereoselective arylation of chiral dihydrofurans **37** with neutral and electron rich aryl diazonium salts **30** (Scheme 17).[76] The authors noticed that, depending on the coupling partner, either Pd(II)



R	Yield [%]
4-OMe	95
4-Cl	32
4-NO_2	48

Scheme 16. Arylation of 2,3-dihydrofuran by Correia et al.[75]

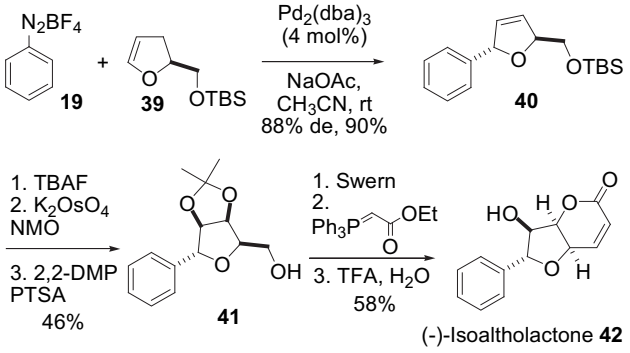


R	R^1	Pd	Additive	dr [%]	Yield [%]
H	H	2% $Pd_2(dba)_3$	--	84	53
4-OMe	H	2% $Pd_2(dba)_3$	--	86	63
4-$NHCO_2Me$	H	2% $Pd_2(dba)_3$	--	84	70
4-OMe	TBS	4% $Pd(OAc)_2$	anisole	90	86

Scheme 17. Arylation of chiral 2,3-dihydrofurans by Correia et al.[76]

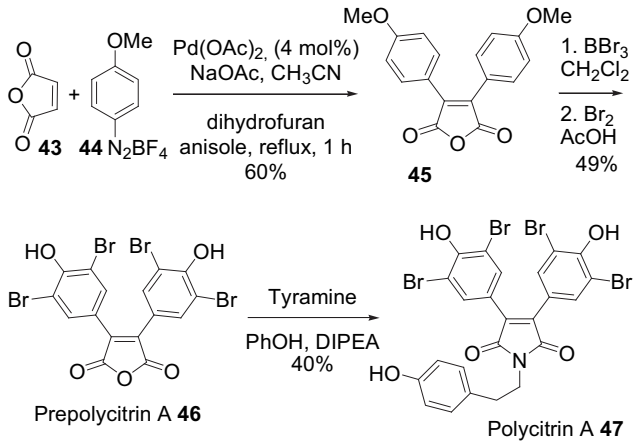
or Pd(0) pre-catalyst were required for optimal results. When a Pd (II) was used, such as $Pd(OAc)_2$, for instance, it was in situ reduced by an equimolar amount of dihydrofuran and the generated Pd(0) nanoparticles were stabilized by addition of anisole.

This synthetically relevant methodology was applied to the total synthesis of (−)-isoaltholactone **42** (Scheme 18). Arylation of dihydrofuran **39**, easily obtained from L-glutamic acid in five steps, with benzene diazonium tetrafluoroborate **19** was performed in basic acetonitrile to give the corresponding dihydrofuran **40** in an excellent yield (90%) and good diastereoselectivity (88% dr). TBAF-mediated desilylation gave the free alcohol, which served as a directing group for the dihydroxylation step with potassium osmate. After protection of the triol as an acetonide **41**, the unprotected primary alcohol was oxidized by the Swern protocol. The resulting aldehyde was reacted with ethyl [bis(3-methylphenoxy) phosphoryl]acetate to give the expected *cis*-olefin. The final ring-closing followed by the acetonide deprotection were realized one-pot under acidic conditions with aqueous TFA to give (−)-isoaltholactone **42**.



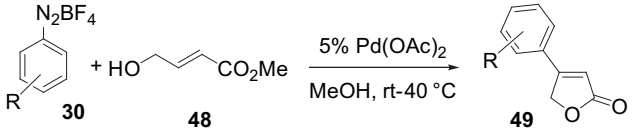
Scheme 18. Total synthesis of (−)-Isoaltholactone **42** by Correia et al.[76]

Still using analogous protocols, the same research group also reported the selective mono- or di-arylation of maleic anhydride.[77] However, only the diarylation was synthetically useful since the monoarylation required a substoichiometric amount (0.05 equiv) of the diazonium salt. This methodology was applied to a short synthesis of the marine alkaloids prepolycitrin A **46** and polycitrin A **47** (Scheme 19). Arylation of maleic anhydride with 4 equiv of 4-methoxybenzene diazonium tetrafluoroborate **44** was best performed using an in situ dihydrofuran-mediated reduction of Pd $(OAc)_2$, giving Pd(0) nanoparticles stabilized with anisole. Demethylation of both methyl ethers with BBr_3 cleanly furnished the corresponding bis-phenol, which was brominated with Br_2 to give the unstable natural product prepolycitrin A **46**. This latter was transformed into polycitrin A **47** by reaction with tyramine under basic conditions at elevated temperature (140 °C) with modest yield (40%).



Scheme 19. Total synthesis of Prepolucitrin **46** and polycitrin A **47** by Correia et al.[77]

On the other hand, the arylation of methyl 4-hydroxy-2-butenoate **48** in MeOH with $Pd(OAc)_2$ yielded 4-aryl butenolides **49** through a tandem Heck reaction-cyclization process. The procedure tolerated a wide variety of both electron rich and electron poor aryl diazonium salts **30** (Scheme 20).[78]

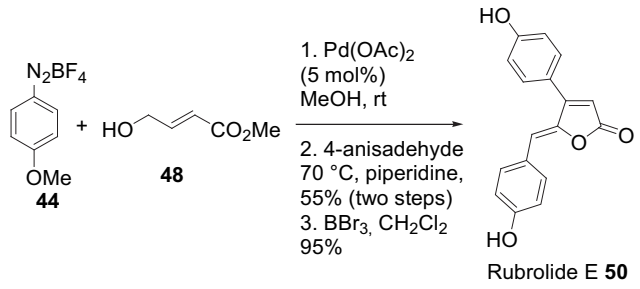


R	Yield [%]	R	Yield [%]
H	91	4-CO_2Me	79
4-OMe	73	4-NO_2	87
2-OMe	67	4-CN	54
4-Me	71	4-COMe	67
4-F	67	3-CF_3	73
4-Cl	81	2,4-Me_2	87
4-Br	86	2-Me-4-F	81
4-I	62	2-Me-4-OMe	75

Scheme 20. Arylation of methyl 4-hydroxy-2-butenoate **48** by Cacchi et al.[78]

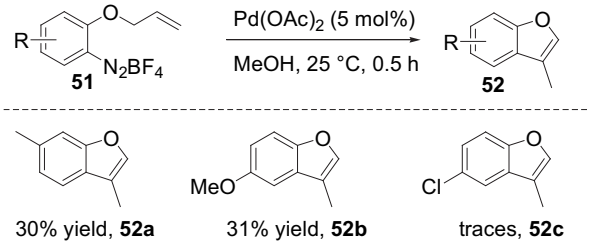
By using this method, authors also reported an expeditious synthesis of rubrolide E, a naturally occurring butenolide (Scheme 21). Arylation of methyl 4-hydroxy-2-butenoate **48** with 4-methoxybenzene diazonium tetrafluoroborate **44** followed by a Knoevenagel condensation with 4-anisaldehyde in the presence of piperidine furnished the protected rubrolide E in 55% yield over the two steps. Final treatment of this latter with BBr_3 gave rubrolide E **50** in high yield (95%).

