

Transition-metal-catalyzed multicomponent coupling reactions with imines and carbon monoxide*

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Abstract: Multicomponent coupling reactions provide a method to combine several substrates in a single reaction. When coupled with transition-metal catalysis, these reactions can be used to both activate and control the assembly of multiple simple building blocks directly into useful products. This account will describe our work in this area, with a focus on the use of palladium catalysis as a tool to couple imines and CO with other substrates into a range of heterocyclic derivatives in one-step reactions.

Keywords: carbonylation; heterocyclic chemistry; multicomponent reactions; palladium.

INTRODUCTION

The development of efficient methods to assemble complex products has become a significant issue in synthetic chemistry. While multistep synthetic methods can generate a diverse variety of compounds, they can also have important limitations, especially as molecules become more complex. This includes diminishing yields with each step, the need for multiple protection/deprotection operations, and creation of waste. In addition, through the sheer number of steps required, they can take many classes of compounds out of realistic access to researchers involved in product discovery. A number of methods have been explored to more directly assemble products from available starting materials. One area that has seen growing interest is the use of multicomponent coupling reactions [1]. Multicomponent reactions provide a route to mediate several bond-forming operations in a single reaction, and can streamline syntheses of molecular complexity, as well as facilitate structural diversification. These transformations do, however, involve the simultaneous combination of several units. As such, they often require elements of control incorporated into the substrates, such that they not only react, but react selectively, within these complex reaction mixtures.

One alternative to traditional multicomponent reactions is to exploit the reactivity of transition-metal catalysis. The last two decades have seen dramatic growth in the use of metal catalysis in synthesis, and in particular bond-forming reactions (e.g., olefin metathesis, cross-coupling reactions, C–H activation, and many more). These rely upon basic organometallic transformations as a tool to activate typically unreactive substrates towards reactions. These features can also be useful in multicomponent coupling reactions, where transition-metal catalysis can not only activate substrates, but also control how multiple variants of these units selectively assemble, via the series of reactions on the metal. This

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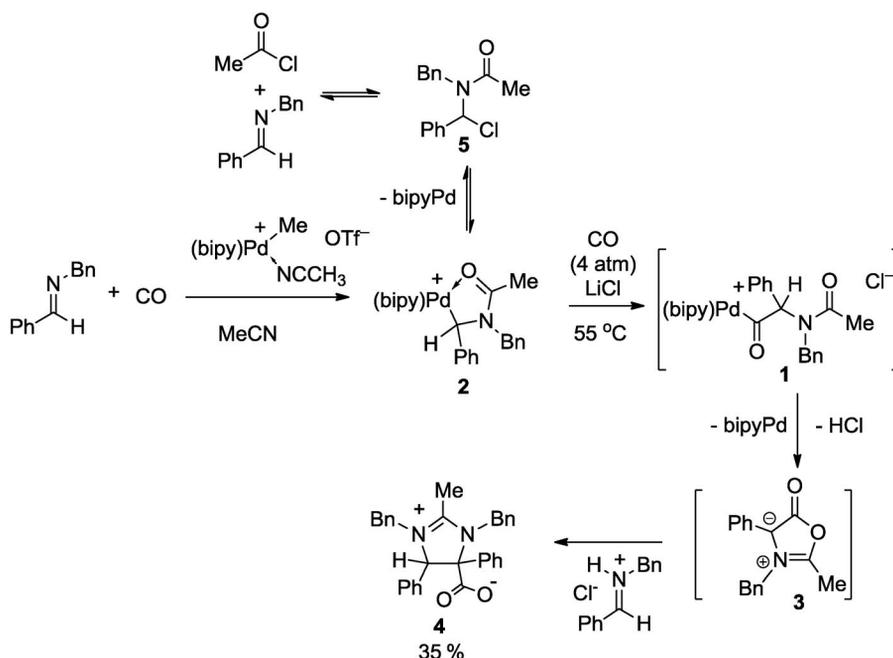
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can provide a route to take multiple simple starting materials and directly convert these in a controlled fashion into complex products.

