



Cite this: *Chem. Commun.*, 2019, 55, 11908

Received 23rd July 2019,
Accepted 8th September 2019

DOI: 10.1039/c9cc05717j

rsc.li/chemcomm

A ruthenium-catalyzed free amine directed (5+1) annulation of anilines with olefins: diverse synthesis of phenanthridine derivatives†

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A ruthenium(II)-catalyzed cross-ring (5+1) annulation between 2-aminobiphenyls and activated olefins is disclosed for succinct synthesis of valuable phenanthridine scaffolds. The protocol avails a common organic functional group, free amine, as a directing group and represents a unique combination of C–H activation/annulation/C–C bond cleavage cascade that bodes well in the production of bioactive alkaloids including trisphaeridine and bicolorine.

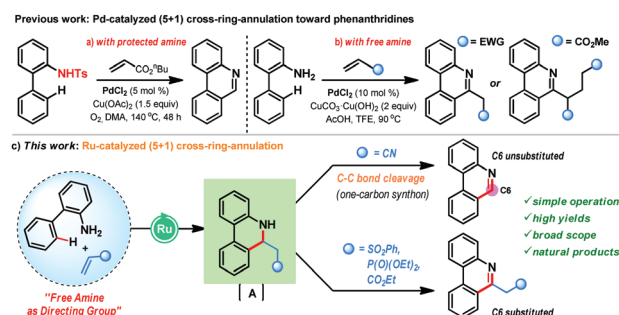
Transition-metal-catalyzed annulation reactions exploiting ubiquitous and otherwise inactive C–H bonds represent an important synthetic strategy to fabricate polycyclic molecular frameworks.^{1,2} Over the years, chemists have compiled a ruthenium-catalyzed reaction compendium that consists of a series of (4+2),^{3a–e} (3+2),^{3f–h} (2+2+2),³ⁱ and (4+1)^{3j} annulations, forging diverse carbocycles and heterocycles. Despite these achievements, to date, ruthenium-catalyzed (5+1) annulation has remained largely underdeveloped.⁴ In these annulation reactions, directing groups play fundamental roles in facilitating the C–H bond activation process and mitigate the problem of regioselectivity. Common organic functional groups like carboxylic acid, ester, amide, ketone, *etc.* are often employed as directing groups.⁵ However, the free amine group (NH₂), one of the most valuable and widely abundant functionalities, has largely been ignored in ruthenium-catalyzed directed C–H bond activation reactions,⁶ probably owing to the challenges associated with its strong coordinating ability with metal catalysts along with the superior nucleophilic reactivity that result in pivotal issues of catalyst deactivation and unwarranted side reactions.^{6c,9b} Thus, there is ample scope in the free amine directed ruthenium(II)-catalyzed regioselective C–H bond activation/annulation manifold and importantly, it could potentially lead to high-value N-heterocycles when the amine directing group becomes the critical component of the ring structure.

Phenanthridine and benzophenanthridine alkaloids signify an important class of organic molecules with promising biological activities.^{7,8} Some of the important natural products are presented in Fig. 1. The biological activities of such alkaloids range from anti-cancer to anti-fungal, and anti-bacterial, to name a few. Consequently, devising novel synthetic strategies towards such molecular frameworks is highly desirable.⁸ Arguably, a C–H bond activation based (5+1) cross-ring-annulation (CRA) reaction of biaryl-2-amines would be a succinct route to access these scaffolds (Scheme 1).

Furthermore, the majority of the naturally occurring phenanthridine alkaloids do not possess any substitution at the C6-position and hence, challenges lie in the strategic design of a suitable one-carbon synthon for the CRA reaction. In 2012, the Li group reported an intriguing Pd-catalyzed (5+1) CRA reaction of biaryl-2-amines with activated alkenes (butyl acrylate) that features the pivotal C–C bond cleavage to offer C6-unsubstituted



Fig. 1 Biologically important phenanthridine alkaloids.



