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Intramolecular Direct Dehydrohalide Coupling Promoted by KO^{t}Bu: Total Synthesis of *Amaryllidaceae* Alkaloids Anhydrolycorinone and Oxoassoanine

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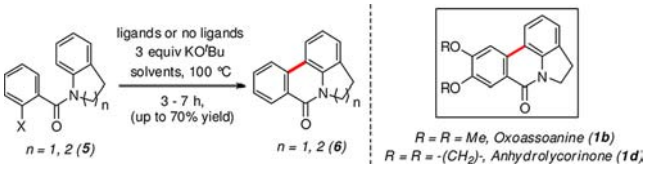
ABSTRACT



A transition-metal-free intramolecular dehydrohalide coupling *via* intramolecular homolytic aromatic substitution (HAS) with aryl radicals has been developed in the presence of potassium *tert*-butoxide and an organic molecule as the catalyst. The methodology has been applied to a concise synthesis of *Amaryllidaceae* alkaloids *viz.* oxoassoanine (1b), anhydrolycorinone (1d), and other related structures. Interestingly, the method also works only in the presence of potassium *tert*-butoxide.

In contemporary organic synthesis, C−C bond-forming reactions[1] through selective functionalization of aromatic compounds *via* C−H bond activation have emerged as an extremely useful exploratory synthetic strategy.[2] Thus, the challenge to devise newer, efficient methods to directly transform C−H bonds to other functional groups motivates synthetic chemists to develop an 'ideal synthetic procedure',[3] which could eventually be applied to natural product synthesis and drug discovery.[4]

Significant effort has already been made in direct C−H bond transformation through traditional demetalhalide cross-coupling utilizing transition metal catalysts.[4] Direct cross-coupling methods, such as demetal hydride,[5] demetal hydroxide,[6] dehydrative,[7] dehydrohalide,[8] and dehydrogenative[9] cross-couplings, have received considerable

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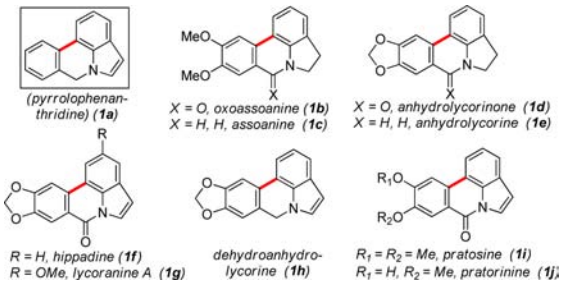
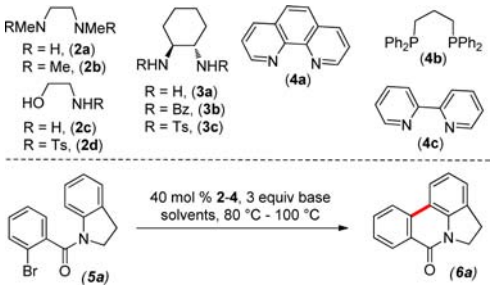


Figure 1. Pyrrolophenanthridine based *Amaryllidaceae* alkaloids.

attention to accomplish this goal. In this context, the synthesis of biaryls through direct C−H bond functionalization[10] is of significant interest because of their wider abundance in natural products, pharmaceuticals, and materials. Recently, Itami et al.[11] first described an unprecedented account on KO^{t}Bu-mediated biaryl coupling of aryl halides and electron-deficient heterocyclic substrates in the absence of a transition metal catalyst. Following this report, a few pioneering reports also revealed that the biaryl couplings could be promoted in the presence of KO^{t}Bu and a diamine ligand.[12] These pairs presumably initiate single electron transfer (SET) to a C−X bond at elevated temperatures,[13a] initially providing a radical anion that gives rise to a radical species for further propagation.[13b]

The impetus for syntheses of biaryl compounds lies in their exhaustive use as building blocks in many alkaloids and natural products. Specifically, here, we have targeted the indole based alkaloids of the *Amaryllidaceae* family having a pyrrolophenanthridinone core such as **1a**−**j** (Figure 1) due to their interesting biological activities, such as cytotoxicity and inhibition of male fertility.[14,15] Herein, we demonstrate a methodology for intramolecular biaryl synthesis from *N*-dihydroindolyl/benzyl amine derivatives, having a halogen at the *ortho*-position, using KO^{t}Bu as the sole coupling promoter in the presence or absence of a catalytic amount of organic molecules. Utilizing this coupling strategy, we were able to synthesize several pyrrolo- and dihydrophenanthridines which are vital structures for several *Amaryllidaceae* alkaloids, through addition of aryl radicals to arene derivatives.