Transition-metal-catalyzed multicomponent coupling reactions are known [2], with classic examples including the Pauson–Khand reaction [3], alkyne trimerization [4], and others [5]. In addition, there have been a wide range of more recently developed variants of these reactions. This article will describe some of our efforts in this area, with a focus on the use of Pd catalysis to selectively couple two simple fragments: imines and carbon monoxide. This has led to the design of a number of new catalytic multi-component routes to heterocyclic products.

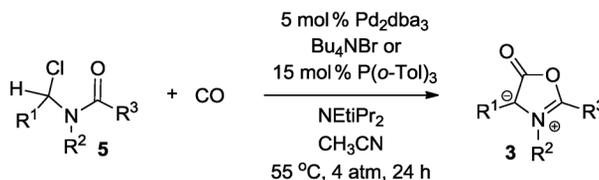
PALLADIUM-MEDIATED IMINE/CO/ACID CHLORIDE COUPLING

Imines and carbon monoxide are attractive building blocks in synthesis. CO is a commodity chemical, while imines are easily synthesized from available aldehydes and amines. In addition, the coupling of these units provides a potential route to build up metal-bound amino acid derivatives (**1**, Scheme 1). We [6] and others [7] suggested several years ago that imines and CO might be combined via sequential insertion into metal–carbon bonds, in direct analogy to olefin/CO alternating copolymerization. As shown in Scheme 1, cationic Pd complexes can mediate these reactions to generate Pd-chelated amides. The addition of CO to **2** does not lead to the simple CO insertion product **1**. Instead, similar to α -amido acid chlorides, complex **1** undergoes spontaneous cyclization to form the dipole containing heterocycle **3**. The latter is subsequently trapped by cycloaddition with a protonated imine to form the imidazolium carboxylate **4** in 35 % yield [8]. An interesting feature of this reaction is the presence of imine to undergo cycloaddition, since imine was not added to the reaction of **2**. Mechanistic studies show that this imine also arises from palladacycle **2**. This occurs via the reversible reductive elimination of an α -chloroamide **5**, which is itself the equilibrium product of imine and acid chloride.



Scheme 1 Pd-mediated imine/CO coupling to imidazolines.

While the reaction above is complex, stoichiometric in Pd, and low yielding, it provides a route to couple imines and CO in a selective fashion. In addition, it can be made much more efficient. As shown in the mechanism, palladacycle **2** is formed in equilibrium with **5**. This suggests it should be possible to simply add an α -chloroamide to a Pd(0) source in the presence of CO to form these products in one step. In addition, since Pd is liberated in this transformation, this is a reaction that can be catalytic. Using these two features, and by adding base to remove the acid formed and inhibit imine dipolar cycloaddition, we were able to develop a Pd-catalyzed cyclocarbonylation of α -chloroamides to generate the dipole **3** (Scheme 2) [9].

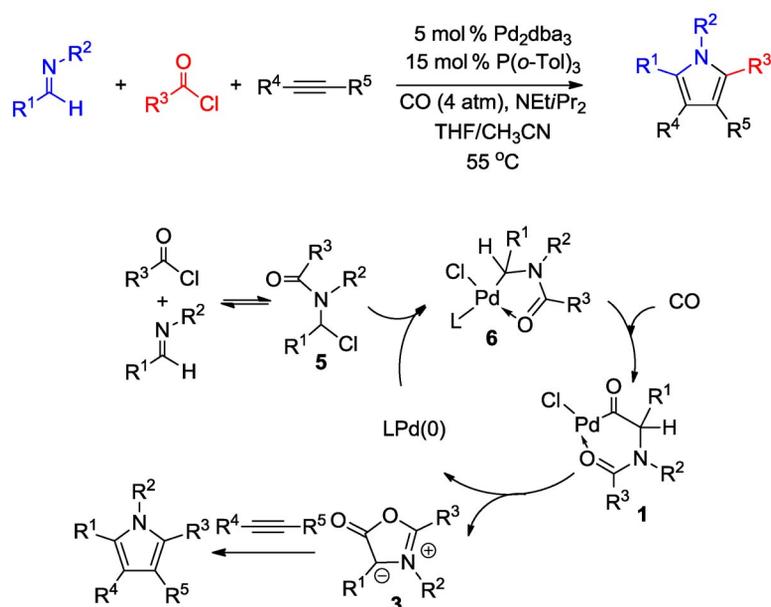


Scheme 2 Pd-catalyzed synthesis of Münchnones.

