ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2024, **60**, 8904

Received 7th May 2024,
Accepted 18th July 2024

DOI: 10.1039/d4cc02215g

rsc.li/chemcomm

A diastereoselective strategy for dihydrophenanthrene-fused spirooxindoles *via* [1,2]-phospha-Brook rearrangement†

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A highly diastereoselective, one-pot strategy for spirooxindoles bearing dihydrophenanthrenes from readily available isatins and *p*-quinone methides (*p*-QMs) has been disclosed. Here, a sequential umpolung process *via* [1,2]-phospha-Brook rearrangement followed by Lewis acid-mediated intramolecular cyclization was employed to furnish the desired spiro product. This protocol provides access to potential medicinally relevant varieties of spirooxindolyl dihydrophenanthrenes in good to excellent yields and diastereoselectivity (>20 : 1).

Integration of one carbocyclic ring with another ring can lead to different scaffolds based on their joining patterns such as fused, bridged bicyclic, and spirocyclic. Spirooxindoles are a unique class of spirocyclic compounds bearing a joining point at the C-3 position of the oxindole core.[1] These privileged heterocyclic molecular motifs represent central cores in natural products[2] and bioactive compounds[3] capable of showing anti-tumor,[4] antimalarial,[5] and anticancer activities[6] (Scheme 1(i)). In the past few decades, several elegant strategies have been developed for stereoselective access of different types of spirooxindoles bearing three-, four-, five- and six-membered unified rings.[7] Despite significant advancement in the area of stereoselective synthesis of spirooxindoles, modular and selective approaches for dihydrophenanthrene-fused spirooxindoles are less explored. In 2016, Lautens and Garcia-Lopez independently disclosed two protocols for dihydrophenanthrene-fused spirooxindoles from acrylamides and benzyne precursors using palladium catalysis (Scheme 1(iii)(a) and (iii)(b)).[8] Later, Yang *et al.* also demonstrated a route to access dihydrophenanthrene-fused spirooxindoles *via* multicomponent coupling of acrylamide and iodobenzene (Scheme 1(iii)(c)).[9] Although these reports showcased interesting reaction pathways involving domino Heck-type coupling and intramolecular C–H activation,[10] several drawbacks such as high catalyst loading, multi-step synthesis of acrylamide, and harsh reaction conditions limit its practical utility. Apart from these three reports with a Pd-based catalytic system, there are no reports on unifying carbocyclic rings and heterocycles to achieve dihydrophenanthrene-fused spirooxindoles.

One strategy (Scheme 1(iv)) for achieving spirooxindole cores can be from commercially available isatin and easily accessible *p*-QMs[11] *via* recently developed unusual [1,2]-phospha-Brook rearrangement guided synthesis.[12] In this, it is envisioned that the metal-free synthetic method using isatin and *p*-QMs would involve two subsequent stepwise rearrangements to deliver the intended outcome (Scheme 1). Based on the literature, mechanistically, it can be proposed that at first $P(NMe_2)_3$-mediated [1,2]-phospha-Brook rearrangement of isatin with *p*-QMs would give the dispirocyclopropane intermediate, which on Lewis acid-mediated selective spirocyclization through the aza-xylylene intermediate would generate the desired product. However, in this strategy, several other possibilities exist making the reaction challenging. For instance, an inefficient ring opening of the cyclopropyl intermediate can lead to other undesired products. In addition, the cyclopropane-adduct can transform into various intermediates *via* either biaryl cyclization on the proximal cyclopropyl position leading to substituted fluorene or indoyl aryl ring C–C bond migration leading to a disubstituted quinone methide (Scheme 3). Herein, we describe a highly diastereoselective, one-pot strategy for synthesis of spirooxindoles from readily available isatins and *p*-quinone methides (*p*-QMs).

We commenced our optimization studies using isatin (**1a**) and 2-phenyl-*p*-QMs (**2a**) as model substrates and keeping in consideration the route to conversion and the formation of the possible intermediates. After a brief reaction condition screening, it was observed that using conditions mediated by $P(NMe_2)_3$ at −78 °C to room temperature yielded the dispirocyclopropane adduct **5a** *in situ* (confirmed by NMR and HRMS), followed by $BF_3{\cdot}Et_2O$ (2 eq.) mediated spirocyclization, furnishing the desired product **3a** in 84% yield (Table 1, entry 1). A controlled experiment without $P(NMe_2)_3$ resulted in a lack of intended product formation and the presence of the dispirocyclopropane intermediate (Table 1, entry 2). Additionally, in the absence of $BF_3{\cdot}Et_2O$ while the dispirocyclopropane adduct was recovered, the spiro product was not observed (Table 1, entry 3).

