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Metal-Catalyzed One-Step Synthesis: Towards Direct Alternatives to Multistep Heterocycle and Amino Acid Derivative Formation

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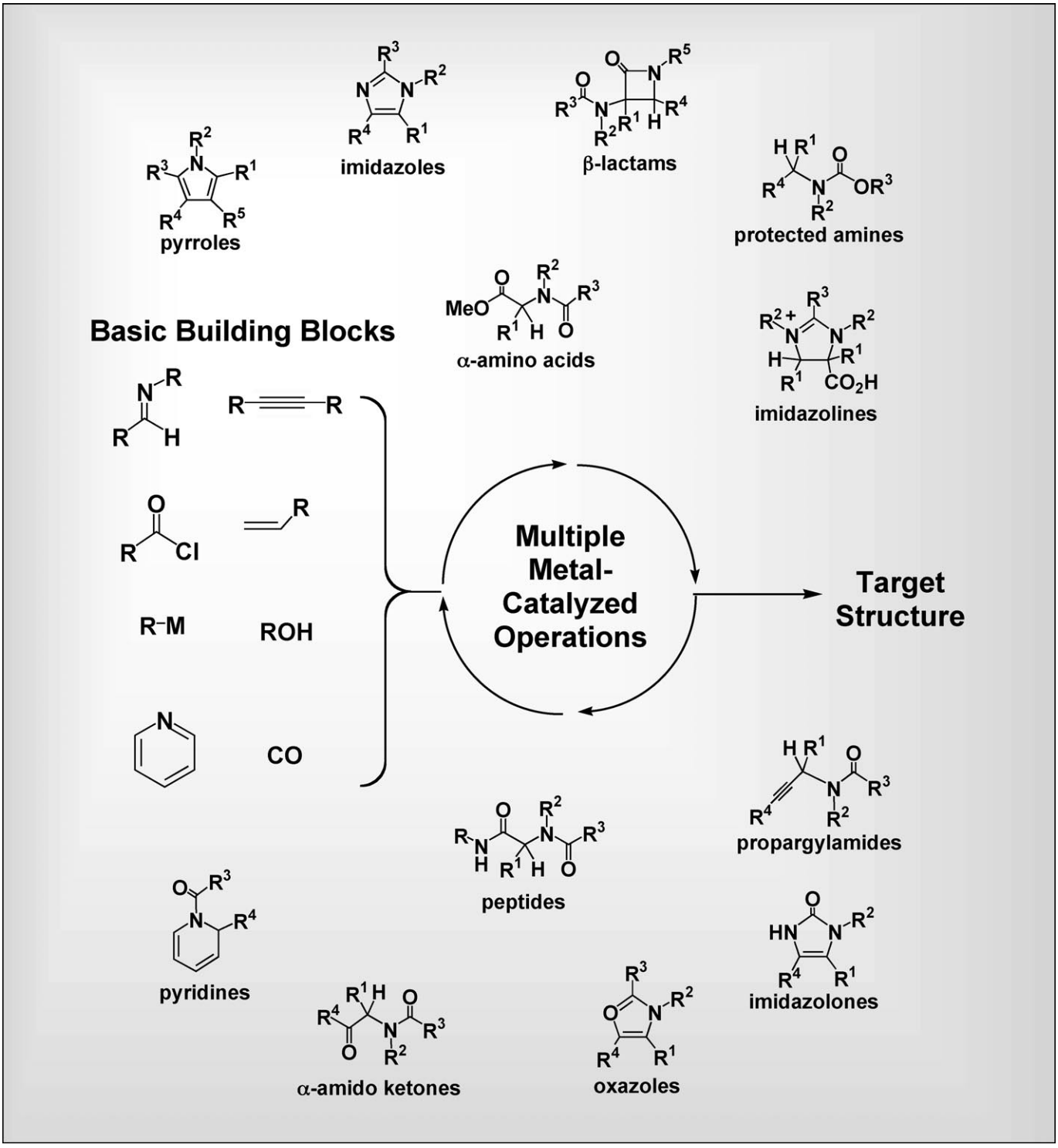

Abstract: The growing understanding of transition-metal catalysis has provided the opportunity to design reactions that convert simple, readily available building blocks in one step into an array of biologically relevant products. Described herein is the application of this approach to the construction of various biologically relevant products, including pyrroles, imidazoles, β-lactams, oxazoles, α-amino acids, propargyl amides, functionalized pyridines, and others. These catalytic reactions rely upon several synthetic operations occurring in sequence, in which the reactivity of transition-metal complexes both activates basic building blocks towards reaction, and controls how multiple versions of these substrates come together. Overall, this allows the synthesis of each these products in one step, in high yield, with minimal waste, and with straightforward access to product diversity.

Keywords: carbonylation · green chemistry · heterocycles · metal catalysis · multicomponent reactions

Introduction

The ability to efficiently access complex molecular scaffolds has become a central research issue in many areas of chemistry. In topics ranging from pharmaceuticals and biomolecule design, materials science, nanotechnology, polymer synthesis, or others, as target structures become more complex and with further refined features, the traditional methods available for their construction can rapidly become very involved. This can make these syntheses not only challenging to perform (e.g., through a growing number steps), but also complicate product discovery, since this sequence of steps must often be repeated to modify structures. In addition, these multistep syntheses tend to rely heavily on reagents not fully incorporated into the product, repeated solvent use, and suffer from diminishing yields, each of which has led to growing environmental concerns. The above issues have created a significant challenge, which is to bring greater levels of molecular complexity with realistic access to chemists, for both product discovery and their ultimate production. As such, a major emphasis has been placed on devising methods to construct compounds with minimal steps, limited waste, as well as structural flexibility, and brought such topics as atom economy,[1] ideal syntheses,[2] click reactions,[3] green chemistry,[4] tandem reactions,[5] and others[6] to the forefront in the design of new synthetic methods.

In principle, an attractive alternative to classical multistep synthesis would be to prepare complex core structures directly from several readily available building blocks brought together at once. Transformations of this form are well established in the field of multicomponent coupling reactions. These include such classic examples as the Strecker reaction,[7] Ugi and Parsini couplings,[8] Hantzsh reaction,[9] and others.[10] However, a challenge is how to design such syntheses in a general fashion. Firstly, for many products, their assembly requires the simultaneous reaction of multiple different substrates. This can lead to the need for "programmed" building blocks that are designed to react selectively within a complex mixture. These substrates often must themselves first be synthesized, which can diminish the benefits of assembling the final product in a multicomponent fashion. In addition, many fundamental building blocks desirable for synthesis (olefins, alkynes, aldehydes, amines, alcohols, etc.) are not generally reactive, yet must both react, and react selectively, in such transformations.