The transformation in Scheme 2 is analogous to a number of Pd-catalyzed cyclocarbonylation reactions. However, there are features of this reaction that make it more broadly useful. As mentioned above, the α -chloroamide reagent **5** is the equilibrium product of imine and acid chloride coupling, which occurs rapidly under the reaction conditions. Thus, this reaction simply requires the mixing of three available units: imines, acid chlorides, and CO, which are in one step converted into **3**. In addition, **3** is not a typical heterocyclic product, but is instead a mesoionic commonly referred to as a Münchnone. Münchnones were found by Huisgen in Munich in the 1960s to undergo facile 1,3-dipolar cycloaddition reactions with unsaturated substrates (typically followed by CO₂ loss) to generate 5-membered ring nitrogen heterocycles [10]. As such, the reaction in Scheme 2 provides an efficient Pd-catalyzed method to generate a product that is itself an intermediate. This opens the opportunity to add further operations to this reaction manifold.

GENERAL PLATFORM FOR METAL-CATALYZED MULTICOMPONENT SYNTHESIS

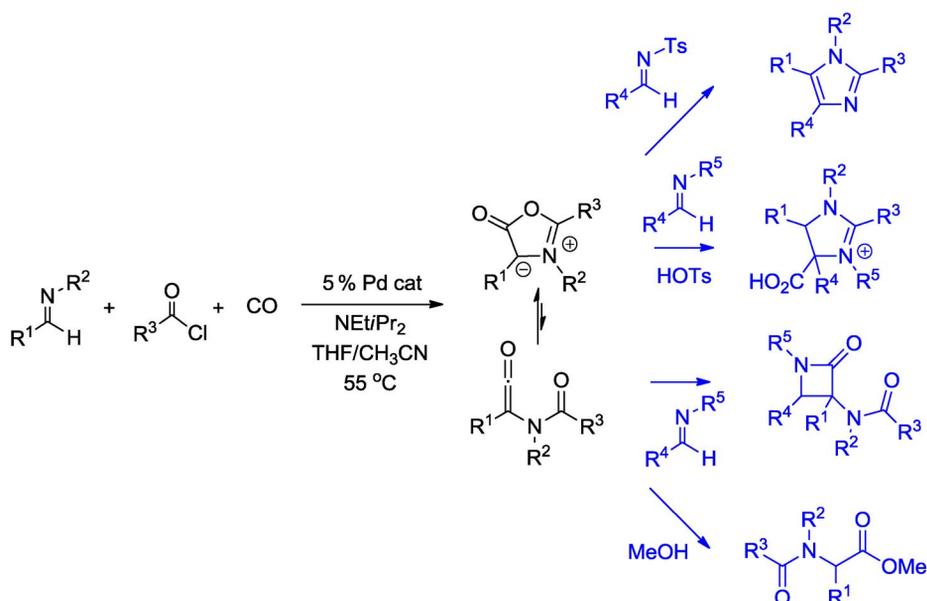
Münchnones are established to undergo 1,3-dipolar cycloaddition with alkynes. This can be combined with the Pd-catalyzed generation of **3** as a route to assemble pyrroles. As shown in Scheme 3, this reaction sequence requires a number of operations to not only occur, but do so in the correct order. However, these are each mechanistically distinct steps, and every component plays a different role. For example, there is only one nucleophile, an imine, and one electrophile, an acid chloride, in the mixture, and these react within minutes to form in equilibrium the α -chloroamide **5**. Once **5** is formed, its only viable reaction partner is the Pd catalyst. Control experiments show that this oxidative addition is also rapid (30 min to 1 h at ambient temperature), presumably due to the generation of a stable Pd-chelated amide. CO is the most reactive insertion substrate in this system, and reacts with complex **6** followed by spontaneous cyclization to form the Münchnone. The latter undergoes dipolar cycloaddition with the only other component in the system, the alkyne. Thus, while it is a complex series of steps, these all occur with high selectivity, and provide a method to couple an imine, acid chloride, and alkyne into poly-substituted pyrroles in high yield [11].



Scheme 3 Multicomponent synthesis of pyrroles.

