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Second-Generation Palladium Catalyst System for the Transannular C–H Functionalization of Azabicycloalkanes

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Abstract

This Article describes the development of a second-generation catalyst system for the transannular C–H functionalization of alicyclic amines. Pyridine- and quinoline-carboxylate ligands are shown to be highly effective for increasing the reaction rate, yield, and scope of Pd-catalyzed transannular C–H arylation reactions of azabicyclo[3.1.0]hexane, azabicyclo[3.1.1]heptane, azabicyclo[3.2.1]octane, and piperidine derivatives. Mechanistic studies reveal that the pyridine/quinoline-carboxylates play a role in impeding both reversible and irreversible catalyst decomposition pathways. These ligands enable the first reported examples of the transannular C–H arylation of the ubiquitous tropane, 7-azanorbornane, and homotropene cores. Finally, the pyridine/quinoline-carboxylates are shown to promote both transannular C–H arylation and transannular C–H dehydrogenation on a homotropene substrate.

Graphical abstract

INTRODUCTION

Alicyclic amines appear in a wide variety of bioactive molecules for the treatment of diverse indications, including Parkinson's disease, depression, pain, obesity, and drug addiction (Figure 1).¹ Indeed, alicyclic amine scaffolds feature in over 20% of the top 200 pharmaceuticals.² Traditional synthetic approaches to alicyclic amines involve multi-step sequences to build up the amine core.³ This is exemplified by Corey's synthesis of epibatidine, wherein the bicyclic amine scaffold is assembled in 7 steps starting from 6-chloronicotinaldehyde (Scheme 1a).⁴ While this represents an elegant approach to this specific target, it is not well-suited for the rapid synthesis of analogues bearing different

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Experimental details, characterization, NMR and X-Ray data for isolated compounds (PDF)

(hetero)aryl substituents, since de novo synthesis would be required to access each new derivative.

In this context, C–H bond functionalization could serve as a complementary and enabling approach for the late-stage derivatization of alicyclic amines. As shown in Scheme 1b, pre-assembly of the amine core and subsequent C–H arylation would enable the rapid preparation of analogues bearing diverse substituents. This approach has been widely used for the introduction of functional groups onto alicyclic amines at the activated C–H sites α to nitrogen.⁵ In contrast, selective C–H functionalization of alicyclic amines at unactivated C–H sites that are remote from nitrogen remains much more challenging.^{6,7,8,9,10}

Our group recently reported a Pd-catalyzed method for the selective transannular C–H arylation of alicyclic amines.¹¹ As summarized in Scheme 2, this approach leverages coordination of the amine nitrogen atom in combination with a tethered secondary directing group (DG) to direct C–H activation via a boat conformer. Our first-generation catalyst system proved effective for the transannular C–H arylation of a variety of alicyclic amine scaffolds, and this method was utilized to access arylated analogues of bioactive molecules such as amitifadine, varenicline, and cytosine.

However, there were a number of key limitations associated with this first-generation method. For instance, the yields were often modest, particularly with bicyclic amines like varenicline. In addition, most of the reactions required high temperatures (>140 °C) and large excesses of the aryl iodide oxidant. Further, a number of important alicyclic amine cores (e.g., tropane, homotropene, and 7-azanorbornane derivatives) exhibited very low reactivity (Scheme 3a). Finally, the original reaction was limited to C–H arylation, and no other C–H functionalization products were accessed.

This Article focuses on the development of a second-generation catalyst system that addresses many of these limitations. A variety of reports from our group¹² and others^{13,14,15} have shown that pyridine and carboxylic acid-based ligands can be used to enhance reactivity and modulate selectivity in other Pd-catalyzed C–H functionalization reactions.¹⁶ We demonstrate herein that ligands that combine these two functional groups are effective for increasing the reaction rates, yields, and scope of the Pd-catalyzed transannular C–H functionalization of alicyclic amines. Most notably, we show that pyridine-carboxylate and quinoline-carboxylate derivatives enable the first reported examples of transannular C–H functionalization on the ubiquitous tropane core (Scheme 3b). We also present studies on the role of these pyridine/quinoline carboxylates and show that they impact both reversible and irreversible catalyst decomposition pathways.