Table 1. Optimization of Organocatalytic Dehydrohalide Coupling



entry[a]	catalyst	base	solvent	temp	time	yield (%)[b]
1	**2a** (40 mol %)	KO^{t}Bu	toluene	100 °C	6 h	45
2	**2a** (40 mol %)	KO^{t}Bu	benzene	80 °C	7 h	51
3	**2a** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	6 h	**63**[c]
4	**2b** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	9 h	21
5	**2c** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	8 h	52
6	**2d** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	6 h	30
7	**3a** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	7 h	36
8	**3b** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	9 h	23
9	**3c** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	7 h	21
10	**4a** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	6 h	**64**[d]
11	**4a** (40 mol %)	KO^{t}Bu	benzene	80 °C	8 h	53
12	**4b** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	8 h	23
13	**4c** (40 mol %)	KO^{t}Bu	mesitylene	100 °C	7 h	58
14	**4c** (40 mol %)	KO^{t}Bu	benzene	80 °C	9 h	45
15	**2a** (40 mol %)	NaO^{t}Bu	mesitylene	100 °C	8 h	trace
16	**4a** (40 mol %)	NaO^{t}Bu	mesitylene	100 °C	7 h	trace
17	no catalyst	NaO^{t}Bu	mesitylene	80 °C	9 h	trace
18	no catalyst	KO^{t}Bu	mesitylene	100 °C	6 h	**67**[e]
19	no catalyst	KO^{t}Bu	benzene	80 °C	6 h	62

[a] Reactions were carried out with 0.25 mmol of **5a**, 0.10 mmol of catalyst, and 0.75 mmol of KO^{t}Bu in 2 mL of solvent in a sealed tube at 80−100 °C for a specified time, unless otherwise stated. [b] In most of the cases the reactions were associated with the cleavage of amides, yielding 18−20% of indoline. [c] Condition A. [d] Condition B. [e] Condition C.

Our studies began with 2-bromobenzoylindoline (**5a**) as the substrate in the presence of **2**−**4** and KO^{t}Bu to access corresponding pyrrolophenanthridine (**6a**) (Table 1). After extensive optimization, 40 mol % of DMEDA **2a** with 3 equiv of KO^{t}Bu in mesitylene (condition A) as solvent afforded the required product in 63% yield (entry 3, Table 1). Thus, mesitylene was chosen for further optimization studies (entries 1−3). Under similar conditions, **2b**, **2c**−**d**,

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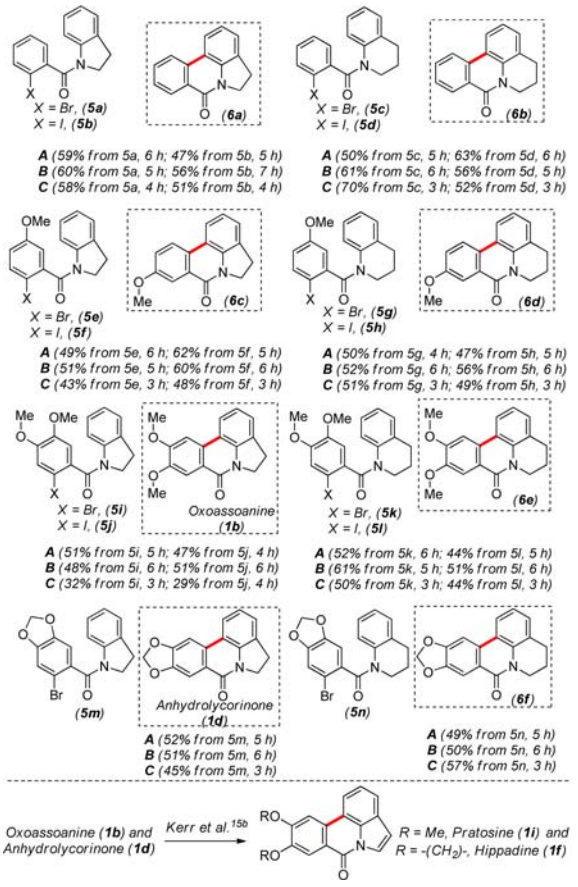

Figure 2. Initial exploration of the substrate scope.

and **3a**–**c** afforded products in 21–52% yields (entries 4–9). The reaction could be performed with almost similar efficiency using 40 mol % of 1,10-phenanthroline **4a** (condition B) and bipyridine **4c** (entries 10 and 13, respectively). However, dppp **4b** was found to be inferior in terms of catalytic activity (entry 12). The reactions were associated with 18–20% of indoline due to cleavage of the amide linkage of the substrate in the presence of KO^{t}Bu. A noteworthy observation was that the reaction could also be performed only in the presence of KO^{t}Bu (condition C) to afford products with similar efficiency (entry 18). This demonstrated that KO^{t}Bu is solely responsible for the biaryl coupling.[16]