An intramolecular approach for the synthesis of dihydrobenzofurans and benzofurans has been reported by Correia et al.



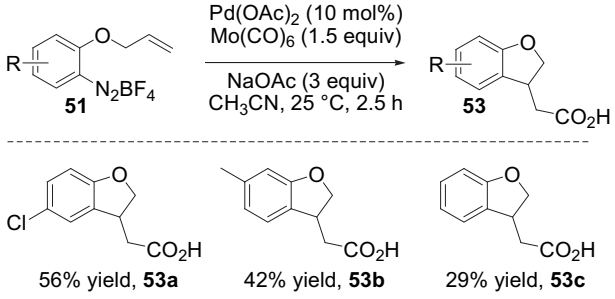
Scheme 21. Synthesis of rubrolide E **50** by Cacchi et al.[78]

(Scheme 22).[79] The intramolecular cyclization of 2-allyloxyaryl diazonium tetrafluoroborates **51** under palladium catalysis in MeOH at 50 °C without base gave low to modest yields of the corresponding benzofurans **52**.



Scheme 22. Synthesis of benzofurans **52** by Correia et al.[79]

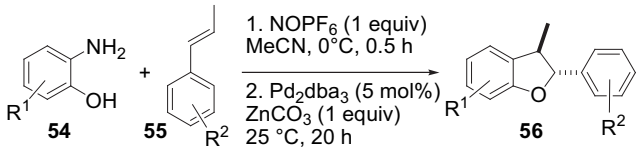
On the other hand, working in CH_3CN with NaOAc as base, Pd $(OAc)_2$ as catalyst and $Mo(CO)_6$ as CO source allowed sequential carbocyclization–carbonylation reactions for the preparation of dihydrobenzofurans (Scheme 23).



Scheme 23. Synthesis of dihydrobenzofurans by Correia et al.[79]

Sefkow et al. developed an intermolecular synthesis of benzofurans **56** via diazotation and palladium-catalyzed oxyarylation in a one-pot process from 2-aminophenols **54** and arylpropenes **55** in CH_3CN.[80] The procedure involves the conversion of 2-aminophenols **54** to the corresponding diazonium salts with $NOPF_6$ as NO source in CH_3CN. For safety reasons, diazonium salts are not isolated and Pd_2dba_3 as catalyst, $ZnCO_3$ as base, and arylpropenes **55** are added to the mixture for the oxyarylation step. With this procedure in hand, authors reported the use of a variety of 2-aminophenols **54** and arylpropenes **55** with, however, a quite limited scope (Scheme 24).

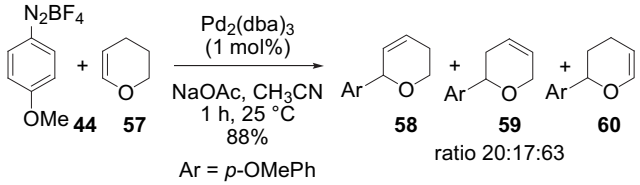
2.1.2. Six-membered oxygen heterocycles. Correia reported that the arylation of the simple 2,3-dihydropyrane **57** with 4-methoxybenzene diazonium tetrafluoroborate **44** occurred in CH_3CN with significant double-bond migration, giving a synthetically useless



R^1	R^2	Yield [%]	R^1	R^2	Yield [%]
4-Cl	4-OMe	79	H	2-Me	26
5-NO_2	4-OMe	49	H	2,4,6-OMe	18
5-CO_2H	4-OMe	59	H	2,5-OMe	26
4-CO_2H	4-OMe	44	H	3,4,5-OMe	70
5-CO_2Me	4-OMe	79	H	4-OH,5-OMe	81
4-CO_2Me	4-OMe	64	H	3,4-OMe	81
H	H	0	H	3,4-OCH_2O	80

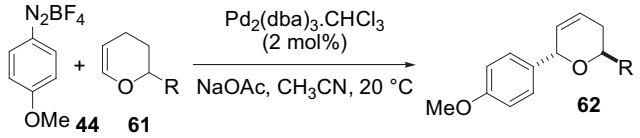
Scheme 24. Synthesis of dihydrobenzofurans **56** by Sefkow et al.[80]

mixture of three *C*-arylated dihydropyrans **5860** with, however, a good overall yield (88%) (Scheme 25).[75]



Scheme 25. Arylation of dihydropyran **57** by Correia et al.[75]

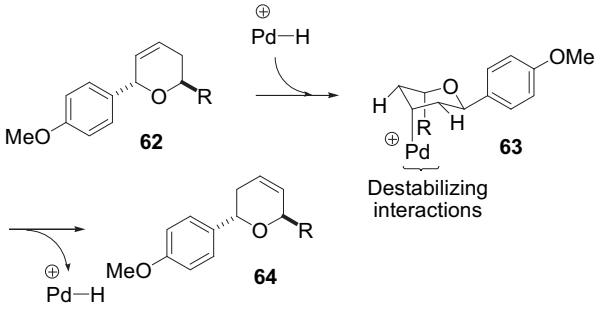
By contrast, the double-bond migration was not observed on substituted dihydropyrans. Indeed, Schmidt et al. reported that 6-substituted-2,3-dihydropyrans **61** could be arylated with high trans diastereoselectivity (>12:1) in CH_3CN with NaOAc as a base and $Pd_2(dba)_3{\cdot}CHCl_3$ as catalyst at room temperature (Scheme 26).[81]



R	Yield [%]
-$(CH_2)_4$-CH_3	82
-$(CH_2)_2$-Ph	80
-$(CH_2)_2$-Ph-4-OMe	83

Scheme 26. Arylation of racemic dihydropyrans by Schmidt et al.[81]

The double-bond migration, induced by Pd/H species, occurs from the formation of a σ-alkyl complex **63**, which upon *syn*-β-H-elimination give the isomerized product **64** (Scheme 27). In the presence of substituents (R≠H), the hydropalladation leading to



