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Metal-free tandem carbene N–H insertions and C–C bond cleavages†

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A metal-free C–H [5 + 1] annulation reaction of 2-arylanilines with diazo compounds has been achieved, giving rise to two types of prevalent phenanthridines *via* highly selective C–C cleavage. Compared to the simple N–H insertion manipulation of diazo, this method elegantly accomplishes a tandem N–H insertion/S_EAr/C–C cleavage/aromatization reaction, and the synthetic utility of this new transformation is exemplified by the succinct syntheses of trisphaeridine and bicolorine alkaloids.

Introduction

Carbene conversion represents one of the most fundamental and synthetically useful reactions in modern organic syntheses.[1] Of particular interest are diazo compounds, a class of "smart" carbene precursors that are being extensively utilized as versatile synthetic feedstock in the chemical as well as biological arena.[2] A myriad of synthetically significant applications of diazo compounds have been realized in Wolff rearrangements,[3] cyclopropanations,[4] ylide formations,[5] X–H insertions,[6] C–H functionalizations[7] and so forth (Scheme 1a). Regarding these examples, it is well known that metal-carbenes play a pivotal role; namely, diazo chemistry mainly relies on metal catalysts (*e.g.* Rh, Ru, Pd, Ir, Ag, Cu and Co) for arriving at the carbenoid reactivity. On account of strict constraints imposed by trace levels of metals in pharmaceuticals and also reaction economy,[8] however, this "metal-engaged" mode of reactivity dramatically overshadows the prospective applications of diazo chemistry. In striking contrast, the evolvement of metal-free technologies heavily lags behind, albeit several elegant yet sporadic reactions have emerged in recent years.[9] Moreover, these studies commonly refer to a "one-fold" operation forming only a single chemical bond within the entire process.[10] Against this background, the exploration of more synthetically innovative streamlined approaches and strategies through multiple bond breaking/forming events in the absence of transition metals, such as domino and cascade reactions of diazo compounds, would be a desirable goal. In this paper, we report a new platform for upgrading a transform of model diazo compounds through a Brønsted acid-promoted N–H insertion/S_EAr/C–C cleavage/oxidative aromatization four-fold domino reaction in a single chemical operation.

It is worth noting that N–H insertion/conversion is among the most promising platforms for constructing the ubiquitous C–N bonds widely encountered in an enormous number of bioactive molecules and countless top-selling marketed drugs, and this mode of reactivity has attracted significant endeavors in recent years and has been used to build numerous natural products.[11] To date, while impressive progress has been made in the systems capitalizing on metal catalysts,[12] there are only a handful of metal-free transformations between amines and diazo compounds[13] (Scheme 1b). Pertinent work was done by Davies[14] in 2012, wherein a thermolysis strategy enabled donor/acceptor carbenes to couple with amines. More recently, the groups of Davies[15] and Jurberg[16] demonstrated a blue LED-triggered N–H insertion reaction with amines and carbazoles, respectively. Notwithstanding the fundamental challenges in metal-free carbene insertions, these cases simply operated by N–H insertion and no further derivatization took place, which sharply hampered the formation of highly functionalized, structurally complex nitrogen-containing molecules, such as N-heterocycles. Indeed, these examples could be merely applied to more active, more nucleophilic, donor/acceptor carbenes. Within our recent strong interest in aniline chemistry,[17] herein, we report an unprecedented Brønsted acid-promoted divergent [5 + 1] annulation between 2-arylanilines and acceptor/acceptor diazo carbenes in the absence of transition-metal catalysts (Scheme 1c), which fully differs from the precedent reaction versions between 2-arylanilines and diazo compounds mediated by metal catalysts (Scheme 1d). This newly established methodology performs a highly selective C–C bond cleavage with diazo compounds in a divergent, substrate-controlled mode, thus rapidly building two types of prevalent phenanthridine cores that are persistent in natural products