RESULTS AND DISCUSSION

Ligand identification

Our initial investigations focused on probing ligand effects on the C–H arylation of the benzo-fused azabicyclo[3.2.1]octane substrate **S1**. This substrate was selected as a model system based on its modest reactivity under the first generation Pd(OAc)₂-catalyzed C–H arylation conditions, which afforded just 46% yield of the C4-arylated product **1a** at 150 °C

using 30 equiv of PhI as the arylating reagent and solvent (Table 1, entry 1). Monodentate pyridine-type ligands were explored first, based on their well-established utility in enhancing both reactivity and selectivity in related Pd-catalyzed C–H functionalization reactions.^{12–16} However, as shown in Table 1, the addition of 5 mol % of monodentate pyridine, quinoline or acridine derivatives **L1–L5** had minimal impact on the yield of **1a** (entries 2–6).

We hypothesized that the bidentate coordination of substrate **S1** might out-compete the binding of monodentate pyridine derivatives.^{10g,17} As such, we next explored a series of quinoline-oxazoline and quinoline/pyridine-carboxylate ligands exemplified by **L6–L9** in Table 1. The addition of 5 mol % of quinoline-oxazoline **L6**¹⁸ resulted in an improvement in the yield of **1a** compared to the ligand-free reaction (56% versus 46%, respectively, entry 7). Even more significant increases were observed with quinoline/pyridine-carboxylate ligands **L7–L9**.¹⁹ In particular, the use of 5 mol % of 2-picolinic acid (**L8**) or of 2-quinaldic acid (**L9**) resulted in an approximately 80% yield of **1a** (entries 9 and 12). With picolinic acid, the reaction was sensitive to the ligand loading, and the yield of **1a** dropped to 24% upon the addition of 20 mol % of **L8** (entry 11). In contrast, varying **L9** from 5–20 mol % had minimal impact on the yield of **1a** (77–85%, entries 12–14). Using 20 mol % of **L9**, **1a** was isolated in 82% yield²⁰ (entry 14), which represents an almost doubling of the yield relative to the ligand-free reaction.

We next sought to lower the reaction temperature from 150 °C as well as to move away from the use of solvent quantities of PhI. As shown in Table 2, with 5 mol % of **L9**, this reaction proceeded at temperatures as low as 100 °C and with just 3 equiv of PhI in *t*-amyl alcohol solvent. Under these conditions **1a** was obtained in 84% yield (entry 8). Nearly identical yield was obtained using picolinic acid (**L8**) under these conditions (entry 9). In contrast, in the absence of **L8/L9**, **1a** was obtained in just 29% yield (entry 10).

Use of **L8/L9** with other substrates

We next explored the application of **L8/L9** in the transannular C–H arylation of other substrates. Initial investigations focused on alicyclic amines that underwent moderate-to-low yielding C–H arylation under our first-generation conditions.¹¹ The addition of 5 mol % of **L8** or **L9** to these reactions under otherwise identical conditions to the first-generation system resulted in increases in the yield of transannular C–H arylation products across the board. Notably, **L8** and **L9** afforded very similar results in most cases; thus, only the results with **L8** are shown in Table 3. The observed increases in yield were particularly dramatic in the formation of products **3–5**, where the yields were more than doubled. In addition, C–H arylation to form derivatives of the bioactive molecules varenicline and amitifadine (**8** and **9**, respectively) proceeded with significantly enhanced yields relative to the first generation conditions.

Mechanistic role of **L9**

We next probed the mechanistic role of the ligand in this transformation. At the outset, we considered two general possibilities, which are summarized in Scheme 4. In the first (mode A), **L9** could bind to the Pd catalyst at some stage of the catalytic cycle for C–H arylation, thereby enhancing the rate and/or selectivity of a key step (for example, C–H activation).

Alternatively, in the second (mode B), **L9** could play a role outside of the primary catalytic cycle by limiting product inhibition, slowing catalyst decomposition, or rescuing other off-cycle intermediates. Notably, there is precedent for both mode A^{12,13,17c,e,21} or mode B^{14,15,17f} in other Pd-catalyzed C–H functionalizations as well as related reactions. We conducted a series of different experiments to differentiate these possibilities.