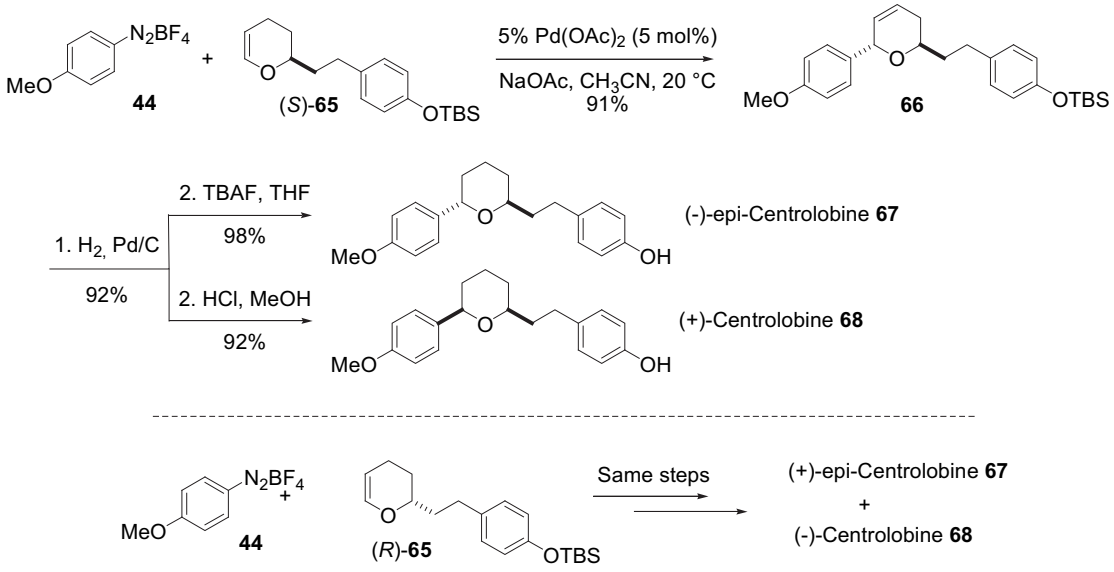
Scheme 27. Rational for the double-bond migration.

complex **63** would be strongly disfavoured due to destabilizing interactions between the Pd and R.

This synthetic methodology has been applied to the arylation of chiral dihydropyrans for the preparation of all four stereoisomers of centrolobine (Scheme 28).[82] Although the reason was not specified in the publication, $Pd(OAc)_2$ was preferred to $Pd_2(dba)_3 \cdot CHCl_3$. The mild conditions required for this reaction (room temperature) allowed excellent yields of arylated pyranes with very high diastereoselectivity (>98/2). A similar approach was also reported for the synthesis of *rac*-de-*O*-methyl centrolobine.[26]

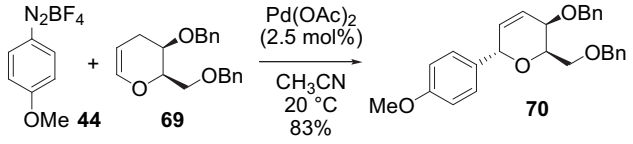
A new entry to Kavalactone natural products has been made possible by arylation of the pyranone **76** with $Pd_2(dba)_3$ as catalyst in PhCN and under microwave heating.[84] With this procedure yangonine **77** and (±)-dihydromethysticin **79** natural products have been prepared with good efficiency (Scheme 31).

The coupling of coumarin diazonium salts with styrene derivatives has been studied in a paper reporting the relationship between fluorescence properties and structure of substituted styrylcoumarins.[85] Fast reactions were observed in MeOH at 40 °C with $Pd(OAc)_2$ under base-free condition (Scheme 32). It is interesting to note that this work is one of the rare examples where the heterocyclic moiety is borne by the diazonium salt partner.



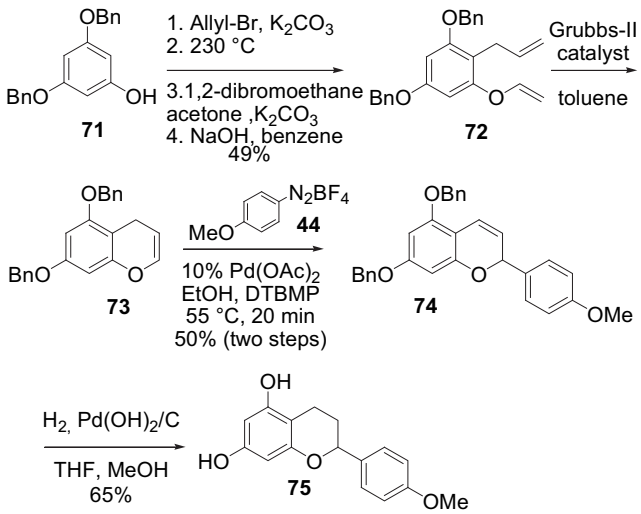
Scheme 28. Total synthesis of the four stereoisomers of centrolobine by Schmidt et al.[82]

The same group developed a related strategy for the preparation of the *C*-arylated glycoside **70** from the functionalized dihydropyran **69** (Scheme 29).[83] Authors showed that the use of a base was unnecessary and that isomerization of the double bond does not occur due to sterical hindrance.



Scheme 29. Synthesis of a *C*-aryl glycoside by Schmidt et al.[83]

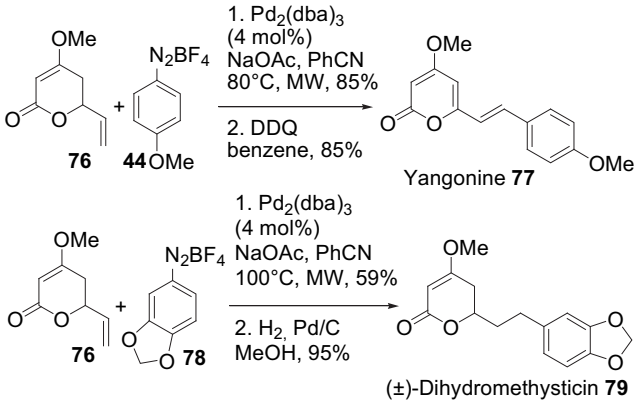
On the other hand, chromenes proved to be useful substrates where double-bond migration cannot occur.[75] Unfortunately, optimization studies showed that experimental conditions were quite substrate-dependant particularly concerning the choice of the solvent. Although yields were modest (50–60%), an interesting application was disclosed with the total synthesis of the natural flavan **75** isolated from Amazonian Shrub (Scheme 30). The 4*H*-chromene **73** was easily prepared in five steps from the 3,5-bis (benzyloxy)phenol **71** using a ring-closing metathesis as a key step. Arylation of the 4*H*-chromene **73** was realized in EtOH with 2,6-di-*tert*-butyl-4-methylpyridine as proton sponge. In this case, EtOH was preferred to CH_3CN as solvent likely due to the enhanced reactivity of the Ar/Pd^+ intermediate in this media toward the 4*H*-chromene **73**. A final cleavage of benzyl protecting groups and hydrogenation of the double bond by the aid of $Pd(OH)_2/C$ under H_2 atmosphere furnished the targeted natural flavan **75**.



