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Synthesis of Aminated Phenanthridinones via Palladium/Norbornene Catalysis

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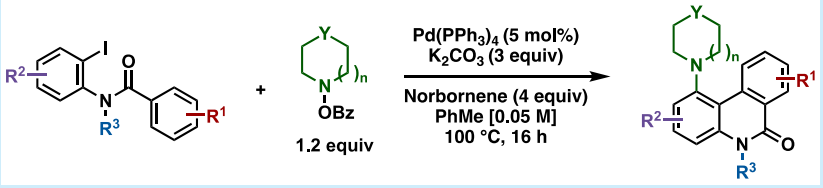

ABSTRACT: An *ortho*-amination, *ipso*-C−H arylation mediated by palladium/norbornene cooperative catalysis is reported. This reaction proceeds through a sequential intermolecular C−N bond formation process followed by intramolecular C−H activation of a tethered arene. The products, aminated phenanthridinones, were generated in moderate to good yields. This method is also applicable to the formation of dibenzazepinones.

Transition-metal-catalyzed domino reactions have emerged as useful approaches to construct complex molecules in a single step without having to isolate intermediates.[1] The merging of C−H activation with diverse reactions has allowed chemists to access different mechanistic pathways and to serve as a complementary means to cross-coupling reactions.[2] In contrast to chelated-assisted reactions,[3] the absence of a directing group offers a powerful and useful strategy since the resulting molecule does not require a subsequent deprotection or functional group interconversion step. A transient directing group is known to be an applicable approach, yet selectivity issues may arise and as such constitute a significant disadvantage.[4]

One extremely powerful reaction in its use of a transient C−H bond activating agent is the Catellani reaction,[5] also described by some as palladium/norbornene (Pd/NBE) cooperative catalysis, a well-known methodology that allows dual functionalization at the *ortho*- and *ipso*-positions of aryl halides through C−H bond activation.[6,7] The functionalization typically employs electrophilic reagents which react at the *ortho* position with the aid of a norbornyl fragment as a transient directing group and traditional palladium(0) cross-couplings to functionalize the *ipso* position.[8] This type of domino reaction enables otherwise challenging disconnections, and notably, it represents a novel route toward functionalized heterocycles. We have been exploring the synthetic potential of the annulative Catellani reaction since our first report in 2000 and C−H terminating reactions since 2005, and now report a new route to the phenanthridinone skeleton.[9−11]

The phenanthridinone motif is found in natural products as well as anticancer drugs.[9,10] Examples include the PJ34 PARP inhibitor,[12,13] a therapeutic agent for hepatitis C,[14] and pancratistatin, which displays antitumor activity (Figure 1).[15]

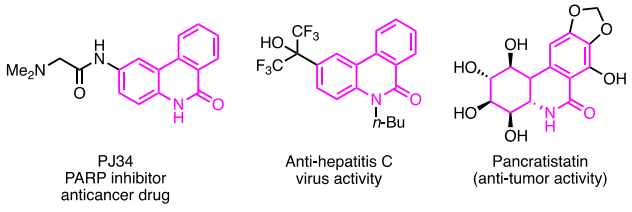

Figure 1. Selected examples of bioactive phenanthridinones.

In 2004, Catellani reported the Pd/NBE-catalyzed synthesis of phenanthridinones through *ortho* intermolecular arylation followed by intramolecular C−N coupling (Scheme 1a).[16] More recently in 2016, Jiao constructed the same type of compounds via a Pd/NBE-catalyzed intermolecular *ortho* acylation followed by intramolecular C−H arylation (Scheme 1b).[17]

Until 2013, functionalization at the *ortho*-position via this approach was broadly limited to carbon substituents.[8] That year, Dong reported *ortho*-amination was feasible using *O*-benzoylhydroxylamines as coupling partners.[18] Since then numerous *ipso* functionalizations have been paired with the *ortho* amination method including vinylation,[19−21] arylation,[22] alkynylation,[23,24] cyanation,[25,26] alkylation,[27,28] and borylation.[29] Cyclizations making use of *ortho*-amination have also been reported such as a phenol dearomatization and a C(sp^3)−

