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# Temporary Intramolecular Generation of Pyridine Carbenes in Metal-Free Three-Component C–H Bond Functionalisation/Aryl-Transfer Reactions

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**Abstract:** Nucleophilic addition of pyridines to benzyne generates zwitterionic adducts that evolve by a rapid intramolecular proton shift to produce the corresponding pyridine carbenes, *N*-phenyl pyrid-2-ylidenes. In the presence of electrophilic ketones (isatin derivatives), the pyridylidenes can further react by an original bis-arylation reaction of the carbonyl compounds involving a formal pyridine C–H bond functionalisation. The overall transformation is an unprecedented three-component reaction featuring a carbene intermediate. The mechanism of this transformation was examined in detail by using both experimental and theoretical approaches. It was found that the generation of *N*-phenyl pyrid-2-ylidene from pyridine and benzyne is energetically favoured, and that the corresponding carbene dimer can also form easily. Under the three-component reaction conditions, the pyridylidene preferentially adds to the ketone group of the isatin derivative to produce a zwitterionic adduct amenable to an intramolecular aryl transfer reaction by a concerted nucleophilic aromatic substitution. This peculiar reactivity for a carbene was compared to possibly competitive known reactions of stable carbenes with carbonyl compounds, and the reaction was found to be under thermodynamic control. The reported method of generation of *N*-phenyl pyrid-2-ylidenes and their reactivity with carbonyl compounds unlock new perspectives in organic synthesis.

**Keywords:** aromatic substitution · arynes · carbenes · C–H activation · multicomponent reactions

## Introduction

*N*-Heterocyclic carbenes (NHCs), that are essentially diaminocarbenes, are now firmly established as valuable transition-metal ligands with outstanding applications in organometallic chemistry and catalysis, essentially due to their strong σ-donating properties.[1] Since the ground-breaking discovery of their isolation as stable free carbenes,[2] NHCs have also found spectacular applications as organocatalysts.[3] In recent years, the catalogue of available cyclic stable singlet carbenes has been substantially expanded, notably to carbenes stabilised by only one nitrogen atom as in cyclic (amino)(alkyl)carbenes (cAACs).[4] These carbenes feature even stronger σ-donating properties as ligands with extended applications in organometallic chemistry.[5] However, their known applications in organic chemistry are limited to the activation of small molecules (CO, $H_2$, $NH_3$, $P_4$) and the stabilisation of highly reactive intermediates.[6] Pyridylidenes (e.g., **I**, **II**, and **III**) represent an unusual and relatively rare class of monoamino carbenes that can exist as three different regioisomers with the carbenic atom at the 2-, 3- or 4-position (Figure 1). Calculations have shown that the pyrid-2-ylidene **I** is more stable than its isomers **II** and **III** by approximately 15 kcal mol$^{-1}$ (for R = H).[7] Pyridylidenes have not been isolated, and so far, they have only been obtained as transition-metal complexes,[4a,8] their organic chemistry remaining unexplored. Recently, the groups of Cabeza[9] and Segawa-Itami[10] reported a new method for the preparation of pyrid-2-ylidene ruthenium, gold and pal-

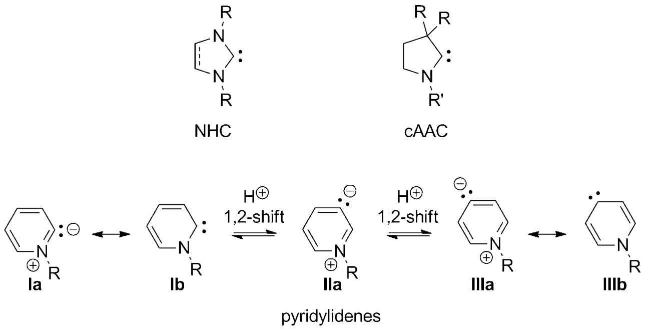

Figure 1. Some nitrogen-stabilised carbenes. General formula for a NHC, cAAC and the three possible regioisomeric pyridylidenes.