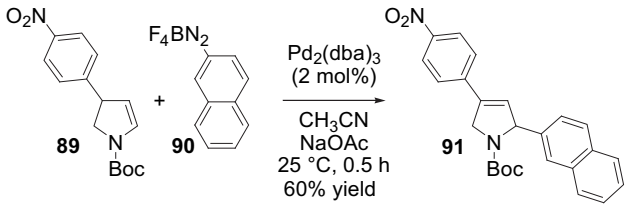
Scheme 30. Arylation of chromene **73** by Correia et al.[75]

2.2. Nitrogen heterocycles

Nitrogen heterocycles are found in a number of alkaloid natural products[86] and pharmacologically active compounds.[87] In this context, efficient synthetic strategies devoted to their preparation are of crucial importance.[88]



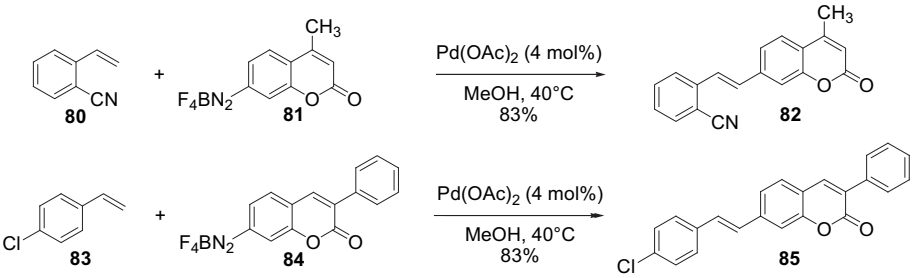
Scheme 31. Synthesis of Kavalactones **77** and **79** by Correia et al.[84]



Scheme 34. Second arylation of 2,3-dihydropyrroles by Correia et al.[90]

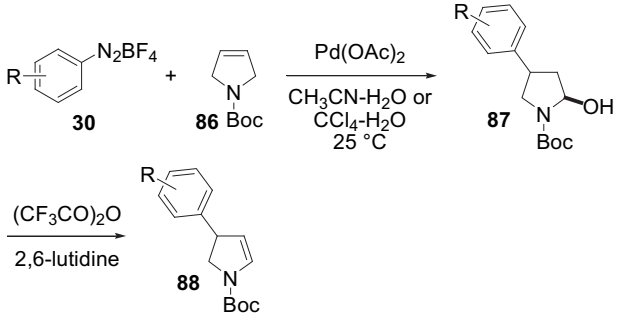
authors, require $Pd_2(dba)_3$ as palladium source and NaOAc as a base in CH_3CN.

This methodology has also been applied to the synthesis of natural product-like compounds.[91] For instance, a short approach to aryl pyrrolizidines has been developed (Scheme 35).[92] Indeed, the enecarbamates **88a**,**b** were subjected to a [2+2] cycloaddition step with



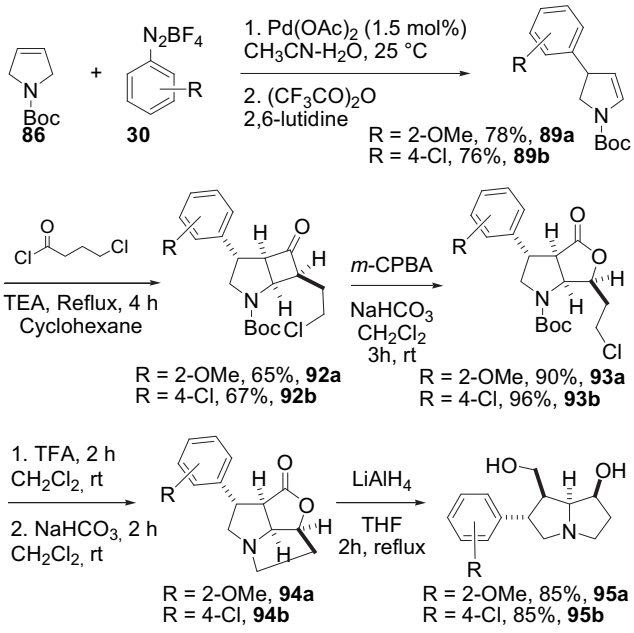
Scheme 32. Selected examples of styrylcoumarins by Xu et al.[85]

2.2.1. Five-membered nitrogen heterocycles. Arylation of 2,5-dihydropyrroles with aryl halides and aryl triflates gave rise to a mixture of isomerized and diarylated products allowing the isolation of compound **88** in modest to good yields (40–70%).[89] Moreover, the 'traditional' conditions required phosphine ligands, a large excess of the olefin (10 equiv) and elevated temperatures (100 °C). Correia et al. have thus intensively studied this approach by using aryl diazonium tetrafluoroborates as arylating agents. Toward this end, the Brazilian group developed an aqueous biphasic catalytic system made of $Pd(OAc)_2$ as palladium source under ligand-free and base-free conditions at room temperature (Scheme 33).[90] As a base was omitted, the 2,5-dihydropyrrole **86** was smoothly converted to the corresponding arylated lactamols **87**, which was rapidly submitted to dehydration with TFAA and 2,6-lutidine to produce the expected arylated pyrroles **88** in good overall yields.



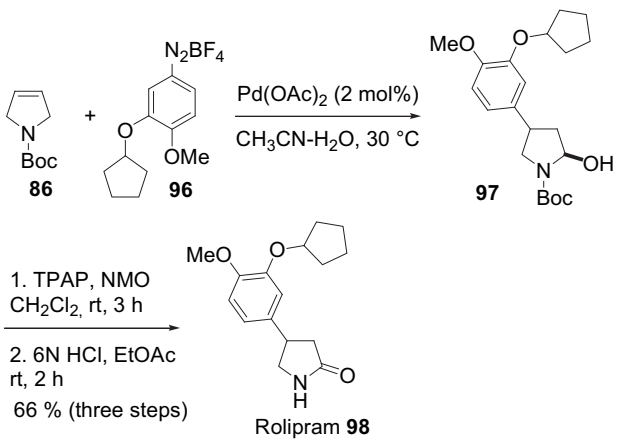
Scheme 33. General strategy for the arylation of 2,5-dihydropyrroles by Correia et al.[90]

A second arylation can be carried out on the 3-arylated-2,3-dihydropyrrole **89** to provide the corresponding 2,4-diarylated product **91** (Scheme 34). The best conditions reported by the the 2-chloroethyl ketene, in situ generated, from 4-chlorobutanoyl chloride and triethylamine to give the *endo*-(2-chloroethyl)cyclobutanones **92a**,**b**. These later were then submitted to a highly regioselective Baeyer–Villiger ring expansion with *m*-CPBA, furnishing the lactones **93a**,**b** with good yields. Acidic cleavage of the Boc-protecting group followed by an intramolecular cyclization gave the tricyclic compounds **94a**,**b**. Last, reductive cleavage of the lactone functionality provided the corresponding aryl pyrrolizidines **95a**,**b**.



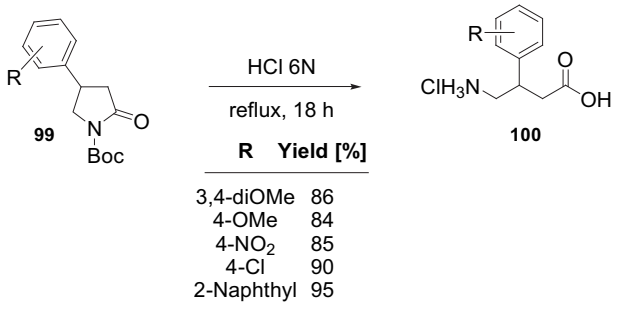
Scheme 35. Synthesis of aryl pyrrolizidines by Correia et al.[92]

Alternatively, the lactamol intermediate can be oxidized into the corresponding lactam. This methodology has been applied to the preparation of Rolipram **98**, a PDE4-inhibitor used as an anti-inflammatory drug (Scheme 36).[93] Arylation of the 2,5-dihydropyrrolidine **86** with the diazonium salt **96** led to the lactamol **97**, which was isolated and quickly oxidized in the presence of TPAP and NMO to give the corresponding lactam. Acidic cleavage of the Boc-protecting group furnished Rolipram **98** in quantitative yield.