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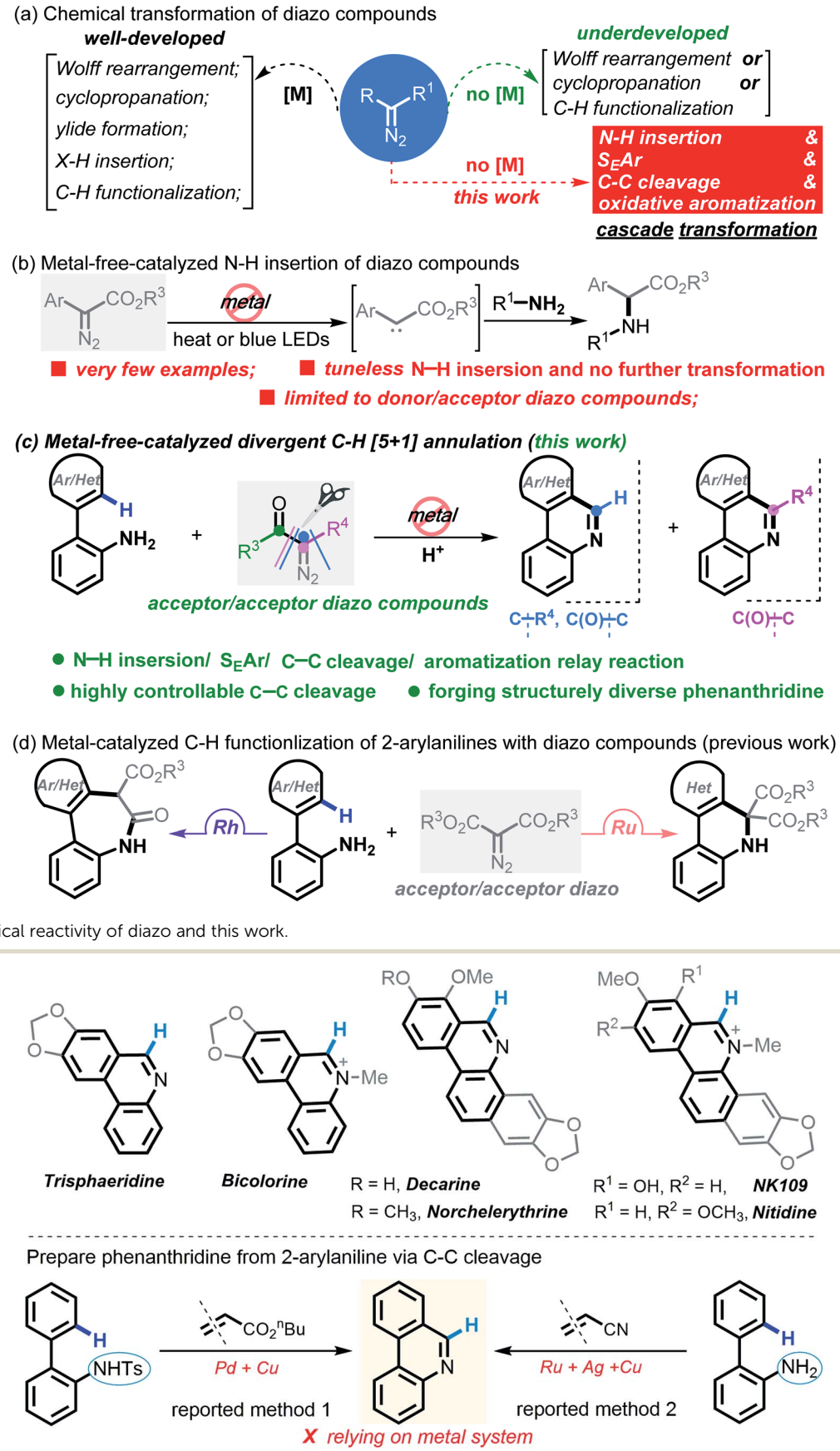
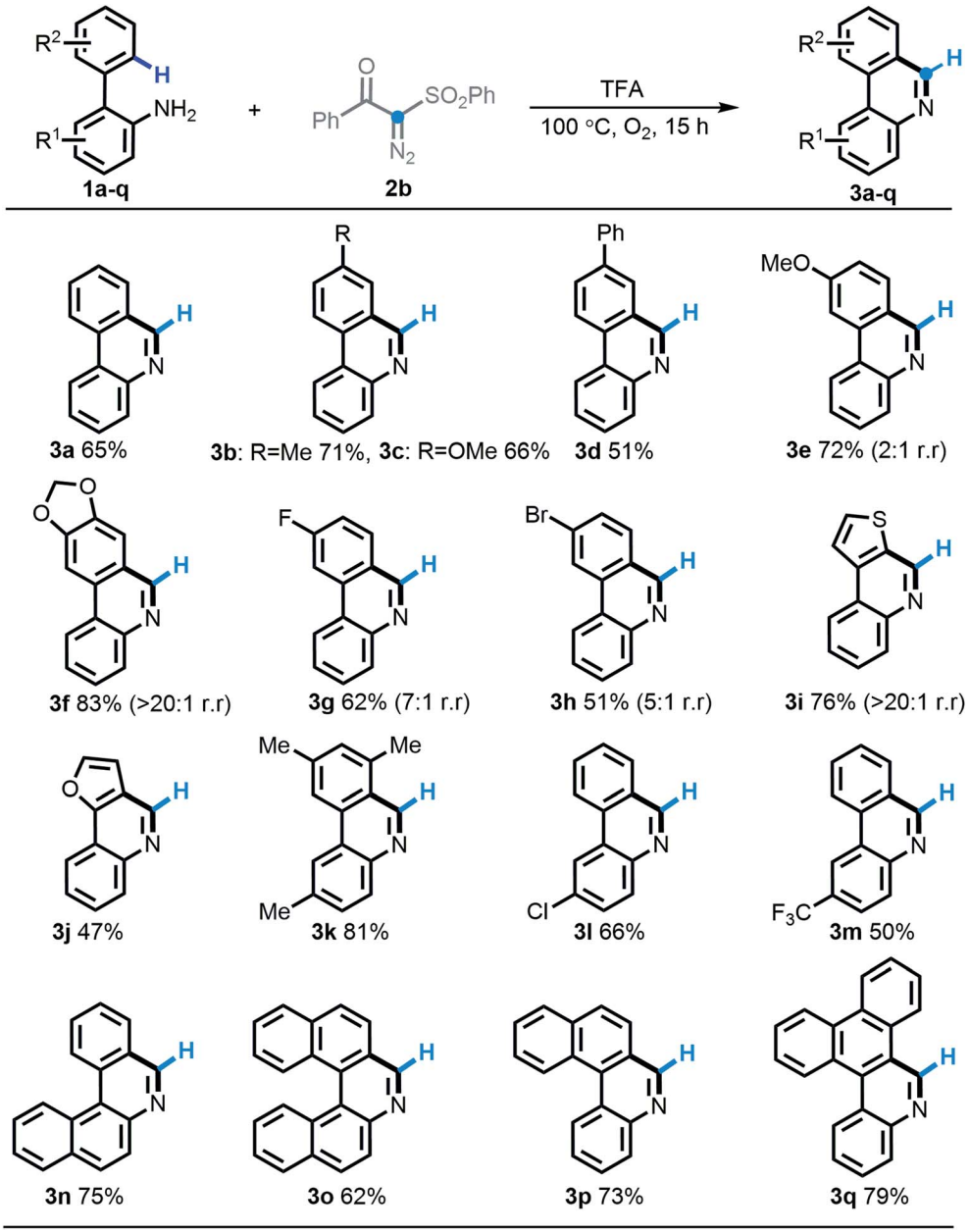


