Domino Reactions

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Palladium-Catalyzed Domino Direct Arylation/N-Arylation: Convenient Synthesis of Phenanthridines**

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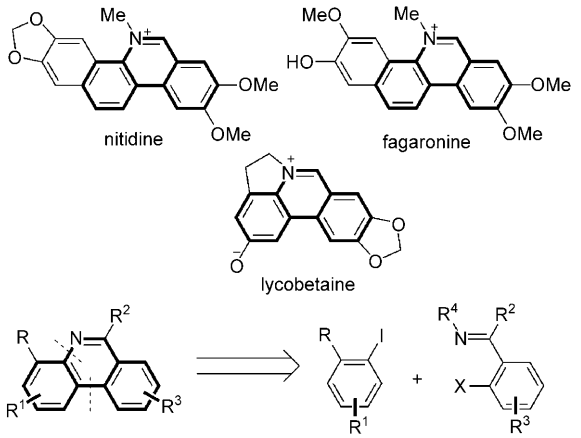
The phenanthridine unit represents an important structural motif found in natural products and biologically relevant compounds (Scheme 1). Molecules containing this motif are

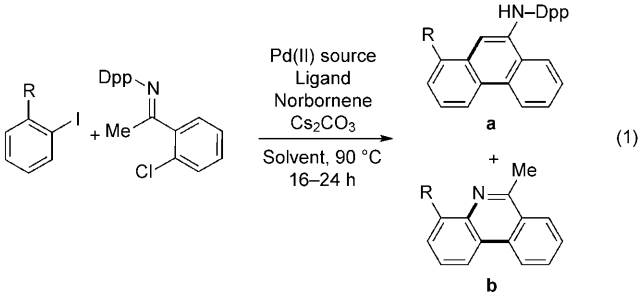


Scheme 1. Examples of biologically relevant benzo[*c*]phenanthridine and pyrrolophenanthridine alkaloids.

the subject of considerable interest as potent antitumor, antimicrobial, and antiviral agents.[1] Much effort has been invested in the synthesis of derivatives of these compounds to deduce structure-activity relationships and discover new analogues with improved properties.[1]

Although a number of methods are available for the synthesis of these phenanthridines, many are limited because of the lack of generality, limited functional group tolerance, and lengthy synthetic sequences.[1–3] Palladium-catalyzed approaches have addressed issues of functional group tolerance, however, lengthy synthetic sequences are still associated with the generation of functionalized coupling partners. Methods employing direct arylation allow for the use of simplified starting materials and offer a more atom economical approach relative to traditional metal-catalyzed cross-coupling reactions.[4] Catellani and co-workers have reported a powerful strategy involving a sequence of domino *ortho* functionalization with subsequent terminal cross-coupling processes for the synthesis of diversely substituted aromatic compounds.[5] Our group has employed this strategy in devising alternative processes for the efficient construction of heterocyclic compounds.[6]

We envisioned applying a C–H activation/cross-coupling approach toward the synthesis of diversely substituted phenanthridine derivatives, whereby a sequence of *ortho* arylation and subsequent N-arylation would provide the desired compounds in one step (Scheme 1).



(1)

The feasibility of this approach was suggested by the unexpected reactivity observed during our previous investigations [Eq. (1)].[7a] During these studies a number of different imine derivatives were investigated and an interesting side-product was observed when *N*-diphenylphosphinoylimines (*N*-Dpp imines) were employed. With these imine derivatives, arylation occurred at the expected α-position [Eq. (1), **a**] accompanied by a small amount of an N-arylated product [Eq. (1), **b**]. It was reasoned that silylimines would favor the product of N-arylation because they are nucleophilic at the nitrogen atom and the silyl group can be easily cleaved under the reaction conditions.[8a,9] To test this hypothesis silylimine **2a** (Table 1) was synthesized and reacted with iodonaphthalene under our previously developed reaction conditions, smoothly providing the desired benzo[*c*]phenanthridine **3a** in 72% yield.[7b]

Herein we report our efforts toward the development of a highly efficient method for the construction of diversely substituted phenanthridine derivatives employing N-unsubstituted and *N*-silylimines based on this reaction protocol. To the best of our knowledge this report represents the first application of these imine derivatives in the metal-mediated synthesis of heterocycles. Furthermore, we introduce the N-arylation of *N*-silylamidines, thereby expanding the range of