Transition-metal catalysis can provide a useful potential tool to mediate such reactions. The unique reactivity of transition metals has stimulated tremendous growth in the design of new metal-catalyzed methodologies that efficiently generate structures. Equally important are the major strides made in developing a mechanistic insight of how these transformations occur. This has resulted in an understanding of the factors that govern such fundamental reaction steps as ligand substitution, oxidative addition/reductive elimination, migratory insertion, cycloaddition, and nucleophilic/electrophilic attack on ligands (Figure 1).[11] While a relatively concise list, this reactivity provides the potential to perform most classes of bond manipulation with the correct metal complex.

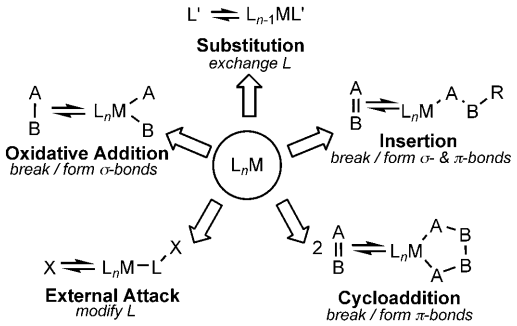

Figure 1. Diversity of transition-metal-based reactions.

This diverse reactivity, along with its mechanistic understanding, suggests the interesting potential of designing new synthetic methods that use a series of sequential metal-based operations to activate fundamental building blocks to-

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wards reaction, and at the same time control how multiple versions of these substrates come together. If done within a catalytic cycle, this could enable the assembly of several classic starting materials directly into a target structure (i.e., a direct synthesis, Figure 2). These reactions could proceed

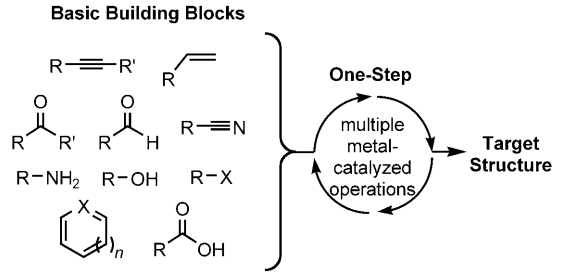
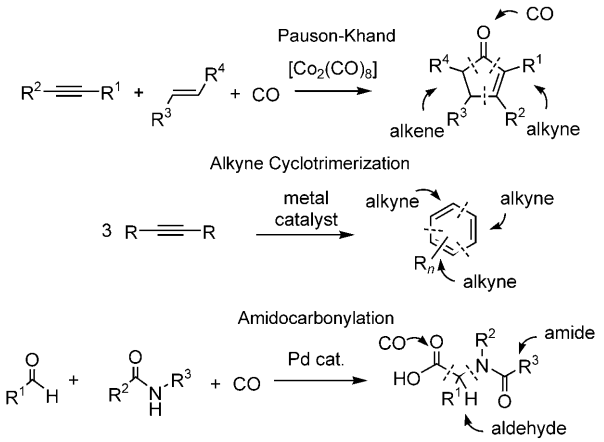


Figure 2. One-step synthesis by metal catalysis.

in a similar fashion to such known processes as the Pauson–Khand reaction,[12] alkyne trimerization,[13] aldehyde amidocarbonylation[14] (Scheme 1), as well as a growing list of



Scheme 1. Representative examples of metal-catalyzed multicomponent syntheses.

efficient, more recently developed metal-catalyzed multicomponent reactions.[15,16] Importantly, this approach has the potential to display many of the features desired in synthetic methods, including the ability to access products in minimal steps, a modular synthesis that relies upon substrates available in many forms, high overall yields, and because of their efficiency, ultimately less waste.

This article will outline our efforts to exploit transition-metal catalysis as a tool to build up families of reactions in which useful structures can be generated from readily available building blocks. These are directed towards the assembly of a number of common structural motifs found in biologically relevant products, including pyrroles, imidazoles, lactams, amino acids/peptides and related products. As described below, by developing mechanistic insights into a simple coupling reaction of imines and carbon monoxide, and assembling differing combinations of metal-based operations into catalytic cycles, one-step routes to each of these products have been designed.

The Direct Synthesis of Peptide-Based Products

Synthetic peptides and α-amino acid containing products are central structures in the study of biological systems and drug design, as well as other important applications.[17] Peptides are typically constructed by the use of α-amino acids as synthons. While this approach is very effective, there are certain important limits. For example, for non-natural amino acid residues, the amino acid derivative must itself be synthesized first; this procedure can often involve multiple steps. However, we noted some time ago that the structure of a peptide might in principle be considered to arise from two much simpler building blocks: imines and carbon monoxide (Figure 3). In the light of the availability of both imines and CO, and their ease of diversification through imine formation, this could provide an efficient alternative route to assemble a peptide unit.

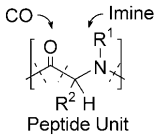
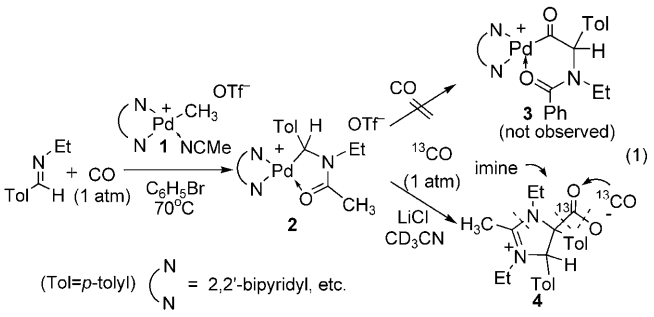


Figure 3. A potential imine/CO approach to peptides.

Initial studies, in both our laboratory[18] and others,[19] in this area demonstrated that imines and CO can be selectively coupled by their sequential insertion into the palladium–carbon bond of **1** [Eq. (1)]. Interestingly, this chelated



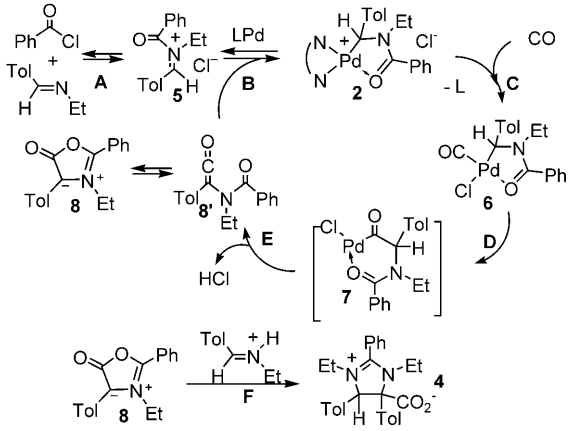
(1)

product is directly analogous to that observed in olefin and carbon monoxide copolymerization.[20] Despite this similarity, the reaction of **2** with further carbon monoxide did not result in its insertion into the palladium–carbon bond to form **3**. This presumably arises from the strong chelation of the amide oxygen to palladium, which blocks the generation of an empty coordination site.[21] While neither modification of the ligands on palladium, addition of Lewis acids, nor the incorporation of electron-withdrawing groups on the chelated amide allowed further CO insertion, simply exchanging the weakly coordinating triflate counteranion in **2** with the

slightly more coordinating chloride does allow a reaction with CO to occur. This results in the formation of the non-palladium bound, amino acid based heterocycle **4**.[22]

