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# Intramolecular Direct C–H Bond Arylation from Aryl Chlorides: A Transition-Metal-Free Approach for Facile Access of Phenanthridines

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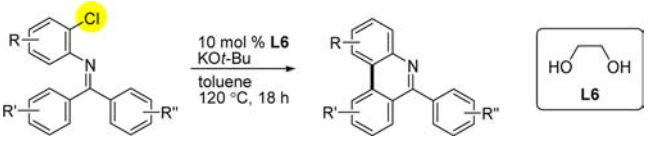
## ABSTRACT




**A C–H arylation with aryl chloride is made viable through a transition-metal-free approach. In the presence of a simple diol associating with KO*t*-Bu, various phenanthridine derivatives can be conveniently accessed. In particular, only 10 mol % of simple and inexpensive ethylene glycol is required for this protocol. These results represent the first general examples of aryl chloride/C–H coupling under transition-metal-free conditions.**

Cross-coupling constitutes a powerful protocol for the synthesis of biaryl motifs, in which these subunits are often found in numerous pharmaceuticals, natural products, and advanced materials.[1] Substantial efforts have been undertaken by researchers aiming to activate aryl chlorides[2] for widespread application in cross-coupling reactions. Despite remarkable advances, the frequently needed high catalyst loading (e.g., in Cu or Fe catalysis) or typically required specially designed ligands (e.g., in Pd catalysis) in these processes render such protocols cost-intensive and affect their practicability. Indeed, the strict demand for the absence of transition metal impurity in the final pharmaceutical products inspired chemists to develop alternative coupling synthetic routes. Thus, the search for other approaches toward biaryl synthesis is highly desirable. In this context, the transition-metal-free protocols appear to be particularly attractive. In 2008, Itami and co-workers reported the transition-metal-free arylation of an activated C–H bond (heterocycles) using aryl iodides.[3] In 2010, Hayashi/Shirakawa,[4] Lei/Kwong,[5] and Shi[6] independently disclosed further advancements of this methodology to unactivated arenes. When a high catalytic loading of DMEDA or phenanthroline derivatives (20–40 mol %) was employed under KO*t*-Bu-mediated conditions, aryl iodides and some aryl bromides were coupled with benzene.[7] Since then, considerable attention has been focused by chemists toward this newly emerged methodology.[8,9] Yet, the general application of an aryl chloride as a substrate in this transition-metal-free coupling remains limited and highly challenging. Only recent examples of a heteroarene containing acidic C–H bond were reported under cryogenic conditions using lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as a base.[10]

Phenanthridines are essential core structures found in a variety of natural product and other pharmaceutically

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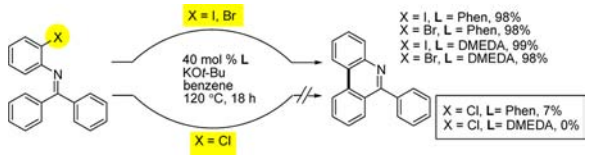
**Scheme 1.** Initial Test of Transition-Metal-Free Aryl Halide Couplings Using Previously Known to Be Successful Additives (Phen and DMEDA)