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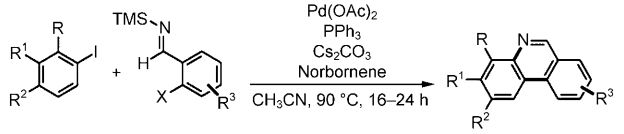
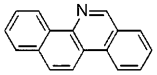
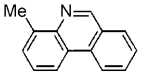
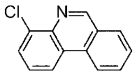
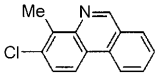
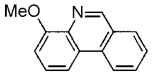
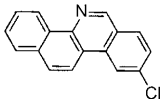
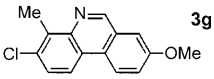
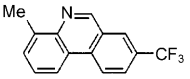
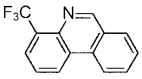
Table 1: Synthesis of 6-H-substituted phenanthridines.[a]



Entry	Aryl iodide R, R^1, R^2	Silylimine X, R^3	Product		Yield [%][b]
1	R, R^1 = 	X = Cl, R^3 = H **2a**		**3a**	85
2	**1a**	X = Br, R^3 = H **2b**	**3a**		75
3	R = Me, R^1 = R^2 = H **1b**	**2a**		**3b**	75
4	R = Cl, R^1 = R^2 = H **1c**	**2a**		**3c**	56
5	R = Me, R^1 = Cl, R^2 = H **1d**	**2a**		**3d**	86
6	R = OMe, R^1 = R^2 = H **1e**	**2a**		**3e**	81
7	**1e**	**2a**	**3e**		74[c]
8	**1e**	**2b**	**3e**		76
9	**1a**	X = Cl, R^3 = Cl **2c**		**3f**	39
10	**1d**	X = Br, R^3 = OMe **2d**		**3g**	39
11	**1b**	X = Br, R^3 = CF_3 **2e**		**3h**	31
12	R = CF_3, R^1 = R^2 = H **1f**	**2b**		**3i**	34

[a] Reaction conditions: Aryl iodide (0.2 mmol, 1.0 equiv), silylimine (1.1 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (25 mol%), Cs_2CO_3 (3.0 equiv), and norbornene (8.0 equiv) in MeCN (0.05 M) were heated in a sealed tube at 90 °C for 16–24 h. [b] Yield of isolated product. [c] Reaction scaled up (2 mmol). TMS = trimethylsilyl.

imine derivatives capable of participating in palladium-catalyzed cross-coupling processes.[8]

In examining the reaction parameters, it was found that solvent, concentration, and the amount of norbornene used had the greatest influence on the yield. Polar solvents such as *N*,*N*-dimethylformamide, *N*-methylpyrrolidone, and acetonitrile were found to be beneficial for the transformation. Furthermore, increasing the amount of norbornene had a positive effect on the yield of the reaction. It was possible to find conditions which provided benzo[*c*]phenanthridine **2a** in 85% yield (Table 1, entry 1). With these conditions in hand, a substrate study was undertaken to investigate the generality of this transformation.

A range of phenanthridines and benzo[*c*]phenanthridines could be formed in moderate to good yields from readily available *N*-silylaldimines and aryl iodides. Notably, the aryl iodides employed are commercially available and the *N*-silylaldimines are available from the corresponding aldehyde in one step.[9c] The *ortho*-chloro- and *ortho*-bromo-*N*-silylaldimines could serve as coupling partners, with *ortho*-chloro-*N*-silylaldimines generally demonstrating better performance (Table 1, entries 1, 2, 6, and 8). Aryl iodides of varying steric and electronic properties could be successfully employed as coupling partners. Furthermore, the protocol is readily scalable; increasing the reaction scale ten-fold did not affect the yield significantly (Table 1, entry 7).

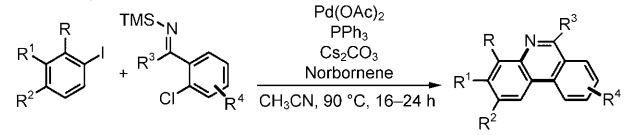
Encouraged by these results we sought to investigate the possibility of substitution at the 6-position of the phenanthridine ring system. Subjecting iodonaphthalene and the *N*-silylketimine **2f** to the reaction conditions yielded benzo[*c*]phenanthridine **3j** as the sole product (Table 2, entry 1). Groups of differing steric and electronic properties such as alkyl, alkenyl, aryl, and amino groups could be installed efficiently (Table 2). Significantly, *N*-silylamidines were demonstrated to be suitable coupling partners and the catalyst loading could be decreased to 2.5 mol% (Table 2, entry 5).