Labeling studies on this reaction demonstrate that CO is incorporated into **4** as shown in Equation (1), suggesting that CO insertion has occurred, presumably to form **3**, followed by further chemistry. Imidazolines such as **4** are found in numerous biologically relevant molecules, with carboxylate-substituted imidazolines attracting attention as peptide bond isoteres, and as potent cell sensitizers for cancer treatment.[23] In addition, the synthesis of **4** in Equation (1) is ultimately the result of coupling simple substrates: imines and carbon monoxide. However, the heterocycle is formed in low yield (40%), and results from a multistep process that is stoichiometric in palladium complex **1**. Despite these issues, insight into the mechanism of this reaction can be utilized to transform this into an efficient synthesis.

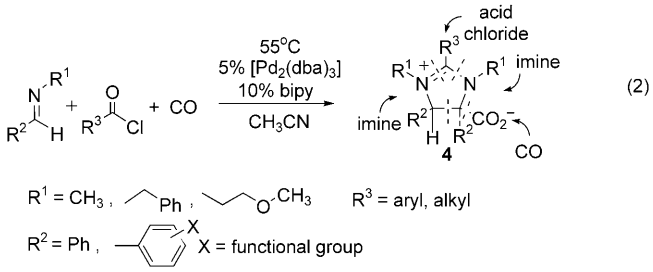
As shown in Scheme 2, complex **2** is believed to be the source of two competing processes: one to generate imine and acid chloride upon reductive elimination (steps **A** and



Scheme 2. Mechanism of imidazoline formation.

B), and a second to generate this mesionic dipole **8** (through CO insertion and β-hydride elimination, steps **C**–**E**). Control experiments demonstrate that these two fragments are ultimately coupled to generate **4**, by 1,3-dipolar cycloaddition of the protonated imine to **8**, followed by C–O bond cleavage, which affords imidazoline **4** in near quantitative yield (step **F**).[24]

On examining this mechanism, it was noted that the dynamic equilibrium between complex **2** and imine, acid chloride, and Pd^0 suggests that mixing these three reagents with carbon monoxide could allow the direct formation of imidazolines. Since Pd^0 is ultimately liberated after β-hydride elimination (step **E**), this process also holds the potential to be catalytic. As shown in Equation (2), the one-pot reaction of imine, acid chloride, and carbon monoxide in the presence of a commercially available $[Pd_2(dba)_3]\cdot CHCl_3$ (dba = dibenzylideneaceton) provides a high yield, catalytic method to construct imidazolines.[22]



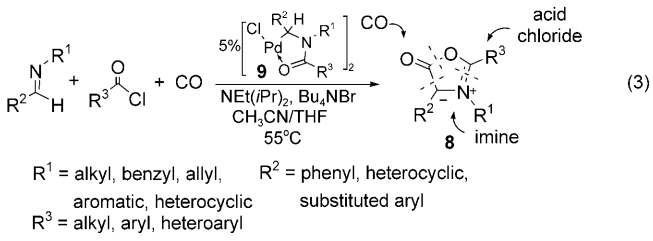
(2)

This reaction is an example of a direct synthesis outlined in Figure 2. Because of the building blocks employed (two imines, acid chloride, carbon monoxide), it can also be applied to the synthesis of a range of imidazolines. This includes the incorporation of imines of various aromatic aldehydes, *N*-alkyl or *N*-functionalized imines, as well as alkyl or aryl acid chlorides. Considering the ready availability of these building blocks, and the mild conditions employed (1 atm CO, 55 °C, palladium catalysis), this represents a useful alternative to traditional multistep routes to these products.

Münchnones: The development of this palladium-catalyzed synthesis of imidazolines has provided the basis for the synthesis of a range of other useful core structures. As can be seen in Scheme 2, the role of palladium catalysis is to couple an imine, an acid chloride, and CO together to generate a mesoionic 1,3-oxazolium-5-oxide (**8**), commonly referred to as a münchnone. Münchnones are versatile 1,3-dipolar addition substrates, and have proven key in the construction of a range of natural products and heterocycles.[25] Alternatively, their ketene tautomer can serve as a precursor to α-amino acid and peptide derivatives.

The diversity of products accessible from münchnones makes them attractive synthetic targets. However, their preparation to date has typically involved multistep reactions, most commonly through the dehydration of appropriately substituted and pre-synthesized *N*-acyl amino acid derivatives.[25,26] In contrast, the addition of amine base to the palladium-catalyzed reaction in Equation (1) eliminates the possibility of generating a protonated imine for münchnone trapping (blocking step **F**). This has been used to design a catalytic method to synthesize münchnones in one step and from available building blocks [Eq. (3)].[27]

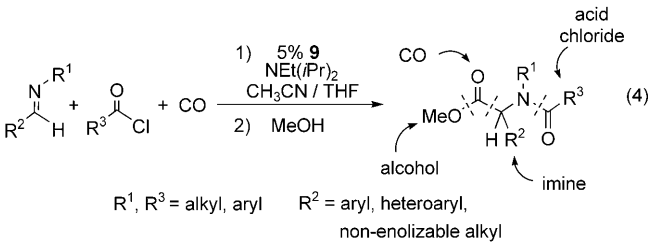
This reaction can be catalyzed by simple $[Pd_2(dba)_3]$, however, a more efficient catalyst is $[Pd(\eta^2\text{-}CR^2HNR^1COR^3)Cl]$



(3)

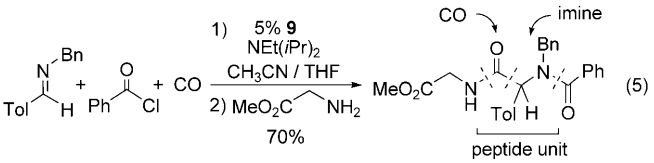
(**9**). The latter represents an intermediate in the catalytic cycle, and can be formed by pre-treating $[Pd_2(dba)_3]\cdot CHCl_3$ with imine and acid chloride. This serves to remove dba from the reaction system, and is believed to facilitate CO coordination during catalysis by removing any other coordinating ligand from the reaction mixture (step **C**, Scheme 2). With this catalyst, a range of stable *C*-aryl imines and acid chlorides can be employed in this chemistry. Subsequent studies have shown that the addition of bulky phosphines (e.g., $P(o\text{-Tol})_3$), can enhance the activity of this catalyst.[28] Since these systems can more effectively compete with a background *N*-acyl iminium salt decomposition, this can allow lower catalyst loadings to be employed, and the use of less stable reagents. Such reagents include various aryl or alkyl acid chlorides, as well as a diverse combination of *C*-aryl, -heteroaryl or -tertiary alkyl imines.

