Expeditious approach to the *Amaryllidaceae* alkaloids, crinasiadine and its analogues, via a palladium-catalyzed intramolecular direct C-H arylation

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A simple and efficient approach to the core skeleton of various *Amaryllidaceae* alkaloids such as phenanthridones, phenanthridines and 5, 6-dihydrophenanthridines has been achieved. The methodology involves a palladium catalyzed direct biaryl-coupling of 2-halobenzoylamines/2-halobenzylamine derivatives.

**Keywords:** Catalysis, Biaryl-coupling, Palladium, Alkaloids, Arylation, Crinasiadine, Phenanthridone, Phenanthidine, Dihydrophenanthridine

Development of novel methods for the formation of carbon-carbon (C–C) bonds continues to be a challenge in synthetic organic chemistry. Towards this, synthesis of biaryl scaffolds, found in a variety of natural products, is of great synthetic interest especially those having phenanthridine/phenanthridone moiety constituting the basic skeleton of wide range of biological active *Amaryllidaceae* alkaloids.\(^1\) Till date, more than 500 *Amaryllidaceae* alkaloids representing 18 skeletal types have been isolated and are reported to have several biological activities such as acetylcholinesterase (AChE) inhibitory, analgesic, antibacterial, antifungal, antimalarial, antitumor, antiviral and cytotoxic activities.\(^2\) In general, isoquinolin-1(2H)-one derivatives such as crinasiadine (1a) and its derivatives (Fig. 1) have been identified as ligands for a variety of receptors and as agents for the treatment of a number of pathologies.\(^3\)

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**Fig. 1 – Naturally occurring phenanthridones and phenanthridines (1a-n).**

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R = H, crinasiadine (1a)  
R = Me, N-methylcrinasiadine (1b)  
R = i-pentyl, N-isopentylcrinasiadine (1c)  
R = -CH<sub>2</sub>CH<sub>2</sub>Ph, N-phenethylcrinasiadine (1d)  
n = 1, N-ethoxy carbonyl ethyl crinasiadine (1e)  
n = 2, N-ethoxy carbonyl propyl crinasiadine (1f)

R = H, arolycoricidine (1g)  
R = OH, narciprimine (1h)  
5,6-dihydrobicolarine (1i)  
R = H, ismine (1j)  
R = Me, O-methyl ismine (1k)

trispheridine (1l)  
bicolorine (1m)  
asiaticumine A (1n)
The most common approaches known in literature for the synthesis of phenanthridines include cyclization of \( N-(o\text{-halobenzyl}) \) arylamines through a benzyne mechanism,\(^4\) reduction of phenanthridones,\(^5a\) intramolecular radical cyclizations of \( N-(o\text{-halobenzyl}) \) arylamines,\(^5b\text{-}c\) photocyclization of benzanilides and benzylideneanilines.\(^5d\) Other strategies include Bischler-Napieralsky and directed metalation for cyclization of 2-substituted biphenyls,\(^6a\text{-}c\) microwave-mediated [2+2+2] cyclotrimerization of a diyne,\(^6d\) different photochemical approaches,\(^6e\text{-}h\) annulation between \( o \)-alkynylanilines and \( o \)-alkynyl benzaldehydes,\(^7a\) or nickel-catalyzed iminoannulation of internal alkynes\(^7b\) and hypervalent iodine chemistry from \( N-(o\text{-halobenzyl}) \)-arylamines as starting materials.\(^7c\)

The carbon-carbon (C–C) bond-forming reactions through selective functionalization of aromatic compounds via C–H bond activation have emerged as an extremely useful exploratory synthetic strategy in contemporary organic synthesis.\(^8\) Along this direction, phenanthridines and related structures have been prepared from homolytic aromatic substitution (HAS) reactions\(^9\) and various Pd-catalysis pathways.\(^10\) Harayama and coworkers\(^11\) have reported synthesis of phenanthridones via Pd-mediated direct arylation approaches using 1,3-bis[diphenylphosphino]propane (dppp) and \( n \)-Bu\(_3\)P as ligands. In 2005, Harayama and coworkers\(^12\) reported a regioselective biaryl-coupling of \( 2a \) in presence of stoichiometric and catalytic amount of Pd-source (Scheme 1). Towards developing a new method for the synthesis of biaryls based on Pd-catalyzed intramolecular direct C–H arylation, herein, we report a versatile one-step methodology for a highly regioselective direct biaryl-coupling approach for the synthesis of phenanthridone (such as \( N \)-methylcrinasiadine \( 1b \)) and dihydrophenanthridine (such as 5,6-dihydrobicolorine \( 1i \)) in presence of catalytic Pd(\( PPh_3 \))\(_4\). During this study, we also envisioned the synthesis of phenanthridine (such as trispheridine \( 1l \)) via a direct biaryl-coupling followed by aerial oxidation in presence of catalytic Pd(\( PPh_3 \))\(_4\).