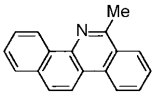
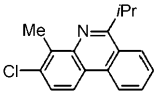
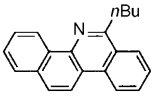
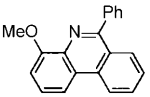
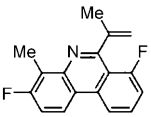
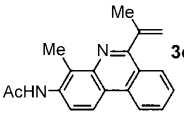
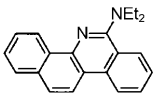
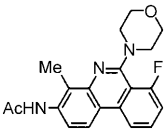
Varying the substituent at the 6-position was readily accomplished by employing the desired *N*-silylketimine or amidine which was prepared from the reaction between the corresponding benzonitrile and organolithium reagent.[9d] Formation of the imine derivatives takes place smoothly without the formation of many byproducts, although NMR spectra may be complicated by the presence of tautomers and geometric isomers with the distribution being a function of the temperature.[9] Fortunately, subjecting the isomeric mixtures of imines to the reaction conditions provided the desired phenanthridines in consistently high yields. It is likely that the isomers equilibrate under the reaction conditions.[9] It was found that the *N*-silylketimines could be employed without their prior purification (Table 2, entry 4); however this was not the case with the *N*-silylaldimines, where the best yields were achieved with prior purification of the imine.

Two requirements became apparent for the success of this reaction: a suitable imine derivative must be chosen such that it possesses a group on the nitrogen atom which can be cleaved at some point in the catalytic cycle, and only *ortho*-substituted aryl iodides were suitable coupling partners under the developed reaction conditions as complex mixtures were obtained in the absence of an *ortho* substituent.

The unsubstituted aldimines are generally not available as they are often unstable species, however, unsubstituted ketimines are easily synthesized, isolable compounds. Unsubstituted ketimines **2o** and **2p** were synthesized and subjected to the reaction conditions. They are indeed suitable substrates for this transformation, providing the desired products in comparable yields to the trimethylsilylimines (Table 3, entries 2 and 3). It is advantageous to utilize such unsubsti-

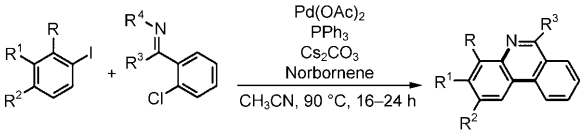
Table 2: Synthesis of 6-substituted phenanthridines.[a]



Entry	Aryl iodide R, R^1, R^2	Silylimine R^3, R^4	Product		Yield [%][b]
1	**1a**	R^3 = Me, R^4 = H **2f**		**3j**	86
2	**1d**	R^3 = *i*Pr, R^4 = H **2g**		**3k**	91
3	**1a**	R^3 = *n*Bu, R^4 = H **2h**		**3l**	79
4	**1a**	**2h**	**3l**		82[c]
5	**1a**	**2h**	**3l**		69[d]
6	**1e**	R^3 = Ph, R^4 = H **2i**		**3m**	68
7	R = Me, R^1 = F, R^2 = H **1g**	R^3 =  R^4 = F **2j**		**3n**	91
8	R = Me, R^1 = NHAc, R^2 = H **1h**	R^3 =  R^4 = H **2k**		**3o**	98
9	**1a**	R^3 = NEt_2, R^4 = H **2l**		**3p**	58
10	**1h**	R^3 =  R^4 = H **2m**		**3q**	76