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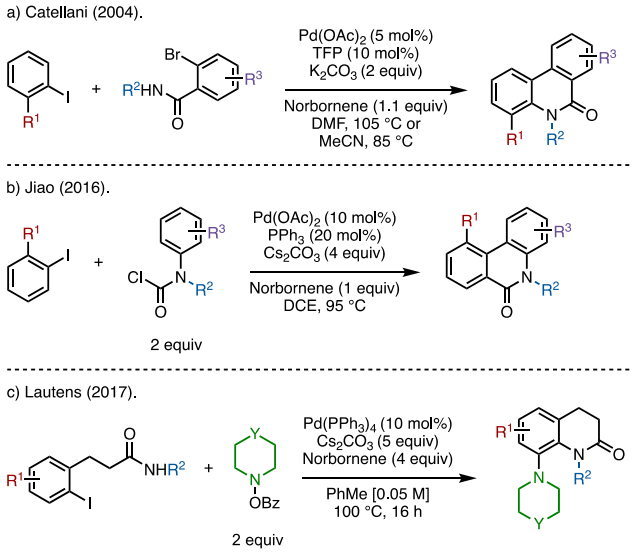
Scheme 1. Previously Reported Pd/NBE-Catalyzed Domino Reactions

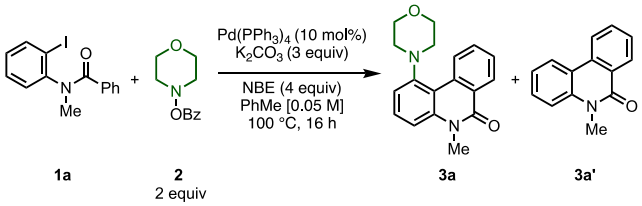


H arylation.[30,31] Our group has long been interested in the application of the Catellani reaction toward the synthesis of heterocycles. In 2017 we reported a Pd/NBE-mediated *ortho*-amination *ipso*-amidation wherein sequential inter- and intramolecular C−N bond formations took place (Scheme 1c).[32]

We wondered whether it would be possible to synthesize phenanthridinone-type molecules, e.g. **3a**, by means of a different sequence of bond-forming events via Pd/NBE cooperative catalysis, such as *ortho*-amination followed by intramolecular C−H arylation (Table 1). To the best of our knowledge, there are no reports of 1-amino-substituted phenanthridinones. As such, these molecules constitute unexplored chemical space.

We began investigating the assembly of *ortho*-aminated phenanthridinones by reacting benzamide **1a** with *O*-benzoylhydroxylamine **2** using conditions resembling Dong's initial report (see Supporting Information for more details). We started with 2 equiv of **2**, 10 mol % of $Pd(PPh_3)_4$, 3 equiv of K_2CO_3, and 4 equiv of norbornene in toluene [0.05 M] at 100 °C for 16 h, which gave **3a** in 77% yield (Table 1, entry 1). Single-crystal X-ray diffraction was performed on **3a** (see the Supporting Information for details). Testing PivOH as an additive decreased the yield of **3a** to 62% while generating the direct-cyclization side-product **3a′** in trace amount (entry 2).[33] Replacing K_2CO_3 with Cs_2CO_3 or reducing the equivalence of base led to no improvement in yield (entries 3−4). Increasing the temperature, concentrating the reaction, or reducing the equivalence of norbornene (entries 5−7) all resulted in lower yields. However, further studies demonstrated that 5 mol % of $Pd(PPh_3)_4$ was sufficient for just a slightly lower yield of **3a** (entry 8). Combining this reduced catalyst loading with only 1.2 equiv of **2** resulted in an isolated yield of 74% (entry 9).

Table 1. Effect of Varying Reaction Conditions



entry	variation(s)	3a (%)[a]	3a′ (%)[a]
1	none	77	0
2	PivOH as additive (30 mol %)	62	1
3	Cs_2CO_3 instead of K_2CO_3	77	4
4	K_2CO_3 (2 equiv)	58	0
5	120 °C	75	0
6	[0.1 M]	68	0
7	NBE (3 equiv)	62	0
8	$Pd(PPh_3)_4$ (5 mol %)	75	0
9	**$Pd(PPh_3)_4$ (5 mol %), 2 (1.2 equiv)**	**79 (74)[b]**	**0**

[a]Yields were determined by ^{1}H NMR spectroscopy analysis of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield.