**Material and Methods**

Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under nitrogen atmosphere and stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) and diethyl ether (Et\(_2\)O) were distilled over sodium/benzophenone ketyl, while \( N \), \( N \)-dimethylacetamide (DMA) was distilled over calcium hydride. All other solvents such as DMF, dichloromethane and toluene, and,
Results and Discussion

Recently, we have shown an expeditious approach to the dihydrophenanthridines and pyrrolophenanthridines via a transition metal-free biaryl-coupling\textsuperscript{13}, which is solely promoted by KO\textsubscript{t}Bu in the presence or absence of a catalytic amount of bidentate organic molecules. As a part of our ongoing programme targeted towards synthesis of various Amaryllidaceae alkaloids\textsuperscript{13}, we have examined the Pd-catalyzed direct biaryl-coupling of 2-bromobenzamide (3a) under various conditions to carry out the synthesis of phenanthridone moieties which constitutes the basic skeleton of some members of this family (Table 1). Exhaustive optimization studies revealed that the reaction affords (4a) in excellent yield (96\% yield) when 10 mol\% Pd(PPh\textsubscript{3})\textsubscript{4} was used in the presence of 3 equiv. of K\textsubscript{3}CO\textsubscript{3} in N, N-dimethylacetamide (DMA) at 140 °C for 5 h (Table 1, entry 1). The coupling reaction could be facilitated with almost same efficiency (95\% yields of 4a) when 2-iodobenzamide (3b) was used as substrate (Table 1, entry 2). With these initial results in hand, a variety of 2-halobenzamides having N-alkyl substituents (3a-k) were screened and results are shown in Table 1 (entries 1-11).

Interestingly, in the standard reaction condition, various N-alkylphenanthridones (4b-h) could be achieved in good to excellent yields (82–96\% yield) in presence of 10 mol\% Pd(PPh\textsubscript{3})\textsubscript{4}. As expected, 2-halobenzamides (3l-m) forms the product (4i) in excellent yields (Table 1, entries 12 &13). However, substrates (3n-o) were not suitable under the optimized conditions to afford the products (4j-k), where starting materials were recovered quantitatively (Table 1, entries 14 & 15). A similar difference in the behaviour of 2-halobenzoyldihydroindoles was also observed by Harayama and coworker\textsuperscript{14} even when they used 1 equiv. of Pd(OAc)\textsubscript{2} and ligands.

With the preliminary results in hand, the reaction was extended to a few N-acetyl-2-bromobenzylamines (5a-d) for the synthesis of N-acetyldihydrophenanthridines (6a-d). It was found that reaction is quite general and N-acetyldihydrophenanthridines (6a-d) were obtained in excellent yields (91–93\% yield) (Table 2).

The versatility of our method and reaction conditions was further examined by extending the substrates scope of biaryl-coupling using various 2-halobenzoyl (7a-b)/benzyl (7c-e and 2d-e) substrates (Table 3). Surprisingly, unprotected 2-bromobenzamide...
Table 1 — Substrates scope of Pd-catalyzed biaryl synthesis

<table>
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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Pd source</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
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<td>[Image]</td>
<td>Pd(PPh$_3$)$_4$</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>[Image]</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>5</td>
<td>[Image]</td>
<td>94</td>
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$^a$10 mol% Pd(PPh$_3$)$_4$ was used in each reaction and the yields are reported after column chromatography.

