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From Aryl Iodides to 1,3-Dipoles: Design and Mechanism of a Palladium Catalyzed Multicomponent Synthesis of Pyrroles

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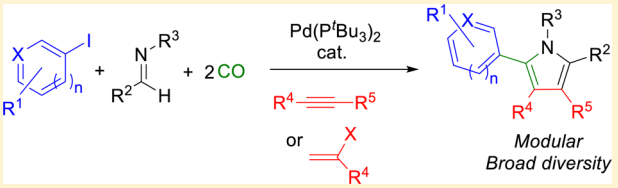
Supporting Information

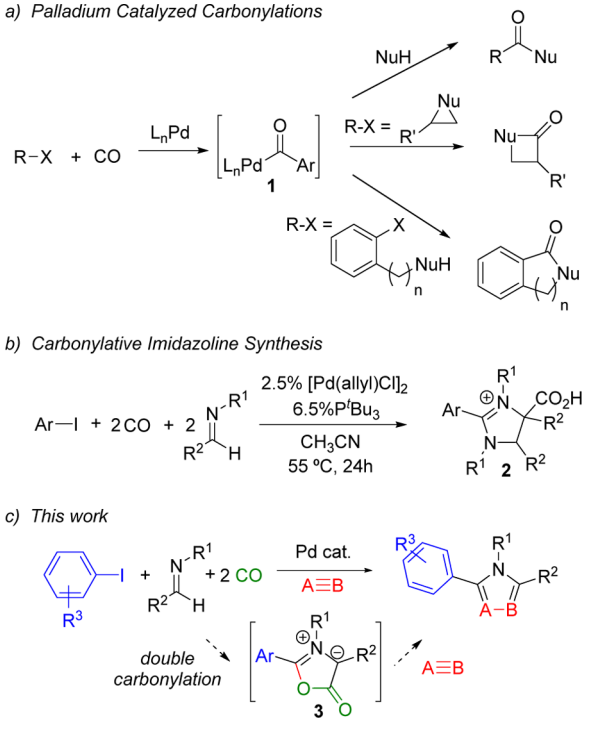
ABSTRACT: A palladium-catalyzed multicomponent synthetic route to polysubstituted pyrroles from aryl iodides, imines, carbon monoxide, and alkynes is described. To develop this reaction, a series of mechanistic studies on the $[Pd(allyl)Cl]_2/P^tBu_3$ catalyzed synthesis of imidazolinium carboxylates from aryl iodides, imines, and carbon monoxide were first performed, including model reactions for each individual step in the transformation. These show that this reaction proceeds in a concurrent tandem catalytic fashion, and involves the in situ formation of acid chlorides, *N*-acyl iminium salts, and ultimately 1,3-dipoles, i.e., Münchnones, for subsequent cycloaddition. By employing a $Pd(P^tBu_3)_2/Bu_4NCl$ catalyst, this information was used to design the first four-component synthesis of Münchnones. Coupling the latter with 1,3-dipolar cycloaddition with electron deficient alkynes or alkenes can be used to generate diverse families of highly substituted pyrroles in good yield. This represents a modular and streamlined new approach to this class of heterocycles from readily accessible starting materials.



INTRODUCTION

Palladium-catalyzed carbonylative coupling reactions with organic halides and pseudohalides have become an important tool in synthetic chemistry. Since its initial discovery by Heck in the mid-1970s, this reaction has been applied to the synthesis of a diverse range of carboxylic acid derivatives (esters, amides, aldehydes, ketones, etc.).[1−3] Carbonylations have also seen rapidly growing use in the assembly of more complex carbocyclic and heterocyclic scaffolds.[4] One approach developed by Alper, Coates, Drent, and others involves the ring expansion of heterocycles to form lactones or lactams.[5] Alternatively, a range of aryl halide carbonylations with intramolecular cyclization have been described,[6] as have sequential or cascade insertions,[7] and reactions involving the subsequent cyclization of the ester or amide products of carbonylation.[8] From a mechanistic perspective, metal-catalyzed carbonylations are typically postulated to involve the in situ formation of metal-acyl complexes (**1**) which subsequently undergo coupling with nucleophiles (Scheme 1a). The reactivity of **1** therefore shows similarity to that of activated carboxylic acid derivatives such as acid chlorides. In considering this analogy, and the broad utility of acid chlorides in synthesis, we recently became interested in the potential use of carbonylations to access products other than carbonyl-containing derivatives. As an initial study toward this reaction, aryl halide carbonylation in the presence of imines results in the generation of imidazolinium carboxylates **2** (Scheme 1b).[9] The latter is based upon the established generation of iminium salts from acid chlorides, and provides a rare example of a five-component coupling reaction, as well as a modular method to assemble these heterocycles.

Scheme 1. Palladium Catalyzed Carbonylation and Heterocycle Synthesis



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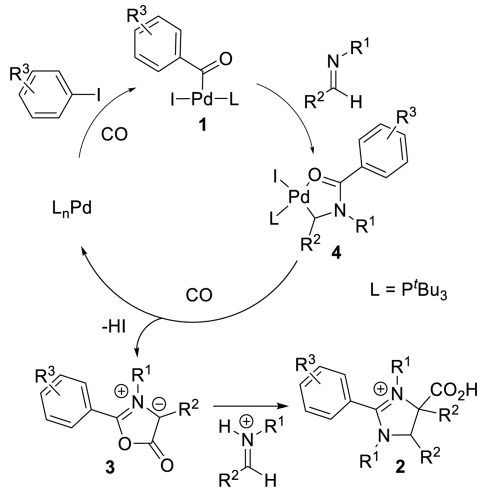
While the imidazolinium carboxylates formed above are limited to symmetrically substituted products, this reaction has prompted us to question if aryl halide carbonylation chemistry might open a more broadly applicable approach to construct heterocycles from fundamental building blocks. Polysubstituted heterocycles, and in particular the aryl-heteroaryl motif, are among the most common structural units found in pharmaceutical development. These products are typically generated via substitution chemistry on presynthesized heterocycles (e.g., cross coupling reactions), or cyclization reactions, both of which require the multistep synthesis of substituted precursors.[10] In contrast, the transformation in Scheme 1b presumably involves the in situ generation of an interesting class of 1,3-dipole: Münchnones (**3**), although these intermediates are not observed. Münchnones are well-known 1,3-dipoles that have been exploited for the convergent synthesis of various classes of heterocycles.[11] One limitation to the use of **3** in heterocycle synthesis is their own formation, as these compounds are typically generated via the cyclization of α-amido acids, which can themselves require a multistep synthesis. While alternative approaches to Münchnones have been described,[12,13] including via the carbonylation of *N*-acyl iminium salts, these also rely upon the use of reactive (and synthetic) building blocks, such as acid chlorides or metal-carbenes. In contrast to each of these reactions, the palladium catalyzed formation of imidazolines suggests that Münchnones can be generated from the carbonylation of aryl iodides and imines. We therefore hypothesized that inhibiting imidazoline formation and generating **3** could provide a general platform to generate aryl-substituted heterocycles from simple combinations of available substrates (Scheme 1c). In addition to the synthetic chemistry, a notable feature of this system would be its use of CO not to generate a carbonylated product, but instead to drive the multicomponent assembly of fundamental building blocks via the ultimate liberation of CO_2.