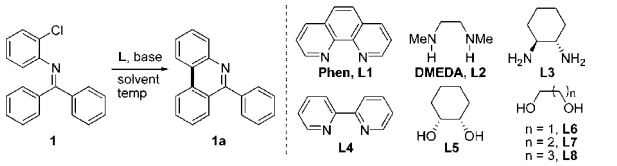



important molecules.[11] They have a wide range of biological activities and applications, including antibacterial, antiprotozoal, and anticancer agents.[12] A well-known member in the phenanthridine class is Ethidium, a common and versatile DNA/RNA intercalator.[13] Previous synthetic methods for preparing phenanthridine scaffolds include radical,[14] benzyne-mediated,[15] photochemical,[16] hypervalent iodine-promoted,[17] and transition metal-catalyzed approaches.[18] Although a number of useful synthetic methods are available, there remain limitations such as multistep synthesis, limited substrate scope, and difficult removal of transition metal impurities. In some cases, harsh reaction conditions are also required. Thus, exploration for a milder and more convenient process from readily available building blocks (e.g., benzophenones and anilines) for the synthesis of a phenanthridine moiety is imperative. In continuing our former focus on transition-metal-free DMEDA-catalyzed C−H arylation of benzene using aryl iodides[5] and arylation of heterocycles,[19] herein we report the development of an intramolecular C−H arylation from aryl chlorides using an ethylene glycol catalyzed system. This method provides a simple synthesis of phenanthridine derivatives from readily available components.

We embarked on this research by testing the feasibility of aryl halide C−H bond coupling for phenanthridine synthesis, using either previously known successful DMEDA or phenanthroline derivatives as promoters (Scheme 1).[4−6]

Disappointingly, apart from an aryl iodide/bromide, an aryl chloride was found to be unsuccessful in this process. In fact, other structurally similar diamines were also inferior in this reaction (Table 1, entries 1−4). In an attempt to make the aryl chloride coupling reaction viable, we surveyed other simple organic molecules which are known to be more effective for promoting aryl radical anion formation (which is believed to be the key species in the homolytic aromatic substitution[8c] /coupling process). Inspired by the

**Table 1.** Screening of Reaction Conditions[a]




| entry | L (mol %) | solvent | base | temp/°C | %yield[b] |
|---|---|---|---|---|---|
| 1 | **L1** (40) | benzene | KO*t*-Bu | 120 | 7 |
| 2 | **L2** (40) | benzene | KO*t*-Bu | 120 | 0 |
| 3 | **L3** (40) | benzene | KO*t*-Bu | 120 | 9 |
| 4 | **L4** (40) | benzene | KO*t*-Bu | 120 | 4 |
| 5 | *t*BuOH (50) | benzene | KO*t*-Bu | 120 | 26 |
| 6 | **L5** (40) | benzene | KO*t*-Bu | 120 | 99 |
| 7 | **L6** (40) | benzene | KO*t*-Bu | 120 | 99 |
| 8 | **L7** (40) | benzene | KO*t*-Bu | 120 | 48 |
| 9 | **L8** (40) | benzene | KO*t*-Bu | 120 | 34 |
| 10 | **L6** (40) | mesitylene | KO*t*-Bu | 120 | 83 |
| 11 | **L6** (40) | toluene | KO*t*-Bu | 120 | 98 |
| 12 | **L6** (40) | DMF | KO*t*-Bu | 120 | 2 |
| 13 | **L6** (10) | toluene | KO*t*-Bu | 120 | 98 (96) |
| 14 | **L6** (10) | toluene | KO*t*-Bu | 100 | 77 |
| 15 | **L6** (10) | toluene | KO*t*-Bu | 80 | 0 |
| 16 | **L6** (10) | toluene | Nil. | 120 | 0 |
| 17 | nil | toluene | KO*t*-Bu | 120 | 0 |
| 18 | **L6** (10) | toluene | $K_2CO_3$ | 120 | 0 |
| 19 | **L6** (2) | toluene | KO*t*-Bu | 120 | 44 |

[a] Reaction conditions: **1** (1.0 mmol), **L** (mol % as indicated), KO*t*-Bu (2.0 mmol), and solvent (8.0 mL) were stirred at specified reaction temperature for 24 h. [b] Calibrated GC yields were reported using dodecane as the internal standard. Isolated yield in parentheses.