While there are a range of synthetic methods to prepare pyrroles, these typically involve either the multistep build-up of a precursor with the correct units to cyclize (e.g., Paal–Knorr pyrrole synthesis), or begin with simple pyrroles, and in a stepwise fashion add substituents. In this regard, the reaction in Scheme 3 provides a simple route to pyrroles where every substituent can be individually modified. This multicomponent synthesis proceeds in highest yields with imines of aromatic aldehydes, although heteroaryl and tertiary alkyl substituents can also be employed. Similarly, cycloaddition proceeds with a range of mono-, di-, and unsubstituted alkynes.

In addition to pyrroles, Münchnones undergo a myriad of cycloaddition reactions (Scheme 4). These can similarly be incorporated into this reaction manifold. For example, the generation of Münchnones in the presence of electron-poor *N*-tosylimines results in cycloaddition to form imidazoles [12]. The addition of imines in the presence of an acid catalyst to **3** leads to the formation of imidazolium salts, which can be subsequently decarboxylated to imidazolines [13]. Münchnones are also known to be in equilibrium with ketenes. Thus, performing Pd catalysis in the presence of another imine leads to amide-substituted β-lactams [14], and the addition of alcohols can be used to catalytically generate α-amido esters derivatives. While these reactions are shown from a mechanistic perspective in Scheme 4, they can all be performed in one pot, and provide multicomponent methods to assemble a range of products.

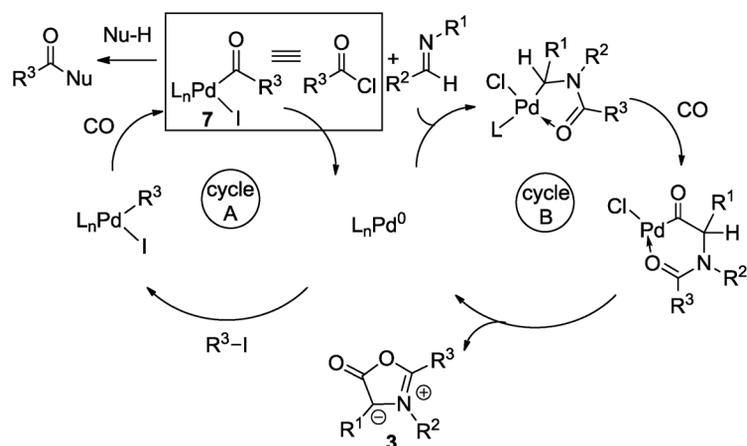


Scheme 4 Pd-catalyzed synthesis of heterocycles.

SIMPLIFIED BUILDING BLOCKS: ARYLHALIDES AS ACID CHLORIDE REPLACEMENTS

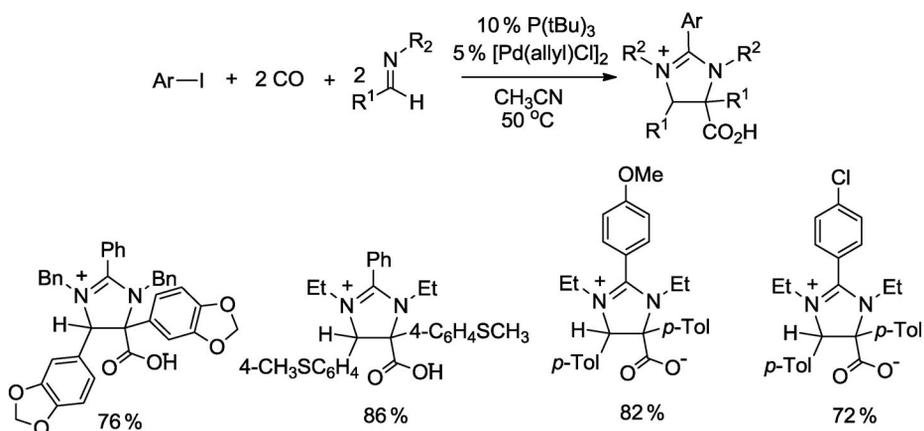
The reactions outlined in Scheme 4 rely upon acid chlorides to activate imines towards oxidative addition. While many acid chlorides are commercially available, they are ultimately generated from the corresponding carboxylic acids with harsh halogenating reagents (thionyl chloride, oxalyl chloride). Thus, while acid chlorides are useful electrophiles, they are not particularly green building blocks, plus they can require special handling. We have more recently become interested in the potential replacement of acid chlorides in this chemistry.