Following optimization, we turned our attention to investigating the scope of the reaction (Scheme 2). Exploring different *N*-substitutions gave products **3b**, **3c**, and **3d** in 85%, 67%, and 82% yields, respectively. Methyl substituents at the *para*, *meta*, and *ortho* positions gave rise to **3e**, **3f**, and **3g** in 74%, 74%, and 69% yields, respectively. A 10:1 regioisomeric ratio was observed for the *meta* product **3f**, likely stemming from steric challenges of C−H activation to the di-*ortho* substituted position. Examples **3h**, **3i**, and **3j** revealed a clear trend with respect to electronic effects of the carbonyl-tethered arene moiety's *para* substituent. Indeed, as the *para* substitutent's electron-withdrawing nature increased, so did the corresponding yield (*p*-OMe, *p*-Me, *p*-H, *p*-F, *p*-CF_3, 63% to 83%). A 1.0-mmol-scale synthesis of **3j** was performed, which resulted in a 63% yield. 2-Naphthyl-derived **3k** was only generated in a low NMR yield of 22%. Heteroaryl motifs were examined, and though thienyl-containing product **3l** was obtained in good yield, product **3m** bearing a pyridine was only generated in 30% yield. In contrast, **3n** and **3o** derived from the corresponding 5-substituted anilines were generated in good yields of 79% and 86%, respectively. It must be noted that the 4-chloroaniline derivative did not manage to furnish the desired product. It is known that bulky and/or non-coordinating *meta* substituents relative to the iodide on the substrate can lead to byproducts retaining the norbornene fragment as steric hindrance prevents *ortho* C−H functionalization.[34,35] We also tried synthesizing **3a** from the corresponding aryl bromide. However, the product was only generated in 13% NMR yield.

Compound **1a** was reacted with various electrophilic amination reagents (Scheme 3). Ketal-protected **3p** was obtained in 50% yield, which can be further deprotected to generate the primary aniline,[29] while the aryl piperazinyl product **3q** was isolated in 72% yield. However, 1,2,3,4-tetrahydroisoquinoline and hexamethylenimine products **3r** and **3s** were only generated in 10% and 12% NMR yields, respectively. As for piperidine and pyrrolidine products **3t** and **3u**, these were obtained in 29% and 17% yields, respectively.

A borane reduction of the phenanthridinone's amide functionality provided access to the amine **4** in 69% yield (Scheme 4).

Inspired by Cramer's work on the formation of dibenzazepinones,[36] we explored the possibility of generating seven-membered heterocycles. As such, triphenylacetic acid derived substrates **5a** (R = H) and **5b** (R = Me) were successfully coupled with **2**, both furnishing the atropisomers **6a** and **6b** in 55% yields (Scheme 5). The presence of three phenyl rings on