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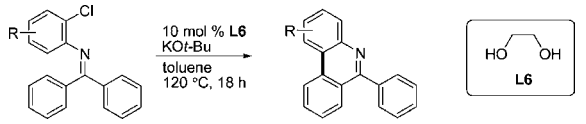
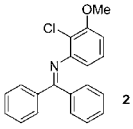
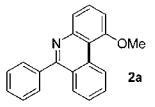
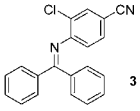
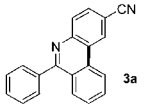
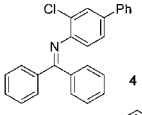
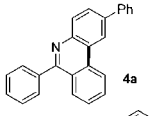
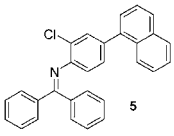
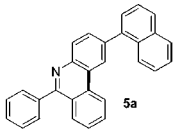
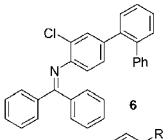
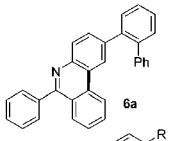
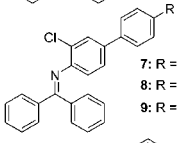
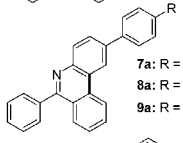
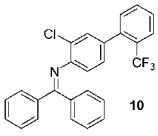
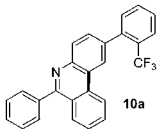
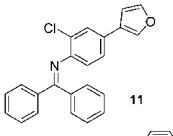
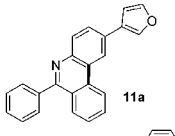
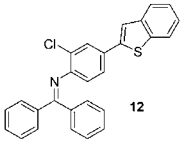
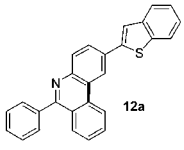
**Table 2.** Transition-Metal-Free KO*t*-Bu/Ethylene Glycol Promoted Intramolecular C−H Coupling of Aryl Chlorides[a]




| entry | ArCl | product | %yield[b] |
|---|---|---|---|
| 1 |  **2** |  **2a** | 94 |
| 2 |  **3** |  **3a** | 88 |
| 3 |  **4** |  **4a** | 90 |
| 4 |  **5** |  **5a** | 85 |
| 5 |  **6** |  **6a** | 85 |
| 6 |  **7**: R = OMe |  **7a**: R = OMe | 84 |
| 7 | **8**: R = $NMe_2$ | **8a**: R = $NMe_2$ | 88 |
| 8 | **9**: R = Me | **9a**: R = Me | 84 |
| 9 |  **10** |  **10a** | 75 |
| 10 |  **11** |  **11a** | 53 |
| 11 |  **12** |  **12a** | 71 |

[a] Reaction conditions: *N*-(2-Chloroaryl)benzophenone imine **2**−**12** (1.0 mmol), **L6** (10 mol %), KO*t*-Bu (2.0 mmol), and toluene (8.0 mL) were stirred at 120 °C for 18 h (see Supporting Information for details). [b] Isolated yields were reported.

requisite of an alcoholic medium for certain efficient electron transfer processes,[20] we thus attempted to add R−OH as an additive to our reaction mixtures. When 50 mol % of *t*-BuOH was added, the product yield slightly increased. Other diol derivatives were also investigated. To our delight, 1,2-diol (e.g., **L5** and **L6**) successfully promoted this aryl chloride coupling (entries 6−7). A diol with a longer chain length did not fully facilitate this reaction (entries 8−9). Presumably the reaction intermediate requires a well-coordinating 1,2-diol anion for potassium. Toluene and benzene were the solvents of choice in this reaction (entries 7 and 10−12). DMF solvent gave a significant amount of dehalogenation side product. Particularly noteworthy is that even 10 mol % of **L6** allowed this reaction to proceed smoothly (entry 13). Lowering the reaction temperature gave poorer substrate conversion (entries 13−15). The control experiment revealed that the absence of KO*t*-Bu or ethylene glycol could not promote this catalysis (entries 16−17). $K_2CO_3$ did not promote this reaction (entry 18). A catalyst loading of 2 mol % **L6** offered moderate conversion (entry 19).