One challenge to the use of this carbonylation chemistry to generate heterocycles is the lack of a complete understanding of how imidazolinium carboxylates are generated, and indeed if Münchnones are intermediates in this reaction. To address this, we have undertaken a series of studies to determine the mechanism of this catalytic transformation. These demonstrate the steps by which the multicomponent coupling occurs, and conditions that can favor the formation of 1,3-dipoles. Based upon this data, we have designed a palladium catalyzed dicarbonylative approach for the synthesis of polysubstituted pyrroles. In contrast to typical procedures, this reaction provides a method to form a pyrrole unit at the same time as the aryl-pyrrole bond, in one pot, and from four simple components: aryl iodides, imines, CO, and alkynes or alkenes.

RESULTS AND DISCUSSION

I. Stoichiometric Model Reactions. Our preliminary mechanistic postulate for the catalytic generation of imidazolines is shown in Scheme 2. Palladacycles of the general form of **4** have been established to undergo cyclocarbonylations to generate Münchnones.[14] We therefore hypothesized that an in situ generated palladium-aroyl complex **1** serves as a precursor to **4** by reacting with imine. In this scenario, the palladium catalyst would mediate both an initial carbonylation of aryl iodide to form **1**, followed by a subsequent cyclocarbonylation to form Münchnone **3** and liberate catalyst. The bulky P^tBu_3 ligand is believed to facilitate catalysis due in part to its lability in palladacycle **4**, which can allow CO association and

Scheme 2. Mechanistic Postulate for Catalysis

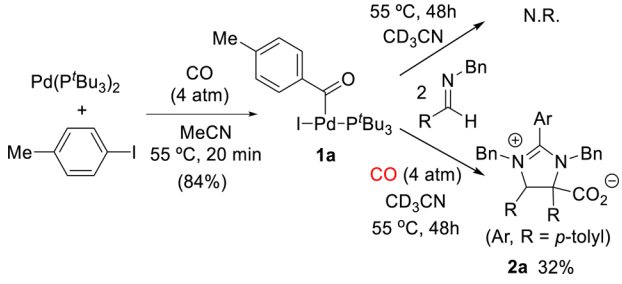


subsequent insertion. While Münchnones are not observed in the reaction, protonated imines are known to undergo rapid cycloaddition to **3**, and upon carbon–oxygen bond scission to form imidazolinium salts.[14]

In order to further probe this mechanism, we first performed a series of model reactions for each of these individual steps.

Reaction of Pd(P^tBu_3)$_2$, Aryl Iodide, CO, and Imine. Our initial studies examined the putative first steps in the catalytic cycle: the formation of palladium-aroyl complex **1** and its reaction with imine. Similar to previous reports,[15] the addition of Pd(P^tBu_3)$_2$,[16] as a model for the in situ generated Pd(0) catalyst, to aryl iodide and carbon monoxide leads to the rapid formation of the three-coordinate palladium-aroyl complex **1a** (Scheme 3). This complex can be easily isolated in high yield

Scheme 3. Reactivity of Pd-Aroyl Complex 1a



upon precipitation with pentane.[15a,b] Interestingly, control experiments show no reaction occurs between **1a** and imine, the postulated next step in catalysis, even upon prolonged heating at 55 °C. However, the addition of the other reagent present in catalysis, CO, initiates the slow disappearance of **1a** and generation of imidazolinium carboxylate **2a** (32% yield). We observe no intermediates in this reaction, indicating that subsequent steps leading to the formation of product are faster than the reaction of imine with palladium-aroyl complex. Although this data demonstrates that **1a** is a viable intermediate in the formation of **2a**, it is notable that the stoichiometric reaction is low yielding and slow (2 days, 55 °C). This suggested that **1a** may not be an immediate precursor to imidazolines during catalysis.

Influence of Chloride. In considering differences between the control experiments in Scheme 3 and catalysis, we noted

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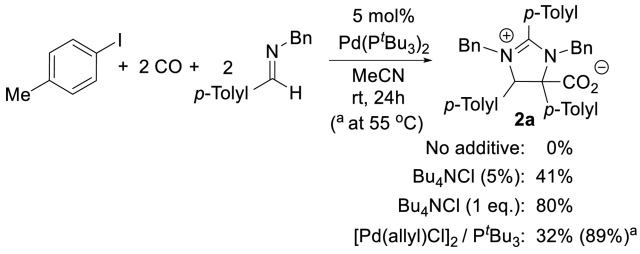
that the catalytic synthesis of imidazolinium carboxylate employs $[Pd(allyl)Cl]_2/P^tBu_3$, rather than $Pd(P^tBu_3)_2$, as the catalyst precursor. While both of these are expected to generate similar P^tBu_3-coordinated Pd(0) catalysts, as shown in Scheme 4, the use of $Pd(P^tBu_3)_2$ as catalyst results in minimal coupling

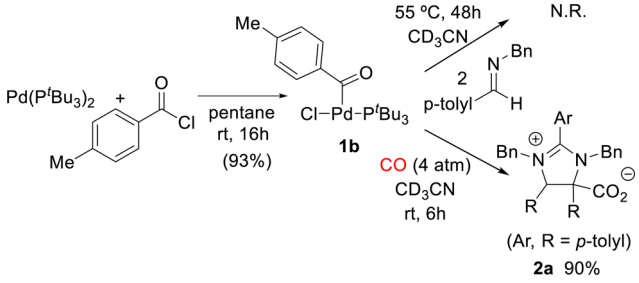
Scheme 4. Influence of Chloride on Catalysis



under identical conditions. One potentially important difference between these two systems is the presence of chloride in the $[Pd(allyl)Cl]_2$ catalyst precursor. To examine the role of chloride in the reaction, 5 mol % Bu_4NCl was added to the catalytic reaction with $Pd(P^tBu_3)_2$. This restores catalytic activity to the level noted with $Pd(allyl)Cl]_2/P^tBu_3$ (Scheme 4). Further, increased chloride concentration results in accelerated reaction.