Scheme 36. Synthesis of Rolipram **98** by Correia et al.[93]

Acidic hydrolysis of the lactam also furnished a novel entry to GABA analogues including Baclofen, a $GABA_B$ receptor agonist used for the treatment of spastic movement disorders (Scheme 37).[94]



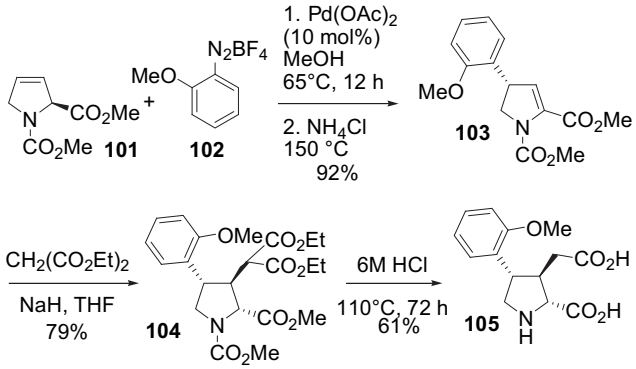
Scheme 37. Synthesis of GABA analogues by Correia et al.[94]

The regio- and stereo-selective arylation of 3-dehydroproline methyl ester **101** allows a rapid entry to aryl kainoids.[95] Indeed, the Heck–Matsuda reaction of **101** with 2-methoxybenzene diazonium tetrafluoroborate **102** gave the α,β-unsaturated ester **103** that underwent a smooth Michael addition reaction with sodium ethyl malonate (Scheme 38). Acidic hydrolysis of the triester **104** was accompanied by a spontaneous decarboxylation to afford the *trans*-aryl kainoid acid **105**.

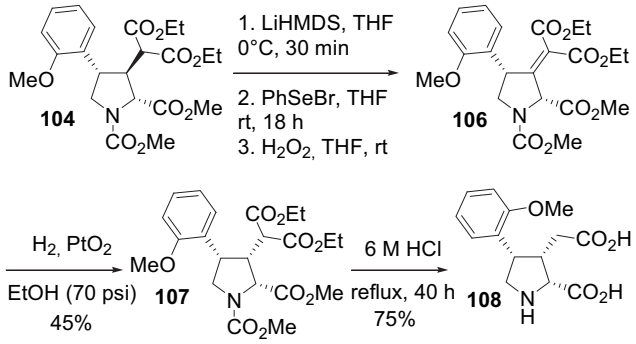
Others stereoisomers were also described by the epimerization of the malonyl substituent at C3 following the strategy of Rubio et al.[96a,b] The phenylselenylated trimester, under oxidative H_2O_2-mediated deselenylation, provided the corresponding olefin **106**, which was stereoselectivity reduced under hydrogen atmosphere. A last sequential hydrolysis–decarboxylation step in acidic media allowed the isolation of the all *cis*-stereoisomer **108** (Scheme 39).

Alternatively, inversion of configuration of ester at C2 produced the C2,C3-*trans*-epimer **109** (Scheme 40).

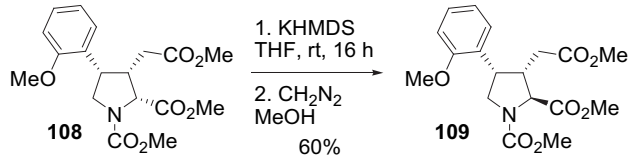
Endocyclic enecarbamates, and especially 4,5-dihydropyrroles, are useful substrates for the Heck reaction with diazonium salts that allow an entry to various pyrrolidine alkaloids. Correia et al.



Scheme 38. Synthesis of aryl kainoids by Correia et al.[95]

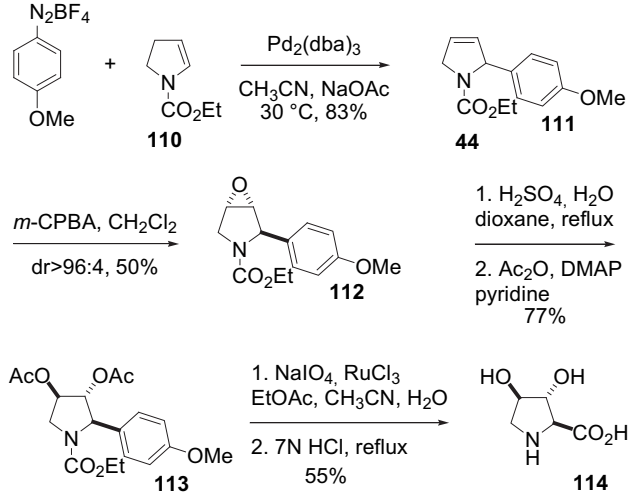


Scheme 39. Synthesis of aryl kainoids by Correia et al.[96a,b]



Scheme 40. Synthesis of aryl kainoids by Correia et al.[95]

reported the preparation of dihydroxylated prolines and iminocyclitols by exploiting the properties of electron rich aromatic rings as latent carboxylic acid mask upon oxidative cleavage (Scheme 41).[97] The arylation step proceeded under mild conditions in CH_3CN with



Scheme 41. Synthesis of dihydroxylated prolines by Correia et al.[97]

NaOAc as a base to avoid any isomerization processes as well as the formation of lactamols. The arylated pyrrolidine **111** can be oxidatively functionnalized by epoxidation or dihydroxylation of the double bond. Then, oxidative cleavage of the aryl ring unmasks the corresponding carboxylic acid **114** that can be further reduced into primary alcohol.

Chiral 4,5-dihydropyrroles can be diastereoselectively arylated with diazonium salts for the preparation of highly substituted pyrrolidine including (−)-codonopsinine **115**, (−)-codonopsine **116**,[98,99] and various *C*-aryl azasugars (Fig. 3).[100]

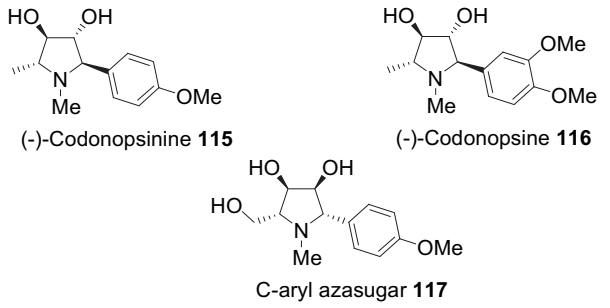
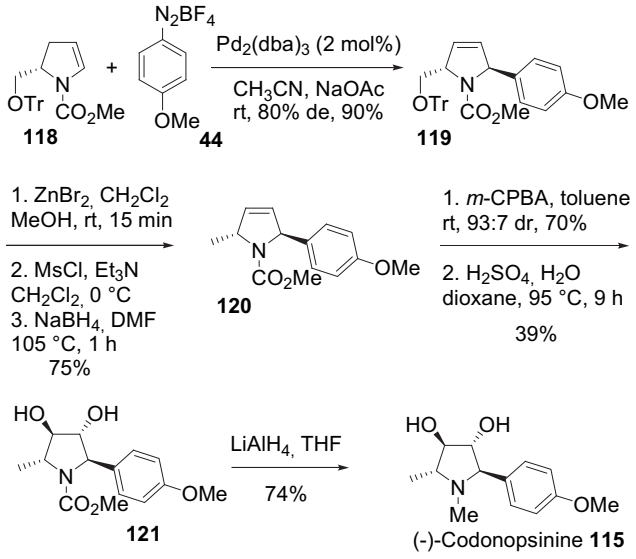


Fig. 3. Structure of (−)-codonopsinine **115**, (−)-codonopsine **116**, and *C*-aryl azasugar **117**.

