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Expeditious Synthesis of Phenanthridines from Benzylamines via Dual Palladium Catalysis

Giovanni Maestri, Marie-Hélène Larraufie, Étienne Derat, Cyril Ollivier, Louis Fensterbank,* Emmanuel Lacôte,* and Max Malacria*

UPMC Univ Paris 06, Institut Parisien de Chimie Moléculaire (UMR CNRS 7201), 4 place Jussieu, C. 229, 75005 Paris, France

louis.fensterbank@upmc.fr; emmanuel.lacote@upmc.fr; max.malacria@upmc.fr

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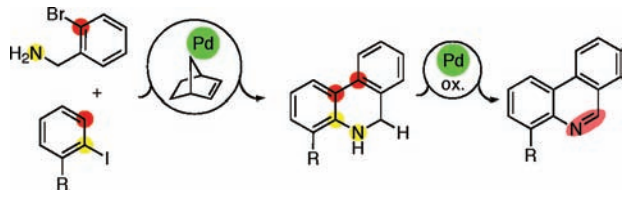
ABSTRACT



A method for the synthesis of phenanthridines from benzylamines and aryl iodides which uses a dual palladium-catalyzed process is developed. The domino sequence ends via an intramolecular amination and an oxidative dehydrogenation. No protecting group or prefunctionalization of the amine is required, and the process uses dioxygen as the terminal oxidant.

Palladium-catalyzed cascades involving direct C−H bond activation have emerged as powerful tools for rapid access to complex polycyclic structures because they bypass the prefunctionalizations required for the traditional cross-coupling methods.[1] In this context, the addition of norbornene as cocatalyst pioneered by Catellani gives access to catalytic sequences uniquely suited to selective sequential bond forming.[2] New syntheses of polycyclic frameworks from simple substrates are thus easily accessible.[3] Yet, despite the variety of possibilities offered by Pd/norbornene catalysis, the introduction of a C-amination step in a cascade has been limited to anilines.[4]

We report herein an example of such a domino reaction. It allows the protecting-group free rapid assembly of phenanthridines, which are attractive targets because of their established significant bioactivities,[5] from single aryls and an amine (Scheme 1).

Reasoning that some Pd(II) complexes could also catalyze oxidative dehydrogenations to generate alkenes,[6] we felt that a

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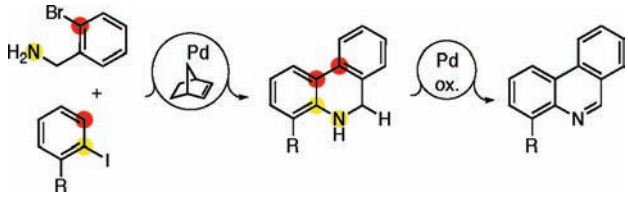
Scheme 1. One-Pot Strategy to Phenanthridines



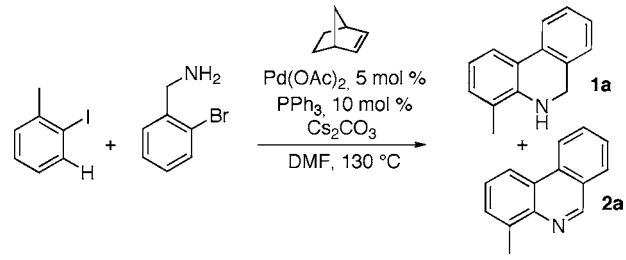
combination of the latter reaction with Pd/norbornene-mediated formations of N-containing heterocycles could drive the reactivity of unprotected benzylic amines directly toward the formation of phenanthridines. To the best of our knowledge, the Catellani−Lautens coupling reaction has never been associated with another metal-mediated reaction in a dual catalytic process.

We selected 2-iodotoluene and 2-bromobenzylamine as representative reagents. Those were reacted in the presence of palladium acetate (5 mol %) and norbornene (1 equiv) as cocatalysts in DMF at 130 °C. The conversion was low (10%), and only dihydrophenanthrine **1a** was obtained in 6% yield (Table 1, entry 1). Addition of triphenylphosphine proved beneficial, yielding 53% of **1a** and 12% of the desired phenanthridine **2a** (entry 2). Lowering the norbornene amount to 50 mol % increased the relative ratio of **2a**, albeit at the expense of conversion beyond that point (entries 3 and 4).

