Synthetic Methods

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Palladium-Catalyzed Dearomative Cyclocarbonylation by C–N Bond Activation

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Abstract: *A fundamentally novel approach to bioactive quinolizinones is based on the palladium-catalyzed intramolecular cyclocarbonylation of allylamines. [Pd(Xantphos)I_2], which features a very large bite angle, has been found to facilitate the rapid carbonylation of azaarene-substituted allylamines into bioactive quinolizinones in good to excellent yields. This transformation represents the first dearomative carbonylation and is proposed to proceed by palladium-catalyzed C–N bond activation, dearomatization, CO insertion, and a Heck reaction.*

Quinolizinones and related molecules that contain an amide group and a nitrogen atom at the ring junction are a unique class of heterocycles with valuable physicochemical properties and are emerging as key pharmacophores for the treatment of Alzheimer's disease, Type 2 diabetes, HIV, and spinal muscular atrophy (Figure 1).[1] In spite of the long-standing biological and synthetic interest in these valuable compounds, it is surprising that a general method for the construction of such bicyclic ring systems has not been reported thus far.[2] Existing methods commonly rely on multistep syntheses, but their widespread use has been precluded by a restricted substrate scope, inconvenient reaction procedures, and lengthy syntheses of the reagents. A general catalytic method to various quinolizinones is therefore in high demand and would also serve to provide a great opportunity to accelerate biological and biosynthetic studies of these valuable compounds.[3]

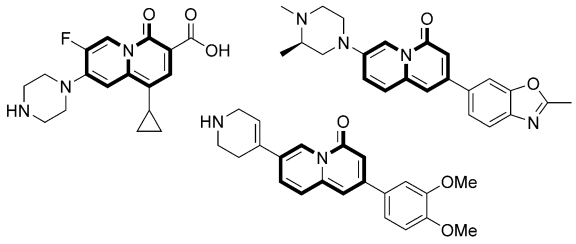
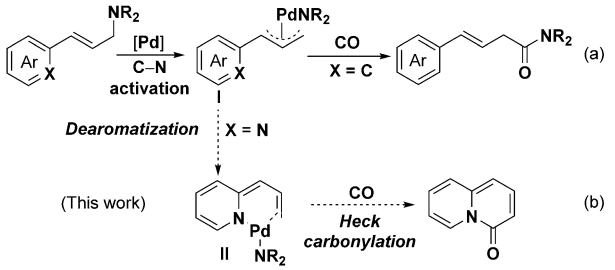


Figure 1. Examples of quinolizinone-containing bioactive molecules.

Transition-metal-catalyzed aminocarbonylation is a versatile process that has been strenuously developed and emerged as a convenient method for the synthesis of amides.[4] Among many efficient methods, the carbonylation of C–N bonds, a strategy that involves transition-metal-catalyzed C–N bond activation followed by insertion of CO to furnish the amide group, has proven to be one of the most direct and promising ways to access a range of valuable amides.[5] Allylamines are suitable substrates for such catalytic processes, as they can smoothly undergo oxidative addition with Pd^0 to cleave the C–N bond for the generation of a π-allylpalladium species **I** and have thus been successfully applied in Pd-catalyzed aminocarbonylation reactions in the presence of CO (Scheme 1a).[6] However, once an azaarene such as pyridine or quinoline is introduced into the allylamine system, the π-allylpalladium species **I** generated by C–N bond activation might be transformed into the dearomatized palladium amide species **II**, with the shift of the double bond incurred by dearomatization of the heterocycle.[7] We reasoned that the dearomatization process could be further enhanced in the presence of CO, owing to the lower electron density at Pd(CO).[8] Moreover, CO would prefer to insert into the less hindered planar pyridyl N–Pd bond, and the R_2N^- moiety contained in metal complex **II** could then act as an intramolecular base to promote the subsequent Heck reaction. It should thus be possible to realize a catalytic tandem reaction that consists of C–N bond activation, dearomatization, CO insertion, and a Heck reaction for the synthesis of quinolizinones under palladium catalysis. Herein, we report the development of the first palladium-catalyzed dearomative cyclocarbonylation of azaarene-substituted allylamines, which provides biologically active quinolizinones (Scheme 1b). Notably, this transformation is mechanistically unique in comparison with traditional base-promoted pyri-



Scheme 1. Dearomative cyclocarbonylation by C–N bond activation.