Scheme 1 Chemical reactivity of diazo and this work.

Scheme 2 Biologically active phenanthridine derivatives and existing synthetic methods.

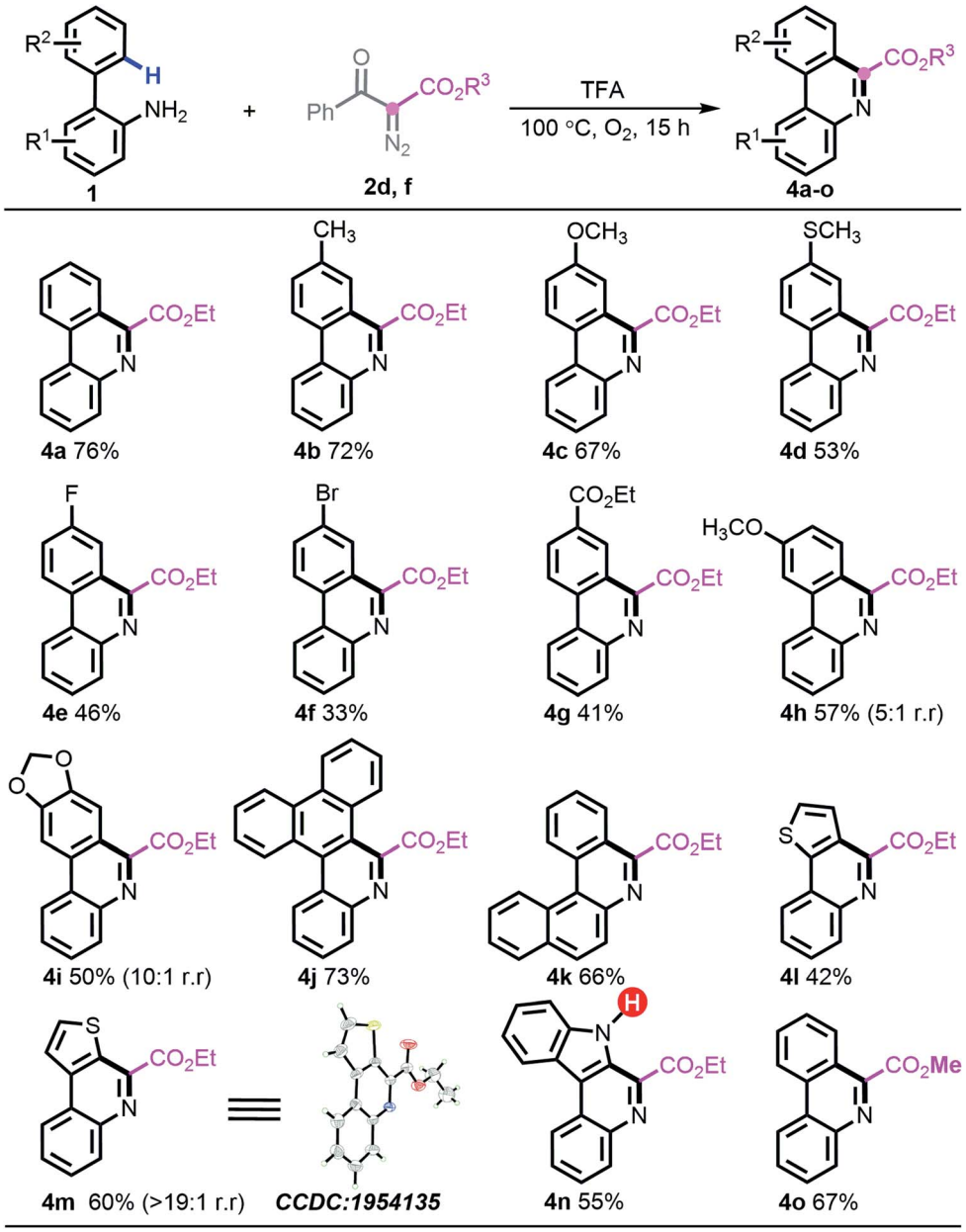


Scheme 3 Substrate scope of [5 + 1] annulation.

and functional materials,[18] but their *de novo* synthesis often requires intricate metal-catalyzed or light-promoted systems[19] (Scheme 2).

Results and discussion

At the outset, we executed this study by reacting 2-phenylaniline **1a** with diazo compound **2a** (Table 1). After investigating several reaction parameters, the desired phenanthridine **3a** was obtained in 50% isolated yield in trifluoroacetic acid (TFA) at 100 °C under O_2 for 15 h (entry 1). Experimental results showed that employing TFA as the reaction solvent was vital, and other common solvents such as DMF, THF, HFIP, toluene, dioxane, and acetic acid were all absolutely futile, wherein only a certain amount of Wolff rearrangement product **6** was formed (entries 2–7). A decreased yield occurred when the reaction proceeded under air atmosphere; especially a nonaerobic system just resulted in 13% yield of **3a** (entries 8–9), which undoubtedly clarified the significance of an aerobic environment. Changing the reaction temperature to either lower or higher levels diminished the efficiency (entries 10–11). When we turned our attention to phenyl-substituted substrate **2b**, gratifyingly, the efficacy of the title transformation improved and yielded the target **3a** in 65% yield (entry 12). Motivated by the above structure–activity relationship, we investigated the ester-modified diazo compound **2c** in an attempt to further the optimization; unexpectedly, this procedure delivered exclusively

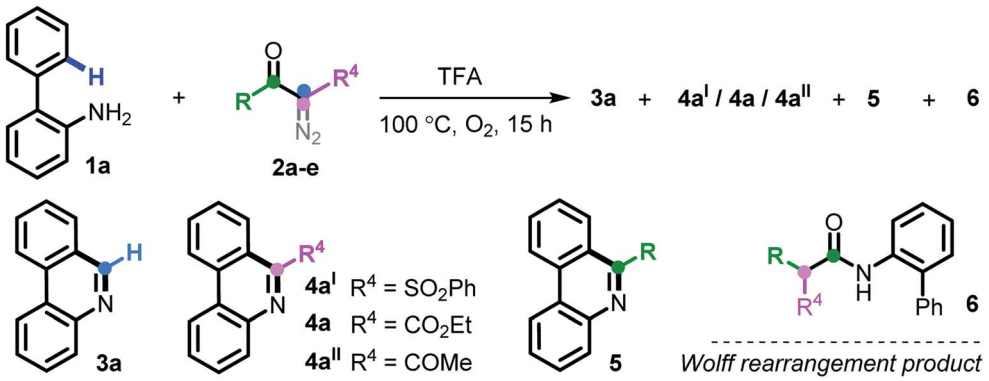


Scheme 4 Substrate scope of deacylative [5 + 1] annulation.