The catalytic transformations above can be considered variants of the more classic Pd-catalyzed arylhalide carbonylation reactions. These were developed by Heck in the 1970s, and are now heavily exploited as a route to prepared carboxylic acid derivatives [15,16]. The carbonylation of arylhalides generates Pd-acyl intermediates, which are subsequently trapped by nucleophiles to form the carbonyl-nucleophile bond (Scheme 5). In this regard, the Pd intermediate **7** can be thought of as synthetic equivalents to acid chlorides, yet are accessible from simple arylhalides and CO. This analogy suggested to us that arylhalide carbonylation might be exploited for more than the generation of carboxylic acid derivatives. Acid chlorides are useful substrates in a range of reactions, including the Pd-catalyzed multicomponent reactions above. In principle, Pd complex **7** could serve as a catalytically generated replacement for acid chlorides in this chemistry (Scheme 5).



Scheme 5 Arylhalide carbonylation as acid chloride replacements.

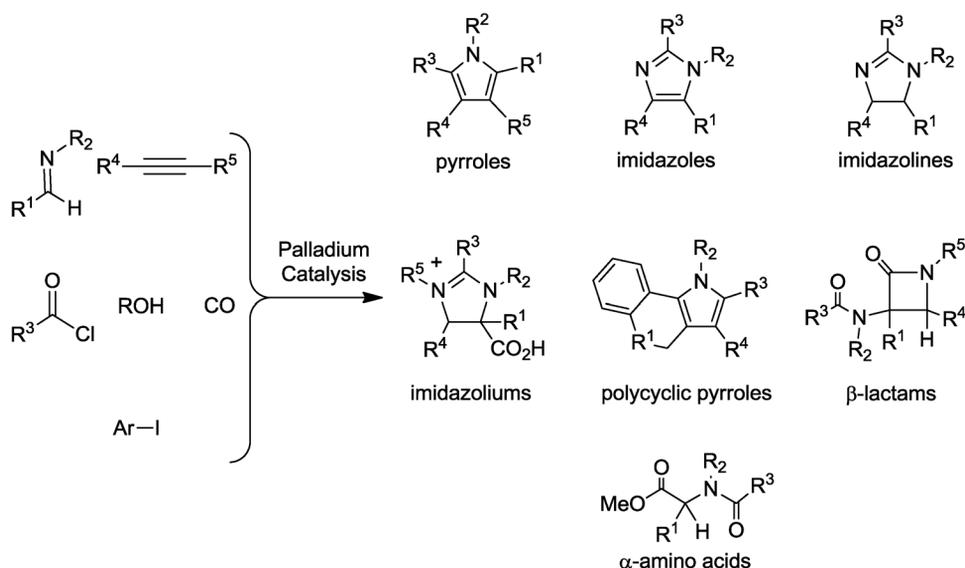
Since both the carbonylation of arylhalides, and of α -chloroamides, are Pd-catalyzed, a single Pd catalyst may be able to mediate both of these cycles. While complex from a mechanistic perspective, this would provide a method to create Münchnones from arylhalides, CO, and an imine. We have recently found that a single catalyst, $[\text{Pd}(\text{allyl})\text{Cl}]_2$ in concert with the sterically encumbered Pt-Bu_3 ligand, can mediate both of these steps. In the presence of excess imine, **3** undergoes spontaneous cyclization to allow the one-step, five-component synthesis of imidazolines (Scheme 6) [17].



Scheme 6 Five-component synthesis of imidazolines.

CONCLUSIONS

In conclusion, the reactivity of Pd catalysts can allow the direct assembly of a range of products from combinations of available building blocks. These reactions rely upon a simple coupling of imines and CO, which can initiate a cascade of operations to form mesoionic Münchnones, which can themselves undergo spontaneous reactions. While these transformations are mechanistically complex, these steps each occur within the context of a catalytic cycle, providing overall straightforward routes to assemble a range of structures directly from available substrates (Scheme 7). Studies directed towards the expan-



Scheme 7 Pd-catalyzed multicomponent syntheses.

sion of this metal-catalyzed multicomponent coupling approach to alternative classes of products [18], as well as their use in the directed synthesis [19], are currently the subject of research in our laboratory.

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