Having the optimized reaction conditions in hand, we next examined the scope of this aryl chloride C−H coupling (Table 2). Sterically hindered aryl chloride furnished the desired product in excellent yield (entry 1). The nitrile group was found to be compatible under these reaction conditions (entry 2, note: this −CN group is not fully tolerable when *n*-BuLi or LiTMP bases are used). No significant effect was observed when other aromatic moieties were incorporated (entries 3−5). Electron-donating substituents provided good yields of the reaction (entries 6−8). Yet, the electron-withdrawing $-CF_3$ group gave a slighly lower product yield (entry 9). Heterocycles such as furan and benzothiophene were feasible substrates (entries 10−11).

With the successful C−H arylation results of *N*-(2-chloroaryl)benzoimines, we began to investigate the substituent effect on the benzoimine scaffold (Table 3). Good-to-excellent yields were generally obtained (up to 98%). Interestingly, a noticeable product scrambling was observed (e.g., entry 1). The location of the *para*-substituent was changed to the *meta*-position (see Scheme 2 for proposed mechanism). Methoxy and diethylamino groups offered similar regioselectivity (entries 2−3). *N*-(2-Chlorophenyl)-9*H*-fluoren-9-imine (**16**) was transformed to the desired polycyclic product in good yield (entry 4). Extended aromatic structures (e.g., with tolyl or thienyl groups) were found to be compatible under these reaction conditions (entries 5−6). The unsymmetrical benzophenone imine afforded high product regioselectivity (10:1), with preferential bond construction at the substituted aryl ring (entries 7−8).[21] Disappointingly, when chloro-substituted triarylethenes were used as the starting materials, no corresponding desired products were observed. Presumably the nitrogen moiety in the substrate scaffold is important to trigger this reaction.

A proposed mechanism of homolytic aromatic substitution[8c] is shown in Scheme 2. The anionic radical **B** is generated from **A** by SET in the presence of KO*t*-Bu(diol). The radical intermediate **C** undergoes a kinetically favored 5-*exo*-*trig ipso* attack[22] to give the spirocyclohexadienyl