α-Amino acids and peptides: Since münchnones can be readily hydrated to generate amino acid derivatives, the coupling of this catalytic formation of **8** with subsequent methanol addition has been used to design a one-pot, catalytic route to construct a range of α-amino acid derivatives from four units: imine, carbon monoxide, acid chloride, and alcohol [Eq. (4)].[27]



(4)

This palladium-catalyzed synthesis of amino acids is reminiscent of the aldehyde amidocarbonylation reaction (Scheme 1), both from a synthetic and mechanistic perspective; in the aldehyde amidocarbonylation reaction amides and aldehydes are coupled with carbon monoxide under palladium catalysis to form α-amido acids.[14] Each reaction has its distinct features. Amidocarbonylation can operate under hydrolytic and acidic conditions, and requires as little as 0.01 mol% palladium loading to proceed in high yield. In addition, amidocarbonylation proceeds with primary amides, allowing the formation of NH substituted amino acids in a single catalytic step. Conversely, while the catalytic formation of münchnones requires higher catalyst loading, this chemistry proceeds under milder conditions, presumably due to the more rapid formation of *N*-acyliminium salt from imine and acid chloride, and provides access to a range of non-natural peptoids that are substituted at nitrogen. Such compounds are difficult to generate by amidocarbonylation. In addition, this catalytic münchnone formation does not result in the liberation of water as in amidocarbonylation. This provides more control in the trapping agents that can be employed. As a simple illustration of this feature, the catalytic formation of münchnone **8** followed by the addition of an N-unprotected amino acid, can be used to directly generate a peptide residue [Eq. (5)].[29] To our knowledge,

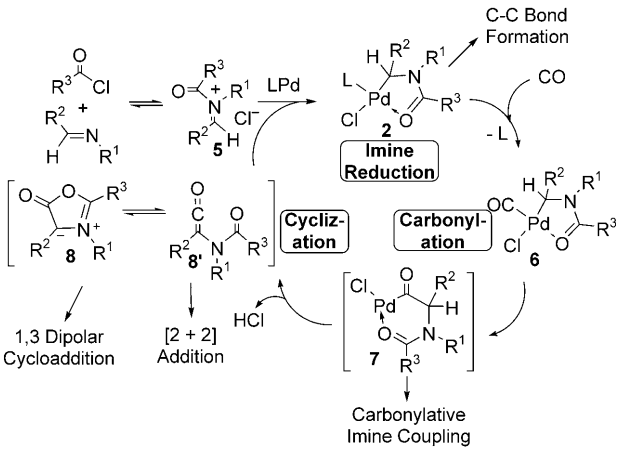


(5)

this represents the first example of the formation of a peptide unit from its two fundamental building blocks: imines and carbon monoxide.

Mechanism—Multiple Metal-Catalyzed Operations

As shown in Scheme 3 the catalytic synthesis of münchnones results from at least seven distinct synthetic steps occurring in sequence. These can be considered to represent a number



Scheme 3. Palladium-catalyzed multiple synthetic operations.

of fundamental synthetic operations. Firstly, mechanistic studies show that the initial step in catalysis involves the reaction of imine and acid chloride to form an *N*-acyl iminium salt (**5**), which undergoes rapid oxidative addition to palladium. This is clearly observed in control experiments, in which the reaction of in situ generated iminium salts with $[Pd_2(dba)_3]$ forms to **2** in near quantitative yield.[30] Overall, this series of steps provides a method to convert imines into a reduced α-palladated amide (imine reduction). Kinetic studies show that this oxidative addition step is at least partially rate determining in the catalytic formation of münchnones. As such, the generation of **2** is likely the source of certain scope limitations in this chemistry, such as the inability to use enolizable imines in the münchnone synthesis (which form enamides more rapidly than react with palladium), or

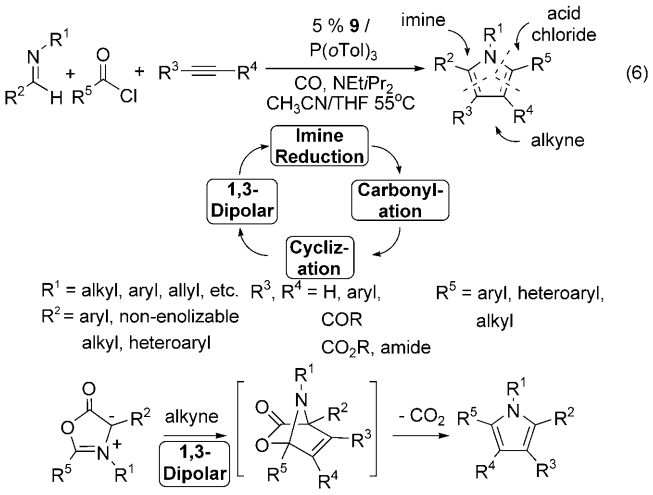
substrates that form iminium salts in poor yield (e.g., poorly nucleophilic or bulky imines).

While compound **2** is a potentially useful product itself (vide infra), its formation in the presence of carbon monoxide allows a subsequent series of reactions to occur: CO coordination to generate palladium complex **6**, followed by migratory insertion. These reactions allow the overall coupling of imine and CO into a palladium-bound peptide unit (carbonylation, **7**). Following carbonylation, base can induce a third operation, elimination of HCl and cyclization, resulting in the generation of the observed münchnone product (cyclization).

The concept of performing multiple synthetic operations within the context of a single reaction can be powerful approach for building up molecular complexity in an efficient fashion.[5,6,10,31] As will described below, the use of various combinations of the imine reduction, carbonylation, and cyclization steps, in concert with subsequent reactions, has opened the door to the catalytic synthesis of a range of products.