This suggested that the excess norbornene in the initial stages of the reaction led to norbornyl-containing byproducts with reactive iodides.[7] We thus decided to keep a slight excess of the aryl iodide over the bromobenzylamine as some of it might be consumed in side reactions. Phenanthridinine **2a** is formed via dehydrogenation of **1a**, which requires a sacrificial olefin to accept the dihydrogen. Part of the norbornene is most probably also consumed for the aromatization of **1a**. If its initial amount drops too low, none is available for further catalysis. Addition of 3 equiv of norbornene at 90% conversion resulted in an increased ratio of **2a** (**1a**/**2a** = 1:4, entry 5).[8]

Addition of more norbornene after full conversion did not change the product ratio. We finally found that simple

Table 1. Formation of Phenanthridines from Benzylamines[a]



entry	norbornene	conv. Ar−I[b]	conv. Ar−Br[b]	yield (%) **1a**[c]	yield (%) **2a**[c]
1[d]	1 equiv	10	7	6	-
2	1 equiv	95	70	53	12
3	0.5 equiv	99	95	58	27
4	0.25 equiv	55	45	20	24
5	0.5 + 3 equiv	99	95	17	65
6[e]	0.5 equiv	99	95	-	85

[a] Reaction conditions: $Pd(OAc)_2$ (0.013 mmol), PPh_3 (0.026 mmol), norborn., Cs_2CO_3 (0.6 mmol), Ar−I (0.29 mmol), Ar−Br (0.26 mmol) in DMF (6 mL) at 130 °C under argon until Pd black precipitation (24−48 h). [b] Determined by GC. [c] ^1H NMR yield using $MeNO_2$ as internal standard. [d] Without PPh_3. [e] O_2 added after full conversion.

induction of oxygen via a balloon at the end of the reaction (evidenced by precipitation of Pd black) allowed us to get rid of any trace of **1a**. In a typical experiment, 1.1 equiv of 2-iodotoluene was reacted with 2-bromobenzylamine in the presence of 5 mol % of $Pd(OAc)_2$, 10 mol % of triphenylphosphine, and 50 mol % of norbornene in DMF at 130 °C under argon for 36 h. Then, after addition of O_2, the reaction mixture was kept overnight at the same temperature. Phenanthridine **2a** was obtained in 85% yield (entry 6).

Good results were obtained with electron-donating substituents, whether alkyl (entries 1−3) or alkoxy (entries 4−5). Benzo[c]phenanthridines were also prepared in high yields (entries 5 and 6). On the other hand, iodides bearing electron-withdrawing groups at the *ortho* position led to moderate to poor yields (Table 2, entries 8 and 9). This reflects previous results on similar reactions.[1c,9] As before, omission of the oxygen resulted in phenanthridine/dihydrophenanthridine mixtures.

Diversely 6-substituted phenanthridines were obtained with excellent yields from both secondary α-methylbenzylamine (Table 3, entries 1−3) and dibenzylamine derivatives (entries 8 and 9). Aromatic substituents of different electronic and steric properties did not disrupt the reaction, which proved much more tolerant of substitution of the benzylamine part (entries 4−7) than it was of substitution of the iodide partner. Electron-donating and -withdrawing groups worked equally well, independently of the substitution on the other partner. Again, this is in agreement with both previous findings[3a,9] and the proposed reaction mechanism (vide infra). Note that our method is thus suitable for the synthesis of fluorinated phenanthridines.

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(8) Diphenylethane was detected in the reaction mixture when stilbene was added at the start of the reaction. This further proves that a metal-catalyzed transhydrogenation reaction is involved.