We first examined the initial rate of the C–H arylation of substrate **S1** in the presence and absence of 5 mol % of **L9**. As shown in Figure 2, the initial rate with **L9** is approximately double that without it (0.0013 versus 0.00062 mol·L⁻¹·min⁻¹, respectively). This led us to an initial hypothesis that the role of **L9** might be to accelerate the turnover-limiting step of the catalytic cycle.

Recent DFT calculations of these transannular C–H arylation reactions have suggested that C–H activation is turnover-limiting.²² To test for this experimentally in our system, we first determined the hydrogen/deuterium kinetic isotope effect (k_H/k_D) for the ligand-free Pd-catalyzed C–H arylation of **S1** versus **S1-d5** (Scheme 5).²³ In the absence of **L9**, a k_H/k_D of 3.3 was observed. The magnitude of this value is consistent with a primary isotope effect,²⁴ and provides experimental evidence supporting C–H cleavage as the turnover-limiting step of this reaction.

We next probed the isotope effect in the presence of 5 mol % of **L9**. As shown in Scheme 5, these experiments show a k_H/k_D value of 3.2. Again, this result is consistent with turnover limiting C–H activation. However, we note that the magnitudes of the KIE values in the ligand-free and **L9** conditions are virtually identical. This is in marked contrast to other Pd-catalyzed C–H functionalization reactions, in which added ligands often have a dramatic impact on k_H/k_D .^{13b,17c} These changes in k_H/k_D are generally rationalized based on the ligand playing an integral role in the nature/position of the transition state for the C–H cleavage step.^{10g} Conversely, the lack of such a change in our system suggests that the ligand may not be involved in C–H activation.

We next conducted rate studies to examine the full reaction profile of the ligand-free and **L9**-containing reactions. In the ligand-free reaction (Figure 3, blue curve), the concentration of product starts to plateau after approximately 60 min, and the reaction completely stalls after 480 min to afford a maximum concentration of 0.035 M of product **1a** (29% yield). In contrast, in the presence of 5 mol % of **L9** (Figure 3, red curve) the reaction continues to progress over 1200 min to afford 0.1 M **1a** (84% yield).

One possible explanation for the observed stalling of the ligand-free reaction would be product inhibition via, for example, the formation of an off-cycle adduct between the product and the Pd catalyst. To preliminarily test for product inhibition in the conversion of **S1** to **1a**, we added varying amounts of a closely related product (**1b**) at the reaction onset. We then compared the yield of product **1a** at an early time point (45 min) as well as the initial reaction rates. Notably, this approach has been used previously to probe for product inhibition in related Pd catalyzed C–H functionalization reactions.¹⁵ As summarized in Table 4, the addition of 0.012–0.09 M of **1b** (0.1–0.75 equiv relative to **S1**) had essentially no impact on the yield after 45 min, either in the presence or absence of ligand. Furthermore,

nearly identical initial reaction rates were observed in the presence and absence of 0.06 M **1b** (Figures SI-9 and SI-10). Overall, these results suggest against product inhibition in this system.

Experimentally, we observe that the ligand-free reaction changes from a yellow homogeneous solution to a dark heterogeneous mixture over approximately 30 min at 100 °C. This suggests that catalyst deactivation might be the reason for the stalling of the ligand-free reaction. In this scenario, the role of **L9** could be either prevent/slow an irreversible catalyst deactivation pathway or to recover Pd catalyst that is sequestered reversibly as an off-cycle intermediate (mode B in Scheme 4).

To preliminarily test for these possibilities, we conducted the ligand-free reaction of **S1** with PhI for 240 min (the time at which the reaction stalls at [**1a**] = 0.035 M; 29% yield) and then added 5 mol % of **L9**. As shown in Figure 4, the addition of **L9** resulted in significant recovery of catalytic activity (final [**1a**] = 0.07 M; 58% yield). This provides preliminary evidence that **L9** plays a role in reversing the deactivation of the Pd catalyst. However, the final yield is not as high as that obtained when **L9** was present at the start of the reaction (0.1 M **1a**; 84% yield), suggesting that an irreversible catalyst decomposition pathway is likely occurring as well.