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† Electronic supplementary information (ESI) available. CCDC 2322903. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4cc02215g

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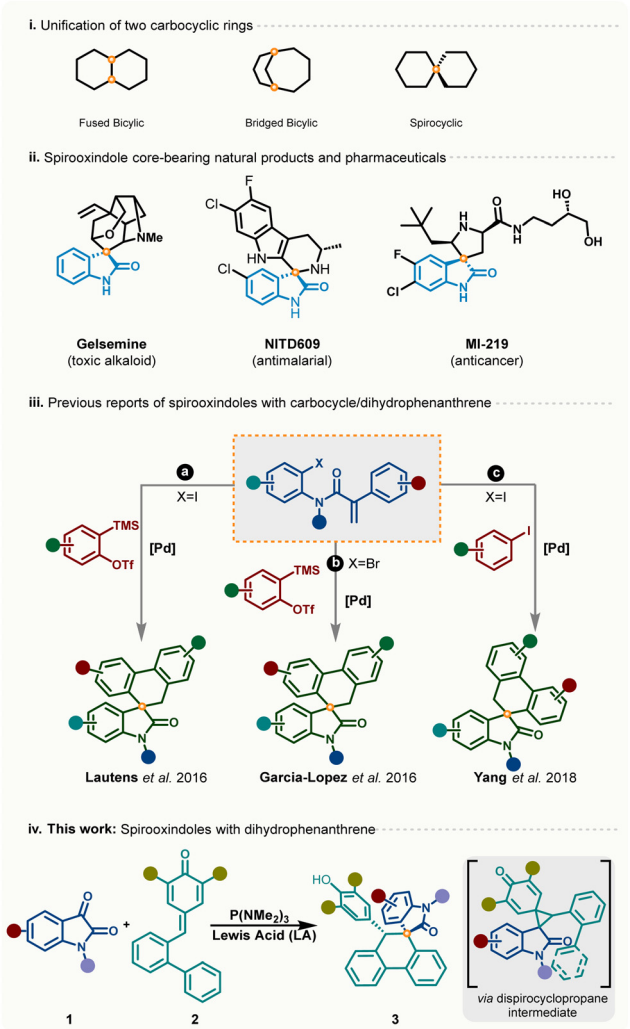


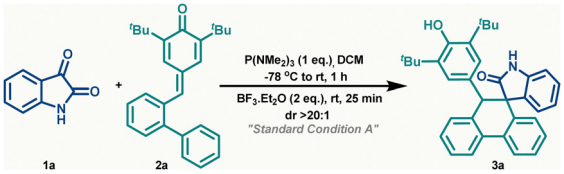
Scheme 1 (i) Unification of carbocyclic rings; (ii) representative examples of bioactive molecules containing the spirooxindole core; (iii) recent reports on spirooxindoles with carbocycle/dihydrophenanthrene; (iv) this work.

These two control experiments indicate that both $P(NMe_2)_3$ and $BF_3{\cdot}Et_2O$ are essential for the transformation.

The use of 0.2 eq. of $In(OTf)_3$ as a Lewis acid afforded **3a** in 25% yield, whereas increasing the loading of $In(OTf)_3$ showed enhanced reactivity, furnishing **3a** in 33% yield (Table 1, entries 4 and 5). Further optimization with an uneconomical high loading of metal triflate was avoided and other Lewis acids were tested. Subsequently, lowering in the equivalents of $BF_3{\cdot}Et_2O$ decelerated the reactivity drastically and hampered the product yield (Table 1, entries 6, 7 and 8). In addition to the Lewis acid, the desired reaction took place in the presence of 1 eq. of trifluoroacetic acid albeit in 42% yield after 24 h. An attempt to use PPh_3 and $P(OEt)_3$ in place of $P(NMe_2)_3$ did not provide **3a** as the cyclopropanation adduct was not formed (Table 1, entry 10).

