Synthesis of enamines, enol ethers and related compounds by cross-coupling reactions

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Received (in Cambridge, UK) 15th October 2004, Accepted 29th November 2004
First published as an Advance Article on the web 17th January 2005
DOI: 10.1039/b415954c

For several decades, enamines and related compounds have been used as intermediates in organic synthesis and many methods are known for their preparation. Most of the synthetic protocols, however, require harsh reaction conditions. Recently, a new approach has emerged, inspired by the analogous arylation of amines catalysed by palladium or copper complexes (Buchwald–Hartwig reaction). Simultaneous and independent work from several research groups has led to the development of very powerful protocols for the preparation of enamines and their derivatives that require only readily available starting materials and proceed under very mild reaction conditions. Noteworthy is the fact that in less than five years an almost unknown reaction has reached such a high level of scope and generality that it is now very frequently applied in total syntheses of natural products.

Introduction

In the last few decades, metal-catalysed conversions of unsaturated organohalides into other heteroatom functionalised products has attracted much attention.[1] In particular the findings by Buchwald and Hartwig led to a broadly applicable methodology for cross-couplings of aryl halides and sulfonates with nitrogen- and oxygen-containing substrates giving anilines and phenyl ethers, respectively.[2] In the light of this development and with the goal of efficiently synthesizing pharmaceutically attractive natural products such as antibiotics[3] or the antitumor macrolides lobatamides and oximidines (Fig. 1),[4] several groups have recently focused on investigating palladium- and copper-catalysed coupling reactions of vinylic substrates leading to enamines, enamides, and enol ethers (Fig. 2).

In general, enamines (**1**) and their *N*-acylated derivatives (enamides, **2**) have long been known as valuable synthetic intermediates, which found numerous applications in organic synthesis.[5,6] Most commonly, the former are prepared by condensation reactions of secondary amines with carbonyl compounds in the presence of a water scavenger and a Brønsted or Lewis acid. The relatively harsh reaction conditions generally required for this transformation cause low functional group tolerance, and prompted the development of alternative methods, such as hydroaminations of alkynes[7] or methylenations of amides.[8] Enamides (**2**) can be obtained by *N*-acylations of imines,[5] and the oxygen analogues of

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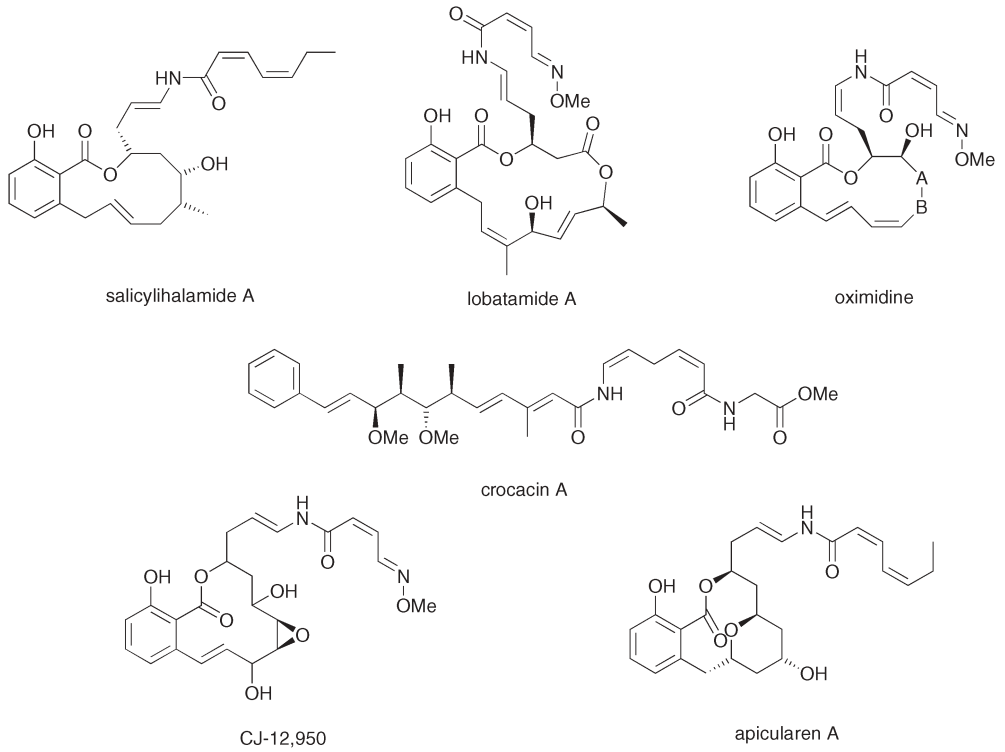


Fig. 1 Naturally occuring enamides.

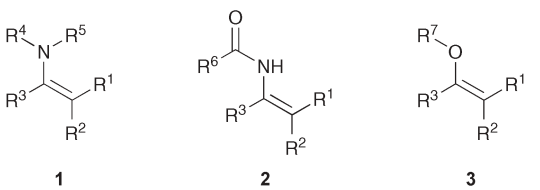


Fig. 2 Enamines, enamides and enol ethers.

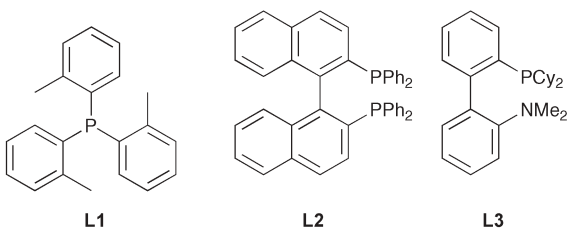


Fig. 3 Representative examples of successfully applied phosphines for the Buchwald–Hartwig arylation of amines: P(*o*-tolyl)$_3$ (**L1**), BINAP (**L2**) and 2-dicyclohexylphosphino-2′-dimethylaminobiphenyl (**L3**).

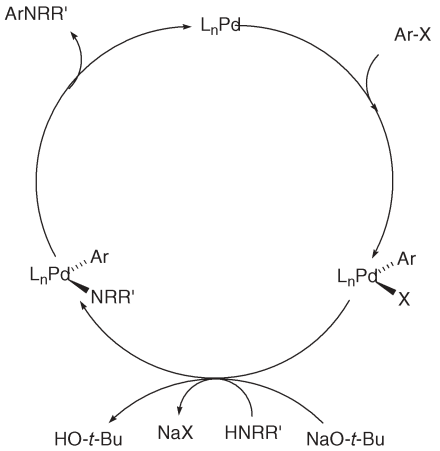
enamines, enol ethers, **3**, are commonly prepared by *O*-alkylation of enolates or base-catalysed addition of alkanols to acetylene.[9] More recently, vinyl esters and iridium catalysts have been used for their synthesis.[10] Industrially, enol ethers are particularly important, finding applications as monomers in the production of oxygen-containing vinyl polymers.

In this review, the recently developed alternative enamine, enamide, and enol ether syntheses using cross-coupling reactions starting from vinyl halides and sulfonates are summarised. Furthermore, we illustrate the value of this novel methodology by describing total syntheses of biologically active natural products, which were previously more difficult to prepare or even remained inaccessible.