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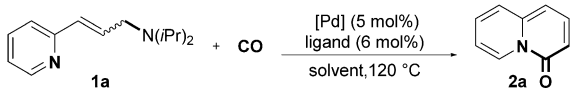
dine dearomatization processes that involve C–N bond activation.[7]

Our investigations began with the direct cyclocarbonylation of *N*,*N*-diisopropyl-3-(pyridin-2-yl)prop-2-en-1-amine (**1a**) in toluene by palladium catalysis under CO atmosphere at 120 °C (Table 1). After an extensive screening of catalysts, which features a larger bite angle, was used as part of the catalyst system, product **2a** was obtained in 59% yield. Moreover, further increasing the steric bulk and bite angle of the phosphine ligand by using Xantphos led to a substantial increase in catalytic activity, and the desired carbonylation product **2a** was isolated in 81% yield (entry 12). When NiXantphos, with a very similar bite angle, was used, the desired product was formed in an almost identical yield. The exceptionally high reactivity of the Xantphos-containing catalyst might be due to the unique structure of the ligand, which is capable of forming both *cis* and *trans* Pd complexes, thus facilitating the catalytic process. The huge bite angle of 154.78° can be clearly seen in the X-ray structure of $[Pd(Xantphos)I_2]$.[10] Screening some representative solvents revealed that the reaction was most efficient in toluene, in which the desired product **2a** was obtained in good yield (entry 12). The reaction reached completion in one hour to yield the corresponding product in 87% yield (entry 20).

With optimized reaction conditions in hand, substrates with various leaving groups were subjected to the standard conditions. As summarized in Table 2, substrates containing

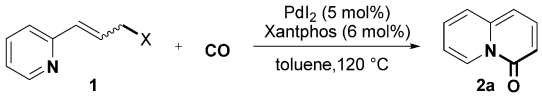
Table 1: Optimization of the reaction conditions.[a]



Entry	[Pd]	Ligand	Solvent	Yield[b] [%]
1	$PdCl_2$	–	toluene	< 5
2	$PdBr_2$	–	toluene	14
3	PdI_2	–	toluene	67
4	$[Pd(cod)I_2]$	–	toluene	63
5	$[Pd(CH_3CN)_2Cl_2]$	–	toluene	< 5
6	$[\{Pd(allyl)Cl\}_2]$	–	toluene	< 5
7	PdI_2	DPPE	toluene	< 5
8	PdI_2	DPPP	toluene	< 5
9	PdI_2	DPPB	toluene	59
10	PdI_2	DPPF	toluene	< 5
11	PdI_2	BINAP	toluene	< 5
12	PdI_2	Xantphos	toluene	84 (81)
13	PdI_2	NiXantphos	toluene	83
14	PdI_2	DPEphos	toluene	42
15	PdI_2	Xantphos	xylene	83
16	PdI_2	Xantphos	mesitylene	82
17	PdI_2	Xantphos	benzene	84
18	PdI_2	Xantphos	$PhCF_3$	80
19	PdI_2	Xantphos	NMP	70
20[c]	PdI_2	Xantphos	toluene	91 (87)
21	–	–	toluene	0

[a] Reaction conditions: **1a** (0.5 mmol), [Pd] (0.025 mmol), ligand (0.03 mmol), solvent (2 mL), CO (10 atm), 120 °C, 24 h. [b] Yields were determined by GC analysis using *n*-hexadecane as an internal standard; yields of isolated products are given in parentheses. [c] One hour. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, DPEphos = bis[2-(diphenylphosphino)phenyl] ether, DPPB = 1,4-bis(diphenylphosphino)-butane, DPPE = 1,2-bis(diphenylphosphino)ethane, DPPF = 1,1′-bis(diphenylphosphino)ferrocene, DPPP = 1,3-bis(diphenylphosphino)propane, NiXantphos = 4,6-bis(diphenylphosphino)phenoxazine, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