With the optimized conditions in hand, the reactivity of various substituted isatins was examined to check the viability of the reaction conditions. Isatin bearing electron-donating methyl and methoxy groups at the 5-position afforded the corresponding spirooxindoles **3b** and **3c** in 87% and 89% yields

Table 1 Optimization of reaction conditions



Entry	Deviation from standard condition A	Yield (%)[a]
1	None	84
2	Without $P(NMe_2)_3$	n.d.
3	Without $BF_3{\cdot}Et_2O$	n.d.
4	$In(OTf)_3$ (0.2 eq.) instead of $BF_3{\cdot}Et_2O$	25
5	$In(OTf)_3$ (0.3 eq.) instead of $BF_3{\cdot}Et_2O$	33
6	$BF_3{\cdot}Et_2O$ (0.2 eq.) instead of 2 eq.	28
7	$BF_3{\cdot}Et_2O$ (0.2 eq.) instead of 2 eq.	47
8	$BF_3{\cdot}Et_2O$ (0.2 eq.) instead of 2 eq.	60
9	TFA (1.0 eq.) instead of 2 eq.	42
10	$P(OEt)_3$, PPh_3 instead of $P(NMe_2)_3$	n.d.

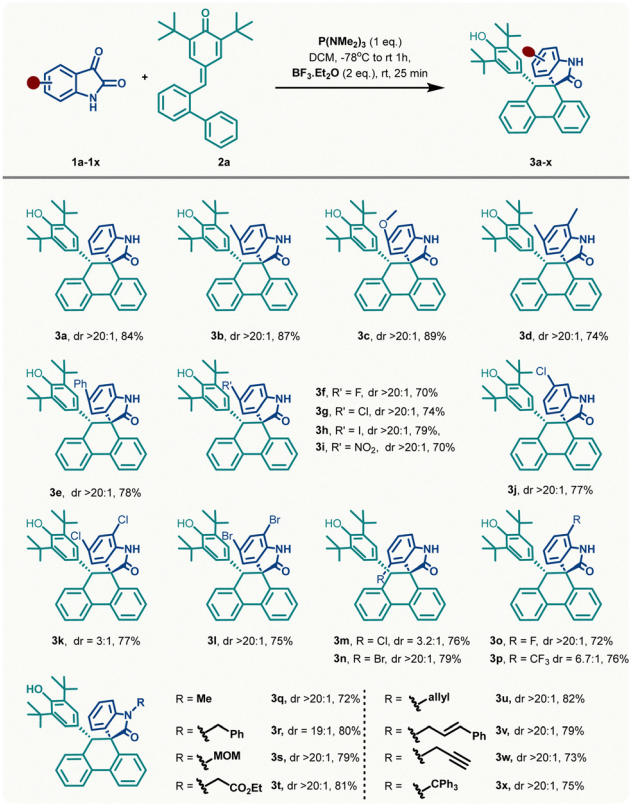
All reactions were performed under an argon atmosphere, **1a** (0.1 mmol) and **2a** (0.11 mmol) were dissolved in solvent (1 mL) and cooled to −78 °C followed by the addition of $P(NMe_2)_3$ (0.1 mmol), and then a Lewis acid was added at rt. Diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [a] Isolated yield.

with excellent diastereoselectivity (Table 2). Similarly, isatin having 5,7-di-methyl substitution and 5-phenyl group substitution furnished the intended products **3d** and **3e** in good yields of 74% and 78%, respectively, with excellent stereoselectivities.

Interestingly, the developed reaction conditions tolerate halogen groups such as fluoro, chloro, and iodo at the 5-position of isatin to deliver the desired spirocyclized products **3f–3h** in good yields (70–80%) and selectivity. Moreover, 5-nitro isatin was amenable to the described protocol allowing the formation of spirooxindole **3i** in 70% yield with >20:1 diastereoselectivity. Additionally, 6-chloroisatin, 5,7-dichloroisatin, and 5,7-dibromoisatin also exhibited good reactivity, furnishing the desired products **3j–3l** in 77–75% yields with good selectivity.

Furthermore, when evaluating the reactivity of 4-chloro and 4-bromo isatins under the same reaction conditions, they were found to be good reacting partners providing the desired spiro products **3m** and **3n** in 76% and 79% yields, with moderate diastereoselectivity for **3m** but excellent selectivity for **3n** (Table 2). Similarly, substituting electron-withdrawing groups such as fluoro and trifluoromethyl at the 7-position of isatin also furnished the corresponding spirooxindoles **3o** and **3p** in 72% and 76% yields. Unfortunately, **3p** gave slightly moderate diastereoselectivity values. Next, the generality of the protocol for various *N*-protected isatins and *p*-QMs (Table 2) was examined. For example, methyl-, benzyl-, and MOM-protected isatins smoothly took part in the intended reaction to furnish the corresponding spirooxindoles **3q–3s** in 72–80% yields with high selectivity. Moreover, the ester, allylic, and propargylic groups on the N-atom of the isatin were tolerated by the developed protocol to give spiroproducts **3t–3w** in good yields (71–82%). Bulky groups such as trityl **3x** also worked well under the developed protocol. Additionally, other variations with one nucleophilic site containing 2,4-dimethylaryl and 2-isopropyl gives the desired spiro-adducts **4a** and **4b** in 77% and 69% yields and excellent selectivity, respectively (Table 3).