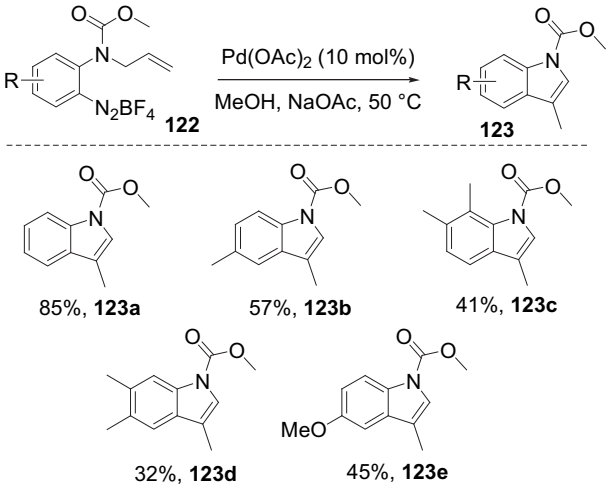
The results reported by the authors are a little bit confusing since initial optimization studies[98] described the arylation of endocyclic carbamates having a protected hydroxymethyl group at C5 with a perfect diastereoselectivity in EtOH, with 2,6-di-*tert*-butyl-4-methylpyridine as base and $Pd(OAc)_2$ as catalyst. However, in a subsequent publication[99] authors reported the same coupling with a 65–75% diastereoisomeric excess (de), still in favour of the trans-isomer. Interestingly, an alternative catalytic system using Pd_2dba_3 as catalyst and NaOAc as a base in CH_3CN at room temperature allowed lower palladium loading (1–2 mol %) again with similar de.

This methodology has been applied to the synthesis of (−)-codonopsinine **115** (Scheme 42).[79] Arylation of endocyclic enecarbamates **118** with 4-methoxybenzene diazonium salt **44** provided the corresponding dehydropyrrolidine **119** in good yield with 80% de in favour of the *trans*-stereoisomer. Cleavage of the trityl group with $ZnBr_2$ followed by deoxygenation via sequential mesylation–reduction steps furnished the compound **120**. Epoxidation of the double bond with a 86% de in favour of the required isomer followed by an acidic hydrolysis allowed the installation of the targeted *trans*-diol function **121**. Last, the methylcarbamate was reduced with $LiAlH_4$ to provide (−)-codonopsinine **115** in 19% yield over seven steps from **118**. A similar synthetic route was employed for the synthesis of (−)-codonopsine **116**.



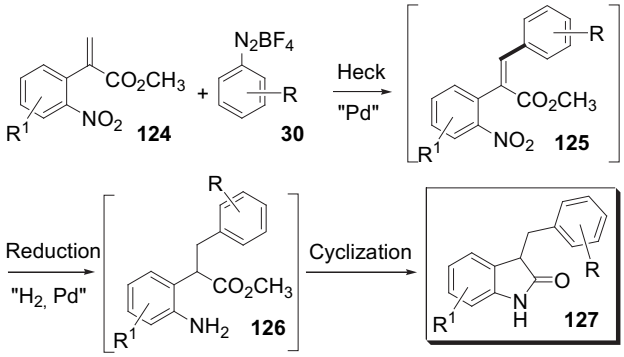
Scheme 42. Synthesis of dihydroxylated prolines by Correia et al.[99]

The preparation of indoles has also been described by Correia et al., based on the methodology developed for the synthesis of benzofurans.[79] Intramolecular cyclization of 2-*N*-allyl aryl diazonium tetrafluoroborates **122** in MeOH, with NaOAc and a high loading of $Pd(OAc)_2$ (10 mol %) furnished the corresponding indoles **123a–e** with modest to good yields (Scheme 43). Unfortunately, the reaction yields are highly structure-dependant and the scope of this methodology appears to be quite narrow. In some cases, the skip of MeOH by CH_3CN can improve the yield of this transformation.



Scheme 43. Synthesis of indoles by Correia et al.[79]

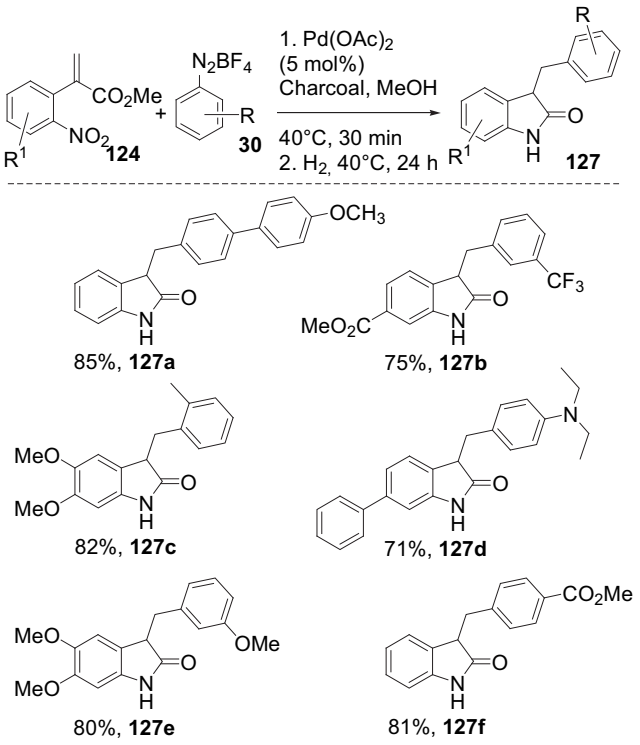
Our laboratory has developed a one-pot tandem Heck-reduction-cyclization (HRC) sequence from a single bifunctional, in situ generated, Pd(0)/C catalyst for the preparation of C3-benzylated oxindoles (Scheme 44).[101]



Scheme 44. Overall HRC strategy by Felpin et al.[101]

This one-pot sequence takes advantage of the following features: (1) the simple experimental conditions (without any ligand and base) required for the coupling of diazonium salts with highly functionalized olefins, (2) the dual reactivity of the Pd(0)/C catalysts (coupling vs reduction). Extensive optimization studies showed