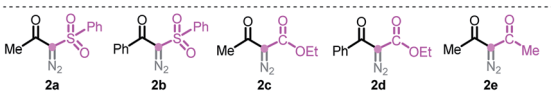
another type of phenanthridine **4a** in 37% yield (entry 13). In this method, phenyl-ester diazo compound **2d** also behaved more efficiently and led to 76% yield (entry 14). Interestingly, persistency with diketo-derived diazo compound **2e** failed to generate the corresponding **3a** and **4a**$^{\mathrm{II}}$; however, the third chemoselective product **5** was furnished in 18% yield (entry 15). Apparently, this divergent outcome hinges upon the exact structure of the diazo precursor to construct structurally distinct phenanthridines.

Having identified the optimal reaction conditions, we firstly strived to test the substrate scope of this acid-induced [5 + 1] annulation reaction by choosing benzoyl-phenylsulfonyl diazo compound **2b** as a synthetic partner. Overall, an extensive range of 2-arylanilines (**1a–1q**) participated in this predicted transformation quite well, furnishing the homologous phenanthridine products **3a–3q** in 51–83% yields. With respect to either an *ortho*-arene system or an aniline segment, the substituted functionalities with different electronic groups including methyl (**3b**, **3k**), methoxy (**3c**, **3e**), phenyl (**3d**), methylenedioxy (**3f**), fluoro (**3g**), bromo (**3h**), chloro (**3l**), and trifluoromethyl (**3m**) were all compatible to undergo this protocol efficiently. As expected, the electron-deficient substrates behaved slightly less expediently. Gratifyingly, heterocyclic substrates such as thienyl (**2i**) and furyl (**2j**) were also efficient in this [5 + 1] annulation procedure. Notably, 2-arylanilines **2f–2i**, possessing two potential C–H cyclization sites, preferentially operated at the least sterically congested position with excellent regioselectivity, except for the less selective performance with

Table 1 Optimization of reaction conditions



Entry	Variation from the assigned conditions	Yield[b] (%) 3a	4	5	6
1[a]	None	50	**4a**^{I}/n.d	n.d	n.d
2	DMF + TFA(10.0 equiv.)	n.d	**4a**^{I}/n.d	n.d	14
3	THF + TFA(10.0 equiv.)	n.d	**4a**^{I}/n.d	n.d	33
4	HFIP + TFA(10.0 equiv.)	5	**4a**^{I}/n.d	n.d	6
5	Toluene + TFA(10.0 equiv.)	5	**4a**^{I}/n.d	n.d	35
6	Dioxane + TFA(10.0 equiv.)	n.d	**4a**^{I}/n.d	n.d	46
7	AcOH + TFA(10.0 equiv.)	n.d	**4a**^{I}/n.d	n.d	20
8	Air instead of O_2	43	**4a**^{I}/n.d	n.d	n.d
9	N_2 instead of O_2	13	**4a**^{I}/n.d	n.d	n.d
10	80 °C instead of 100 °C	33	**4a**^{I}/n.d	n.d	n.d
11	120 °C instead of 100 °C	26	**4a**^{I}/n.d	n.d	n.d
12	**2b** instead of **2a**	65	**4a**^{I}/n.d	n.d	n.d
13	**2c** instead of **2a**	n.d	**4a**/37	n.d	n.d
14	**2d** instead of **2a**	4	**4a**/76	n.d	n.d
15	**2e** instead of **2a**	n.d	**4a**^{II}/n.d	18	n.d