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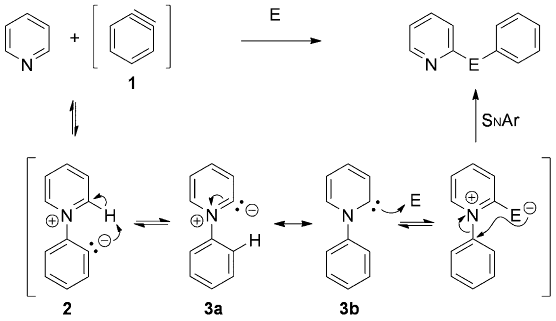
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303359. It contains general experimental information, full characterisation data for all compounds,[18] detailed analyses of HRMS experiments, geometries of all stationary points for the mechanistic theoretical computational study and copies of $^1H$ and $^{13}C$ NMR spectra.

ladium complexes, respectively, by treatment of a N-substituted pyridinium cation with a base in the presence of an electrophilic transition-metal complex.

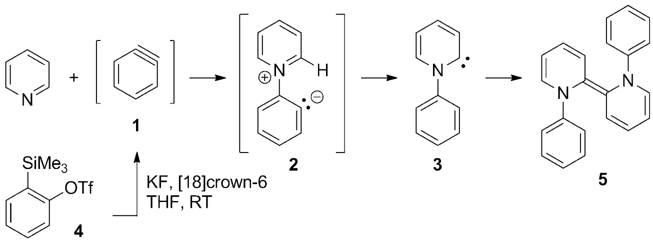
The invention of new reactions and the discovery of unprecedented reactivities are crucial to expand the retrosynthetic tree, and more generally, for progress in synthetic chemistry. At the forefront of modern organic synthesis is the selective and controlled functionalisation of unactivated chemical bonds, such as C−H bonds, under mild conditions. For the work reported here, it was hypothesised that a temporary intramolecular generation of pyrid-2-ylidenes (e.g. **3**, Scheme 1) could result in an original bis-arylation reaction of organic compounds involving a peculiar reactivity of carbenes. This three-component strategy is based on the electrophilic character of arynes[11] (e.g. **1**) that could easily add pyridine to produce the zwitterionic putative adduct **2**. In the absence of any proton source[12] or tethered electrophile,[13] the pyrid-2-ylidene **3** would form by a rapid intramolecular proton shift[14] and add to an external electrophile, operating an aryl transfer in an irreversible thermodynamically favoured $S_NAr$ step.



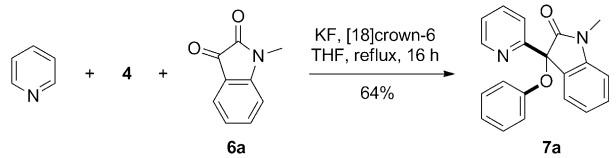
Scheme 1. Proposed bis-arylation strategy via the temporary intramolecular generation of a pyridylidene.