Palladium-catalysed cross-coupling reactions

Tremendous progress has been achieved in the field of palladium-catalysed cross-coupling reactions in the last decades.[1] In this context, the discoveries by Buchwald and Hartwig led to the development of a large variety of catalysts for the amination of aryl halides under mild reaction conditions, which have a rather wide substrate scope.[2] Although the experimental details can vary depending on the substrate structures, the typical procedure involves the use of catalytic amounts of a palladium source [commonly $Pd(OAc)_2$ or Pd_2dba_3] in combination with a phosphine ligand (for some representative examples, see Fig. 3), and an excess of base (*i.e.* NaO-*t*-Bu or Cs_2CO_3) in refluxing toluene.

Mechanistic details of palladium-catalysed amination reactions of aryl halides have extensively been studied, especially for the "first generation" catalysts.[11] The generally accepted mechanism is depicted in Scheme 1. It involves a phosphine–palladium(0) complex (either formed by reduction of Pd(II) or by simple ligand exchange, when a Pd(0) source is used), which undergoes oxidative addition of the aryl halide. In the presence of an amine and a base the resulting palladium(II) complex is then converted into the corresponding arylpalladium amide. Reductive elimination finally yields the aryl amine and regenerates the palladium(0) complex, closing the catalytic cycle.



Scheme 1

Although no kinetic or mechanistic studies of the analogous vinylation reaction of amines and amides have yet been reported, it seems reasonable to assume that similar catalytic cycles operate here as well. It is therefore not surprising that all methodologies developed so far utilise similar reagent combinations as in the aryl amination reactions.

Enamines

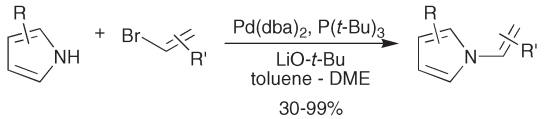
Although vinyl halides had been known to be suitable partners in cross-coupling reactions (such as Heck, Suzuki, Sonogashira couplings, *etc.*),[1] it was not until 2002 that they were used in palladium-catalysed C–N bond-forming reactions. In that year, Voskoboynikov described the preparation of *N*-vinyl azoles (Scheme 2), which served as monomers for the synthesis of poly(*N*-vinylazoles) to be used as semiconductors and photosensitive materials.[12] For the cross-coupling of indole and *trans*-β-bromostyrene, a combination of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ in a mixture of toluene and DME proved to be optimal. Interestingly, the nature of the base played a major role. Both too weak and too strong bases lowered the yield, the latter due to competitive β-eliminations. Finally, use of LiO-*t*-Bu (or preformed indolyllithium) as base gave the desired product in quantitative yield. The reaction was stereospecific and proceeded with complete retention of configuration at the double bond. Other azoles (including pyrrole, carbazole and derivatives) and vinyl bromides (*trans*-β-bromostyrene, α-bromostyrene, 2-bromopropene and vinyl bromide) were successfully coupled at temperatures ranging between 50 and 100 °C.[12]

A few months later, Barluenga communicated for the first time on the cross-coupling of alkenyl bromides and non-aromatic secondary amines (Scheme 3). A catalyst screening with morpholine and α-bromostyrene as substrates in toluene showed that use of both $Pd(OAc)_2$ and $Pd_2(dba)_3$ gave similar results. As in the amination of aryl bromides, BINAP (**L2**) and biphenyl monophosphine **L3** were the most effective ligands. The catalyst loading could be as low as 0.5 mol%, and it was possible to perform the reaction at lower temperature (40 °C). *N*-Methylaniline and dialkyl amines were also suitable substrates. Noteworthy, both stereo-(*Z*/*E*) and regiochemistry (internal/external) of the vinyl bromides were retained throughout the coupling process. Another significant feature of this method was the mildness of the work-up, which was required due to the sensitivity of enamines towards acids and water. Thus, simple filtration over celite yielded essentially pure products.[13]

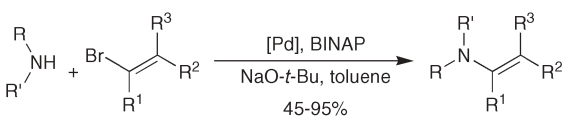
In a subsequent study it was shown that couplings of primary amines such as anilines and benzylamines yielded, after tautomerisation, the corresponding imines. The reaction time was short (15 min) and the catalyst loadings relatively low (0.1 mol% of palladium).[14] The overall transformation is shown in Scheme 4.

The high reactivity of vinyl bromides had already been investigated by Jutand. Kinetic studies showed that the oxidative addition to palladium(0) complexes, which is the rate determining step in Buchwald–Hartwig couplings, was 3–4 orders of magnitude faster than the one of aryl bromides.[15] This was further analysed in competitive studies between 4-bromobiphenyl and α-bromostyrene with either morpholine, *N*-methylaniline or 4-methoxybenzylamine. In all cases the only product observed by NMR or GC was the one stemming from the amination of the vinylic substrate (Scheme 5). The authors suggested that the oxidative addition occured faster with bromostyrene than with the aryl bromide (and irreversibly), and that this high reactivity led to the exclusive formation of the enamines.

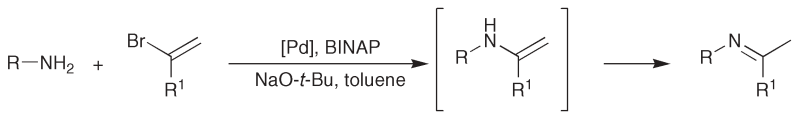
In continuation of these studies, Barluenga explored the possibility of using vinyl chlorides, which are much more readily available and stable, although less reactive, than the corresponding vinyl bromides.[16] In this case, a combination of Pd_2dba_3 (1 mol%) and biphenyl amino phosphine **L3** (4 mol%)



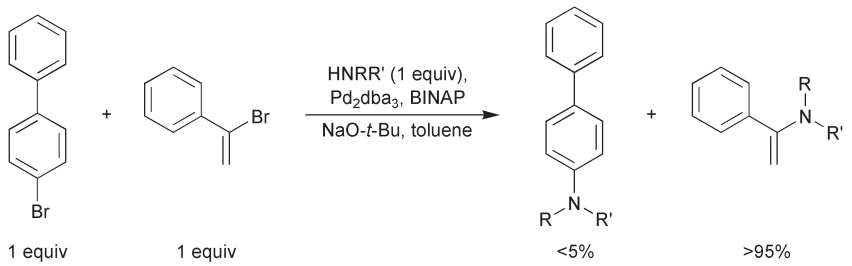
Scheme 2



Scheme 3



Scheme 4

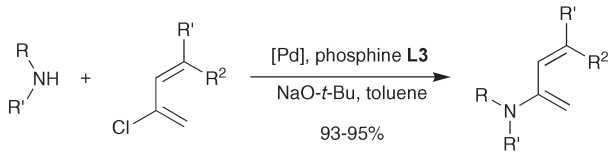


Scheme 5

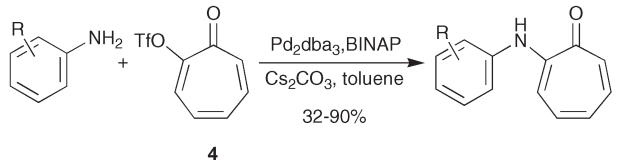
led to the best catalyst. The reaction had to be carried out at 90 °C, since negligible conversions were observed at room temperature. Again excellent yields (up to 96%) were obtained for different enamines, as far as the amine substituents are not too bulky. Use of primary amines afforded (after tautomerisation) the corresponding imines. A major synthetic advantage of this approach is the possibility of preparing 2-amino-1,3-butadienes, which are useful dienes in cycloaddition processes (Scheme 6).