The Direct Synthesis of Heterocycles

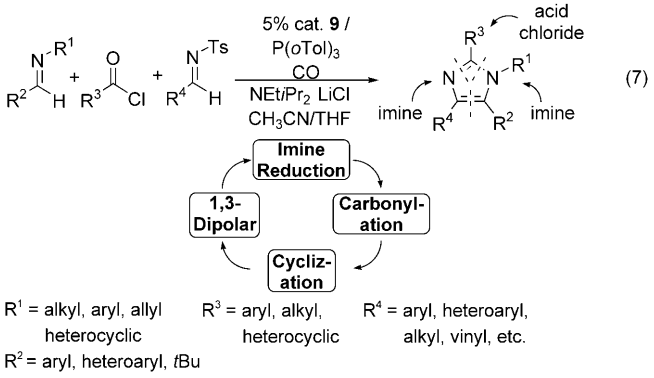
Pyrroles: Pyrroles are among the more common heterocyclic structures in biologically relevant products.[32] Methods to construct diversely substituted pyrroles typically require multiple steps to build up a substrate for cyclization. In contrast, coupling the series of palladium-catalyzed operations to form Munchnone **8** with subsequent 1,3-dipolar cycloaddition of alkynes, has provided a method to synthesize these products directly from three available building blocks [Eq. (6)].[30]



Interestingly, initial attempts to perform this reaction under the conditions used to form münchnones [e.g., Eq. (3)] yielded only traces of pyrrole. This illustrates a challenge in designing catalytic transformations of this form; in this case four separate reagents, base, and a catalyst are all required to selectively proceed through over eight separate (and sequential) steps. This suggests the potential for numerous other unwanted reactions. Closer examination of this reaction shows the build-up of *N*-acyl iminium salt **5** after catalysis, implying the alkyne may be inhibiting oxidative addition to Pd^0 (step **B**, Scheme 2), perhaps through the formation of an alkyne complex. By employing bulky phosphine ligands such as P(*o*-Tol)$_3$, which can coordinate to the catalyst to favor oxidative addition of **5** while retain sufficient lability to subsequently be displaced by CO (step **C**), this side process can be blocked, and allows the generation of a catalytic route to pyrroles.

Because of the building blocks employed, this provides a route to variously substituted pyrroles in a single reaction. For example, imines of aromatic, heteroaryl and non-enolizable alkyl aldehydes can be employed in the reaction, as can similarly substituted aryl and alkyl acid chlorides. Alkyne dipolar cycloaddition proceeds in highest yield with electron poor substrates, though electron neutral acetylene and phenyl acetylene can also be employed. While with unsymmetric alkynes regiochemical mixtures can arise, for many substrates this reaction can be induced to proceed to single pyrroles in high yields. Overall, this provides a route to construct pyrroles where each of the five substituents can be independently varied by tuning of the imine, acid chloride or alkyne used.

Imidazoles: The imidazole core is also accessible from this direct metal-catalyzed approach, and with the same type of modularity as the other product classes. By performing the palladium-catalyzed coupling in the presence of *N*-tosyl-substituted imines, which undergo 1,3-dipolar addition to münchnones followed by CO_2 and sulfinic acid loss to aromatize,[33] a palladium-catalyzed synthesis of these heterocycles can be generated from three available building blocks [Eq. (7)].[34] This catalysis incorporates similar catalytic



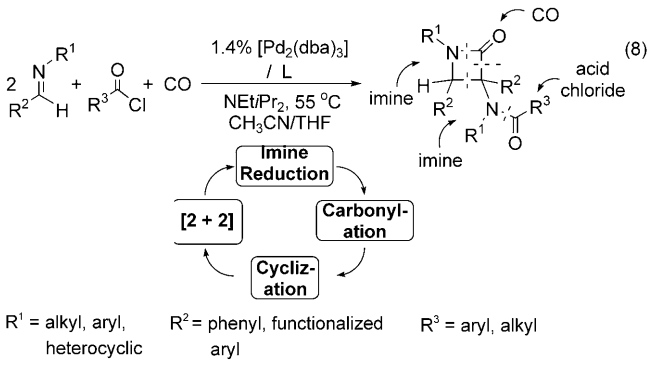
operations to that of pyrroles, but employing an imine in dipolar cycloaddition rather than an alkyne.

As with pyrroles, the presence of this fourth *N*-tosyl-substituted imine component leads to side reactions from the central catalytic cycle (Scheme 3). This includes the reaction

of the in situ generated iminium salt **5** with the liberated sulfinate anion to form an α-sulfonyl amide. It was found that the addition of LiCl, which favors the equilibrium regeneration of **5**, can allow catalysis to proceed, leading to the high yield, catalytic formation of imidazoles.

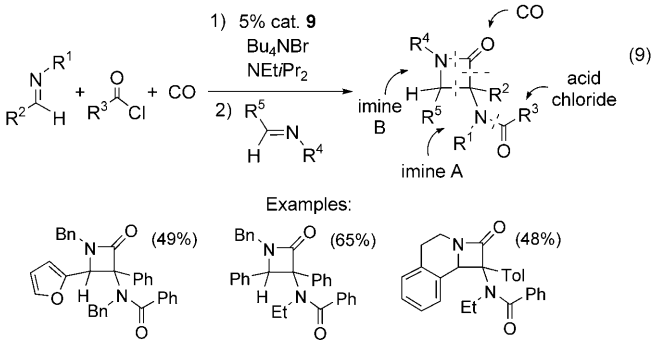
From a mechanistic perspective, this imidazole synthesis represents an unusual example of a catalytic multicomponent reaction that allows the simultaneous and intermolecular incorporation of two different imines selectively into the product. This often leads to product mixtures unless the substrates are tethered to undergo intramolecular reactions, as exploited in catalytic alkyne trimerization reactions.[12] In this case, the selectivity appears to result from the reaction mechanism. The electron-poor tosyl-substituted imine cannot react with the acid chloride (step **B**), and is therefore not incorporated into münchnone. However, this more electron-deficient imine reacts much more rapidly with münchnone than do *N*-alkyl or *N*-aryl imines (step **F**). Overall, this provides not only for two different imines in the heterocyclic core, but also allows for perfect regiocontrol of all the substituents about the imidazole from differing imines and acid chlorides.

β-Lactams: This same direct catalytic approach can also be applied to the synthesis of β-lactams. Münchnones are established to display ketene reactivity,[35] presumably through a dynamic equilibrium with the tautomeric ketene isomer **8′** (mechanism of Scheme 3). Thus, simply performing the catalytic operations to form münchnones in the presence of a second imine equivalent, which can undergo a formal [2+2] cycloaddition with the in situ generated ketene, provides a route to directly access the β-lactam core [Eq. (8)].[36] Notably, these are the same components employed to generate imidazoline carboxylates [Eq. (2)]. Thus, by modulating role of acid in catalysis, two different classes of products can be accessed from the same substrates (β-lactams or imidazolines).



(8)

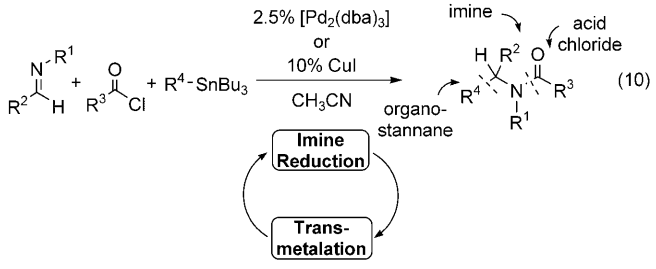
While there have been a growing number of syntheses of β-lactams, including those utilizing catalysis,[37] a useful feature of this methodology is its simplicity, which employs commercially available or readily prepared building blocks, as well as a commercial metal catalyst, and in one step brings these together to directly generate a β-lactam. In addition, this reaction provides direct access to the peptide-like amide-substituted β-lactam core, which is the functional structure of a range of antibiotics (e.g., penicillin, nocardicins, etc.). The reaction in Equation (8) does require the incorporation of two identical imines (the use of two distinct imines leads to the formation of mixtures of β-lactam products); however, by first catalytically generating a münchnone, then adding a second imine, lactams incorporating two separate imines can be generated [Eq. (9)]. This last type of reaction provides a method to construct a β-lactam with control of five separate substituents in a single reaction.