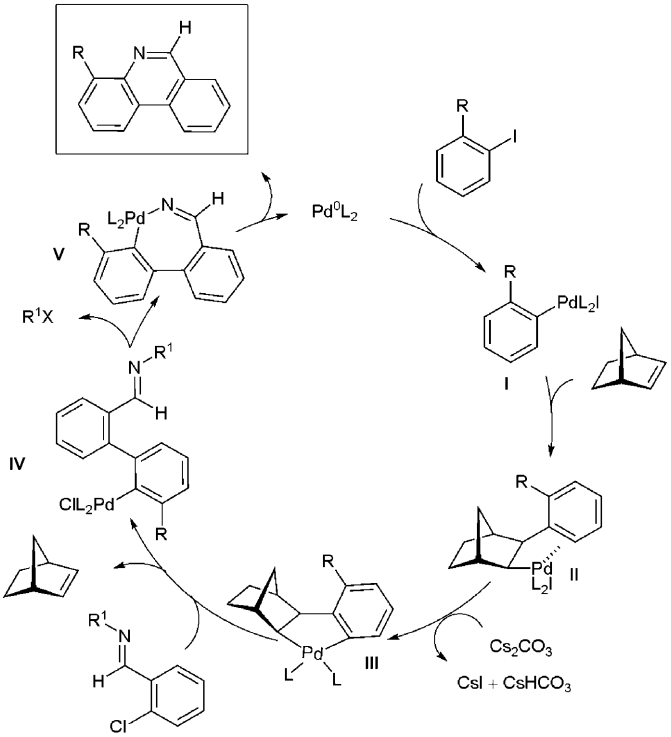
[a] Reaction conditions: see Table 1. [b] Yield of isolated product. [c] Silylimine not isolated. [d] $Pd(OAc)_2$ (2.5 mol%), MeCN (0.27 M) used.

Table 3: Variation of the imine derivative.



Entry	Aryl iodide R, R^1, R^2	Imine R^3, R^4	Product	Yield [%][b]
1	**1a**	R^3 = *n*Bu, R^4 = TBDMS **2n**	**3l**	41
2	**1a**	R^3 = *n*Bu, R^4 = H **2o**	**3l**	76
3	**1e**	R^3 = Ph, R^4 = H **2p**	**3m**	60

[a] Reaction conditions: see Table 1. [b] Yield of isolated product. TBDMS = *tert*-butyldimethylsilyl.



Scheme 2. Proposed catalytic cycle.

tuted imines as the production of waste is minimized. Other trialklysilylimine derivatives could be employed (Table 3, entry 1), however, a lower yield was observed, which may be a result of the enhanced stability of the TDBMS group.

A simplified catalytic cycle can be proposed on the basis of the mechanistic work carried out independently by Catellani et al.,[5] Hartwig et. al.,[8c] and Barluenga et al.[8a] (Scheme 2). Oxidative addition of the aryl iodide would yield the aryl–palladium intermediate **I** which can subsequently undergo carbopalladation with norbornene to yield the intermediate **II**. Electrophilic metalation followed by deprotonation can generate the palladacyclic intermediate **III**. Reaction of the imine with the intermediate **III** would result in arylation of the *ortho*-position of the aryl iodide. The arylation may be proceeding through a palladium(IV) intermediate, in analogy to what has been observed for *ortho* alkylation.[5d] Subsequent decarbopalladation then provides the intermediate **IV**. Cleavage of the N–H or N–Si bond can result in the formation of the palladium–imido intermediate **V**, and subsequent reductive elimination from this intermediate, releases the product, regenerating palladium(0) which goes on to continue the cycle.

In conclusion, we have developed a practical and efficient method for the preparation of diversely substituted phenanthridines and benzo[*c*]phenanthridines from readily available precursors. This methodology will surely aid in the effort to generate more interesting structures for use in biological studies. Furthermore, we have also expanded the synthetic utility of imine derivatives in metal-catalyzed cross-coupling reactions and broadened the range of imine derivatives utilized in such processes.

Experimental Section

Typical procedure for domino direct arylation/N-arylation:
A 5 mL microwave vial equipped with a magnetic stirring bar and septum was flame-dried and then cooled under a stream of argon by venting through a needle in the septum. The vial was then charged with palladium acetate (10 mol%), triphenylphosphine (25 mol%), cesium carbonate (3 equiv), and norbornene (8 equiv). The vial was then sealed and flushed with argon for 1 min. Dry acetonitrile was added (0.05 M, based on aryl iodide) and the solution was stirred at room temperature for 10 min. The imine (1.1 equiv) and aryl iodide (1.0 equiv, 0.2 mmol scale) were then added sequentially via syringe (alternatively, if one of the components was a solid it was weighed along with the other solids, or transferred to the reaction mixture as a solution in acetonitrile). The reaction vessel was then immersed in an oil bath, which was preheated at 90 °C, for 16–24 h. After this time the reaction mixture was cooled to room temperature and then filtered through a short pad of silica with ethyl acetate washings (ca. 60 mL). Concentration of the filtrate by rotary evaporation provided a residue which was purified by column chromatography.

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