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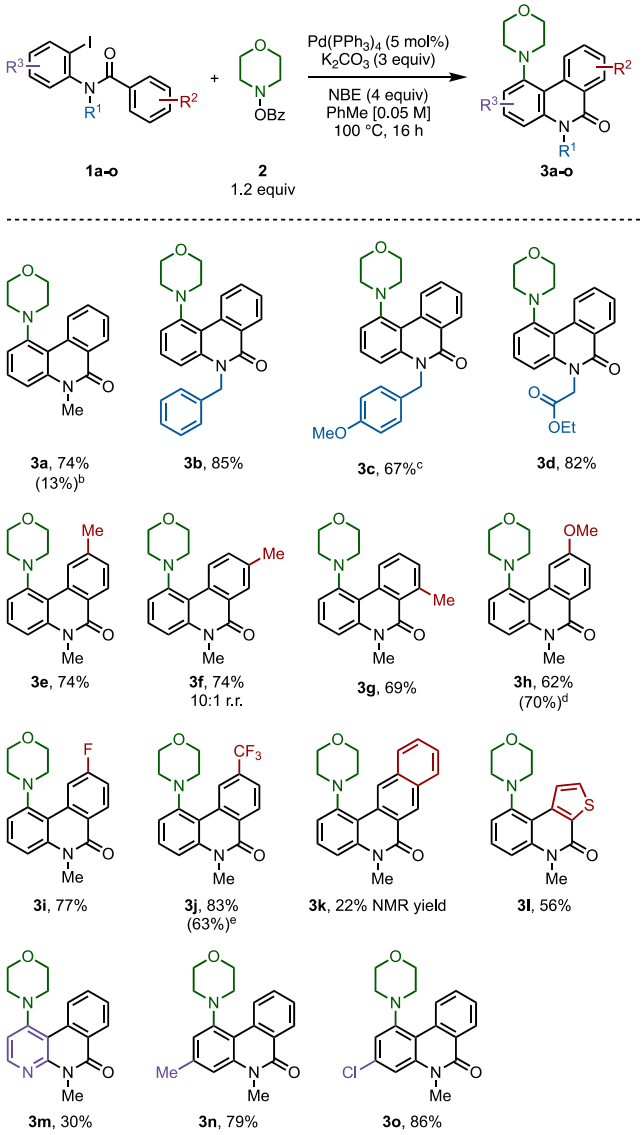
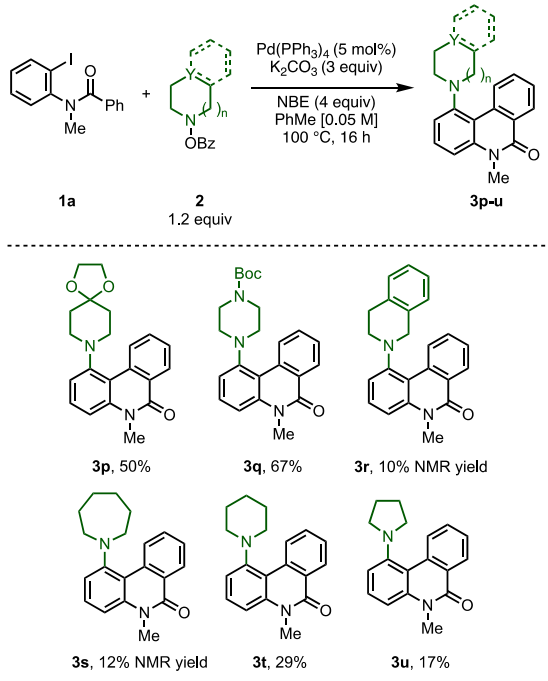
Scheme 2. Substrate Scope[a]



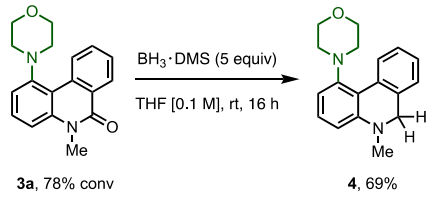
[a]Reactions were performed on a 0.2 mmol scale according to the standard conditions shown above; isolated yields are shown. [b]The corresponding aryl bromide was used instead. [c]1.0 equiv of **2** was used. [d]10 mol % of $Pd(PPh_3)_4$ was used. [e]1 mmol scale.

Scheme 3. *O*-Benzoylhydroxylamines Scope[a]



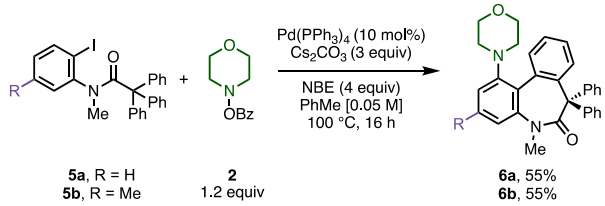
[a]Reactions were performed on a 0.2 mmol scale according to the standard conditions shown above; isolated yields are shown.

Scheme 4. Derivatization of Compound 3a[a]



[a]Reaction was performed on a 0.2 mmol scale according to the conditions shown above; isolated yield is shown.

Scheme 5. Dibenzazepinones Synthesis[a]



[a]Reactions were performed on a 0.2 mmol scale according to the conditions shown above; isolated yields are shown.

the starting material was essential for good yields (see the Supporting Information for details).

The synthesis of **8** from **7** was attempted to generate other isomers of the phenanthridinone (Scheme 6a). However, **8** was only formed in 28% yield (by ^{1}H NMR). During the elaboration of this project, a carboxylate-assisted Pd/NBE-catalyzed *ortho*-amination followed by C(sp^2)−H arylation methodology in order to synthesize 1-amino substituted dihydrophenanthridines, phenanthridines, and 6*H*-benzo[c]-chromenes was reported by Liang.[37] Attempted synthesis of one of the products included in the authors' table, under our conditions at 110 °C (Scheme 6b), gave **10** in 42% yield from **9**, compared to the reported yield of 59%.