Other common substrates in cross-coupling reactions are vinyl triflates.[17] Jutand has recently shown that their oxidative addition to palladium(0) complexes in DMF is, actually, 4 orders of magnitude higher than the one of the corresponding vinyl bromides.[15]

One of the very first examples of palladium-catalysed amination reactions of vinylic substrates was, in fact, the coupling between anilines and 2-triflatotropona **4** (Scheme 7). Tropona derivatives are interesting compounds due to their homoaromaticity and the presence of this structural entity in biologically active natural products. The preparation of



Scheme 6



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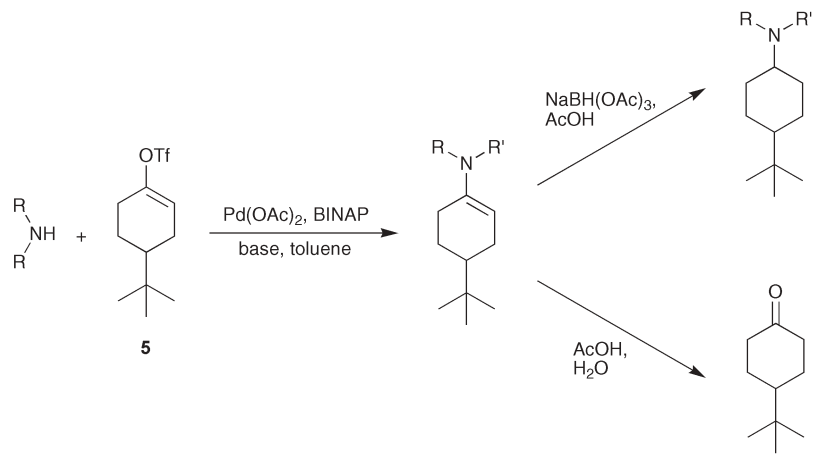
Scheme 7

aminated compounds by cross-couplings was considered as a promising approach, since other substitutions usually lead to mixtures of regioisomers. Under standard Buchwald–Hartwig conditions (Pd_2dba_3, BINAP, Cs_2CO_3, toluene), several anilines could effectively be coupled giving the desired products in up to 90% yield. The regioselectivity was complete.[18]

Willis carried out palladium-catalysed cross-coupling reactions of secondary amines (either alicyclic or aniline derivatives) with cyclic vinyl triflates, such as **5**. The optimised conditions involved the use of $Pd(OAc)_2$ (5 mol%), BINAP (10 mol%), together with Cs_2CO_3 or NaO-*t*-Bu as a base in toluene at 80 °C.[19] Moderate conversions were also observed at room temperature (Scheme 8). The difficulties in isolating the resulting enamines prompted the authors to reduce the products to the corresponding secondary amines, which were then obtained in 34–60% overall yield. This instability proved, on the other hand, useful for the preparation of ketones, since the direct hydrolysis of vinyl triflates is not a straightforward transformation, and usually results in decomposition.



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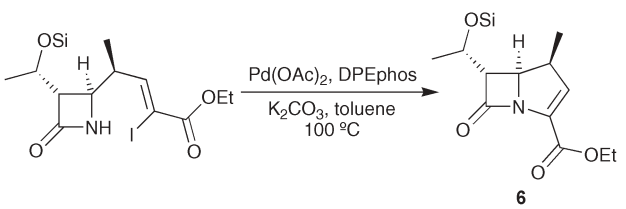
Scheme 8

Enamides

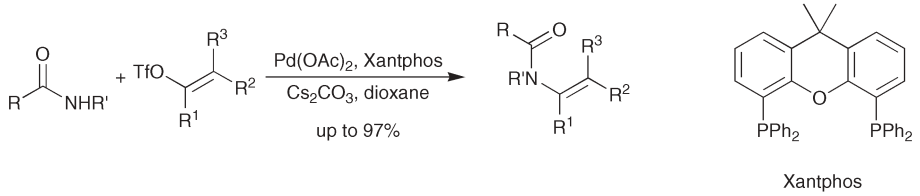
Intramolecular cross-coupling reactions of β-lactams with vinyl halides (bromides and iodides) giving enamide-type products were reported by Mori.[20] In this case, using $Pd(OAc)_2$ in combination with DPEphos gave much better results than with BINAP, DPPF or PPh_3. As a base, K_2CO_3 was the reagent of choice. Although both halides gave the expected coupling products, the iodide proved to be more effective. The experimental procedure for the *in situ* preparation of the complex seemed to be crucial in order to obtain high conversions. The methodology was used in the preparation of 3-alkoxycarbonyl-1β-methylcarbapenem **6** (Scheme 9), which is a compound with promising antibiotic activity.[20]

A more general method for the synthesis of enamides was reported from the Merck laboratories starting from vinyl triflates.[21] This approach makes use of the fact that the selective formation of a single enol triflate from a ketone relies on a simple kinetic *versus* thermodynamic control, thus allowing the regioselective preparation of the corresponding enamides. The best results were obtained with $Pd(OAc)_2$ and Xantphos in dioxane. The judicious selection of the base (Cs_2CO_3) was of utmost importance. Amines did not promote the reaction, and KO-*t*-Bu yielded the corresponding alkyne (by elimination of the triflate). Under the optimised conditions, several carboxamides, lactams, carbamates and sulfonamides were successfully coupled with a variety of cyclic and acyclic vinyl triflates giving enamides in up to 97% yield (Scheme 10).[21] Furthermore, retention of configuration at the double bond was achieved by carrying out the reaction at room temperature.

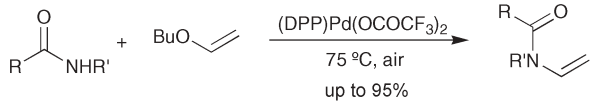
Another preparative approach towards enamides and analogous compounds was found by Stahl during his studies of oxidative aminations of olefins.[22] Quite surprisingly, when vinyl ethers were used as substrates under aerobic conditions, a vinyl transfer occurred (Scheme 11). This result is remarkable, because (a) many palladium-catalysed processes are incompatible with the oxygen atmosphere used in this experiment, and (b) enol ethers are not expected to undergo efficient oxidative addition to palladium complexes. Optimisation studies led to



Scheme 9



Scheme 10



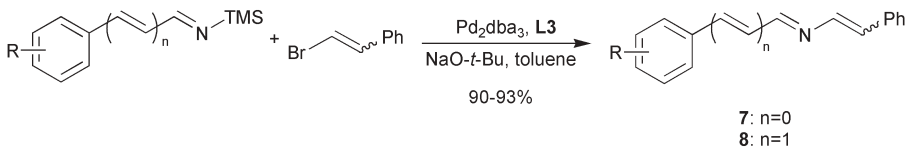
Scheme 11

the identification of $(DPP)Pd(OCOCF_3)_2$ as the best catalyst (DPP = 4,7-diphenyl-1,10-phenanthroline). The vinyl ether was used in large excess and served also as solvent. Mechanistically, this process differs from the other cross-coupling reactions (with vinyl halides or triflates) in that the palladium remains in the +2 oxidation state throughout the entire catalytic cycle.[22]