A visual inspection of the stalled ligand-free reaction showed the formation of a dark precipitate (**I**). This material was isolated by centrifugation and analyzed by ICP-OES, which showed the presence of palladium.²⁵ Analysis of **I** via NMR spectroscopy and mass spectrometry did not provide conclusive evidence regarding the structure of the Pd-containing material.²⁶ Nonetheless, we hypothesized that **I** might contain the off-cycle Pd-intermediate(s) that are being recovered by the **L9** in the experiment in Figure 4. To test this hypothesis, we explored the ability of the precipitate (**I**) to catalyze the C–H arylation of **S1** (Scheme 6, C and D). These reactions were conducted using 4-iodoanisole as the aryl iodide coupling partner in order to distinguish the product (**1b**) from residual **1a** that was formed in the initial precipitate-generating reaction with PhI (Scheme 6, A). In the absence of **L9**, the **I**-catalyzed reaction of **S1** with 4-iodoanisole afforded <10% yield of **1b**, suggesting that only a small amount of the Pd present in the precipitate is accessible to catalyze C–H arylation (Scheme 6, C). However, upon the addition of 5 mol % of **L9** under otherwise analogous conditions (Scheme 6, D), this reaction afforded a significantly enhanced 47% yield of **1b**. This result suggests that a key role of **L9** is to rescue off-cycle Pd species from precipitate **I**.

Application of **L8/L9** to expand reaction scope

A final set of studies focused using **L8/L9** to expand the scope of this transformation beyond that of the first-generation system. We were particularly interested in tropane substrate **S10** and derivatives thereof, as the tropane core is the second most common bicyclic heterocycle in US FDA approved drugs.^{1,27} In particular, 3 β -arylated tropanes have applications in radiology as well as in the treatment of cocaine addiction, obesity, Alzheimer's and Parkinson's diseases (see Figure 1 for examples).²⁸

As shown in eq. 1, under our first-generation, ligand-free conditions, **S10** showed very low reactivity, affording only 4% of the C-3 arylation product **10a**. Similarly poor results were obtained with the related alicyclic amine cores **S11** and **S12**, which are also of high interest due to their prevalence in alkaloids and other bioactive molecules.^{4b,29,30} Notably, under the ligand-free conditions, all of these reactions showed the formation of a dark precipitate similar to that described above, suggesting that catalyst deactivation is limiting the yields in these systems. As such, we hypothesized that **L8/L9** would be effective in enhancing reactivity in these systems.

Indeed, the addition of 5 mol % of **L8** to the C–H arylation of **S10** under otherwise identical conditions to those in eq. 1 resulted in 49% isolated yield of the C–H arylation product **10a**.³¹ As shown in Table 5, this second-generation catalyst system could be applied to the 3 β -arylation of **S10** using electronically diverse aryl and heteroaryl iodides to form products **10b–10j**. Additionally, several tropane derivatives as well as a homotropane **S12** underwent remote arylation to form **13a–15a**. All of these reactions afforded moderate to good isolated yields, and provided a single detectable diastereomer of product. As such, this method represents a versatile and expedient route to diverse 3 β -aryl tropanes.

We also applied the second-generation catalyst to the selective C–H arylation of the azanorbornane scaffold (**S11**), which is the core of epibatidine and epiboxidine (Figure 1 and Scheme 1).^{4,29} Notably, **S11** afforded <10% yield of the C–H arylation product **11a** under the first-generation conditions. In contrast, upon the addition of 5 mol % of **L9**, product **11a** was isolated in 42% yield (eq. 2).