Table 2: Influence of the leaving group.[a]



Entry	Substrate	X	Yield[b] [%] 1 h	24 h
1	**1a**	$N(iPr)_2$	91	–
2	**1b**	NEt_2	80	–
3	**1c**	$N(Cy)_2$	81	–
4	**1d**	NPh_2	< 5	16
5	**1e**	NBn_2	< 5	55
6	**1f**	OH	< 5	15
7	**1g**	OAc	< 5	73
8	**1h**	Cl	< 5	13

[a] Reaction conditions: **1** (0.5 mmol), PdI_2 (0.025 mmol), Xantphos (0.03 mmol), solvent (2 mL), CO (10 atm), 120 °C. [b] Yields were determined by GC analysis using *n*-hexadecane as an internal standard. Bn = benzyl, Cy = cyclohexyl.

to our great delight, the desired product **2a** was obtained in 67% yield in the presence of a catalytic amount of PdI_2 (5 mol%) and CO (10 atm). $[Pd(cod)I_2]$ was also an effective catalyst of this reaction, giving the carbonylation product in 63% yield. As expected, no carbonylation took place without a catalyst (entry 21), and representative palladium catalysts, such as $PdCl_2$, $PdBr_2$, $[Pd(CH_3CN)_2Cl_2]$, and $[\{Pd(allyl)Cl\}_2]$, were not effective (entries 1, 2, 5, and 6). Inspired by this promising lead, we next sought to improve the efficiency of the reaction. Various phosphine ligands were then screened in combination with PdI_2 as the catalyst precursor, and the transformation was found to be sensitive to the bite angle of the bis(phosphine) ligand (entries 7–14).[9] Catalysts derived from bis(diphenylphosphino)-type ligands, such as DPPE, DPPP, DPPF, or BINAP, resulted in low conversion into the desired product based on GC analysis. However, when DPPB, different leaving groups (**1a**–**1h**) gave the desired product in distinctly different yields. For allylamines with $N(iPr)_2$, NEt_2, or $N(Cy)_2$ as the leaving group, the cycloadduct **2a** could be obtained in high yields even in one hour (entries 1–3). However, when other leaving groups, such as NPh_2, NBn_2, OH, OAc, or Cl, were installed in the allylic skeleton, the conversion was dramatically lower under identical reaction conditions (entries 4–8). The lower activity of these substrates might be attributed to either the difficult cleavage of the corresponding C–X bonds or their reluctance to undergo a late-stage Heck reaction.[11]

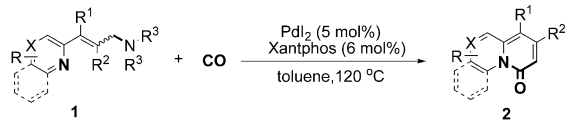
On the basis of the results described above, a variety of azaarene-substituted allylamines with $N(iPr)_2$ as the leaving group were submitted to the Pd-catalyzed dearomative cyclocarbonylation reaction to investigate its substrate scope and generality (Table 3). A series of substituents on the