Table 2 Substrate scopes of substituted isatins

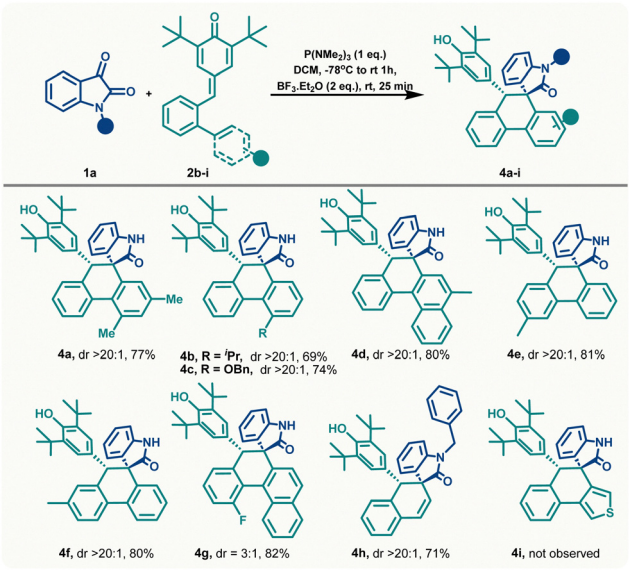


All reactions were performed under an argon atmosphere, **1a** (0.1 mmol) and **2a** (0.11 mmol) were dissolved in DCM (1 mL) and cooled to −78 °C followed by the addition of $P(NMe_2)_3$ (0.1 mmol), and then $BF_3{\cdot}Et_2O$ (0.2 mmol) was added at rt. Diastereomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures. Isolated yields for **3a–x**.

Additionally, substituting the bulkier benzyloxy group at the *ortho*-position of the aryl group of *p*-QM showed good reactivity and selectivity despite having only one nucleophilic centre to afford the adduct **4c** in 74% yield. Variation of other substituents such as *ortho*-naphthyl and 4- and 5-methyl also afforded **4d–4f** with good reactivity and selectivity. Unfortunately, the 5-F variation obtained **4g** with moderate selectivity but with an excellent yield. The reaction also worked well for *o*-vinyl substituted *p*-QMs. Substitution of the internal nucleophile with a vinyl group instead of an aryl group was used to evaluate the suitability of the reaction conditions for generating the corresponding saturated framework. It was observed that, similar to the aryl, the vinyl group was a good reacting partner and afforded the desired product **4h** in 71% yield. Unfortunately, *ortho*-heteroaromatics such as thiophene did not show any reactivity towards the developed protocol **4i**. The structure of the spiroadduct was established by the single crystal X-ray analysis of **4h** (Table 3; CCDC 2322903) (see the ESI†).

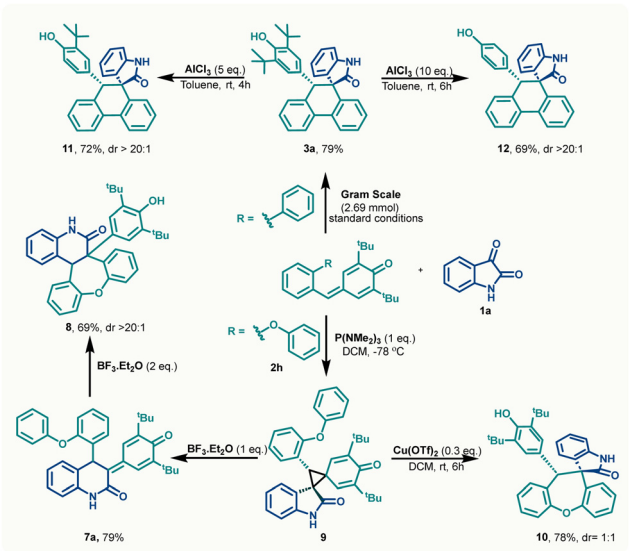
Next, in order to expand the product diversity, a similar strategy was implemented to obtain a seven-membered heterocyclic product by introducing an oxygen atom between the two aryl rings of *p*-QM. A reaction between isatin (**1a**) and *ortho*-phenoxy *p*-QM (**2h**) under standard conditions led to the formation of quinolinone product **7** instead of the desired