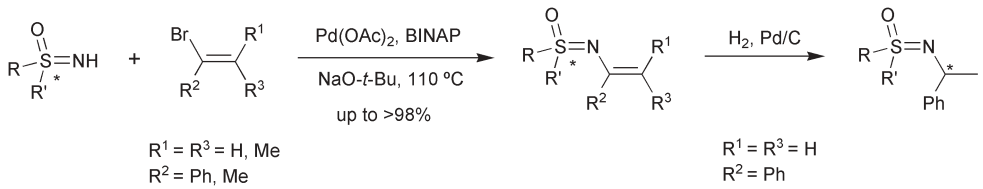
Other nitrogen compounds

Although the vast majority of palladium-catalysed amination reactions of vinylic substrates makes use of amines or amides as coupling partners, a few examples have recently appeared in the literature that involve couplings with less common nitrogen- or oxygen-containing compounds. In some cases the resulting enamines spontaneously tautomerise under the reaction conditions giving the corresponding imines. In the search for an alternative and efficient approach towards *N*-substituted aldimines, Barluenga utilised *N*-trialkylsilyl imines as surrogates for the unstable NH-aldimines in the Buchwald–Hartwig arylation reaction.[23] The possibility to use the same compounds in vinylation reactions was shown using β-bromostyrene as substrate. In combination with silyl imines derived from benzaldehyde and cinnamaldehyde the reactions yielded the corresponding 2-azadienes **7**, and 3-azatrienes **8**, respectively (Scheme 12), which are versatile reagents in hetero-cycloaddition reactions. For avoiding the formation of β-elimination products, biphenyl phosphine **L3** was used as ligand for Pd_2dba_3.[23]

Sulfoximines, which are sulfur-based reagents with a formally sp^2 hybridised nitrogen atom, have also been used as nucleophiles in cross-coupling reactions with vinylic substrates.[24] Due to their low nucleophilicity, the options for introducing substituents on the sulfoximine nitrogen are limited. Only recently, the development of a general process for the *N*-arylation of sulfoximines (based on the Buchwald–Hartwig chemistry),[25] allowed sulfoximines to compete with other well-established ligand structures in asymmetric catalysis.[26] Encouraged by these results, the possibility of extending this methodology towards the synthesis of *N*-vinyl sulfoximines was explored. Contrary to enamines and enamides, such products were previously unavailable by other means. After testing various reagent combinations, mixtures of

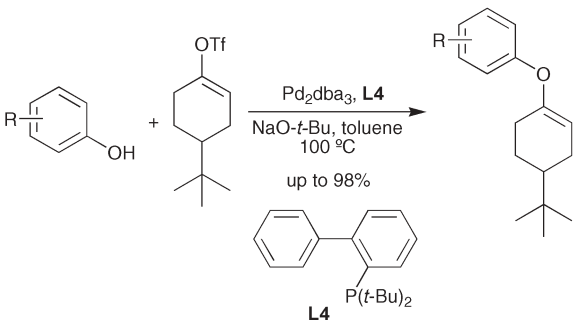


Scheme 12



Scheme 13

$Pd(OAc)_2$, BINAP (at loadings as low as 0.5 and 0.75 mol%, respectively) and NaO-*t*-Bu in refluxing toluene proved applicable, and various sulfoximines could be coupled with internal vinyl bromides (Scheme 13). Furthermore, the same procedure was applied for the sulfoximidation of a vinyl triflate, albeit in this case the base had to be changed to Cs_2CO_3 in order to avoid the hydrolysis of the substrate. Finally, hydrogenation of the vinyl moiety opened a new way to α-branched *N*-alkyl sulfoximines,[27] which are compounds that have previously been difficult to prepare.[28]



Scheme 14

Enol ethers

Although less applied than their nitrogen counterparts, alcohols can also be used as nucleophiles in cross-coupling reactions.[2a,29] Not surprisingly, transformations of vinylic derivatives are not fully developed yet, but, nevertheless, some illustrative examples of enol ethers syntheses have recently been described in the literature.

Already in 1996, Rossi studied the carbon–oxygen bond forming reactions using activated vinyl halides (usually acrylates and derivatives thereof) with alkoxystannanes catalysed by tetrakis(triphenylphosphine)palladium in NMP (*N*-methyl pyrrolidinone) at room temperature.[30] The reaction proceeded with retention of configuration at the double bond and was highly chemoselective. Electron-poor positions were favored, which allowed the monosubstitution of 1,2-dibromoolefins. In some cases, however, the high basicity of the alkoxy reagents caused *trans*-elimination. The products thus obtained were structural analogues of strobilurin A and other important agrochemicals.

Continuing his studies on cross-coupling reactions of vinyl triflates with heteroatom-containing nucleophiles, Willis reported on palladium-catalysed aryl enol ether syntheses. The use of a combination of Pd_2dba_3 (2 mol%), biphenyl phosphine **L4** (3 mol%) and NaO-*t*-Bu led to reactions between various phenols and vinyl triflates in up to 98% yield (Scheme 14). Both electron-poor and electron-rich phenols were well accepted as substrates, although the latter caused lower yields, most likely due to the instability of the resulting enol ethers. Furthermore, steric hindrance played a major role for the outcome of the reaction. *Meta* and *para* substituents were well tolerated, while use of *ortho*-substituted phenols usually led to low conversions (<40%). Finally, the reaction was carried out on a 1 g scale, demonstrating the synthetic utility of the process.[31]

In contrast to the palladium-catalysed conversions of enol ethers into enamides, which are thermodynamically favourable, enol ether formations with alcohols have an equilibrium constant of *ca.* 1, and they can therefore be driven to either side simply by applying the alcohol or the vinyl ether in excess, ideally as the solvent. Traditionally, such reactions have been carried out using mercuric salts of carboxylic acids as catalysts,[32] which, however, should be avoided in large-scale applications. Weintraub therefore developed an alternative approach based on palladium catalysis and prepared stereoidal vinyl ethers, such as **9** (Fig. 4), which can be regarded as

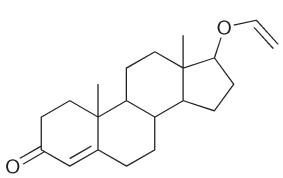


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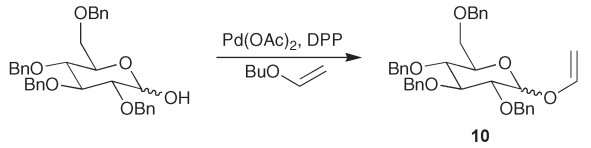
Fig. 4 A steroid derivative obtained by palladium-catalysed vinylation of the corresponding alcohol.