Three sets of reaction conditions were chosen *viz*. KO^{t}Bu with **2a** (condition A) and **4a** (condition B) as well as KO^{t}Bu alone (condition C) in mesitylene, and the results obtained are summarized in Figure 2. Noticeably, 2-haloarylamides prepared from indoline (**5a**–**b**, **5e**–**f**, **5i**–**j**, and **5m**) and 1,2,3,4-tetrahydroquinoline (**5c**–**d**, **5g**–**h**, **5k**–**l**, and **5n**) underwent smooth reactions to afford a wide range of products. As a preview of the usefulness of this methodology, we could successfully carry out the total syntheses of oxoassoanine (**1b**) and anhydrolycorinone (**1d**) (Figure 2). Natural products **1b** and **1d** are in fact advanced intermediates for the synthesis of pratosine (**1i**) and hippadine (**1f**), respectively.

To make our strategy practically viable, the reaction was also conducted with 8 mmol of **5a**, affording **6a** in 55% yield along with 20% of indoline.

To further explore the strategy, a few *N*-substituted isatins **5q**–**r** and 2-oxindoles **5o**–**p** were subjected under the optimized conditions to afford the biaryl products (Figure 3). However, contrary to our assumption, **5o**–**p** afforded tetracyclic *O*-arylated products **6g**–**h** instead of C-arylated products. In these cases, *O*-arylation takes place presumably due to the presence of a sufficiently acidic proton at the 3-position of 2-oxindole derivatives. The X-ray crystal structure of tetracyclic **6g** provided unambiguous proof of this unusual *O*-arylation process. Surprisingly, under identical conditions **5q** and **5r** yielded a mixture of products.

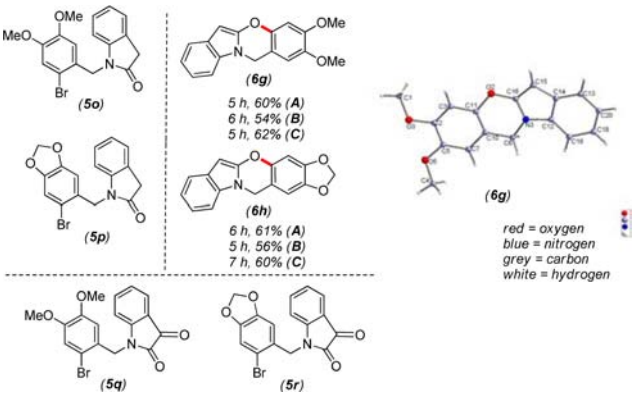

Figure 3. Substrates scope for biaryl syntheses.

To show the versatility of our approach, the strategy was further utilized for the synthesis of dihydrophenanthridines, structurally similar to a number of *Amaryllidaceae* alkaloids (see **7a**–**c**; Figure 4).

To our delight, under optimized conditions B and C the *N*-aryl-2-bromobenzylamines (**5s**–**da**) afforded various dihydrophenanthridines (**6i**–**p**) in moderate to good yields (up to 70% yield) as shown in Figure 5.[12e] Interestingly, just the presence of KO^{t}Bu was sufficient to effect this coupling (condition C; Figure 5). However, condition A was found to be unsuitable for this reaction yielding products in poor yields (~12–24% for **5s**–**t**). The strategy provides a ready access to 5,6-dihydrobicolorine (**7c**) in up to 70% yield starting from **5y**–**z**. On extending the reaction to substrates **5ca**–**da** with electron-withdrawing groups, we found that only **5ca** affords product **6p** in 34% yield under condition B, whereas **5da** simply leads to

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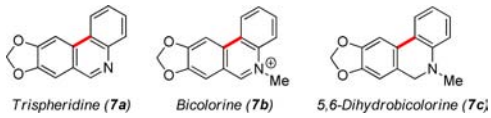

Figure 4. Phenanthridine based *Amaryllidaceae* alkaloids.