A final set of studies focused on substrate **S12**, which contains two equivalent transannular C–H sites that could potentially react to afford diarylated product **12a** (eq. 3). While **12a** was formed in 15% yield under the second generation conditions with ligand **L8**, this was not the major product. Instead, the major products were **12-ene** (24% isolated yield) and **12-ene-OPiv** (31% isolated yield), in which a single C–H arylation occurred along with a second, completely different transannular C–H functionalization reaction. In the formation of **12-ene**, this second reaction involves dehydrogenation at the C-6–C-7 position,³² presumably via transannular C–H activation and subsequent β -hydride elimination.³³ Product **12-ene-OPiv** is then formed via an allylic C–H pivaloylation of **12-ene**. Consistent with this proposal, subjecting **12-ene** to the reaction conditions yielded **12-ene-OPiv** in 30% yield based on ¹H NMR spectroscopic analysis. Control experiments show that Pd(OAc)₂ is required for the conversion of **12-ene** to **12-ene-OPiv**, although **L9** is not necessary for this transformation. Overall, these results open the door for exciting new classes of transannular C–H functionalization reactions of alicyclic amines, which will be pursued independently.

(3)

CONCLUSIONS

In summary, this Article describes the development of a second-generation Pd catalyst system for the transannular C–H functionalization of azabicycloalkanes. The addition of 2-pico-lic acid or 2-quinaldic acid was found to dramatically improve reactivity, and studies suggest that these additives play a key role in recovering active catalyst from a precipitate that forms over the course of the reactions. Ultimately, this second-generation catalyst system was leveraged to achieve transannular C–H arylation of the tropane, 7-azanorbornane, and homotropene cores, which were not viable substrates with the first generation catalyst system. Finally, preliminary results show that the second-generation catalyst also opens up new transannular C–H functionalization processes, including dehydrogenation to form cyclic alkenes. Future studies will focus on further exploiting this new catalyst to expand the scope of transannular C–H functionalization reactions with alicyclic amines as well as on developing next generation catalysts that exhibit further enhancements in reactivity and selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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33. We cannot rule out the possibility of an initial transannular C–H dehydrogenation, followed by C–H arylation to afford 12-ene.

Figure 1.
Examples of bioactive alicyclic amines.

Figure 2.

Initial rate for reaction of **S1** with PhI in the presence of 5 mol % **L9** (red curve) and absence of ligand (blue curve). Conditions red curve: **S1** (0.03 mmol, 1 equiv, 0.12 M), Pd(OAc)₂ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), **L9** (0.006 M), *t*-amyLOH (0.25 mL), 100 °C. Conditions blue curve: **S1** (0.03 mmol, 1 equiv, 0.12 M), Pd(OAc)₂ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), *t*-amyLOH (0.25 mL), 100 °C.

Figure 3.

Full reaction profile for the reaction of **S1** with PhI in of 5 mol % **L9** (red curve) and absence of ligand (blue curve). Conditions red curve: **S1** (0.03 mmol, 1 equiv, 0.12 M), Pd(OAc)₂ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), **L9** (0.006 M), *t*-amyLOH (0.25 mL), 100 °C. Conditions blue curve: **S1** (0.03 mmol, 1 equiv, 0.12 M), Pd(OAc)₂ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), *t*-amyLOH (0.25 mL), 100 °C.

Figure 4.

Catalyst recovery by addition of quinaldic acid after 4 hours. Conditions: **S1** (0.03 mmol, 0.12 M), Pd(OAc)₂ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), *t*-AmylOH (0.25 mL), 100 °C, 4 h. Then, add **L9** (0.006 M) and heat to 100 °C.

Scheme 1.

(a) Linear synthesis of epibatidine; (b) Late stage C–H functionalization approach to substituted 7-azanorbornanes.

Scheme 2.

First-generation Pd-catalyzed method for transannular C–H arylation of alicyclic amines.

Scheme 3.

Ligand-enabled C–H arylation of tropane, homotropane, and 7-azanorbornane derivatives

Scheme 4. Two Possible Roles for **L8/L9** in C-H Arylation of **S1**.

Scheme 5. Kinetic Isotope Effect for **S1** and **S1-*d*₅** with and without **L9**.^a

^aConditions: **S1** or **S1-*d*₅** (0.03 mmol, 0.12 M), Pd(OAc)₂ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), *t*-amylOH (0.25 mL), 100 °C, with and without **L9** (0.006 M).

Scheme 6.