Scheme 15

synthons for the corresponding cyclopropyl ethers (to be obtained by Simmons–Smith reaction). With ethyl vinyl ether as vinylation reagent the enol ether formation was catalysed by bis(acetate)(1,10-phenanthroline-N^1,N^{10})palladium, which was applied in either recrystallised or crude form, or even prepared *in situ*. Ethyl vinyl ether also served as solvent, although dichloromethane could be present as co-solvent.[33]

Schlaf used this approach for the synthesis of protected monosaccharides, such as **10** (Scheme 15). Contrary to vinylations following the Buchwald-Hartwig mechanism, the presence of oxygen was crucial in order to avoid the decomposition of the catalyst [$Pd(OAc)_2$ and DPP] to palladium(0) by β-elimination and subsequent reductive elimination. Achieving optimal results required the saturation of the solvent with dry oxygen. Comparable results, however, were also obtained by carrying out the reaction in air. Only simple vinyl substituents could be introduced, and other vinyl transfer agents, such as 2-methoxypropene, 2-methoxystyrene or 2-methoxyacrylonitrile did not give the expected products.[34]

Soon after a similar approach was described by the same group for the syntheses of allyl and alkyl vinyl ethers having more general structures.[35]

Copper-promoted cross-coupling reactions

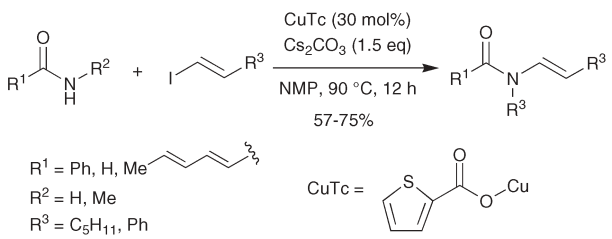
A large variety of inexpensive copper salts is available in large quantities. After his pioneering work on the synthesis of biaryls by copper-mediated homo-coupling reactions between two aryl halides, Ullmann discovered, in 1903, that copper species were also efficient promoters for C–N, C–O and C–S bond formations starting from aryl halides and amines, alcohols or thiols, respectively (Ullmann condensation reactions).[36] Three years later these cross-coupling reactions were extended to amides as coupling partners (Goldberg-modified Ullmann condensation reaction). At that time, however, the reaction conditions were severe (high temperatures, use of strong bases, stoichiometric quantities of copper or copper salts, and long reaction times), and the yields were only moderate. As a result, Ullmann couplings were considered unattractive for the synthesis of complex products. It took almost one century until considerable improvements were made in terms of efficiency (leading to high yields) and conditions (allowing the use of catalytic amounts of copper and weaker bases at moderate temperatures). One of these advances is due to the introduction of amine ligands, some of which are shown in Fig. 5.[36]

Other aryl sources were also found (*e.g.* aryl boronic acids, iodonium salts, siloxanes, stannanes, *etc.*), and nowadays Ullmann couplings are considered as routine synthetic tools.[36]

In the last years, copper catalysts have also been applied to the cross-coupling between amides and vinyl or alkinyl halides, leading to enamides or ynamides, respectively. This methodology has already found interesting applications in total syntheses of natural products, and, moreover, other types of nitrogen donors and alcohols proved to be excellent coupling partners.

Enamides and related compounds

Already in 1991, Ogawa reported the copper iodide-promoted substitution of vinyl bromides by potassium amides to afford enamides.[37] However, the reaction required harsh conditions (in HMPA at 130 °C) and the products were only obtained in low yields (<45%). After this pioneering work, this approach towards enamides remained dormant for almost ten years. It was only in 2000 that Porco began to reinvestigate the copper-mediated cross-coupling reaction between vinyl iodides and amides with the goal of preparing enamides related to salicylate antitumor macrolides.[38] One major point of his study was the control of the *E*/*Z* stereoselectivity of the double bond. Preliminary experiments on simple model substrates revealed that the reaction had to be performed in polar aprotic solvents, such as NMP or DMSO, in the presence of Cs_2CO_3 as a base. Liebeskind's copper(I) thiophene-2-carboxylate (CuTc)[39] was the best promoter for this purpose and only substoichiometric amounts of it (10–30 mol%) were required. Under these conditions, no further ligand had to be added and various enamides were obtained in moderate to good yields (57–75%) (Scheme 16).



Scheme 16

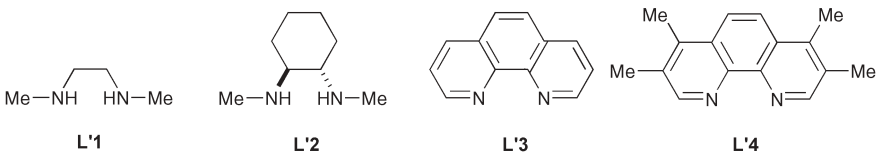
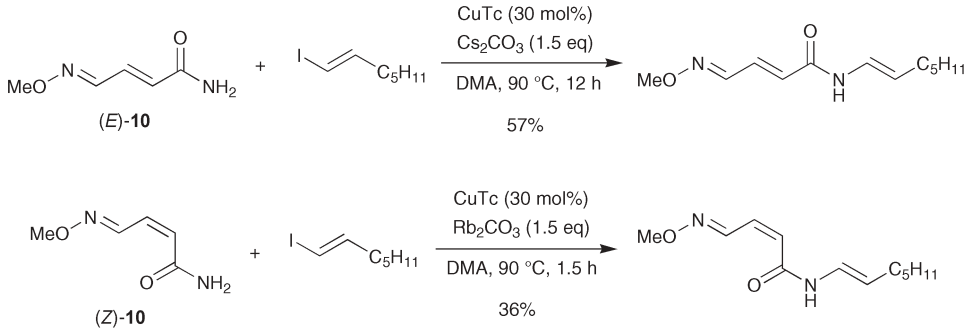


Fig. 5 Representative examples of diamines used as ligands in Ullman-type cross-coupling reactions.



Scheme 17

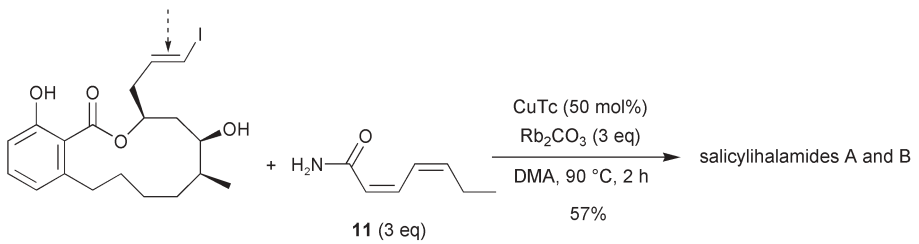
Focusing on syntheses of enamides related to the salicylate antitumor macrolides, (*E*)- and (*Z*)-*O*-methyloximes, amides **10** were tested as substrates with heptenyl iodide as coupling partner. When the reaction was performed in *N*,*N*-dimethyl acetamide (DMA) under the conditions depicted in Scheme 17, use of (*E*)-**10** gave the desired enamide in 57% yield. Unfortunately, under the same conditions, (*Z*)-**10** did not afford any coupling product, although the vinyl iodide was completely consumed. Later experiments showed that the base, Cs_2CO_3, was responsible for the failure of the reaction. Replacing it by Rb_2CO_3 led to the target enamide in 36% yield (Scheme 17).