Scheme 1 Ru(II)-catalyzed free amine directed cross-ring (5+1) annulation towards phenanthridine alkaloids.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9cc05717j

phenanthridines in high yields (Scheme 1a).^{9a} In this case, the use of *N*-protected biaryl-2-amines was necessary as *N*-unprotected biaryl-2-amines gave poor yields. In parallel, the Zhang group also reported (5+1) CRA reaction of biaryl-2-amines with alkenes under Pd-catalysis in trifluoroethanol (Scheme 1b).^{9b} This reaction is effective with unprotected amines, however, they did not observe any C–C bond cleavage phenomenon and, in the case of acrylate coupling partner, a second Michael addition was proposed for the aromatization step *en route* to C6-substituted phenanthridines. Currently, such a CRA reaction manifold for the production of phenanthridines is unknown with Ru-catalysis and herein, we disclose the first example of free amine directed (5+1) CRA reaction of biaryl-2-amines with activated alkenes under Ru-catalysis (Scheme 1c). When acrylonitrile is used as a coupling partner, it acts as a C1-synthone and delivers C6-unsubstituted phenanthridines after the C–C bond cleavage. In contrast, other activated olefins, such as vinyl sulfone, vinyl phosphate, and acrylate, furnished C6-substituted phenanthridines in very high yields.

We commenced our investigations following the model reaction of 2-aminobiphenyl **1a** with acrylonitrile **2a** (Table 1). The choice of acrylonitrile as an olefin coupling partner is intriguing as initially formed dihydrophenanthridine intermediate **A** bearing a cyanomethyl (–CH₂CN) functionality may experience a C–C bond cleavage phenomenon either through a radical pathway or a coordination assisted base promoted elimination mechanism to validate domino C–H activation based (5+1) annulation *en route* to the C6-unsubstituted phenanthridine scaffold (Scheme 1c). Accordingly, when we treated **1a** and **2a** in the presence of [Ru(*p*-cymene)Cl₂]₂ (5 mol%), Cu(OAc)₂·H₂O (2 equiv.), AgSbF₆ (20 mol%), and CH₃CO₂H (1.2 equiv.) in THF solvent, we were delighted to find the desired 6-unsubstituted phenanthridine product **3a** in 52% yield (Table 1, entry 1).

Table 1 Optimization of (5+1) annulation reaction^a

Entry	Acid additive	Solvent	Temp (°C)	Yield ^b (%)
1	AcOH	THF	80	52
2	AcOH	DCE	80	32
3	AcOH	DME	80	38
4	AcOH	Dioxane	80	46
5	MesCO ₂ H	THF	80	72
6	MesCO ₂ H	2-Me-THF	80	37
7	1-AdCO ₂ H	THF	80	12
8	MesCO ₂ H	THF	100/60	62/0
9	MesCO ₂ H	THF	80	16 ^c /11 ^d
10 ^e	MesCO ₂ H	THF	80	—
11 ^f	—	THF	80	< 5
12 ^g	MesCO ₂ H	THF	80	59
13	MesCO ₂ H	THF	80	16 ^h /0 ⁱ /0 ^j

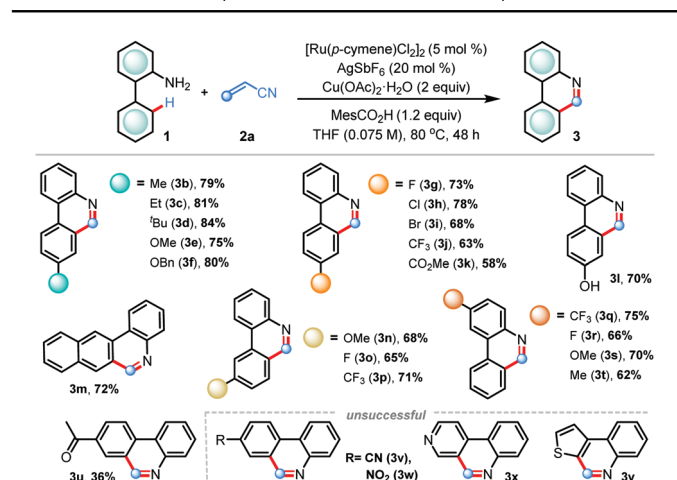
^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), solvent (4.2 mL) for 48 h under an argon atmosphere. ^b Isolated yields. ^c AgBF₄ (20 mol%) was used as an additive. ^d CuO (2 equiv.) was used as an oxidant. ^e Reaction without [Ru(*p*-cymene)Cl₂]₂ catalyst or Cu(OAc)₂·H₂O oxidant or AgSbF₆ additive. ^f Reaction without MesCO₂H (mesitoic acid) additive. ^g 2 equiv. of water was added. ^h With Pd(OAc)₂. ⁱ With (Cp*IrCl₂)₂ catalyst. ^j With (Cp*IrCl₂)₂ catalyst.