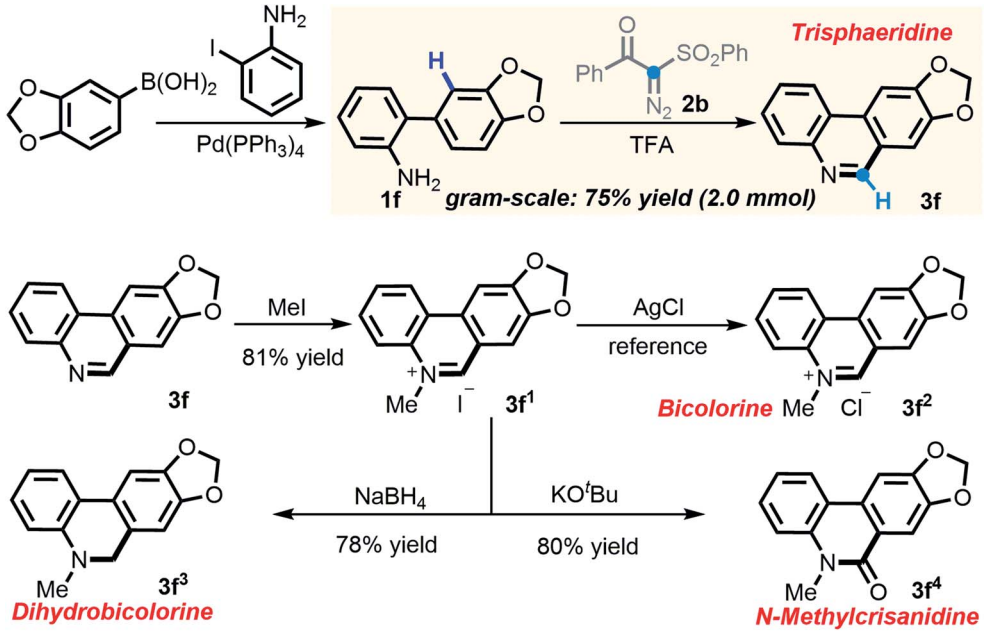


[a] Assigned conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), TFA (1.6 mL), 100 °C, 15 h, and O_2 atmosphere. [b] Isolated yields (n.d: not detected).

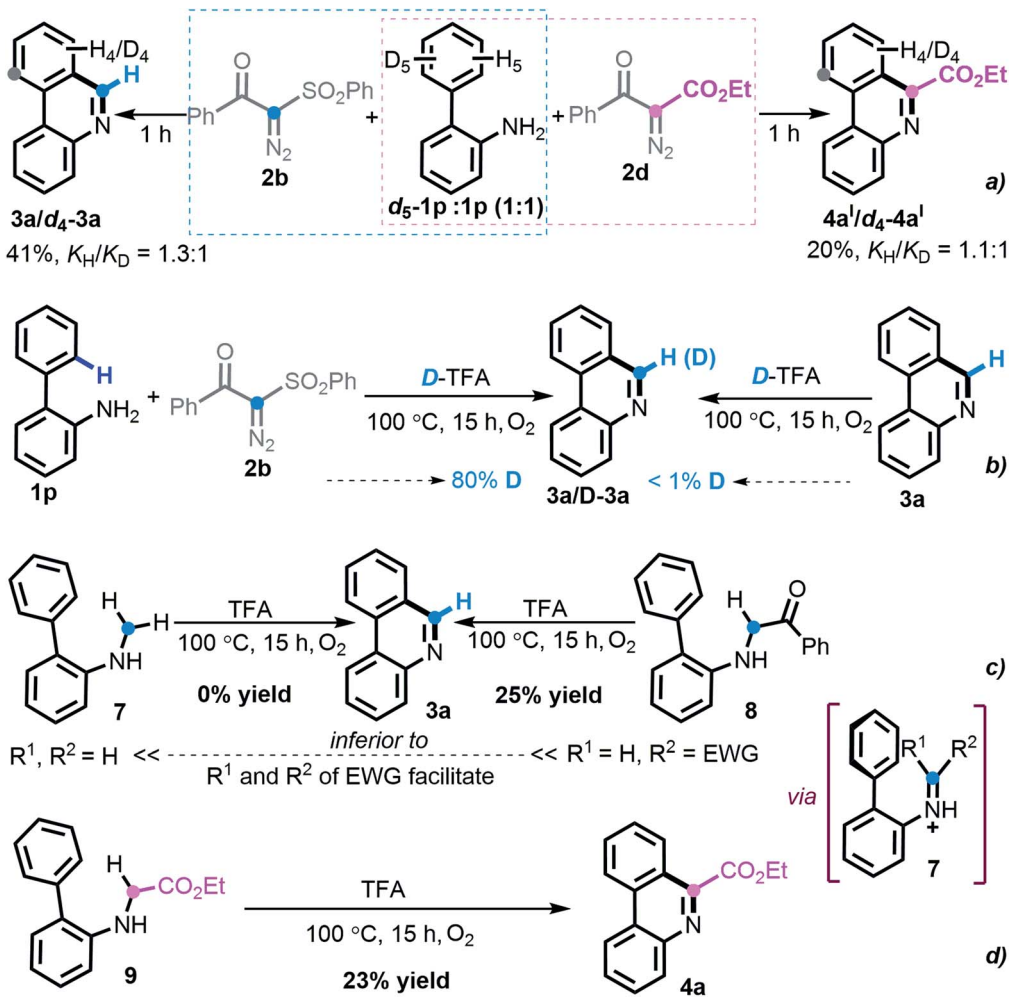
substrate **2e**. More strikingly, the very useful π-extended phenanthridines widely found in functional materials, such as tetracycles (**3n**, **3p**) and pentacycles (**3o**, **3q**), were also efficiently obtained according to this highly selective [5 + 1] annulation in good yields.