Following Porco's work, this methodology was applied as a key step in various total syntheses. For example, Fürstner reported the stereospecific preparation of salicylihalamides A and B (which differ by the configuration at the double bond indicated in Scheme 18; see also Fig. 1) using the copper-catalysed cross-coupling as the final step.[40]

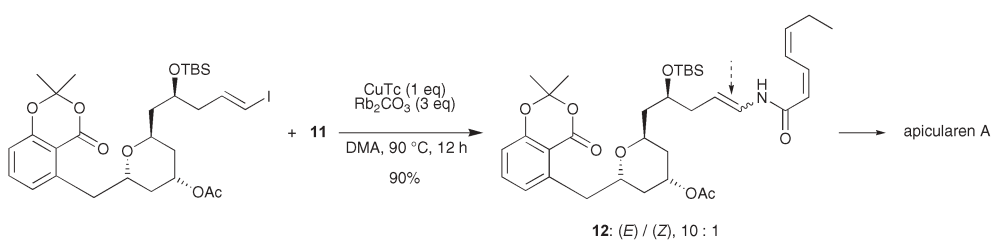
The reaction proceeded cleanly and was compatible with the presence of hydroxyl groups. Due to an isomerisation of the double bond of the vinyl iodide a 2.5 : 1 mixture of salicylihalamides A and B was formed (57% yield). Such isomerisation was also observed by Nicolaou, who used related reaction conditions (employing stoichiometric quantities of CuTc), in the total synthesis of apicularen A (Scheme 19; Fig. 1).[41] The reaction afforded intermediate **12** (in a 10 : 1 *E*/*Z* ratio) in 90% yield, and apicularen A was then obtained from (*E*)-**12** in one step.

The total syntheses of oximidine II[42] and lobatamide C[42] (Fig. 1) have been reported by Porco. In the latter, a considerable optimisation was required for the cross-coupling reaction, and the presence of 1,10-phenanthroline (**L′3**) proved essential. Finally, the vinylic coupling of **13** with (*E*)-*O*-methyloxime amide *E*-**10** then to a 45% yield of intermediate **14**, along with 10% of the (*Z*)-oxime isomer (Scheme 20).[43]

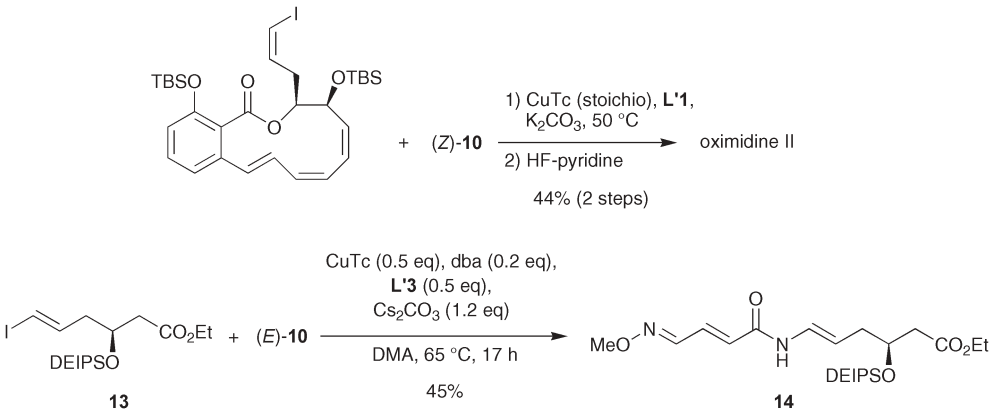
Porco extended the C–N bond formation methodology to the coupling of amides with β-iodo-acrylates and acrylamides, affording *N*-acyl vinologous carbamic acids and ureas.[44] Preliminary assessments revealed that $Cu(CH_3CN)_4PF_6$ was a suitable catalyst and that 3,4,7,8-tetramethyl-1,10-phenanthroline (**L′4**) was the most efficient ligand (Scheme 21).



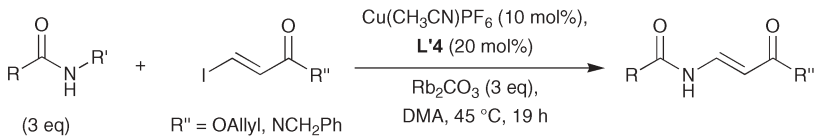
Scheme 18



Scheme 19



Scheme 20



Scheme 21

The reaction gave also good results with benzamides and lactams as substrates.[44] In the case of aliphatic primary amides (*e.g.* with R = alkyl), the presence of an oxygen atom on the substituent R was required. Otherwise the conversion was low, and it was suggested that this oxygen atom stabilised the putative copper intermediate. Using these conditions a route to the antibiotic CJ-15,801 was described.[44]

Coleman reported syntheses of side chains of salicylate enamide macrolides. As an alternative to previous strategies (*vide supra*), use of hemi-aminal **15** derived from maleimide (instead of a methyloxime amide) as a coupling partner for vinyl iodide **16** was proposed.[45] An adjustment of the reaction conditions proved essential. CuTc and CuI in combination with **L′2** and K_3PO_4 in dioxane at 90 °C gave good results (Scheme 2).

Interestingly, this reaction was only possible with copper catalysts, and all attempts to use palladium catalysts failed. Oxime formations of the coupling products (*E*)- and (*Z*)-**17** then led to the side chains of oximidines, lobatamides and CJ-12,950. Alternatively, Wittig olefinations of the cyclic hemi-aminals **17** afforded the side chains of salicylihalamides.[45]

The most general and straightforward method for the coupling of amides with vinyl halides has been reported by Buchwald (Table 1).[46]

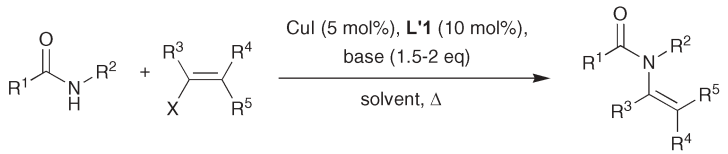
The reaction is catalytic in copper and proceeds under very mild reaction conditions. In the presence of CuI (5 mol%), ligand **L′1** (10 mol%) and K_2CO_3 in refluxing toluene, the cross-coupling of vinyl bromides with amides or carbamates affords the corresponding products in high yields (76–95%; Table 1, entries 1–5). With primary amides, in presence of an excess of alkenyl halide, double vinylation products are formed in small amounts. It is worth noting that this is the first report of a copper-catalysed amidation of an unactivated vinyl bromide. Acyclic secondary amides are unsuitable substrates, most likely due to their increased level of steric hindrance. In contrast, the size of the vinyl halides is less critical. Thus, the coupling of a fully substituted vinyl bromide was accomplished for the first time (entries 1 and 2). Notably, an amide with a free anilino group was also successfully coupled with complete chemoselectivity. With vinyl iodides as substrates, Cs_2CO_3 must be used as base, and the reaction proceeds at lower temperature (<70 °C) in THF. Of particular synthetic value is the preparation of a dehydro-β-amino ester (entry 6), which is the precursor for a β-amino acid. In all of these examples, the configuration of the double bond of the vinyl halide was retained. Similar results were obtained by Ma, who used CuI in combination with *N*,*N*-dimethylglycine and Cs_2CO_3 in dioxane.[47] These conditions were effective for both vinyl iodides and bromides.