(9)

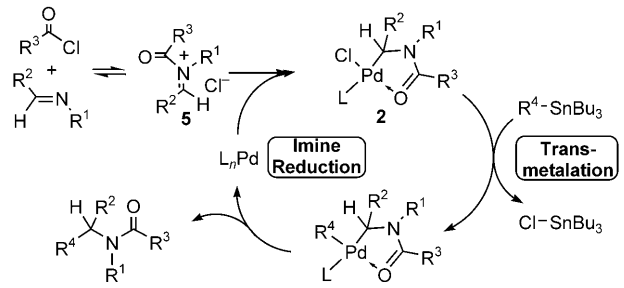
Direct Routes to α-Substituted Amides

The diversity of products available within this catalytic reaction manifold can be broadened beyond münchnone- and ketene-derived compounds, and provide direct routes to α-substituted amides and amine derivatives, by the application of cross-coupling chemistry. As shown in Scheme 3, palladium catalysis is initiated by the oxidative addition of *N*-acyl iminium salt **5**, leading to the generation of the palladium–carbon bonded intermediate **2**. By coupling this reaction step with the subsequent transmetalation of organotin reagents, this can provide a mild, palladium catalyzed Stille-type cross coupling method to construct α-substituted amides [Scheme 4, Eq. (10)].[30]



(10)

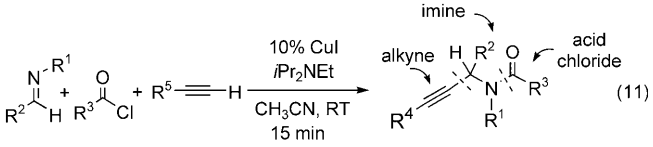
This reaction provides an unusual route to use multiply bonded electrophiles (i.e., imines) in a palladium-catalyzed cross-coupling reaction. In general, while cross-coupling re-



Scheme 4. Mechanism of Stille-type coupling with imines.

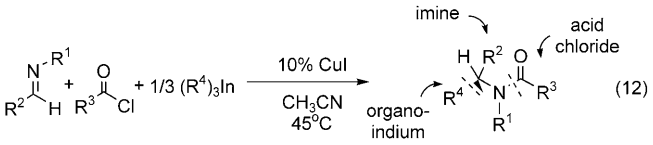
actions have become an important method to construct carbon–carbon bonds with R–X electrophiles,[38] one traditional limitation of this process is its inability to mediate similar bond formation with multiply bonded substrates. This results from the inability of these substrates to undergo direct addition to palladium to generate a Pd–C bond. In this case, by the simple addition of acid chlorides, imines not only add to palladium, but do so rapidly (ambient temperature). As a result of this rapid oxidative addition, selective carbon–carbon bond formation occurs even in the presence of classic Stille coupling partners, such as aryl iodides, and under mild conditions (ambient temperature cross coupling without added ligands).[30] In addition to palladium, copper(I) salts, such as CuI, can also catalyze this reaction, and do so with an even greater diversity of organotin reagents.[39] The latter likely occurs through a mechanism different than in Scheme 4, involving an initial transmetalation to create an organocopper intermediate, which reacts with the in situ generated *N*-acyl iminium salt.

Similar catalytic approaches can be used to couple other reagents with imines. As an example, the one-step coupling of imines, acid chlorides, and terminal alkynes under copper catalysis provides a route to generate propargylamide building blocks [Eq. (11)].[40] Alternatively, organoindium re-



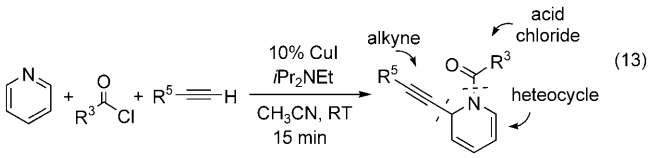
(11)

agents can be employed in this chemistry to access a range of α-substituted amides and carbamates; in this case with 1/3 of an equivalent of $InCl_3$ as the sole byproduct [Eq. (12)].[41] In addition to imines, various aromatic nitro-



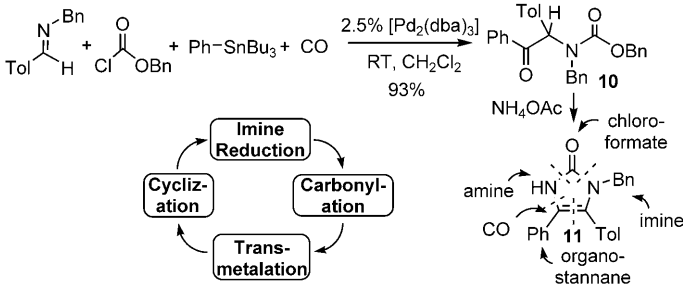
(12)

gen-containing heterocycles can also participate in these coupling reactions. This provides, for example, a method to directly functionalize pyridines without initial halogenation or strong nucleophiles [Eq. (13)].[42]



(13)

Since these carbon–carbon bond-forming reactions occur with a transition-metal catalyst, they are amenable to incorporating further levels of molecular complexity. For example, combining the iminium salt oxidative addition with carbonylation, followed by a Stille-like coupling, provides a method to generate α-amido ketones (Scheme 5). This represents a relatively rare four-component cross-coupling reac-