A plausible role of chloride in catalysis would be to exchange with iodide on palladium and therefore modulate reactivity.[17] To test this, the analogous chloride coordinated palladium-aroyl complex **1b** was generated by the oxidative addition of acid chloride to $Pd(P^tBu_3)_2$ (Scheme 5). This chloride

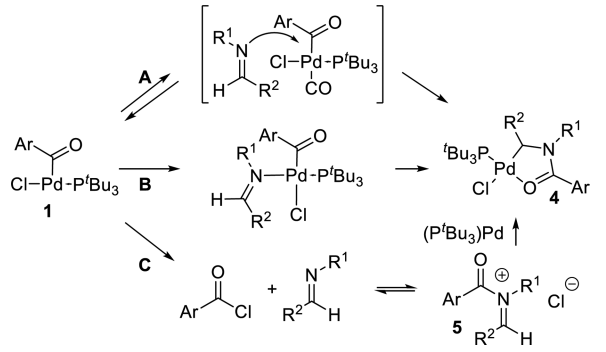
Scheme 5. Reactivity of Pd-Aroyl Complex 1b



coordinated **1b** also does not directly react with imine. However, the addition of carbon monoxide results in the room temperature formation of imidazolinium carboxylate **2a** in high yield (90%). The latter transformation is much more rapid (6 h, rt) than that with the iodide complex **1a**, and of sufficient rate to be a viable step in the catalytic reaction.

Acid Chloride Intermediates. The above data suggest that both chloride and carbon monoxide can facilitate the reaction of imines with palladium-aroyl complexes, and in particular carbon monoxide is required for any reaction to occur. One rationale for these effects is that chloride and/or carbon monoxide coordination exert an influence on the reaction of imine with the palladium-aroyl complex. The latter may occur via a direct nucleophilic attack on the electrophilic aroyl ligand (Scheme 6, path A), or, in analogy to previous reports with cationic palladium-acyl complexes, coordination and migratory insertion (path B).[18] However, we have recently noted that chloride and carbon monoxide in concert with the P^tBu_3 ligand can accelerate palladium catalyzed aryl halide carbonylations by allowing the generation of acid chlorides.[19] As such, an

Scheme 6. Mechanism of Imine Reaction 1

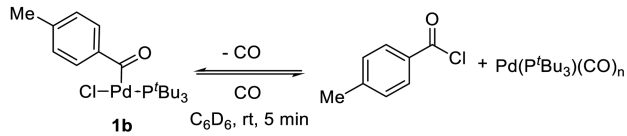


alternative postulate for the influence of chloride is that it allows the in situ generation of acid chlorides for reaction with imine (path C).

Insight into the pathway followed in this transformation can be obtained by simply omitting the addition of imine to the reaction of palladium-aroyl complex **1b**. The addition of CO to **1b** leads to the rapid, equilibrium formation of acid chloride (Scheme 7a). Removal of CO from the reaction allows the

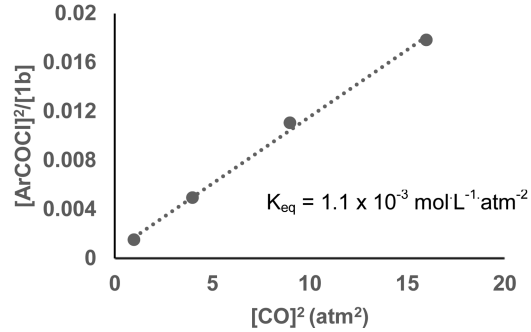
Scheme 7. Generation of Acid Chlorides from 1b

*a) Equilibrium Elimination of Acid Chloride from **1b***



CO (atm)	% acid chloride
1	18%
2	30%
3	42%
4	52%

b) Plot of Acid Chloride Formation vs. $[CO]^2$



quantitative reformation of **1b**, while increasing CO pressure results in the further favored generation of acid chloride. A plot of the ratio of product vs CO pressure provides a linear fit to $[CO]^2$ (Scheme 7b), implying that two CO ligands may bind to the Pd(0) complex. Notably, no reaction is noted for the analogous iodide complex **1a**, nor with **1b** in the absence of CO. The rapid formation of acid chloride from **1b** provides a rationale for the role of chloride in catalysis, and a reasonable pathway for coupling with imine, as acid chlorides are established to react rapidly with imines to form *N*-acyl iminium salts (**5**, path C).[20] The intermediacy of **5** in this chemistry is further examined below.

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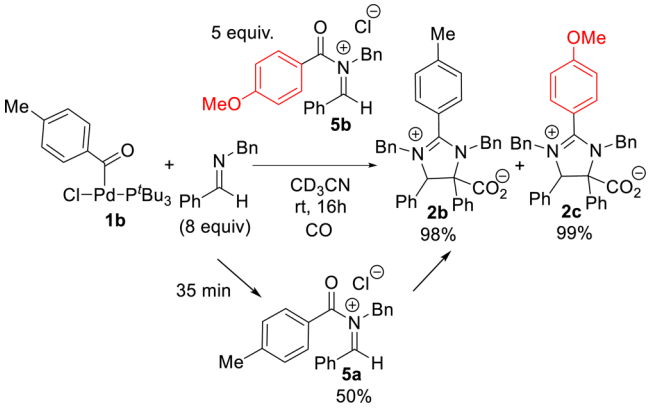
N-Acyl Iminium Salts. We see no evidence for the formation of *N*-acyl iminium salts, or any intermediate, by monitoring the stoichiometric reaction of **1b**, imine, and carbon monoxide by ^{1}H NMR analysis. To probe for their intermediacy, we therefore employed scrambling experiments with a labeled iminium salt (**5b**, Scheme 8). The latter could exchange with