pyridyl ring of the allylamine were well tolerated regardless of whether they were electron-donating or -withdrawing, providing the desired quinolizinones in good to excellent yields (53–93%). The reactivity was not affected by the *E*/*Z* ratio of the allylamines, and both the *E* and *Z* isomers could be efficiently converted into the desired cycloadducts. The position of the substituent on the pyridyl ring of the allylamine appeared to influence the reactivity. For example, substrate **1i**, with a methyl group in the *ortho* position of the pyridyl ring, gave the corresponding product in a rather low yield (**2i**). Typical functional groups, such as fluorine and chlorine substituents, were also tolerated under the reaction conditions (Table 3, entries 6–9), giving ample opportunities for further elaboration by transition-metal-catalyzed couplings or other transformations. To our delight, substrate **1q**, which contains a hydroxymethyl group, also underwent this cyclocarbonylation, giving the desired product **2q** in 73% yield. The free hydroxymethyl group contained in the product is amenable to further elaboration by cross-coupling reactions. Furthermore, allylamines bearing an alkyl group on the double bond were also feasible substrates, affording the cyclocarbonylation products **2s**, **2t**, and **2u** in excellent yields (entries 12–14). However, azaarene-substituted allylamines with a substituent in the α-position of the amine, such as *N*,*N*-diethyl-1-phenyl-3-(pyridin-2-yl)prop-2-en-1-amine and *N*,*N*-diisopropyl-4-(pyridin-2-yl)but-3-en-2-amine, could not be converted into the desired products (see the Supporting Information). When the pyridine core was replaced with a pyrazine or quinoline, the cyclocarbonylation reaction still took place to give the corresponding carbonylation products **2v** and **2w** in 44% and 52% yield when the reaction time was increased (entries 15 and 16). The structures of **2o**, **2q**, and **2w** were confirmed by single-crystal X-ray diffraction.[10]

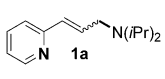
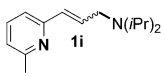
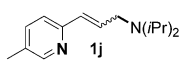
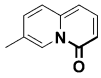
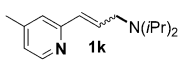
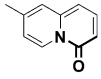
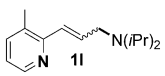
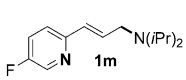
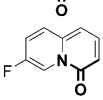
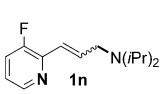
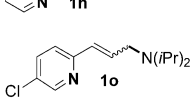
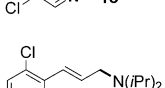
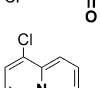
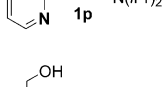
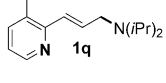
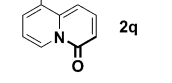
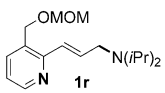
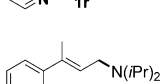
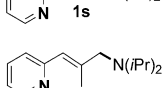
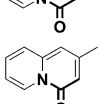
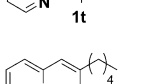
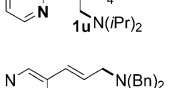
The synthetic versatility of the present catalytic system was next demonstrated through a large-scale reaction and product derivatizations (Scheme 2). The dearomative cyclocarbonylation on a 10 mmol scale was found to be completed in twelve hours, even with a reduced amount of catalyst (1.0 mol%), yielding 1.24 g of cycloadduct **2a** (86% yield). Partial hydrogenation of **2a** catalyzed by Pd/C afforded 3,4-dihydro-1*H*-quinolizin-6(2*H*)-one (**3a**) in 87% yield under 1 atm of H_2 at room temperature. Complete hydrogenation of **2a** to **3b** could also be realized under 10 atm of H_2 at 50°C catalyzed by Pd/C. The desired hexahydro-1*H*-quinolizin-4(6*H*)-one was isolated in 98% yield. Such moieties are common core structures found in numerous alkaloids and biologically active compounds.[12] Moreover, we have also developed an efficient formal synthesis of alkaloid **3d**. As shown in Scheme 2, full hydrogenation of **2q** gave the desired product **3c** in 85% yield; further reduction of **3c** according to a previously reported procedure should then lead to **3d**.[13]

Although the mechanistic details of this transformation are not clear at this stage, on the basis of the present results and precedent reports,[6] a plausible reaction pathway was proposed (Figure 2). Under the reaction conditions, and in the presence of CO, an active Pd^0 species is expected to be formed, which undergoes oxidative addition with allylamine **1a** to give π-allylpalladium intermediate **I** by cleavage of the C–N bond. Dearomatization of **I** quickly takes place under