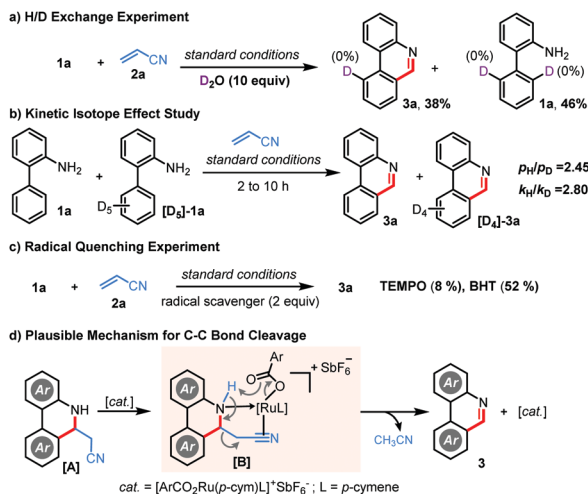
Switching the reaction solvent to DCE, dioxane, and DME furnished inferior results (entries 2–4). Screening of the acid additives revealed mesitoic acid as the best choice, delivering the desired product **3a** in 72% isolated yield (entry 5). Change of the reaction solvent from THF to higher boiling point 2-methyl tetrahydrofuran (2-Me-THF) gave only 37% yield of **3a** (entry 6). Further tuning of the reaction conditions, such as use of 1-AdCO₂H acid (entry 7), increasing or decreasing of reaction temperature (entry 8), utilization of AgBF₄ additive and use of CuO oxidant (entry 9) had detrimental effects. Control experiments revealed that all the components were essential for the success of the reaction (entries 10 and 11). Yield also decreased in the presence of excess water in the reaction medium (entry 12). Other transition metals like Pd, Rh, and Ir based catalysts were ineffective under standard reaction conditions, highlighting the uniqueness of ruthenium in this protocol (entry 13).

Having acquired the optimal conditions, we sought to explore the scope of the (5+1) annulation reaction varying the electronic and steric nature in the arene ring (Table 2). The presence of electron-releasing groups such as alkyl (**3b–d**) and alkoxy (**3e–f**) at the *para*-position gave desired products in uniformly high yields (75–84%). Substrates bearing electron-withdrawing groups, for example halogens (**3g–i**), trifluoromethyl (**3j**), and ester (**3k**) were smoothly reacted to produce C6-unsubstituted phenanthridines in good yields.

Pleasingly, coordinating free-hydroxyl groups did not hamper the reaction, furnishing compound **3l** in 70% yield. When unsymmetrical *meta*-substitution was considered, annulations proceeded selectively at the sterically less hindered site to forge products **3n–p** in good yields. The protocol also worked efficiently with the 2-naphthyl derivative, generating important fused poly-aromatic heterocycle benzo[*j*]phenanthridine (**3m**) in 72% yield. The effect of substituents in the aniline ring was also examined; a host of electron-rich and electron-deficient anilines were effective for this reaction, delivering **3q–t** in 62–75% isolated yields. Synthetically useful yield was also obtained with a sensitive ketone functionality (**3u**). Under the standard conditions, annulations

Table 2 Substrate scope of (5+1) annulation with respect to amines^a





Scheme 3 Control experiments.

In conclusion, an efficient (5+1) cross-ring-annulation (CRA) reaction using readily available 2-aminobiphenyls and activated olefins under common functional group free amine assisted ruthenium(II) catalysis has been accomplished to prepare a library of high-value functionalized phenanthridines in very high yields. Identification of acrylonitrile as a one-carbon synthon was a critical parameter for achieving the concomitant C-C bond cleavage, furnishing 6-unsubstituted phenanthridines in a succinct manner. Also, the applications of this methodology in syntheses of bioactive alkaloids like trisphaeridine and bicolorine add to the fruitfulness of the protocol. Further applications of Ru(II)-catalyzed annulation are currently ongoing in our laboratory.

We gratefully acknowledge SERB-DST for financial support. M. B. also thanks IIT-Madras for the Institute Research Development Award (IRDA). We also thank the Department of Chemistry, IIT-Madras for instrumental facilities.

Conflicts of interest

There are no conflicts to declare.

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