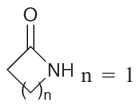
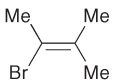
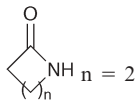
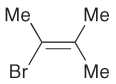
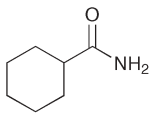
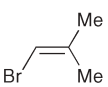
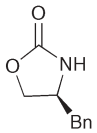
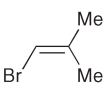
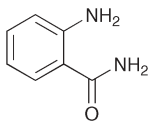
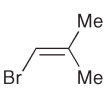
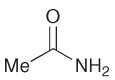
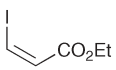
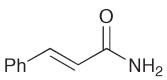
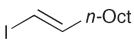
Contrary to the palladium chemistry, only two copper-catalysed cross-couplings involving amines as nucleophiles have been reported. In the first case, the vinylic substrates were uracil derivatives (Scheme 23).[48] Good results were achieved with primary and secondary aliphatic amines as well as with aromatic substrates (61–78% yield).

The other approach using copper catalysis for the formation of enamine-type products was reported by Lam and involves the use of vinyl boronic acids instead of vinyl halides.[49] Apart from ureas, imidazoles and pyrazoles gave excellent results under aerobic conditions (Scheme 24). Since the presence of oxygen (from air) proved essential for the catalysis, the reaction mechanism is believed to involve a Cu(III) species.

Ma developed copper-catalysed vinyl azide syntheses, applying amino acids as ligands.[50] Traditionally these

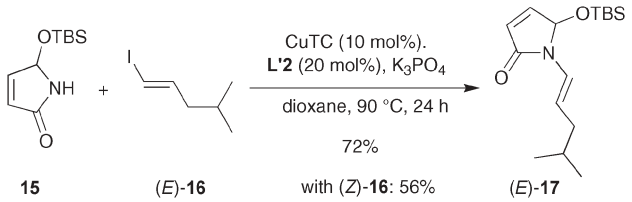
Table 1 Cu-catalysed cross-coupling of amides with vinyl halides



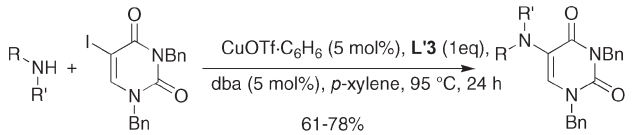
Entry	Amide	Vinyl halide	Base	Solvent	Temp./°C	Time/h	Yield (%)
1	 **a**	 **A**	K_2CO_3	Toluene	110	25	88
2	 **a**	 **A**	K_2CO_3	Toluene	110	21	91
3	 **b**	 **B**	K_2CO_3	Toluene	110	24	84
4	 **c**	 **B**	K_2CO_3	Toluene	110	16	95
5[a]	 **d**	 **B**	K_2CO_3	Toluene	110	16	81
6	 **e**	 **C**	Cs_2CO_3	THF	70	5	67
7	 **f**	 **D**	Cs_2CO_3	THF	70	14	86

[a] 10 mol% of CuI and 20 mol% of **L′1** were employed.

compounds are prepared by elimination of β-iodoazides, which originate from the addition of iodine azide to olefins. This procedure, however, suffers from the occurrence of violent decomposition of iodine azide in some cases.[51] The copper-catalysed coupling of sodium azide with vinyl iodide now offers a safe alternative (Scheme 25). The reaction gives good yields (64–82%) and proceeds with retention of configuration at the double bond.



Scheme 22



Scheme 23

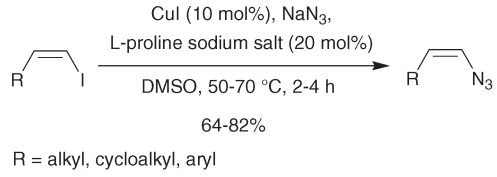
Finally, Bolm utilised copper salts as promotors for the coupling of vinyl bromides with sulfoximines.[52,53] Since a wider range of vinyl bromides (di-, tri-, and tetrasubstituted) can be used, the copper-based methodology offers a more general approach towards vinyl sulfoximines than the analogous palladium-catalysed one (see above). Thus, using CuI (1 eq) in combination with diamine **L′1** (2 eq) and K_2CO_3 in refluxing toluene leads to the coupling products in good to excellent yields (Scheme 26).

Ynamides

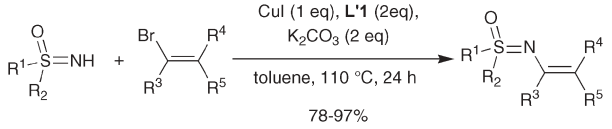
Ynamides are useful building blocks, which found numerous applications in synthetic chemistry (*e.g.* Pauson–Khand reactions, [4 + 2] cycloadditions, *etc.*).[54] However, the difficulty in the preparation of ynamides has limited their utility. In this context, Hsung reported the first cross-coupling between chiral oxazolidinones and alkynyl bromides.[55] The reaction involves CuCN (5 mol%), diamine **L′1** (10 mol%) and K_3PO_4, and is performed in refluxing toluene (Scheme 27).

Originally, the substrate scope was rather limited, and other substrates than oxazolidinones, such as lactams, ureas and acyclic carbamates gave only poor to moderate yields of coupling products. Sulfonamides did not react at all. Later, use of a modified catalyst system consisting of $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline (**L′3**) allowed to convert a wide range of substrates.[56] Moreover, the reaction was then found to proceed at lower temperatures (60–95 °C). A summary of the results is presented in Table 2.

The reaction now affords good to excellent yields (58–95%) of the coupling products with either oxazolidinones, lactams, carbamates, ureas and sulfonamides. Finally, given the pharmaceutical significance of heteroaromatic amines, the method was also applied to the synthesis of novel vinylogous ynamides (entries 7–8).



Scheme 25



Scheme 26

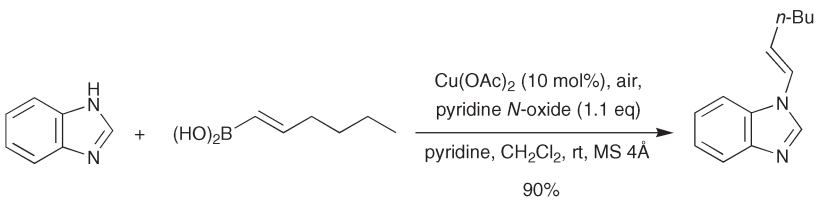
Danheiser reported an alternative method for the same purpose.[57] In this case, the reaction is stoichiometric in copper (CuI), proceeds without ligand, and involves KHMDS as base and pyridine as solvent. One of the main advantages of this protocol is that it can be performed at room temperature.