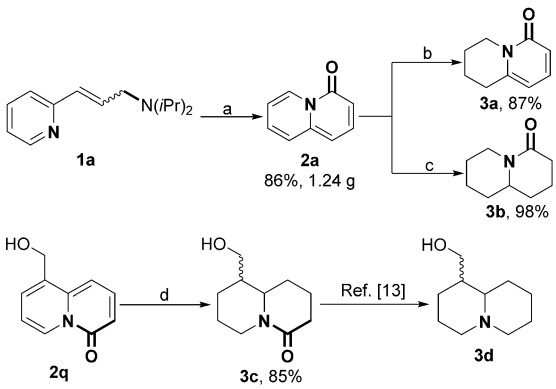
Table 3: Alkene substrate scope.[a]



1 2

Entry	1	t (h)	2	Yield[b] [%]
1		1		87
2		3		53
3		1		88
4		1		84
5		1		88
6		1		82
7		1		84
8		1		75
9		1		64
10		12		73
11		6		91
12		12		92
13		3		83
14		12		93
15		21		44
16		24		52

[a] Reaction conditions: **1** (0.5 mmol), CO (10 atm), PdI_2 (0.025 mmol), Xantphos (0.03 mmol), toluene (2 mL), 120°C. [b] Yield of isolated product. MOM = methoxymethyl.



Scheme 2. Synthetic versatility of the present catalytic system. Reaction conditions: a) **1a** (10 mmol), PdI_2 (1 mol%), Xantphos (1.2 mol%), toluene (15 mL), CO (10 atm), 120°C, 12 h; b) **2a** (0.5 mmol), Pd/C (10%, 7.3 mg), EtOH (1 mL), H_2 (1 atm), RT, 12 h; c) **2a** (1.0 mmol), Pd/C (10%, 14.5 mg), EtOH (2 mL), H_2 (10 atm), 50°C, 12 h; d) **2q** (0.5 mmol), $Pd(OH)_2$/C (25%, 22 mg), EtOH (3 mL), H_2 (40 atm), 80°C, 12 h.

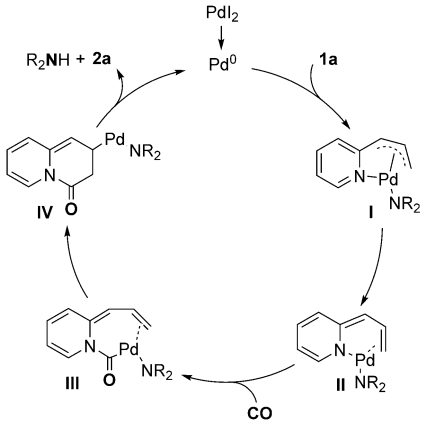


Figure 2. Proposed reaction mechanism. The ligand was omitted for clarity.

CO atmosphere to give rise to intermediate **II**. Selective insertion of CO into the pyridyl nitrogen–palladium bond results in the formation of intermediate **III**. Subsequent double bond migratory insertion leads to intermediate **IV**, which undergoes *syn* β-hydride elimination to deliver the desired product **2a** and reductive elimination to regenerate the active Pd^0 species to complete the catalytic cycle.[14]

In summary, we have developed an unprecedented strategy for the cyclocarbonylation of azaarene-substituted allylamines with CO. This unique reaction was accomplished by synergistically combining palladium-catalyzed C–N bond activation, dearomatization, carbonylation, and a Heck reaction. A wide range of azaarene-substituted allylamines are compatible with this operationally simple and efficient method, which could thus be employed for the synthesis of biologically active quinolizinones with a broad array of substitution and functionalization patterns. Further experiments are in progress to study the scope of this process and the application of this dearomative carbonylation strategy to other reactions.

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Keywords: C–N activation · cyclocarbonylation · dearomatization · palladium · quinolizinones

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[14] Control experiments showed that *N*,*N*-diisopropyl-4-(pyridin-2-yl)but-3-enamide cannot be converted into the desired product **2a** in the presence of base and the Pd catalyst at 120 °C. This result supports the proposed mechanism shown in Figure 2 (see the Supporting Information for details).

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