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Table 2 — Synthesis of N-acetyldihydrophenanthridines from (5a-d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Pd source</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
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<td>5</td>
<td><img src="5a" alt="Image" /></td>
<td>92</td>
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<td>2</td>
<td><img src="5b" alt="Image" /></td>
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<td>5</td>
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</tr>
<tr>
<td>3</td>
<td><img src="5c" alt="Image" /></td>
<td>Pd(PPh$_3$)$_4$</td>
<td>6</td>
<td><img src="5c" alt="Image" /></td>
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<td><img src="5d" alt="Image" /></td>
<td>93</td>
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</table>

$^a$10 mol% Pd(PPh$_3$)$_4$ was used in each case and the yields are reported after column chromatography.
such as 7(a-b) was found inferior and gave back
the starting materials in almost 80–90% isolated
yields (Table 3, entry 1). Noticeably, carbamate
protected 2-bromobenzylamines 7(c,d) afforded
the expected products (8b) and (8d) in 28–33% yield along with trispheridine (11) and (8c) in
32–35% yield (Table 3, entries 2-5). We
hypothesized that the formation of products (11)
and (8c) might be the result of a sequential
Pd-catalyzed direct arylation, cleavage of
carbamate in presence of K$_2$CO$_3$ under heating
followed by oxidation.$^{15}$

| Entry | Substrate | Pd source | Time (h) | Product | Yield (%)$^a$
|-------|-----------|-----------|----------|---------|------------------|
| 1     | ![Substrate](image1.png) | Pd(PPh$_3$)$_4$ | 8 | ![Product](image2.png) | 00$^b$
| 2     | ![Substrate](image3.png) | Pd(PPh$_3$)$_4$ | 8 | ![Product](image4.png) | 00$^b$
| 3     | ![Substrate](image5.png) | Pd(PPh$_3$)$_4$ | 5 | ![Product](image6.png) | ![trispheridine](image7.png) = 32 8b = 29
| 4     | ![Substrate](image8.png) | Pd(OAc)$_2$-PPh$_3$ | 5 | ![Product](image9.png) | ![trispheridine](image10.png) = 35 8b = 33
| 5     | ![Substrate](image11.png) | Pd(PPh$_3$)$_4$ | 9 | ![Product](image12.png) | 8c = 33 8d = 31
| 6     | ![Substrate](image13.png) | Pd(OAc)$_2$-PPh$_3$ | 9 | ![Product](image14.png) | 8c = 32 8d = 28
| 7     | ![Substrate](image15.png) | Pd(PPh$_3$)$_4$ | 4 | ![Product](image16.png) | ![trispheridine](image17.png) = 35$^c$
| 8     | ![Substrate](image18.png) | Pd(PPh$_3$)$_4$ | 9 | ![Product](image19.png) | 32$^c$
| 9     | ![Substrate](image20.png) | Pd(OAc)$_2$-PPh$_3$ | 3 | ![Product](image21.png) | 60

$^a10$ mol% Pd(PPh$_3$)$_4$ was used in each case and the yields are reported after column chromatography.

$^b$Multitude of spots on TLC. $^c$Decomposition of rest of the mass balance.
In fact, unprotected 2-bromobenzylamines (2e and 7e) afforded products (1l) and (8c) in moderate yields under similar conditions (Table 3, entries 6 & 7). The probable mechanism shown in Scheme 2, where compound of the type (7c) could provide intermediate (9a) after oxidative addition in the presence of Pd(0). Intermediate (9a) then undergoes a C–H activation in the presence of K₂CO₃ to form intermediate (9b), which in turn affords the expected product (8b) (29–33% isolated yield) upon reductive elimination. However, due to instability of carbamate (8b) in presence of K₂CO₃ (undergoes cleavage of carbamate protection) to afford intermediate (9c) [React. cond.: 3 equiv. of K₂CO₃ in dimethyl acetamide (DMA) at 140 ºC], could not be obtained, which on aerial oxidation could have efficiently afforded fully aromatized phenanthridines (such as trispheridine 1l). Elaborating our methodology further, we were able to successfully synthesize 5,6-dihydrobicolorine (1i) in 60% yield (Table 3, entry 8).