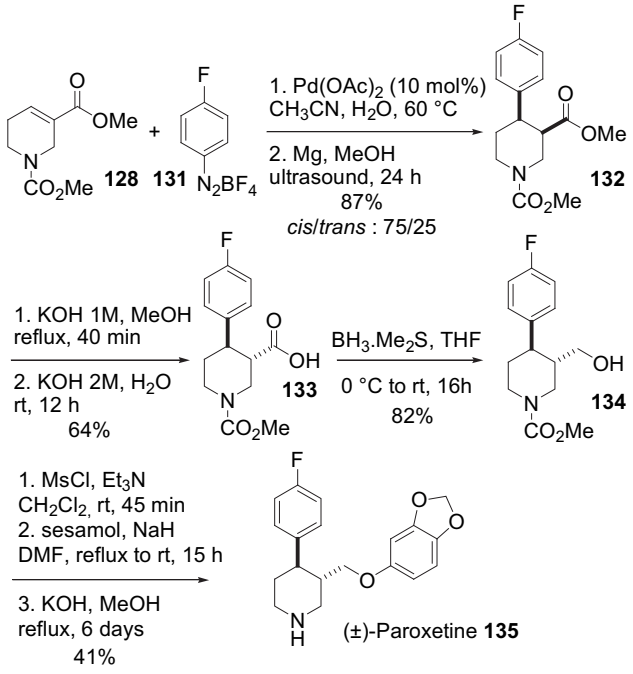
that Pd(II)/C and Pd(0)/C catalysts obtained from commercial sources were ineffective while Pd(0)/C catalyst, in situ generated from $Pd(OAc)_2$ and charcoal, gave excellent results (Scheme 45). It is important to note that the only waste produced during the Heck–Matsuda coupling (i.e., HBF_4) acts as a co-catalyst for the subsequent reduction-cyclization steps. It is one of the rare examples where a waste has such an interesting feature. The role of the support was also evaluated and charcoal was found to be the best one over carbon nanotubes, graphite, polyaniline, and mineral oxides.[102]



Scheme 45. Synthesis of oxindoles by Felpin et al.[101]

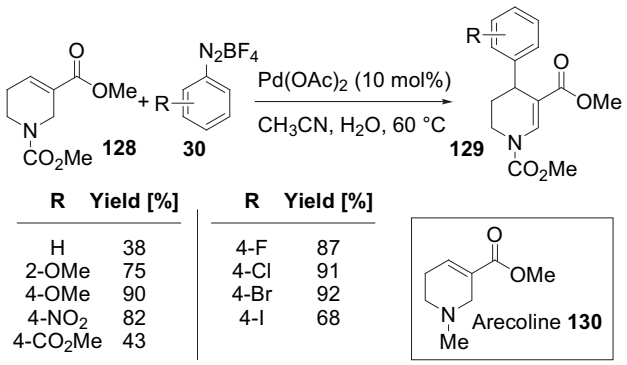
2.2.2. Six-membered nitrogen heterocycles. Arylation of tetrahydropyridines, derived from natural product arecoline **130**, occurred smoothly to give the desired Heck adduct (Scheme 46).[103] Arylations can be carried out in either CH_3OH or CH_3CN/H_2O mixture at 60 °C with good yields. However, faster reaction rates were usually observed with methanol. Protection of the nitrogen as a carbamate was mandatory for the success of the coupling since arecoline **130** as a free base was inert under Heck arylation. The use of a base was not required as it did not affect yields and even caused a decline in reaction rates. In order to attain high conversion, high loading of palladium (5–10 mol %) was needed.

This methodology served as a support for the synthesis of (±)-paroxetine **135**, a selective serotonin reuptake inhibitor antidepressant (Scheme 47).[103] Arylation of tetrahydropyridine **128** followed by the reduction of the enamino-ester with Mg furnished 4-arylpiperidine **132** as a cis/trans (75/25) mixture. The cis/trans mixture was isomerized into the trans-isomer and the ester function was saponified in aqueous KOH to give the corresponding carboxylic acid **133**, which was reduced with borane dimetylsulfide complex into alcohol **134**. After phenylation of **134** and basic hydrolysis of the carbamate function under extensive reflux, (±)-paroxetine **135** was isolated in a fairly good overall yield (19%) for eight steps from the arecoline derivative **128**.

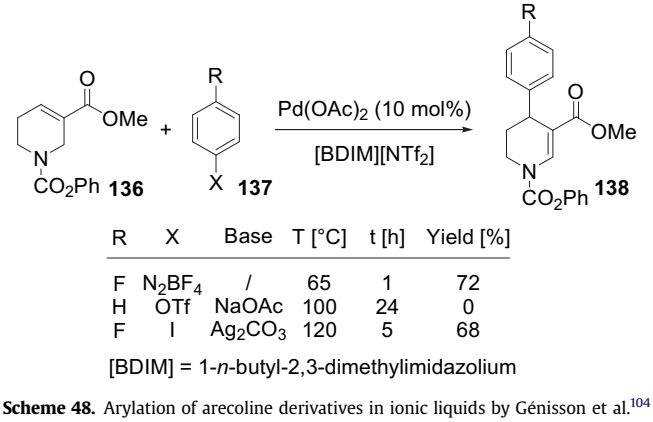


Scheme 47. Synthesis of (±)-paroxetine **135** by Correia et al.[103]

In a related study, Genisson et al. reported the arylation of arecoline derivatives with aryl diazonium salts in various room temperature ionic liquids (Scheme 48).[104] They observed a strong influence of the counterion and found that lipophilic ionic liquids gave the best results. However, in spite of excellent overall catalytic activity with aryl diazonium salts, no asymmetric induction was observed with



Scheme 46. Arylation of arecoline derivatives by Correia et al.[104]



Scheme 48. Arylation of arecoline derivatives in ionic liquids by Génisson et al.[104]

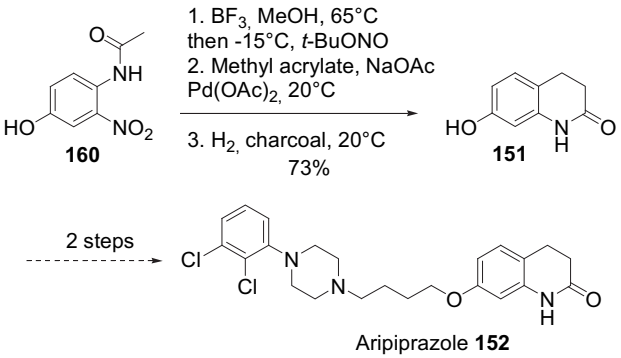
chiral ionic liquids either as solvent or additive. Interestingly, aryl triflates were unreactive in similar conditions and aryl iodides gave usually lower yield and catalytic activity even under more drastic conditions at 120 °C.

Following our Heck-reduction–cyclization (HRC) strategy previously developed for the synthesis of oxindoles, we recently reported the preparation of variously substituted C3-benzylated-2-quinolones[105] and 4-benzyl-1,2-dihydroisoquinolin-3-ones[106] (Scheme 49). While the general synthetic strategy based on the HRC sequence remained similar to the one described for oxindoles,[101] the nature of the coupling partners can be modified in order to diversify the substituents on the heterocycles.