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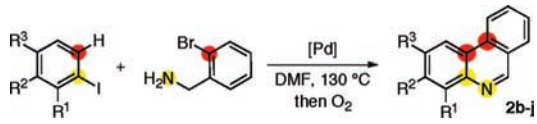
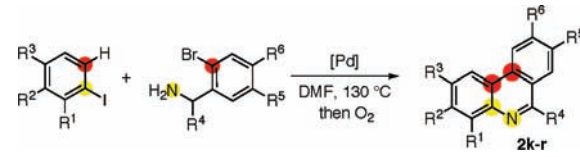
Table 2. Effect of Substituents on the Aryl Iodide Partner



entry[a]	R^1, R^2, R^3	product	yield (%)
1[b]	Et, H, H		**2b**, 82
2[b]	Me, H, Me		**2c**, 81
3[b]	Me, Me, H		**2d**, 91
4	Me, H, OMe		**2e**, 65
5	Me, OMe, OMe		**2f**, 95
6	R^1, R^2 = $(CH)_4$ R^3 = H		**2g**, 80
7	R^1, R^2 = $(CH)_4$ R^3 = OMe		**2h**, 77
8	Cl, H, H		**2i**, 31
9	CF_3, H, H		**2j**, 22

[a] Conditions: see Table 1. An O_2 balloon is introduced after the appearance of Pd black and the reaction left overnight at 130 °C. [b] Without O_2, the phenantr./dihydrophenanthr. ratio was 1:2 (same combined yield).

Table 3. Effect of Substituents on the Aryl Bromide Partner



entry[a]	substituents	product	yield
1	R^1 = R^2 = Me R^4 = Me		**2k**, 90
2	R^1 = Et R^4 = Me		**2l**, 88
3	R^1 = R^3 = Me R^4 = Me		**2m**, 90
4[b]	R^1 = R^3 = Me R^5, R^6 = –OCH_2O–		**2n**, 82
6	R^1 = R^3 = Me R^5 = F		**2o**, 86
7	R^1 = Cl R^5 = F		**2p**, 46
8	R^1 = R^3 = Me R^4 = Ph		**2q**, 97
9	R^1, R^2 = $(CH)_4$ R^4 = Ph		**2r**, 92

[a] Conditions: see Table 2. [b] Without O_2, the phenanthr./dihydrophenanthr. ratio was 1:2 (same combined yield).

A tentative mechanism is depicted in Scheme 2. The *ortho*-substituted aryl iodide first oxidatively adds to Pd(0) to give intermediate Pd(II) complex **A**,[10] which inserts norbornene into the aryl−Pd bond to generate **B**.[11] Arene C−H activation[12] delivers palladacycle **C**.[13] This latter intermediate may react with the aryl bromide possibly affording Pd(IV) complex **D**, in analogy to observations made for *ortho* alkylations (red path),[2b] in which the amine moiety likely completes the Pd(IV) coordination sphere.

An alternative pathway relies on a transmetalation involving two Pd(II) species (blue path).[14] We could not completely rule out this mechanism, although it could hardly account for the observed selectivity in our coupling sequence. Transmetalation among complex **C** and an arylpalladium(II) species would likely result in large amounts of (unobserved) homocoupling byproducts,[3a,7,9b] due to the higher reactivity of aryl *iodides* vs bromides.

On the other hand, the selective formation of the desired compound derives from a faster reaction of the *bromo*benzylamine on complex **C** relative to the aryl iodide. At a higher temperature, the smaller bromide might overcome its inherent lower reactivity and certainly benefit from chelation to compete successfully with the bulkier iodide at the sterically congested center.

Reductive elimination forms biphenyl derivative **E**. Since the norbornyl moiety remains bonded, the steric hindrance in complex **E** causes norbornene to be eliminated to **F**,[2a,1c] which undergoes the final intramolecular amination step from the amine and generates dihydrophenanthridine **1**.