The crystal structure of (8c) (analogue of phenanthridine based Amaryllidaceae alkaloid trispheridine 1l), as shown in Fig. 2, unambiguously proved the unprecedented Pd-catalyzed biaryl-coupling, carbamate deprotection and oxidation processes (Scheme 2). Also, it is well documented in the literature that dihydrophenanthridine can undergo aerial oxidation to form phenanthridine. The obvious reason could be the formation of stable aromatic structure. In addition, the very high stability of phenanthridines could be easily visualized from the crystal packing of compound (8c) using Mercury (as shown in Fig. 3) showing the intermolecular H-bonding and π-π stacking. The important list of interactions in the crystal packing is shown in Table 4.

To further extend the usefulness of our methodology, we applied it for the synthesis of crinasiadine (1a) and its analogues (Fig. 1). Under optimized condition, as expected, compounds (2c) and (3p) afforded biaryl product N-methylcrinasiadine (1b) and (10) in 87–93% yield (Table 5). Phenanthridone (10) could serve as an advanced intermediate for synthesis of various Amaryllidaceae alkaloids (Fig. 1) after deprotection of PMB group.

Finally, one of the biaryl-coupling product (8a) was further reduced to the natural product 5,6-dihydrobicolorine (1i) as shown in Scheme 3, thus illustrating the wide applicability of the aforementioned strategy.

![Scheme 2](image)

Fig. 2 – ORTEP diagram of phenanthridine (8c) (asymmetric unit contains two molecules).
In conclusion, we have established a highly regioselective palladium-catalyzed intramolecular biaryl-coupling reactions of N-aryl-2-bromobenzamides using catalytic Pd(PPh$_3$)$_4$. The methodology provides an expeditious route to access the Amaryllidaceae alkaloids N-methylcrinasiadine (1b) and related...

![Fig. 3 - Intermolecular H-bonding and π-π stacking in the crystal packing of compound (8c) (see CCDC 931413).](image)

**Table 4** - List of intermolecular hydrogen bonds and molecular stacking (π−π) of phenanthridine (8c)

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>D...H (Å)</th>
<th>D...A (Å)</th>
<th>H...A (Å)</th>
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<tr>
<td>C3-H3...O3</td>
<td>1.08</td>
<td>3.30(3)</td>
<td>2.64</td>
<td>118</td>
<td>x, y, z</td>
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<tr>
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<td>3.59(3)</td>
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<td>150</td>
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<tr>
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<td>3.34(4)</td>
<td>2.64</td>
<td>137</td>
<td>-x+1, -y+2, -z+2</td>
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<tr>
<td>C14-H14C...N1</td>
<td>1.08</td>
<td>3.75(4)</td>
<td>2.68</td>
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<tr>
<td>C29-H29A...N2</td>
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<td>3.71(4)</td>
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**Table 5** - Synthesis of N-methylcrinasiadine (1b)

<table>
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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Pd source</th>
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<th>Product</th>
<th>Yield (%)$^a$</th>
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<td>6</td>
<td><img src="image" alt="Product" /></td>
<td>93</td>
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</tbody>
</table>

$^a$10 mol% Pd(PPh$_3$)$_4$ was used in each case and the yields are reported after column chromatography.

**Scheme 3**

Synthesis of 5,6-dihydrobrociloline (11)

**Conclusions**

In conclusion, we have established a highly regioselective palladium-catalyzed intramolecular biaryl-coupling reactions of N-aryl-2-bromobenzamides using catalytic Pd(PPh$_3$)$_4$. The methodology provides an expeditious route to access the Amaryllidaceae alkaloids N-methylcrinasiadine (1b) and related...
analogues in good to excellent yields. The protocol has been extended to the total synthesis of trispiderine (II) and related structures via a one-pot biaryl-coupling, deprotection of carbamate, and oxidation. We could also synthesize the naturally occurring 5,6-dihydrobicolorine (II) applying this strategy. Further application of the Pd-catalyzed one-pot sequential biaryl-coupling, deprotection followed by oxidation approach for the synthesis of a variety of phenanthridine analogues as well as benzo[c] phenanthridines based alkaloids is currently under active investigation.

Supplementary Data  
CCDC 931413 contains the crystallographic data for the compound (8c). These data may be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Other supplementary data containing general experimental procedures and characterization data including 1H NMR, 13C NMR spectra of selected compounds of this article are available in the electronic form at http://www.niscair.res.in/jinfo/ijca/IJC-A_52A(8-9)1093-1102_SupplData.pdf.

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References  