Enol ethers

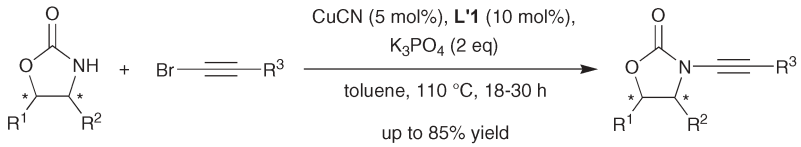
In 1992, Keegstra reported the first copper-catalysed coupling of sodium methoxide with vinyl halides (bromide or iodide) affording vinyl ethers (Scheme 28).[58]

The reaction was performed at 110 °C in a MeOH/NMP solvent mixture and afforded moderate to good yields of enol ethers, with complete retention of configuration at the double bond. This latter fact supported the hypothesis that a catalytic process, rather than a simple nucleophilic substitution, was operative. The direct use of alcohols, instead of alkoxides, has later been reported, when Wan described the coupling between phenol derivatives and vinyl bromides or iodides (Scheme 29).[59]

The reaction was efficient with a wide range of vinyl bromides (di-, tri- and tetra-substituted), and the presence of electron-donating as well as electron-withdrawing groups (EDG and EWG groups, respectively) on the phenol did not affect the transformation. Interestingly, an example involving a thiophenol as substrate was also reported, however this reaction afforded a lower yield than with its hydroxy analogues (41% instead of 81% yield). In this context Lam's copper-promoted cross-coupling between 3,5-di-*tert*-butyl phenol and a vinyl boronic acid is also worth noticing (Scheme 30).[49]

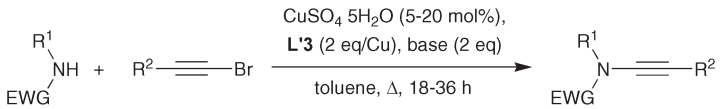


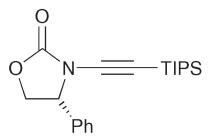
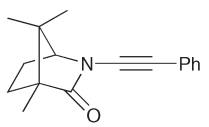
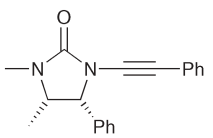
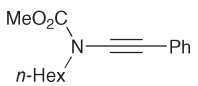
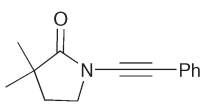
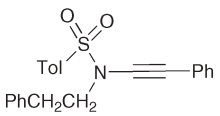
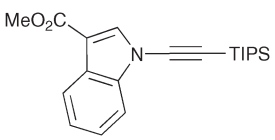
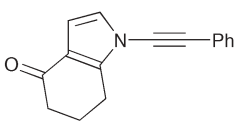
Scheme 24

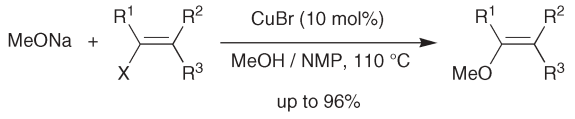


Scheme 27

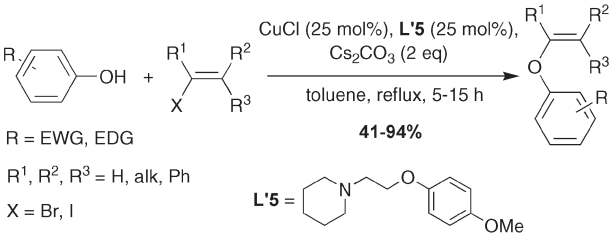
Table 2 Copper-catalysed cross-coupling of various *N*-donors with alkynyl bromides



Entry	$CuSO_4$ (mol%)	Base	Temp./°C	Product	Yield (%)
1	10	K_3PO_4	60–65	**A** 	88
2	5	K_3PO_4	60–65	**B** 	95
3	20	K_3PO_4	60–65	**C** 	86
4	20	K_3PO_4	60–65	**D** 	59
5	20	Cs_2CO_3	60–65	**E** 	58
6	5	K_2CO_3	60–65	**F** 	97
7	10	K_3PO_4	70–80	**G** 	93
8	10	K_3PO_4	70–80	**H** 	93



Scheme 28

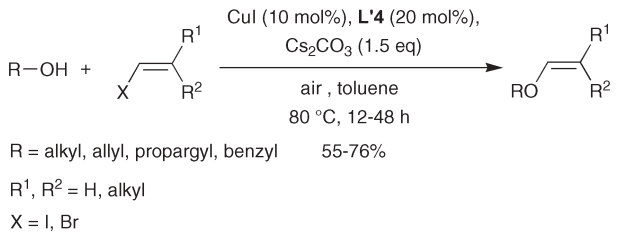


Scheme 29

The same year, Buchwald reported a powerful method for the coupling of alkyl, allyl, propargyl and benzyl alcohol with vinyl iodides and bromides (Scheme 31).[60]

The reaction times for the different types of alcohols varied significantly, generally decreasing in the order of aliphatic > allylic ≈ propargylic > benzylic substrates. One limitation of the reaction was the decomposition of (*Z*)-vinyl iodides under these reaction conditions, presumably by a β-elimination process. In these cases no coupling products could be isolated.

Based on the fact that this reaction gave good results with allylic alcohols as nucleophiles, the idea of performing an *in situ* Claisen-rearrangement of the resulting allyl vinyl ethers emerged.[60] Such a domino process offered an approach towards enals. As expected, performing the cross-coupling reaction at 120 °C in *o*-xylene (instead of 80 °C in toluene) led directly to the product resulting from the thermal Claisen-rearrangement reaction (Scheme 32). Although the coupling reaction could be carried out in an aerobic atmosphere, it was observed that using an inert atmosphere led to better results for the rearrangement reaction.

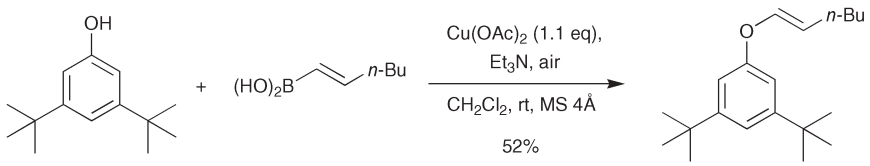


Scheme 31

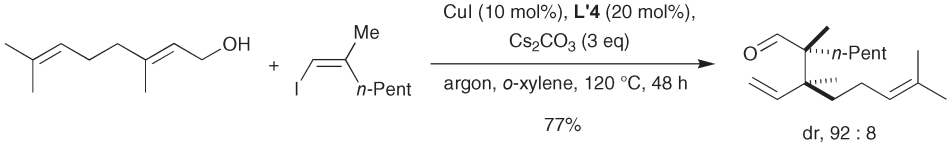
This efficient domino cross-coupling/Claisen-rearrangement reaction allowed the formation of compounds with vicinal quaternary stereogenic centers in a highly diastereoselective fashion.

Conclusions and outlook

Contrary to the arylation reactions of amines and alcohols, which have intensively been studied since the middle of the nineties, the analogous vinylation reactions have remained almost unexplored until the beginning of the 21st century. Independent and parallel research from several groups has led to the development of rather general methodologies utilising palladium or copper complexes in either catalytic or stoichiometric quantities for the synthesis of enamines, enamides, enol ethers and related compounds. It should also be emphasised that this approach has been successful when applied to weaker nucleophiles, such as imine derivatives and sulfoximines, as well. Another important aspect of the vinylations by cross-coupling reactions is the retention of the position and configuration of the C–C double bond of the original vinyl source (except in a few cases), which gives the process an added value, as the regio- and diastereoselective synthesis of enamines is generally difficult to achieve. Despite the "youth" of this methodology, it has already found several applications in total syntheses of natural products. Due to the ubiquity of biologically active compounds bearing the enamide function in nature, great advances can be foreseen in this area in the near future.



Scheme 30



Scheme 32

Acknowledgements

We gratefully acknowledge the Deutsche Forschungsgemeinschaft (SFB 380) and the Fonds der Chemischen Industrie for financial support. J.R.D. and J.L. thank the European Commission and the Alexander von Humboldt Foundation, respectively, for postdoctoral fellowships.

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