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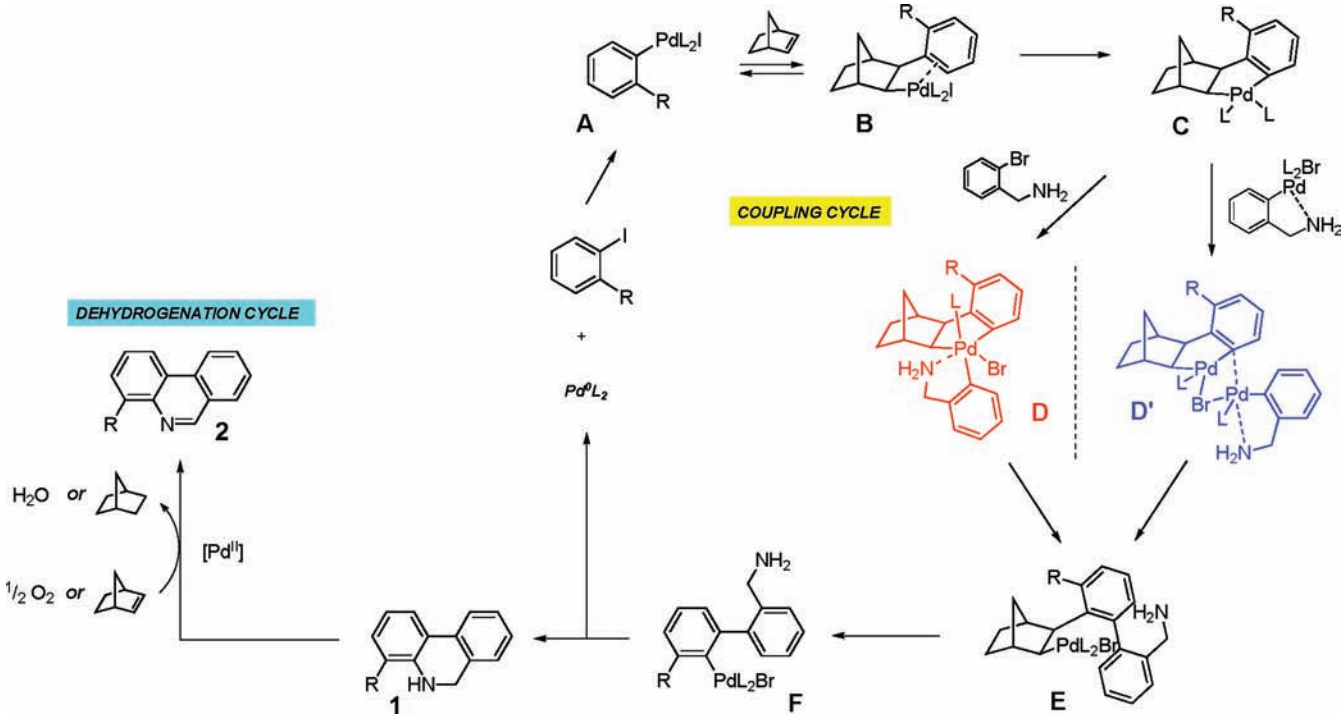
Scheme 2. Proposed Reaction Mechanism



Phenanthridine **2** is formed in the presence of dioxygen (or a sacrificial olefin), which presumably both regenerates a Pd(II) species to switch from one catalytic cycle to the other and acts as the hydrogen scavenger in the dehydrogenation step.[6b]

The isolated **1a** was not oxidized after 24 h at 130 °C in DMF/base under argon without any source of palladium. If dioxygen but no palladium complex was present, then oxidation occurred, but was much slower, confirming the role of the latter in the oxidation step.[6c] We also added an olefin after full conversion, i.e., when no more ArX was present in solution to regenerate a Pd(II) species. This did not favor dehydrogenation and thus tends to confirm that this step is catalyzed by Pd(II).

When norbornene was omitted, low conversions were achieved, and only traces of Ullmann-type coupled biphenyl derivatives were observed. This rules out the possibility that the reaction proceeds via initial amination of the iodide followed by intramolecular ring closure. The *ortho*-substituent on the aryl iodide is necessary to trigger biaryl formation rather than attack of a second aryl halide at the norbornyl site of palladacycle **C**.[15,1c]

As phenanthridines form a well-known class of molecules with biological properties,[5] many protocols for the synthesis of these compounds have been reported.[16] Even if some of these methods are efficient, they usually require prefunctionalization of substrates or the presence of protecting groups, which impact their atom economy. From that perspective also our method compares well to the reported methods.

In conclusion, we have developed a new method for the expeditious synthesis of phenanthridines from benzylamines and aryl iodides, by successfully coupling a palladium/norbornene cocatalyzed domino sequence ending via an intramolecular amination with an oxidative dehydrogenation.

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Supporting Information Available: Experimental procedure, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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