Based on previous work reported by Catellani, our group, and others,[8,18,32,33,38] a plausible mechanism for this transformation is shown in Scheme 7. Substrate **1a** undergoes oxidative addition to furnish aryl-Pd(II) intermediate **I**. Carbopalladation with norbornene forms the *syn* intermediate **II**. A subsequent K_2CO_3-assisted concerted metalation−deprotonation (CMD) process gives rise to the key intermediate in Catellani reactions: an aryl-norbornyl-palladacycle (ANP). C−N bond formation occurs via either a Pd(IV) intermediate **IV** stemming from a second oxidative addition with *O*-benzoylhydroxylamine **2** followed by reductive elimination or direct electrophilic substitution with **2** illustrated as transition state **VI**, both delivering **V**. Norbornene extrusion occurs and leads to **VII** due to the "*ortho* effect". A second K_2CO_3-assisted CMD step as shown in transition state

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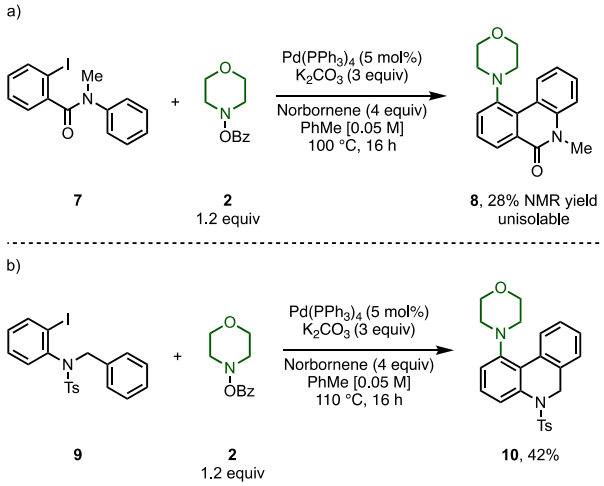
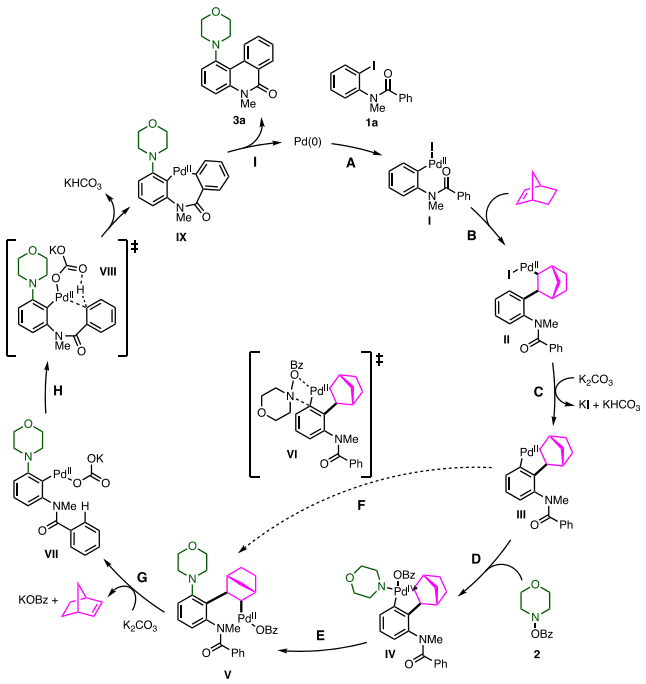
Scheme 6. Synthesis of Analogous Six-Membered Heterocycles[a]



[a]Reactions were performed on a 0.2 mmol scale according to the conditions shown above; isolated yields are shown.

Scheme 7. Proposed Mechanism



VIII forms the seven-membered palladacycle **IX**. Final reductive elimination releases product **3a** and regenerates Pd(0).

In conclusion, we have developed a new variant of the Catellani reaction for the synthesis of aminated phenanthridinones. The use of K_2CO_3 as base was essential to first allow *ortho*-amination, followed by intramolecular C(sp^2)−H arylation, generating the six-membered products. Various functional groups and *O*-benzoylhydroxylamines were compatible with the reaction conditions. Two examples of aminated dibenzazepinones were also synthesized in moderate yields, demonstrating the applicability of this method to the construction of different ring sizes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02850.

Experimental procedures, characterization and X-ray data, and NMR spectra (PDF)

Accession Codes

CCDC 2025322 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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