Considering the distinct chemoselective behaviour with ester-derived diazo compound **2d** (entry 14, Table 1), building highly functionalized 6-phenanthridines, we attempted to assess the generality of the deacylative [5 + 1] annulation process. Under the identified reaction conditions, reacting diazo **2d** or **2f** with a series of 2-arylanilines generated 6-carboalkoxy-phenanthridines (**4a–o**) in generally good yields. Notably, all the vacant carbons around the *ortho*-phenyl ring were applicable to introduce either electron-donating groups (**4b–d** and **4h–i**), electron-withdrawing groups (**4e–4g**), or sterically encumbered phenanthrene scaffold (**4j**). The naphthylamine substrate **1n** was amenable to this programed synthesis smoothly as well. Similar to the preceding desulfonylative/deacylative [5 + 1] annulation, this deacylative protocol generally showed slightly inferior results with electron-deficient substrates, although it is worth nothing that the appendage of bromo (**4f**) and ester (**4g**) groups could be valuable in downstream chemical transformations. Heterocyclic substrates **1v** and **1i** also allowed forming the corresponding products with excellent regioselectivity (>20 : 1). Meanwhile, the structure of **4m** was unambiguously assigned by X-ray crystallographic analysis. It is noteworthy that the unprotected indole substrate **1w** remained intact to produce the anticipated phenanthridine **4n** in 55% yield. Further experimental results also showed that introducing other ester-carrying diazo compounds, such as **2f**, was well supported, giving rise to the expected product **4o** in 67% yield (Scheme 4).

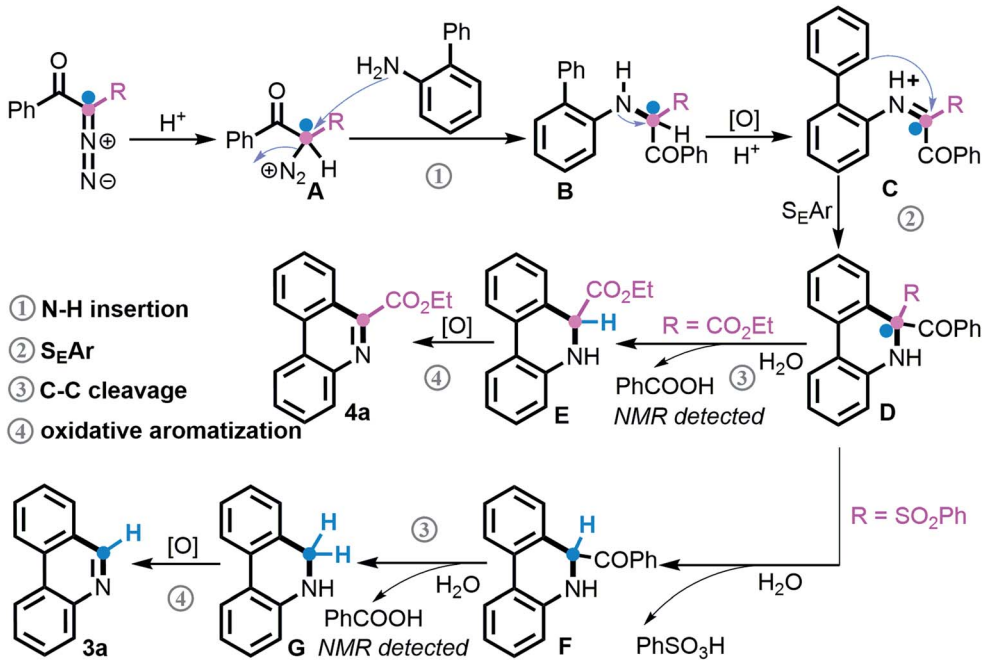
In consideration of the capacity of this newly established method to rapidly assemble phenanthridines, we embarked on building trisphaeridine and other value-added derivatives constituting the core components of Amaryllidaceae alkaloids.[20]



Scheme 5 Synthetic application of established [5 + 1] annulation.