Table 3 Substrate scopes of *N*-protected isatins and various *p*-QMs

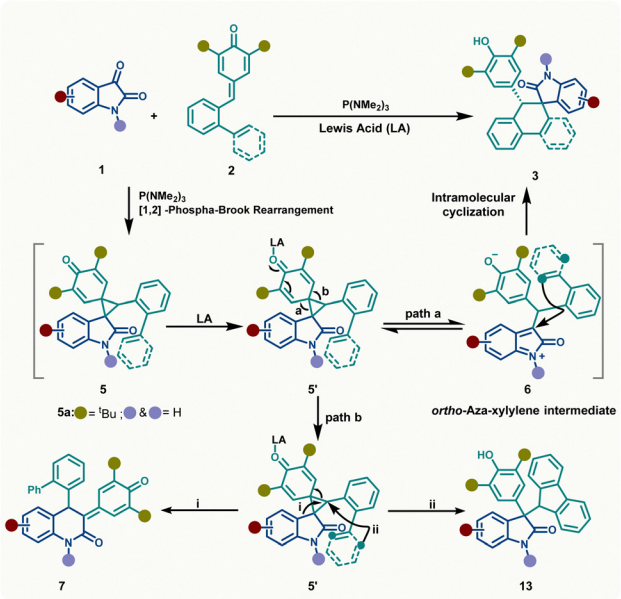


All reactions were performed under an argon atmosphere, **1** (0.1 mmol) and **2** (0.11 mmol) were dissolved in DCM (1 ml) and cooled to −78 °C followed by the addition of $P(NMe_2)_3$ (0.1 mmol), and then $BF_3{\cdot}Et_2O$ (0.2 mmol) was added at rt. Diastereomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures. Isolated yields for **4a–h**.

spirocyclic adduct. Further treatment of $BF_3{\cdot}Et_2O$ (1 eq.) with **7a** resulted in spirocyclic product **8** in 69% yield. When dispirocyclopropane **9** was treated with $Cu(OTf)_2$, formation of spirooxindole-oxepine **10** was observed in 78% yield with 1 : 1 selectivity. Using 5 eq. of $AlCl_3$ in toluene can mono-selectively remove the *tert*-butyl of **3a** to form **11** in 72% yield, whereas increasing the amount of $AlCl_3$ to 10 eq. can deinstall both *tert*-butyl groups to form **12** in 69% yield (Scheme 2). The reaction developed was thus found to be extremely versatile with broad substrate scope and high selectivity.



Scheme 2 Synthetic transformations (for details see the ESI†).



Scheme 3 Possible routes to the spirooxindole adduct transformations.

Supporting the hypothesis of the reaction, it was observed that possible side products relied upon the Lewis acid-mediated selective ring opening of the dicyclopropane **5′**. As discussed earlier, the dicyclopropane intermediate **5′** can transform into different products *via* two competitive pathways (**a** and **b**).

In path **a**, ring-opening leads to the generation of an *ortho*-aza-xylylene intermediate (**6**), which undergoes intramolecular spirocyclization to furnish the intended spirooxindoles (Scheme 3). On the other hand, ring opening of the dispiroadduct intermediate (**5′**) *via* path **b** can further lead to two different possible directions and may result in the formation of 2-quinolinone adducts (**7** *via* route i) and 3,3-disubstituted oxindole cores (**13** *via* route ii). However, during the reactions formation of no undesired products was observed and various control experiments confirmed the preference of path **a** for the developed strategy, which very efficiently resulted in richly substituted spirooxindoles, thus expanding the molecular library with respect to structural complexity.

A direct metal-free protocol has been developed to install the spirooxindole-dihydrophenanthrene scaffolds involving the umpolung process *via* [1,2]-phospha-Brook rearrangement. Here, the sequential addition of phosphine and a Lewis acid was employed to construct the desired scaffold by unifying carbocyclic rings. Broad substrate scopes with substituted oxindoles are demonstrated with good to excellent yields and selectivities. Moreover, synthetic transformations are also carried out to show the utility of the developed reaction.

Generous financial support from SERB-INDIA (CRG/2021/006502 and SERB/SCP/2022/000599) is greatly acknowledged. A. A., H. K. H. and C. B. are grateful to the UGC, CSIR India, and MHRD for the fellowship.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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