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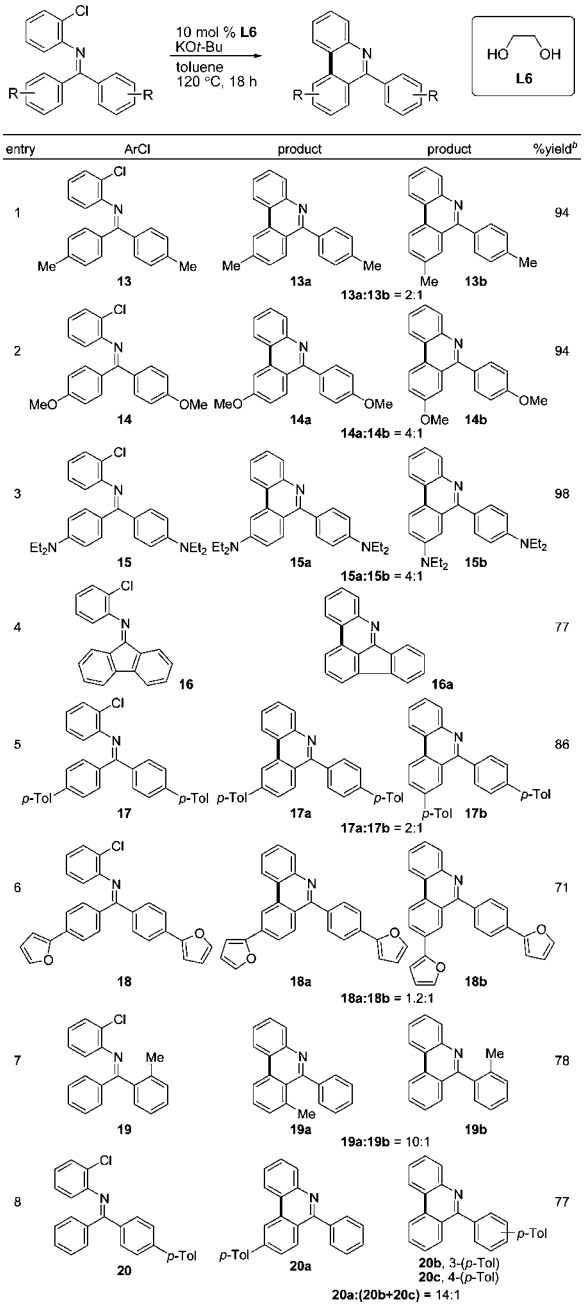
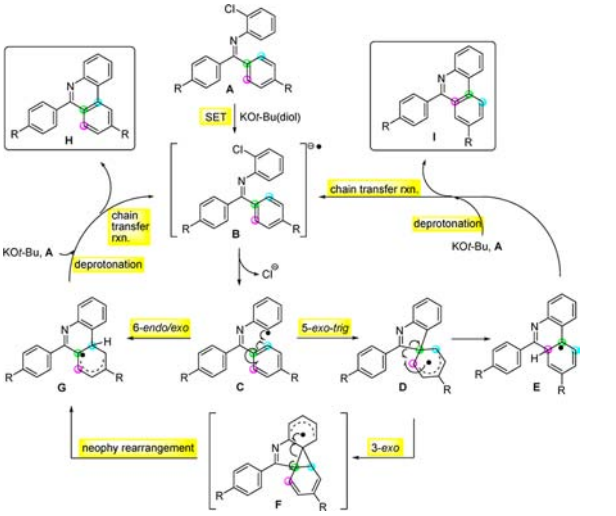
**Table 3.** Transition-Metal-Free KO*t*-Bu/Ethylene Glycol Promoted Intramolecular C−H Coupling Substituted Benzoimines[a]




[a] Reaction conditions: *N*-(2-Chlorophenyl)benzoimine **13**−**20** (1.0 mmol), **L6** (10 mol %), KO*t*-Bu (2.0 mmol), and toluene (8.0 mL) were stirred at 120 °C for 18 h. [b] Isolated yields were reported.

**D**.[23] The intermediate **D** then either proceeds to form a ring expansion[24] intermediate **E** or undergoes a 3-*exo* closure to generate **F**. This intermediate **F** can generate species **G** by neophyl rearrangement.[25] Indeed, the species **G** can also be formed by the 6-*endo*/*exo* pathway from **C**. The final product **H** is afforded by a KO*t*-Bu-assisted deprotonation and chain transfer reaction. Meanwhile, the regioisomeric product **I** is formed from intermediate **E**.

**Scheme 2.** A Plausible Reaction Mechanism




In summary, we have advanced an intermolecular cross-coupling (C−H arylation) from aryl chloride under a transition-metal-free system. Previous successful catalytic systems were found to be only applicable for mainly aryl iodides or bromides. In particular no general examples were reported for aryl chlorides under conventional heating conditions. The key to success is the use of ethylene glycol, which can make the aryl chloride C−H coupling feasible. Particularly attractive is that only 10 mol % of ethylene glycol is sufficient to promote this reaction.[26] Usage of a simple diol (apart from diamine)[27] in this protocol would provide chemists with a new direction for future challenging cross-coupling reactions using inexpensive aryl chlorides under transition-metal-free conditions.

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**Supporting Information Available.** Detailed experimental procedures, compound characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Previous ArI/Br initial examples used a high catalyst loading (20−40 mol% DMEDA or Phen, refs 4−6), or even up to 50 mol % neocuproine (e.g., ref 9e)
(27) Price comparison: ethylene glycol (1 Liter, USD 48), DMEDA (5 mL, USD 45.8), 1,10-phenanthroline (5 g, USD 27.7), from Aldrich catalog.

The authors declare no competing financial interest.