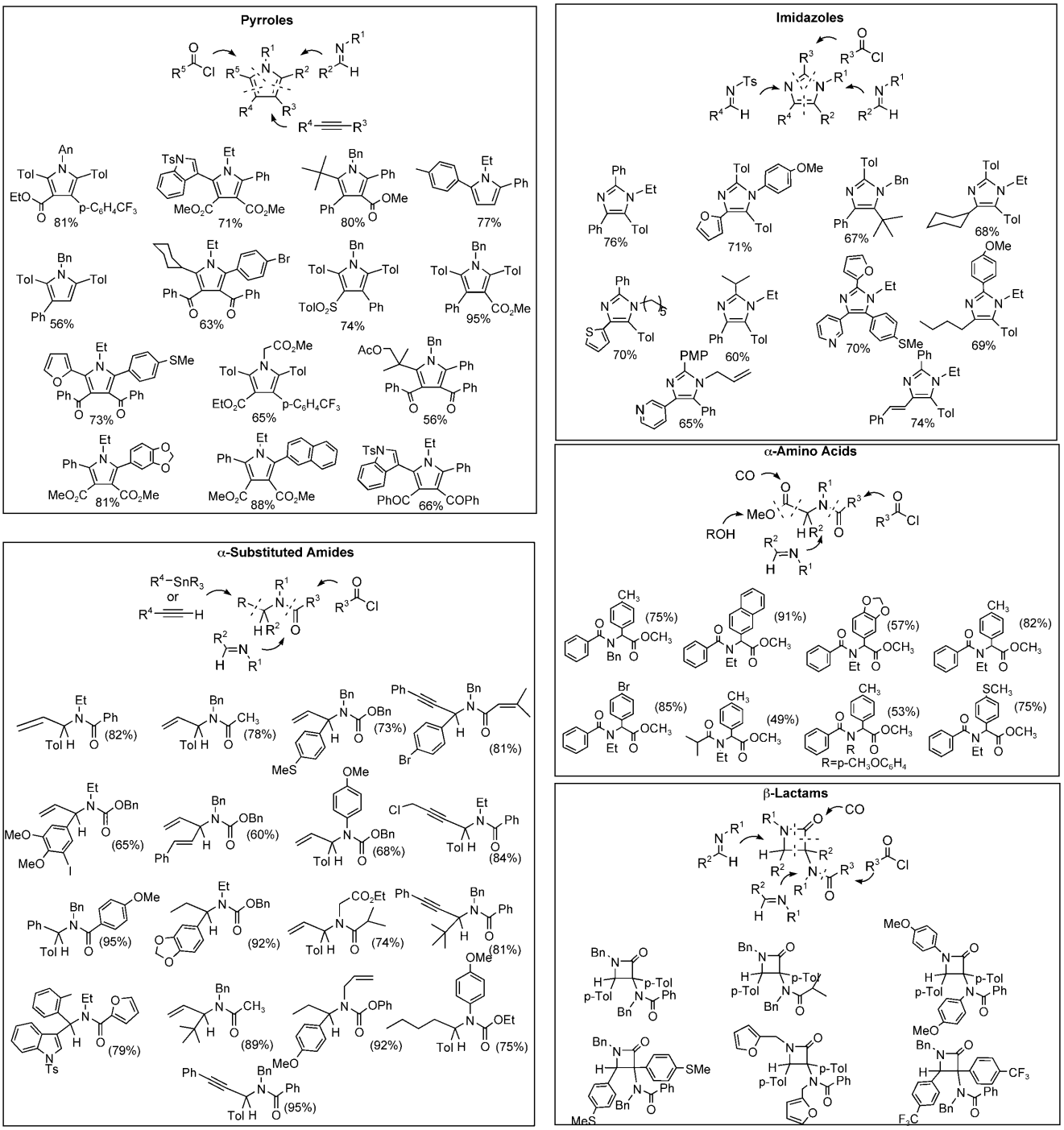
Scheme 5. A one-pot, cross-coupling route to imidazolones.

tion, in which the final product is generated from an imine, chloroformate, an arylstannane, and carbon monoxide. These products are themselves useful building blocks. Thus, the catalytic coupling of these four reagents, followed by the addition of ammonium acetate, initiates a cyclization of **10**. This has been used to design a one-pot route to imidazolones, in this case assembled from five separate units: an imine, acid chloride, carbon monoxide, arylstannane, and ammonia.[43]

Product Diversity

The building blocks incorporated into the reactions outlined above are each readily available, as well as available in many forms, in most cases from commercial sources (e.g., alkynes, aldehydes, amines, alcohols, acid chlorides). Thus, in addition to providing efficient access to these products, these reactions are directly amenable to structural diversification.

For example, in the case of pyrroles, modulating the imine, acid chloride, and alkyne substrates can allow the build-up of arrays of these heterocycles in one-step syntheses (Scheme 6). Representative examples include the use of imines of aromatic, heteroaromatic, or non-enolizable alkyl aldehydes, *N*-alkyl, *N*-benzyl, or *N*-aryl units, and a wide



Scheme 6. Examples of product diversity.

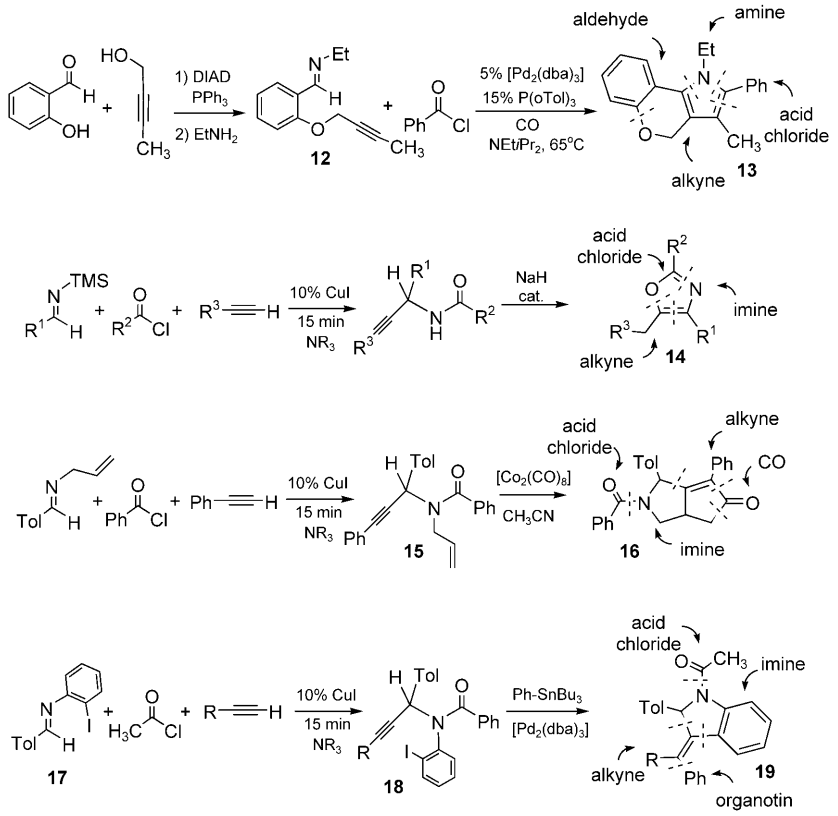
range of electron-poor to moderately electron-rich alkynes.[28] In certain cases, limits are observed with regiochemical selectivity involving unsymmetrical alkynes and münchnones, and for all these products the instability of enolizable imines precludes their use. Nevertheless, this provides, what is to our knowledge, the novel ability to construct pyrroles in which any of the core substituents can be varied in a one-step reaction of available building blocks.