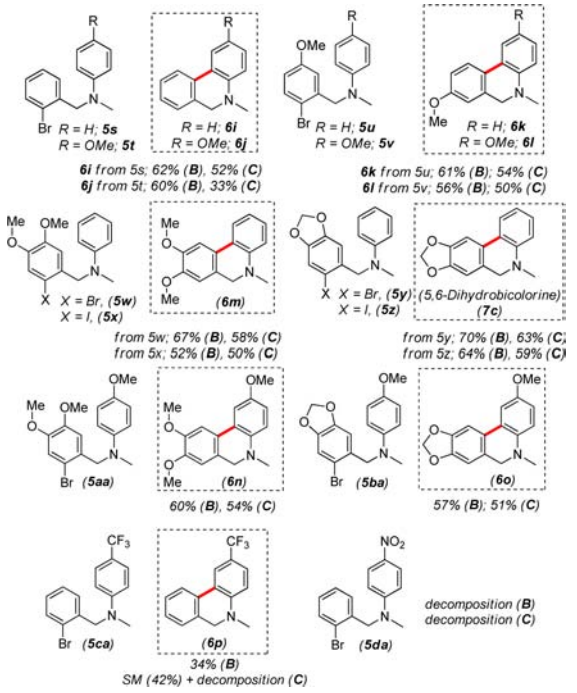

Figure 5. Synthesis of dihydrophenanthridines.

decomposition (Figure 5), indicating the process is probably facilitated by the presence of electron-donating groups.

A tentative mechanism involving SET has been proposed in Figure 6 based on recent mechanistic proposals by Shirakawa–Hayashi et al.[12c] Aryl halides [Ar–X] are transformed to aryl radicals via radical anions (such as **8a**) by reacting with a single electron donor such as metal *tert*-butoxides (**9a**).[16] The radical anion **8a** is then converted into aryl radical **8b** to add intramolecularly at the seventh position of indoline derivatives, providing cyclohexadienyl radical **8c**. Single electron oxidation of **8c** by radical cation **9b** (generated from **9a** or KO^{t}Bu) leads to cyclohexadienyl cation **8d**, which is then deprotonated by *tert*-butoxide to afford coupling product **6** and *t*-BuOH. Cationic metal species **9c** or K^+ reacts with KO^{t}Bu to regenerate metal chelated complex **9a**, which further continues the catalytic cycle. On the other hand, *O*-arylation (**6g–h**, Figure 3) could possibly occur when the intermediate aryl radical **10a** forms a C–O bond with the neighboring carbonyl group to form radical **10b**. This is followed by single electron oxidation of **10b** by **9b** (generated from **9a** or KO^{t}Bu),

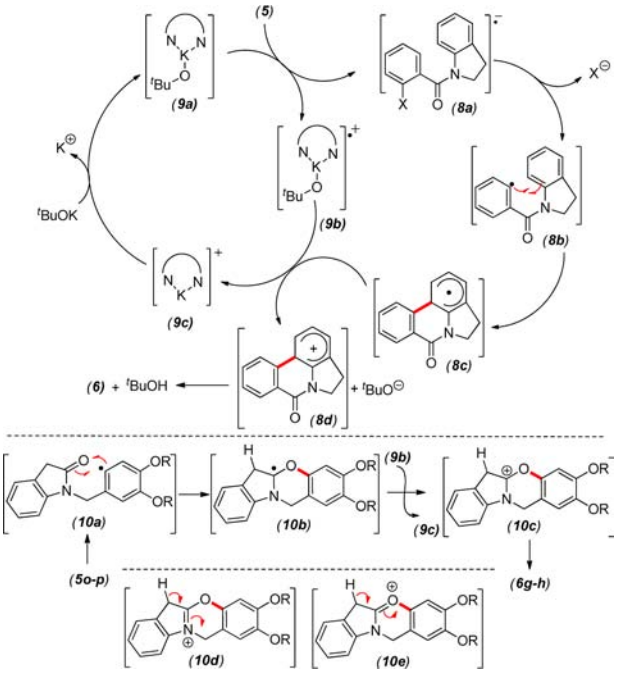

Figure 6. Proposed mechanism of intramolecular biaryl synthesis.

leading to carbocation **10c**. The latter can be stabilized by neighboring nitrogen and oxygen as intermediates **10d** and **10e**, respectively. Ultimately, a deprotonation/aromatization of **10c** affords *O*-arylated product **6g–h** (Figure 6).

To conclude, we report an efficient KO^{t}Bu mediated intramolecular homolytic aromatic substitution (HAS) reaction with or without the aid of a catalytic amount of bidentate organic ligands. Mechanistically, an aryl radical intermediate seems to be involved in the HAS process. The utility of our synthetic protocol is illustrated by the total synthesis of pyrrolophenanthroline based *Amaryllidaceae* alkaloids oxoassoanine (**1b**) and anhydrolycorinone (**1d**) as well as dihydrophenanthridine based skeletons such as 5,6-dihydrobicolorine (**7c**). Further studies in this direction are currently ongoing.

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Supporting Information Available. General experimental procedures and characterization of all new compounds, including a CIF file of **6g**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.