Scheme 6 Mechanistic studies. (a) Kinetic isotope effect experiments. (b) Deuterium-labeling experiments. (c) Investigating intermediate toward phenanthridine **3a**. (d) Investigating intermediate toward phenanthridine **3a**.



Scheme 7 Proposed reaction pathway.

Much to our delight, 2-arylaniline **1f**, which was derived directly from commercially available reagents *via* Suzuki coupling, strongly performed in the scaled-up transformation, yielding trisphaeridine molecule **3f** in 75% isolated yield on a gram scale. More importantly, *N*-methylation of **3f** produced phenanthridine salt **3f**[1] and the subsequent anion exchange gave rise to bicolorine **3f**[2], a natural product which was isolated from *Narcissus bicolor* and shows promising anticancer activity. Additionally, after reduction and carbonyl derivatization, two other alkaloids, dihydrobicolorine **3f**[3] and *N*-methylcrisanidine **3f**[4], were also prepared in good yields (Scheme 5).

To investigate the reaction pathway, a set of preliminary experiments was conducted. As shown in Scheme 6, the values (K_H/K_D = 1.3 : 1 and 1.1 : 1) of kinetic isotope effects implied that S_EAr was not involved in the rate-determining step during this divergent [5 + 1] annulation process (Scheme 6a). Upon treatment with deuterated TFA, the experimental outcome suggested that the hydrogen from TFA participated in the product formation (Scheme 6b). With respect to the formation of phenanthridine **3a**, the hypothetical electronically neutral secondary amine intermediate **7** was synthesized but failed to execute the envisioned cyclization. In contrast, the electron-deficient amine **8** delivered the product **3a**, albeit in a lower yield of 25% (Scheme 6c), which revealed that an imine species might be engaged in the titular transformation and that the more electron-withdrawing substrate nature favors the reaction. Indeed, the prepared secondary ester-carrying amine **9** also led to the construction of phenanthridine **4a** in 23% yield (Scheme 6d). Although our persistent attempts to synthesize other potential intermediates were frustrated, the above-outlined set of uniform experimental results indicated that an imine intermediate containing electron-deficient both R^1 and R^2 might enable this [5 + 1] protocol smoothly.

According to our mechanistic findings and literature precedents,[21] the tentative reaction pathway for assembling the two classes of phenanthridines by divergent [5 + 1] annulation is proposed (Scheme 7). Under acidic conditions, the protonation of a diazo compound initially takes place to deliver species **A**, followed by N_2 extrusion[21a–c] to produce secondary amine **B** *via* nucleophilic attack of NH_2. This key intermediate as verified undergoes oxidation and subsequently performs the S_EAr process, which is supported by the superior result of electron-rich 2-arylanilines in Schemes 3 and 4, to generate C–H functionalization product **D**. At this point, when the R unit consists of an ester group, selective C–C bond cleavage occurs *via* deacylation of the more electrophilic acyl group[21d,e] and concomitant release of benzoic acid that was identified by NMR spectroscopy, followed by oxidative aromatization[21f,g] to give product **4a**. Comparatively, adjusting R to a more active SO_2Ph group promotes a successive de-sulfonylation/de-acylation/oxidative aromatization to finally furnish phenanthridine **3a**.

Conclusions

In conclusion, we have demonstrated a substrate-controlled selective [5 + 1] annulation reaction of 2-arylanilines with diazo compounds by a tandem N–H insertion/S_EAr/C–C cleavage/aromatization under metal-free conditions. Using sulfonyl-derived diazo compounds as the coupling partners, substituent-free phenanthridines are prepared by a dual desulfonylation and deacylation process. Alternatively, introducing ester-derived diazo compounds into the system

divergently leads to the exclusive assembly of C6-carboalkoxy-substituted phenanthridines. Remarkably, the methodology has also been applied to a concise assembly of biologically active trisphaeridine and bicolorine Amaryllidaceae alkaloids as well as their derivatives. This study to the best of our knowledge represents the first example of Brønsted acid-promoted metal-free N–H insertion/multifold bond reorganization of diazo compounds. Metal-free domino transformations of diazo compounds will greatly expand the synthesis of omnipresent synthetic motifs.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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