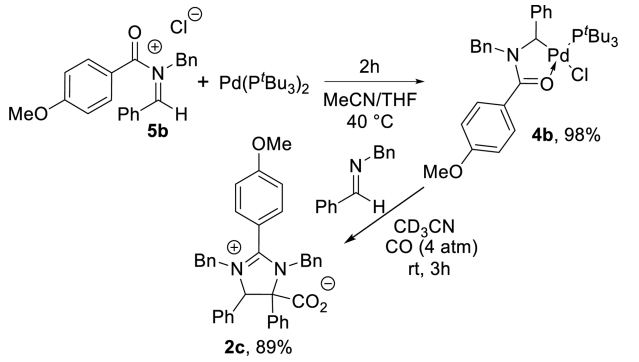
Scheme 8. Intermediacy of *N*-Acyl Iminium Salts



any free iminium salt generated from palladium complex **1b**, and may allow **5a** to build-up in solution. Monitoring the reaction of palladium-aroyl complex **1b** with imine and CO in the presence of an excess of **5b** by in situ ^{1}H NMR analysis reveals that iminium salt **5a** does indeed form in this reaction at short reaction times (50% at 35 min). Allowing the reaction to continue leads to the complete consumption of both iminium salts and generation of two separate imidazolines, **2b** and **2c**.

Palladacycle Formation. The generation of free *N*-acyl iminium salt **5** in this chemistry requires that this intermediate add to palladium for a second carbonylation to ultimately generate imidazolinium carboxylates **2**. Control experiments show that this step is also viable. The addition of *N*-acyl iminium salt **5b** to Pd(P^{t}Bu$_3$)$_2$ leads to the near quantitative formation of palladacyclic complex **4b** within 2h (Scheme 9).

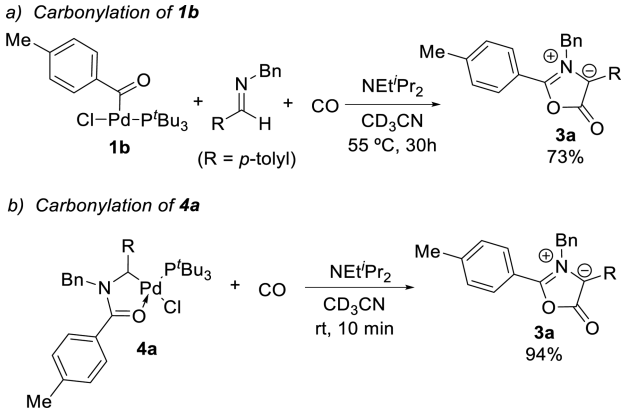
Scheme 9. Synthesis of Palladacyclic Intermediates



This complex displays spectroscopic features similar to previously isolated amide-chelated palladacycles.[12a,18] Complex **4b** is also a viable intermediate in catalysis: the addition of CO to this palladacycle results in its rapid (3 h, rt) conversion into imidazolinium carboxylate in 89% yield.

Münchnone Formation. One intermediate not observed in the stoichiometric chemistry above is Münchnone **3**. Previous studies on 1,3-dipolar cycloadditions with Münchnones have demonstrated that protonated *N*-alkyl imines can undergo very rapid cycloaddition to generate imidazolinium salts.[14] In the chemistry above, acid is generated upon the cyclocarbonylation of palladacycle **4** (Scheme 2), and can presumably protonate imine to allow the generation of **2**. We therefore examined the effect of base on the stoichiometric reactions. As shown in Scheme 10a, the addition of NEt^{i}Pr$_2$ base to the reaction of

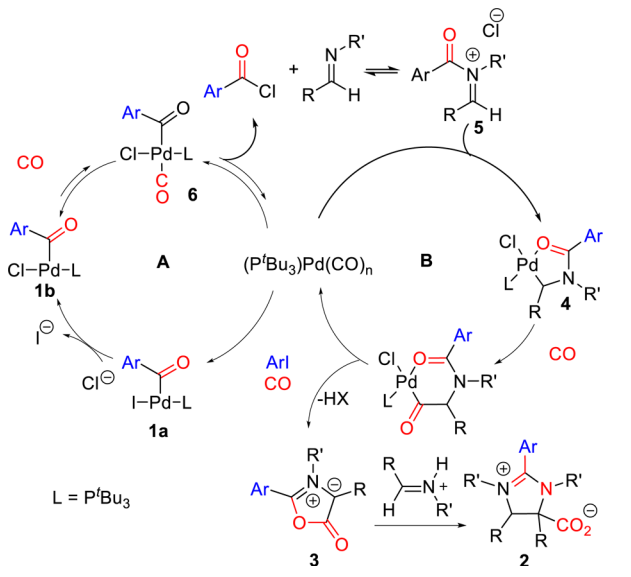
Scheme 10. Stoichiometric Münchnone Generation



palladium-aroyl complex **1b**, imine, and CO inhibits imidazolinium formation and leads instead to the formation of Münchnone **3a**. in 73% yield. A similar effect of base is noted on the reaction with palladacycle **4a** (Scheme 10b).

II. Postulated Mechanism of Imidazolium Formation. The above studies show that several palladium complexes and organic products are each competent intermediates in catalysis: palladium-aroyl complexes (**1a** and **1b**), acid chlorides, *N*-acyl iminium salts **5**, palladacyclic complex **4** and Münchnones. Based upon this data, we can formulate a reasonable mechanism for the multicomponent formation of imidazolines (Scheme 11). In this, the oxidative addition of aryl iodide and CO insertion is rapid, and leads to the generation of the palladium-aroyl complex **1a**. Control experiments demonstrate that complex **1a** does not react rapidly with imine (e.g., Scheme

Scheme 11. Overall Mechanism of Imidazolium Carboxylate Formation



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3). The latter is consistent with many examples in carbonylation reactions, which suggest that palladium-aroyl ligands are only moderately electrophilic, and typically require anionic nucleophiles that can first coordinate to palladium for more facile reductive elimination.[21] Instead, our data is consistent with the reductive elimination of acid chloride from the chloride-coordinated complex **1b**, which can react with the weakly nucleophilic imine away from the palladium catalyst to generate free *N*-acyl iminium salts **5**. The role of CO and P^tBu_3 in the formation of acid chloride is presumably similar to that we have previously noted, where coordination of CO to the T-shaped complex creates a sterically encumbered and electron-poor palladium intermediate **6** for the favored reductive elimination of acid chloride.[19] As such, both chloride and carbon monoxide are critical for the buildup of iminium salts. Once *N*-acyl iminium salt **5** is generated, control experiments suggest that it can undergo rapid oxidative addition to $Pd(P^tBu_3)_2$ to form palladacycle (**4**, Scheme 9) for rapid subsequent cyclocarbonylation to form Münchnone (Scheme 10b). The latter is established to react with protonated imine to generate the observed imidazolinium salt products.[7]