Catalytic activity of precipitate (**I**) for C–H arylation of **S1** with and without **L9**

Conditions **A**: **S1** (0.03 mmol), $\text{Pd}(\text{OAc})_2$ (0.003 mmol), CsOPiv (0.09 mmol), PhI (0.09 mmol), $t\text{-amyLOH}$ (0.25 mL), 100°C , 90 min. Conditions **B**: Centrifuge and decant supernatant. Conditions **C/D**: **S1** (0.03 mmol), precipitate (**I**), CsOPiv (0.09 mmol), with or without **L9** (0.0015 mmol), 4-iodoanisole (0.09 mmol), $t\text{-amyLOH}$ (0.25 mL), 100°C , 18 h.

Table 1

Ligand evaluation with substrate **S1**^a

entry	L	L (mol%)	yield 1a
1	----	----	46%
2	L1	5	44%
3	L2	5	47%
4	L3	5	43%
5	L4	5	40%
6	L5	5	46%
7	L6	5	56%
8	L7	5	68%
9	L8	5	80%
10	L8	10	78%
11	L8	20	24%
12	L9	5	77%
13	L9	10	77%
14	L9	20	85%
(82% ^b)			

^aConditions: **S1** (0.03 mmol, 1 equiv), Pd(OAc)₂ (10 mol %), ligand **L** (5-20 mol %) CsOPiv (3 equiv), PhI (30 equiv), 150 °C.^bIsolated yield of **1a** (0.3 mmol scale).

Table 2

Reaction optimization with **L9**.^a

entry	temp.	solvent	PhI (equiv)	yield 1a
1	150 °C	neat	30	77%
2	120 °C	neat	30	60%
3	120 °C	<i>t</i> -amylOH	30	87%
4	120 °C	<i>t</i> -amylOH	15	85%
5	120 °C	<i>t</i> -amylOH	3	87%
6	120 °C	<i>t</i> -amylOH	1	79%
7	110 °C	<i>t</i> -amylOH	3	86%
8	100 °C	<i>t</i> -amylOH	3	84%
^{9b}	100 °C	<i>t</i> -amylOH	3	85%
^{10c}	100 °C	<i>t</i> -amylOH	3	29%

^a Conditions: **S1** (0.03 mmol, 1 equiv), Pd(OAc)₂ (10 mol %), **L9** (5 mol %) CsOPiv (3 equiv), PhI (1-30 equiv), 100-150 °C. Calibrated GC yields for **1a**.

^b **L8** (5 mol%).

^c No ligand added.

Table 3

Application of pyridine-carboxylates in the transannular C–H arylation of other alicyclic amine substrates

(2) without L8: 62% with L8: 90%	(3) without L8: 35% with L8: 64%	(4) without L8: 34% with L8: 64%	(5) without L8: 33% with L8: 76%
(6) without L8: 55% with L8: 60%	(7) without L8: 74% with L8: 75%	(8) without L8: 45% with L8: 81%	(9) without L8: 40% with L8: 51%

Table 4Addition of **1b** to the C–H arylation of **S1**.^a

entry	[1b] (M)	1b (equiv)	Yield 1a (no ligand)	Yield 1a (5 mol % L9) ^b
1	0	0	13%	28%
2	0.01	0.1	13%	29%
3	0.03	0.25	13%	30%
4	0.06	0.50	13%	28%
5	0.09	0.75	11%	28%

^aConditions: **S1** (0.03 mmol, 1 equiv, 0.12 M), **1b** (0–0.09 M), Pd(OAc)₂ (0.012 M), CsOPiv (0.36 M), **PhI** (0.36 M), *t*-am-yIOH (0.25 mL), 100 °C.

^bReaction with **L9** (0.006 M).

Table 5

Application of Pyridine-Carboxylate Ligands in the Transannular C–H Arylation of Tropane Derivatives

$ \begin{array}{c} \text{10 mol \% Pd(OAc)}_2 \\ \text{5 mol \% L8} \\ \text{3 equiv CsOPiv} \\ \text{45 equiv ArI} \\ \hline \text{140 } ^\circ\text{C, 18 h} \end{array} $			
		10a	49%
		10b	60%
		10c	40%
		10d	46%
		10e	47%
		10f	34%
		10g	54%
		10h	47%
		10i	44%
		10j	42%
		13a	40%
		14a	50%