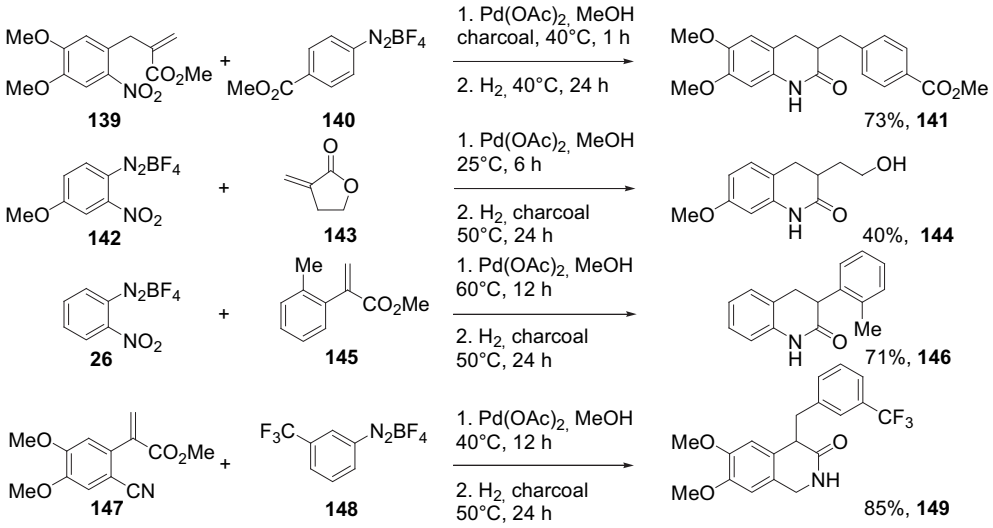
The methodology has been raised to a higher degree of complexity with a Heck-reduction–cyclization–debenzylation (HRCD) sequence leading to quinolone **151**, a known intermediate in the synthesis of the antipsychotic drug aripiprazole **152** (Scheme 50).[105]

The recyclability of the in situ generated Pd(0)/C catalyst was deeply studied (Scheme 51).[105,106] It appeared that the reused catalyst was ineffective for Heck–Matsuda reactions where a Pd(II) pre-catalyst is required.[67] However, the recycled Pd(0)/C showed excellent catalytic activity for reductive processes and Suzuki–Miyaura cross-couplings where a Pd(0) pre-catalyst is usually preferred.[107]

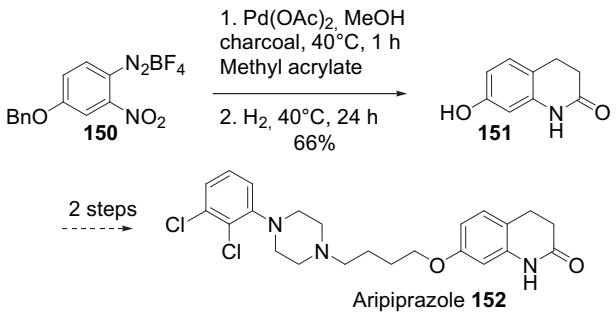
At the same time, Schmidt et al. pursued a strategy that used acetaniline **160** as starting material for the preparation of aripiprazole key fragment **151**.[108] Schmidt's route was realized through one-pot sequential diazotation-Heck-reduction-cyclization reactions (Scheme 51). The elegant one-flask sequence comprises six steps and proceeds in an excellent 73% overall yields. Compared to our strategy, the approach from the Schmidt's group requires neither a benzyl protecting group nor the manipulation of sometimes hazardous crystalline diazonium salts.



Scheme 51. Synthesis of the aripiprazole key fragment **151** by Schmidt et al.[108]



Scheme 49. Synthesis of quinolone skeletons by Felpin et al.[105,106]



Scheme 50. Synthesis of the aripiprazole key fragment **151** by Felpin et al.[105]

3. Conclusion

Although it has been discovered during the seventies, the Heck–Matsuda reaction has been much less studied than the traditional Heck–Mizoroki reaction involving aryl halides as electrophiles. However, it has been observed, in the last ten years, an increasing interest for the chemistry of diazonium salts especially combined with palladium catalysis. The Heck–Matsuda reaction using aryl diazonium salts could, indeed, be considered as an improved procedure over the traditional Heck–Mizoroki coupling since transformations can be carried out at usually lower temperatures (usually 25–60 °C) under ligand-free and even base-free conditions. Although quite high palladium loadings have been frequently reported, recent improvements, especially from our laboratory, have addressed this issue. The synthetic relevance of the Heck–Matsuda reaction can be regarded in the number of recent examples reported in heterocyclic chemistry and natural product synthesis. Further progress would lead to a deeper understanding of the role of the counterion in the catalytic cycle involving cationic palladium species. Moreover, safety issues related to the use of diazonium salts need to be considered, especially for large scale applications. All in all, we believe that the Heck–Matsuda reaction would be an essential tool for every synthetic chemist, from both

academic and industrial laboratories, desiring to create C–C bonds in very mild conditions.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.02.051.

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Biographical sketch

François-Xavier Felpin was born in Villefranche-sur-Saône (France) in 1977. He received his Ph.D. degree in 2003 from the University of Nantes under the supervision of Professor Jacques Lebreton working on synthesis of alkaloids. After his Ph.D., he was engaged in a post-doctoral position with Professor Robert S. Coleman at The Ohio State University working on the synthesis of Mitomycin. In 2004 he joined the University of Bordeaux as an Assistant Professor and he received his habilitation in 2009. His research interests include heterogeneous and homogeneous sustainable catalysis as well as medicinal chemistry.

Luma Nassar-Hardy was born in Khobar (Saoudi Arabia) in 1979. She finished her B.Sc. in chemistry from Beirut Arab University (Lebanon) in 2003, and in 2008 she completed her M.Sc. in organic chemistry from the University of Bordeaux (France). She is now pursuing her Ph.D. at the University of Bordeaux under the direction of Professor Eric Fouquet and Doctor François-Xavier Felpin.

François Le Callonnec was born in Nantes (France) in 1986. In 2008, he graduated his B.Sc., and in 2010 he completed his M.Sc. in organic chemistry from the University of Bordeaux (France). He is now pursuing his Ph.D. at the University of Bordeaux under the direction of Professor Eric Fouquet and Doctor François-Xavier Felpin.

Eric Fouquet was born in Lourdes (France) in 1963. He studied at Paul Sabatier University of Toulouse, where he obtained a DEA in 1987. He moved to the Ecole Polytechnique in Palaiseau to prepare a Ph.D., obtained in 1991 under the direction of Dr. Samir Z. Zard. As he got a position of 'Chargé de Recherche' at the CNRS, in October 1991, he joined the group of Professor Michel Pereyre in the Laboratory of Organic and Organometallic Chemistry in Bordeaux. After spending one year in 1994, as Post-doctoral Research Fellow, in the laboratory of Professor. William B. Motherwell at UCL (London), he went back to his former group in Bordeaux, where he took up in 2000 his present position, as Professor in Organic Chemistry, at the Institute of Molecular Sciences. His scientific interests include all aspects of organotin chemistry, as well as coupling reactions catalyzed by transition metals. He develops as well methodologies for the synthesis of condensed polyphenols (tannins) and rapid chemistry for the introduction of short-lived radiotracers such as ^{11}C and ^{18}F in bioactive compounds.