These data show that catalysis that proceeds via two separate carbonylation cycles (A and B), both of which are mediated by the same palladium catalyst. Monitoring the catalytic reaction by NMR provides some insight into the relative rates of these two cycles. In situ ^{31}P NMR analysis (Figure 1) shows the

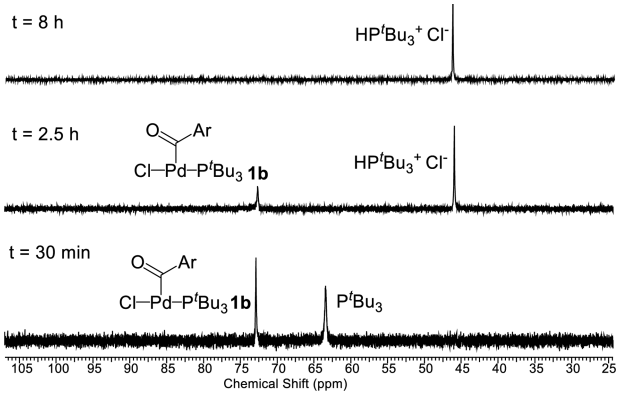

Figure 1. In situ ^{31}P NMR analysis of the catalytic formation of imidazolinium carboxylate in Scheme 4.

generation palladium-aroyl complex **1b** as the only observable intermediate at short reaction times. However, as catalysis proceeds, the buildup of protic acid leads to the equilibrium protonation of the phosphine, and this complex can no longer be observed. The observation of complex **1b** suggests that its subsequent reaction (i.e., with imine) is at least partially rate determining in the overall cycle. ^1H NMR analysis shows no evidence for any organic (e.g., *N*-acyl iminium salt) intermediate during the course of the reaction, and also implies that the consumption of acid chloride and iminium salt (cycle B) is more rapid than their formation (cycle A).

Kinetic analysis of the catalytic reaction provides further insight into the rate-determining step(s) in this system. As illustrated in Figure 2, the catalytic formation of imidazolinium carboxylate proceeds with the first order dependence on imine concentration, aryl iodide concentration, and carbon monoxide pressure. In considering the mechanism in Scheme 11, and the catalyst resting state at **1b**, these results are consistent with *N*-acyl iminium salt **5** formation from **1b** (cycle A) as rate

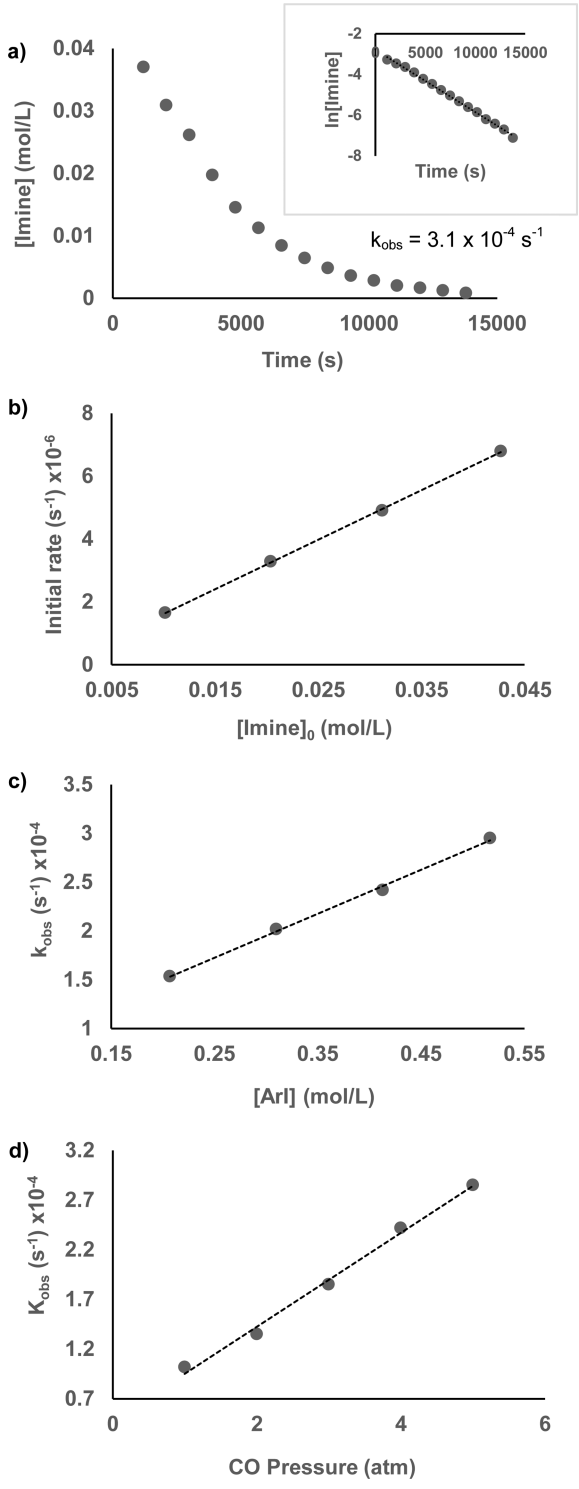

Figure 2. Kinetic analysis of catalytic formation of imidazolinium carboxylate. (a) Typical plot of imine concentration vs time for the reaction in Scheme 3 with 10 mol % $Pd(P^tBu_3)_2$ and 1 equiv of Bu_4NCl at 40 °C. Inset: ln plot of data. (b) Initial rate dependence on imine concentration. (c) Rate dependence on *p*-tolyl iodide concentration. (d) Rate dependence on CO pressure.

determining in catalysis. While acid chloride reductive elimination is rapid, this reaction is in dynamic equilibrium due to the rapid readdition of acid chloride to Pd(0). In this scenario, both imine and aryl iodide concentration can favor *N*-acyl iminium salt generation by trapping the acid chloride and

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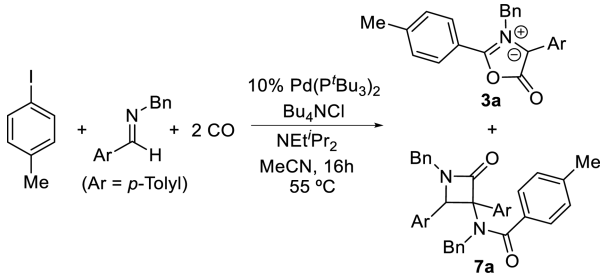
Pd(0), respectively, and carbon monoxide pressure is established to favor this equilibrium by generating a more stable Pd(0)-carbonyl intermediate (Scheme 7).