Notably, each of the products described in the previous sections can be generated with similar modularity and diversity. This includes varying all of four units on imidazoles, five substituents in β-lactams, or four units in α-substituted amides. A potentially useful feature is that many of these products are prepared from similar building blocks. Thus, from a simple set of substituted imines, acid chlorides, alkynes, and organometallic agents, a tremendous variety of

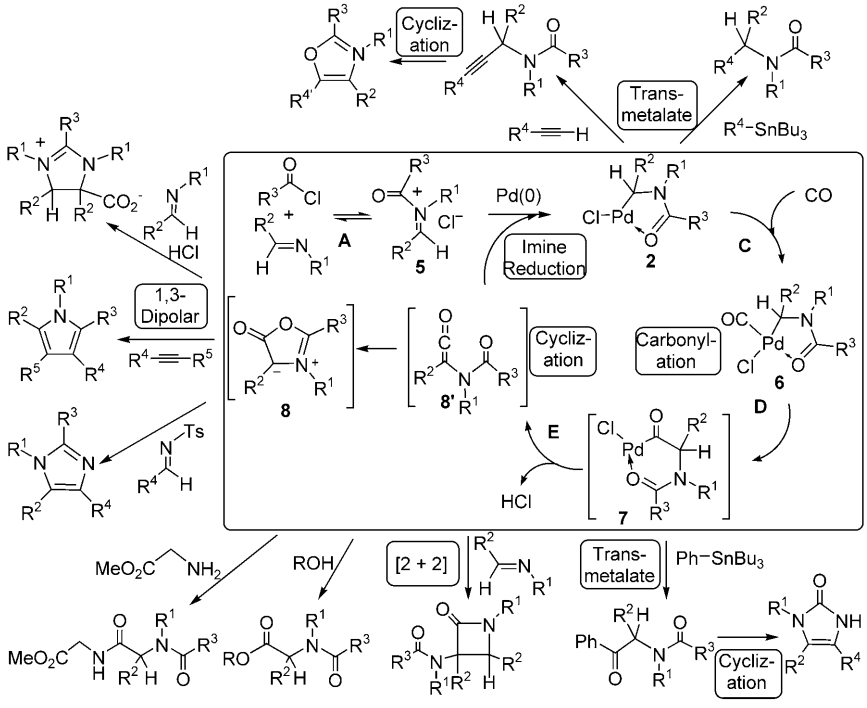
products can potentially be generated. The latter can be important for developing structural diversity.

Adding Further Levels of Molecular Complexity

The ability to directly generate a core structure directly from basic substrates also opens the potential of building in further levels of molecular complexity into these products, by adding in other simple transformations. An example of this can be seen in the direct synthesis of pyrroles from imines, alkynes, and acid chlorides. In addition to simple pyrroles, the initial construction of allyl-substituted imine **12** (by a single-pot Mitsonobu coupling followed by imination), followed by palladium catalysis with acid chloride, provides a method to generate multicyclic pyrroles such as **13** (Scheme 7).[28] This approach displays the same type of modularity as before, in which each of the pyrrole substituents, the arene unit, or linker can be modulated by choice of available compounds, and accesses these structures in three steps.



Scheme 7. One-pot, tandem synthesis of complex structures.



Scheme 8. Mechanistic summary of direct catalytic syntheses.

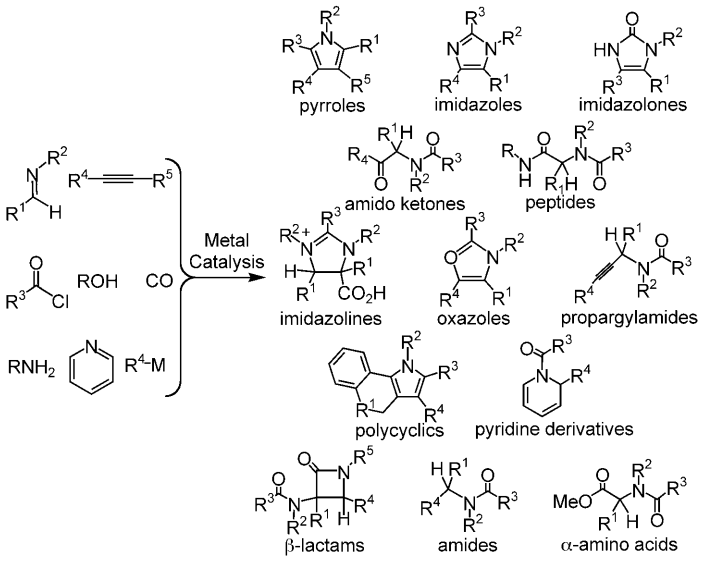
A similar concept has been demonstrated with propargylamides. These products themselves represent useful synthons for a range of important products. For example, the base catalyzed cycloisomerization of propargylamides can provide a one-pot synthesis of oxazoles **14**, in this case generated from an imine, an acid chloride, and a terminal alkyne. Alternatively, the use of allylimine **15** in the alkynylation, followed by a second catalytic Pauson–Khand reaction, provides a two-step procedure to assemble polycyclic amides **16**, while the sequential cross coupling with **17**, in which acid chloride activation first provides for the formation of propargylamide **18** followed by the more classical Stille coupling of the aryl iodide, can be used as a route to generate **19**.[44] Notably, each of these products are generat-

ed in good yield, and every substituent and linker can be modularly changed by choice of commercial starting materials.

Conclusions

These results demonstrate how the reactivity of transition-metal catalysis can be exploited to build up families of useful products in a single step from available building blocks. These reactions rely upon an array of metal-based reactions to occur in a sequential fashion in order to selectively bring these units together. By gaining an understanding of each of these steps, and the various side reactions within these transformations, selective metal-catalyzed routes to a broad range of products can be developed (Scheme 8). For example, this chemistry can be selectively diverted from the central catalytic cycle at the palladium–carbon bonded stage (**2**) to perform carbon–carbon bond-forming reactions, at the carbonylation stage (**7**) to perform carbonylative cross coupling, at the ketene stage (**8′**) to generate amino acid based products, or at the Munchnone stage (**8**) to generate heterocycles.

While the mechanisms of these reactions are complex, the resultant synthetic chemistry is very straightforward, providing metal-catalyzed methods to assemble a diverse array of important core structures (Scheme 9). These processes display many features desired in synthetic protocols (e.g., a one-step synthesis, modular product formation, high overall yields, minimal purification, etc.). As such, these each represent useful alternatives to multistep syntheses. In addition, these reactions, together with other efforts in this area,[12–16] illustrate that the concept of using transition-metal catalysis to assemble products from simple substrates is not only viable, but can be applied to a breadth of structures. Together, these can provide important methods to readily access complex and highly substituted molecular scaffolds, and do so in the diversifiable manner often desired in product discovery.



Scheme 9. Examples of products assembled in one-step, metal-catalyzed reactions.

Acknowledgements

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