III. Catalytic Münchnone Synthesis. We next turned our attention to the potential use of this chemistry as a general route to prepare Münchnones. The data in Scheme 10 shows that amine base can inhibit imidazolinium carboxylate formation and allow the buildup of Münchnone. Similarly, the use of catalytic $Pd(P^tBu_3)_2$ in the reaction of aryl iodide, imine and CO in the presence of NEt^iPr_2 leads to the catalytic formation of Münchnone **2a** (Table 1, entry 1), but in low yield

Table 1. Catalytic formation of Münchnones[b]



entry	CO (atm)	Ar–I (equiv)	% **3a**	% **7a**
1	1	1	20	32
2[a]	1	1	0	0
3	1	3	44	50
4	1	5	50	13
5	4	1	58	19
6	10	1	65	8

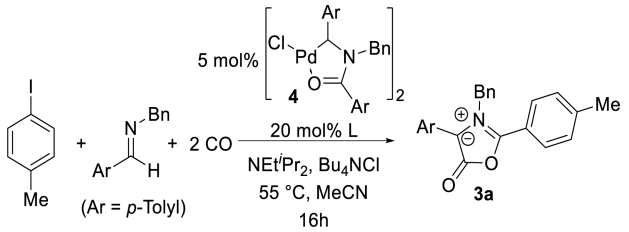
[a]Bu_4NCl not added to the reaction. [b]4-Iodotoluene (55 mg, 0.25 mmol), imine (52 mg, 0.25 mmol), Bu_4NCl (69 mg, 0.25 mmol), NEt^iPr_2 (49 mg, 0.375 mmol), $Pd(P^tBu_3)_2$ (13 mg, 25 μmol), and CO in MeCN (1.7 mL), yields of **3a** and **7a** determined by ^{1}H NMR analysis.

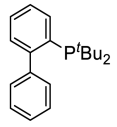
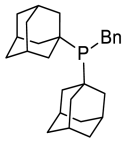
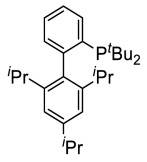
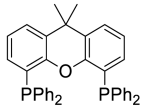
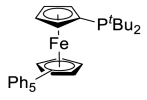
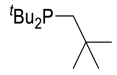
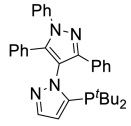
(20%). Instead, we note the buildup of a second product: β-lactam **7a** (32%). The generation of β-lactam presumably arises from the slow [2 + 2] cycloaddition of ketene tautomer of Münchnone with imine.[22] As in the stoichiometric experiments, the omission of chloride completely shuts down catalysis (entry 2).

The formation of β-lactam was an anticipated challenge in this catalytic reaction, where, much like the catalytic formation of imidazolinium carboxylates, the imine itself reacts more rapidly with the Münchnone product than it builds up in the catalytic reaction. One approach to avoid this product would be to accelerate the catalytic formation of Münchnone, and therefore imine consumption. The mechanistic results proved useful in this regard. For example, increasing the concentration of aryl iodide favors the formation and yield of Münchnone (entries 3, 4). The latter is presumably related to the equilibrium formation of acid chloride, where a higher concentration of aryl iodide can better trap Pd(0) and favor catalysis. Similarly, increasing CO pressure leads to the faster generation of Münchnone and significantly limits the formation of β-lactam (entries 5, 6).

The influence of ligands on this transformation was also probed. In order to screen ligands uncomplicated by catalyst activation steps, palladacycle **4** was used as the catalyst precursor, as it also represents an intermediate in the catalytic cycle. The use of common triaryl- or trialkylphosphines completely inhibits catalysis (Table 2, entries 2, 3). This may

Table 2. Ligand Screening for Münchnone Formation[b]



#	Ligand	% 3a (% 7a)	#	Ligand	% 3a (% 7a)
1	-	20 (2)			
2	PPh_3	0 (0)	9		23 (4)
3	PCy_3	0 (0)			
4		0 (14)			
5		3 (2)	10		27 (6)
6		0 (0)	11		57 (14)
7	P(*o*-Tol)$_3$	18 (2)	12		55 (19)
8		24 (6)	13	P^tBu_3	62 (20)
			14[a]	P^tBu_3	80 (4)

[a]Reaction performed at 40 °C, with 4-iodotoluene (164 mg, 0.75 mmol) and CO (10 atm). [b]4-Iodotoluene (33 mg, 0.15 mmol), imine (31 mg, 0.15 mmol), Pd catalyst **4** (6.8 mg, 7.5 μmol), ligand (30 μmol), NEt^iPr_2 (29 mg, 0.23 mmol), Bu_4NCl (42 mg, 0.15 mmol), and CO (4 atm), in MeCN (1 mL), yield determined by ^{1}H NMR analysis.

arise from the strong binding of these ligands to palladacycle **4**, which could inhibit carbonylation. Moving to more sterically encumbered ligands leads to low yield of Münchnones (ca. 20%, entries 7–10), or approximately one to two catalytic turnovers of the palladacycle precatalyst (i.e., cycle B, Scheme 10). In contrast, large bite angle phosphines can lead to double-carbonylative catalysis (entries 11–13), with P^tBu_3 the most active. This ligand is also noted to be key in catalytic acid chloride formation, where its cone angle can create sufficient steric encumbrance on palladium to allow rapid acid chloride formation.[19] Under these combined conditions with excess aryl iodide, the formation of Münchnone is sufficiently rapid to allow us to lower the reaction temperature (entry 14). The latter further suppresses β-lactam formation, and allows the synthesis of Münchnone in high yield.

IV. Catalytic Synthesis of Pyrroles. The reaction in Table 2 provides a new route to form a 1,3-dipole via the carbonylation of aryl iodides with imines. As discussed

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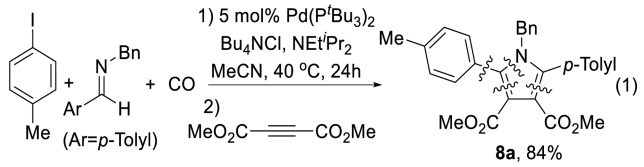
previously, a feature of Münchnones is their ability to participate in cycloaddition reactions to assemble heterocycles. Coupling the catalytic formation of **3** with cycloaddition can therefore provide an alternative to more classical multistep routes to assemble the aryl-heteroaryl motif. As an example, the catalytic generation of Münchnone **3a** followed by the addition of the electron deficient alkyne dimethylacetylenedicarboxylate leads to the generation of 2-aryl substituted pyrrole **8a** in 84% yield (eq 1), where in one pot four bonds are generated from five separate reagents (aryl iodide, imine, alkyne, and 2 equiv of carbon monoxide).

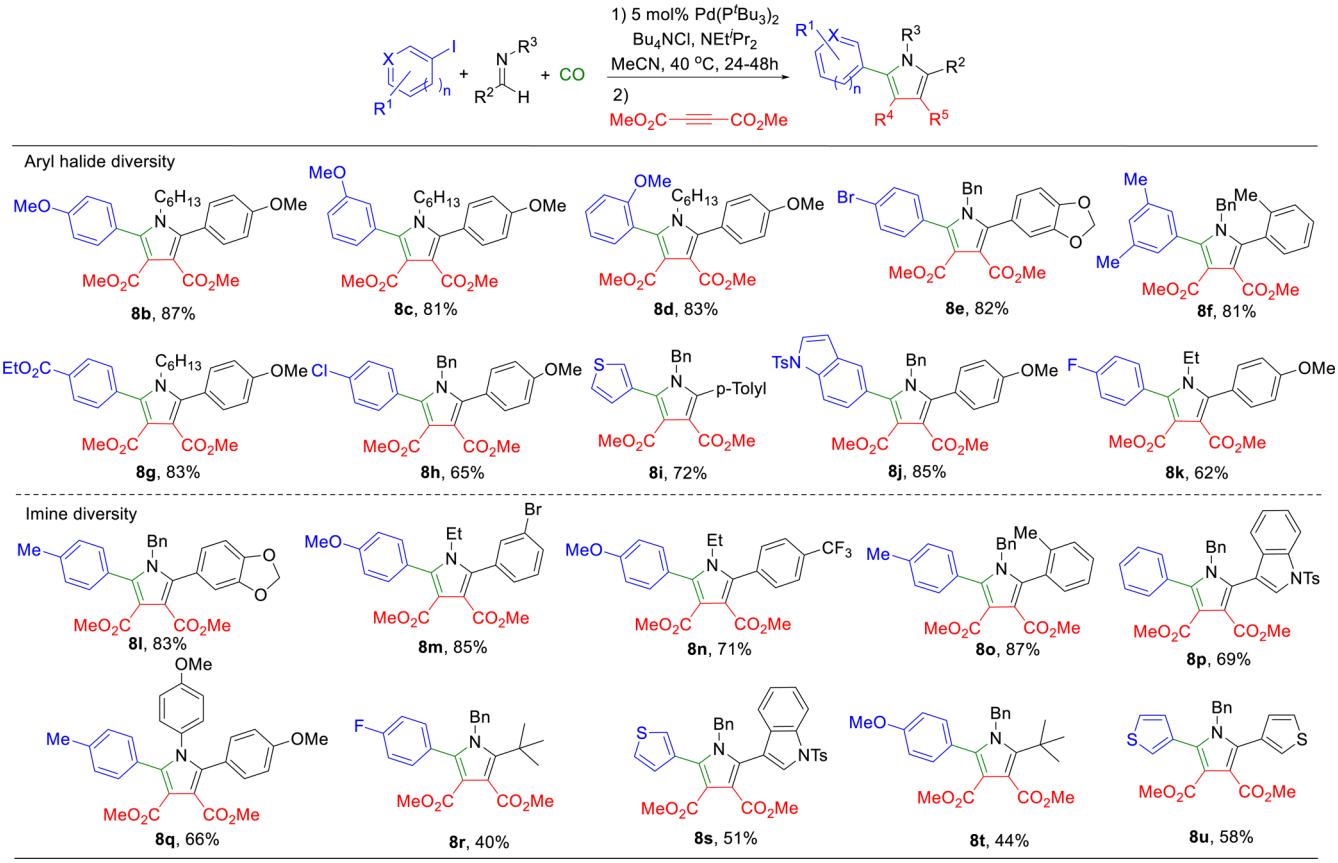


(1)

The pyrrole core, and in particular aryl-substituted pyrroles, represent a useful general class of pharmaceutically relevant heterocycle, and have found significant utility in materials chemistry.[23] In this regard, an aspect of this transformation the ability to access these heterocycles from combinations of available and easily diversified building blocks. This is highlighted in Tables 3 and 4. For example, a number of aryl iodides can be incorporated into this transformation. This includes simple aryl iodides (**8a**), as well as those with electron rich (**8b−d**) and electron poor (**8g,h,k**) substituents. Each of these leads to pyrroles in high overall yield. Potentially palladium reactive aryl bromide functionalities can also be incorporated (**8e**). Interestingly, the reaction can move beyond simple aryl groups and incorporate heteroaryl iodides (**8i,j**). Similar modulation of the imine can be performed. *N*-Alkyl and -benzyl protected imines are viable substrates in this chemistry, as are electron rich *N*-aryl imines (**8l,m,q**). On the imine carbon, an array of electron rich (**8l,q**) or electron poor (**8m,n**) aryl-substituents can be employed, as can heteroaryl imines (**8p,u**) and *t*-butyl substituted reagents (**8r,t**). Conversely, enolizable imines lead to enamides under the reaction conditions.[24] Together, this can allow the assembly of a range of 2,5-aryl, -heteroaryl and/or -alkyl substituted pyrroles.

The dipolarophile can also be tuned in this chemistry (Table 4). Examples of these include a number of substituted electron poor alkynes incorporating ketone (**8v**), ester (**8w,y,z**) or electron deficient arene (**8x**) functionalities. In the case of less electron deficient alkynes (e.g., **8y,aa**), the dipolarophile can be used in the presence of the catalytic synthesis of Münchnone, allowing the one step synthesis of substituted pyrroles. As previously noted, phenyl methylpropiolate and electron poor aryl acetylenes undergo regioselective cycloaddition to unsymmetrical Münchnones.[25] Electron poor alkenes can be similarly used in this platform, and undergo facile acid loss upon cycloaddition to generate tetra- or trisubstituted pyrroles.[26] This can be used to generate 3-substituted pyrroles from vinyl halide derivatives (**8ab,ac**) and nitroalkenes (**8ad**). While acetylene does not react with **3**, the electron deficient

Table 3. Multicomponent Synthesis of Pyrroles: Aryl Iodide and Imine Diversity[a]



[a]Imine (0.50 mmol), aryl iodide (2.50 mmol), Pd(P^{t}Bu$_3$)$_2$ (12.8 mg, 0.025 mmol), Bu$_4$NCl (139.0 mg, 0.5 mmol), NEt^{i}Pr$_2$ (97.0 mg, 0.75 mmol), MeCN (3.3 mL), and CO (10 atm), 40 °C. Quench with DMAD (85.3 mg, 0.60 mmol) at ambient temperature for 15 min.

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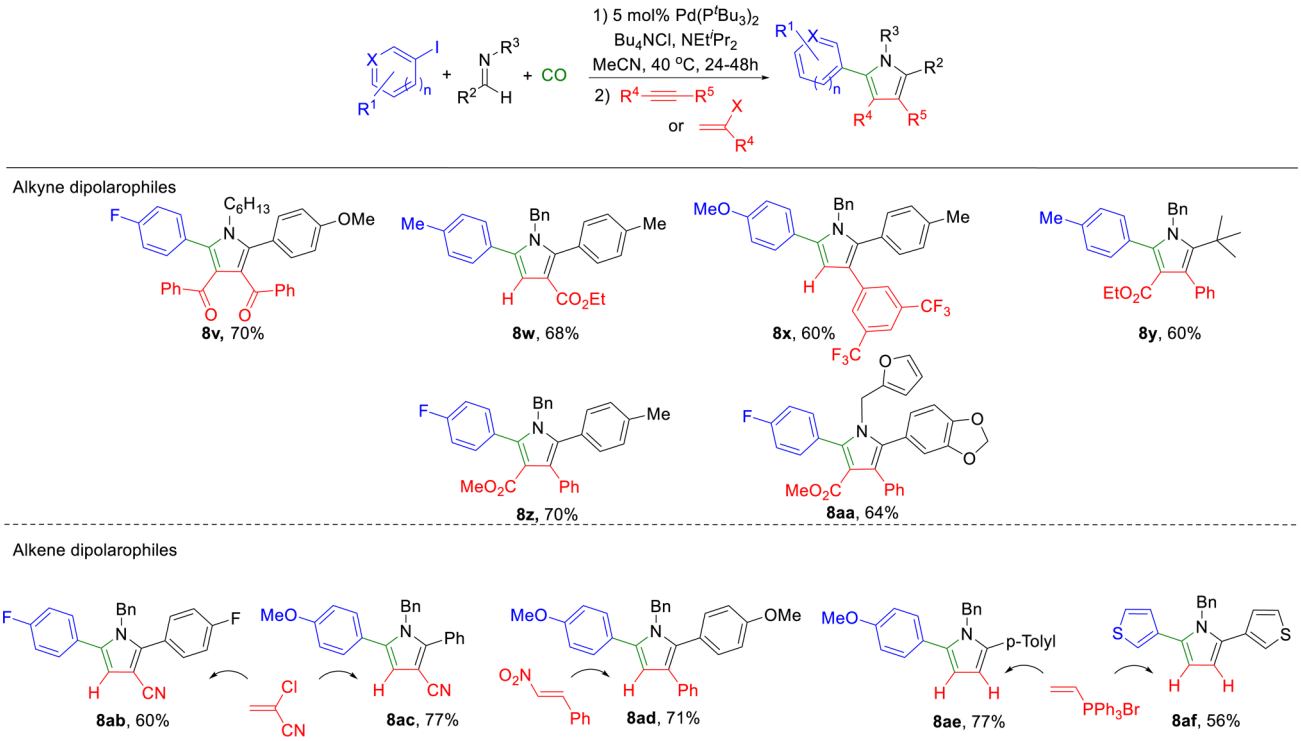
Table 4. Multicomponent Synthesis of Pyrroles: Alkyne and Alkene Diversity[a]



[a]Imine (0.50 mmol), aryl iodide (2.50 mmol), Pd(P^{t}Bu$_3$)$_2$ (12.8 mg, 0.025 mmol), Bu$_4$NCl (139.0 mg, 0.5 mmol), NEt^{i}Pr$_2$ (97.0 mg, 0.75 mmol), MeCN (3.3 mL), and CO (10 atm), 40 °C. For specific conditions for each dipolarophile, see the Supporting Information.

triphenylvinylphosphonium salt can act as an acetylene equivalent upon acid loss to form 3,4-unsubstituted pyrroles (**8ae,af**).

Overall, this provides a method to assemble families of aryl- and heteroaryl-substituted pyrroles with independent control of all five substituents. Within the brief diversity probed in Tables 3 and 4, the combination of substrates provides the ability to generate almost 10^3 structurally different pyrroles in one pot reactions. Considering the broad availability of aryl iodides, imines, and alkynes/alkenes, many more structural combinations are also possible. We are unaware of any other method to construct pyrroles with such broad diversity from aryl halides in combination with other fundamental and stable building blocks.

CONCLUSIONS

In conclusion, we have developed a multicomponent approach for the synthesis of Münchnones from simple aryl iodides, imines, and CO. Mechanistic studies suggest that this reaction proceeds via a tandem catalytic pathway, with the in situ generation of acid chlorides and *N*-acyl iminium salts. The P^{t}Bu$_3$ ligand in concert with chloride is found to be unique in allowing both of these cycles to proceed under mild conditions. This presumably due to the unusual ability of this large ligand to facilitate the reductive elimination of acid chloride from palladium, as well as the lability of this large phosphine, which can allow the carbonylation of palladacyclic intermediates (**4**). Coupling the formation of Münchnones with alkyne/alkene cycloaddition can provide a multicomponent method to generate polysubstituted pyrroles. Notably, this synthesis employs available, inexpensive, and stable reagents (aryl iodides, carbon monoxide imines, alkynes), proceeds with high efficiency, is modular, and generates pyrroles in high overall yield. Studies toward the use of this reaction to access other classes of products are currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02314.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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