## Results and Discussion

To obtain the first proof of concept, the formation of benzyne (**1**), generated by fluoride-induced elimination of *ortho*-silyl phenyltriflate **4**,[15] in the presence of pyridine, was monitored by HRMS (HRMS, positive-mode electrospray ionisation, Scheme 2). Gratifyingly, we clearly observed a signal corresponding to the pseudo-molecular ions [**2**+H]$^+$ and/or [**3**+H]$^+$ ($C_{11}H_{10}N^+$, theoretical *m*/*z*: 156.0808; found: 156.0805) as well as a signal assigned to [**5**+H]$^+$ ($C_{22}H_{19}N_2{}^+$, theoretical *m*/*z*: 311.1543; found: 311.1543), the protonated form of the expected dimerisation[16] product of pyridylidene **3**. A detailed HRMS/MS analysis of the *m*/*z*: 311.1543 ion (see the Supporting Information, Figure S3, Scheme S3 and discussion therein) further supported this assignment, with a fragmentation pattern fully consistent with the proposed structure for compound **5**. The observation of the dimer **5** strongly supports the temporary formation of the pyrid-2-ylidene **3**, and importantly, indicates that it is somewhat persistent, allowing for the exploration of its reactivity with organic compounds. Theoretical calculations predict that pyridylidenes should be very strong σ-donor ligands in metal complexes, as well as strongly basic and nucleophilic species[7] well-suited for the proposed nucleophilic addition/aryl-transfer sequence. Although aldehydes proved to be unproductive electrophiles leading to complex mixtures of products, this unprecedented reactivity was disclosed by studying the formation of **3** in the presence of non-enolisable and highly electrophilic *N*-methyl isatin (**6a**, Scheme 3). The model three-component reaction involved pyridine, the benzyne precursor **4** and the isatin derivative **6a** in refluxing THF with KF/[18]crown-6, and led to the expected bis-arylation product 3-phenoxy-3-(pyridin-2-yl)indolinone **7a** in 64% isolated yield.[17] The structure of **7a** was deduced from its NMR spectroscopic data and confirmed by X-ray diffraction techniques.[18] The most striking feature in **7a** is the new carbon–carbon bond created between the 2-carbon atom of pyridine and the ketone carbon atom in **6a** by an unprecedented mode of C−H bond functionalisation.[19]



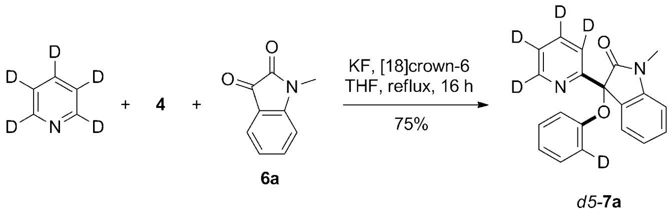
Scheme 2. Reaction of pyridine with benzyne (**1**)[15] leading to *N*-phenylpyrid-2-ylidene (**3**) and its dimerisation product **5**.



Scheme 3. Three-component synthesis of 3-phenoxy-3-(pyridin-2-yl)indolinone (**7a**) via the temporary intramolecular generation of pyridylidene **3**.

So as to gain insights into the involvement of pyridylidene **3** in this reaction, a deuterium-labelled experiment with [$D_5$]pyridine was realised. As proven by $^1$H and $^2$H NMR spectroscopy, the product [$D_5$]-**7a** was obtained in 75% yield with a complete incorporation of a deuterium atom at the *ortho*-position of the phenoxyl group (Scheme 4), which is in perfect agreement with the formation of [$D_5$]-**3** and its reaction as a free nucleophilic carbene in the proposed bis-arylation reaction.

The proposed mechanistic pathway was carefully examined by using computational methods. The identification of all stationary points was first performed by semi-empirical



Scheme 4. Deuterium-labelled experiment with [$D_5$]pyridine.

AM1/RHF methods using the chain algorithm developed by Liotard[20] (AMPAC software, Semichem).[21] The geometries were then refined by using DFT methods and the Gaussian code[22] with the extended base B3LYP 6-311++G** to account for long-range interactions. The combination of semi-empirical and DFT methods was found to be particularly efficient for this study. For all transformations involving important charge effects, DFT calculations were performed using the IEFPCM solvation model for THF.[23] All stationary points were fully optimised and vibrational frequencies were calculated to establish the nature of the stationary points obtained. The results of this computational study provided some strong support for both the formation of the pyridylidene **3** by intramolecular proton shift and its nucleophilic addition to *N*-methyl-isatin (**6a**) to give the intermediate zwitterionic adduct **Za** triggering the final irreversible phenyl transfer with reasonable activation energy barriers for the transition states **TS1**–**TS4** (Figure 2). In particular, these results ruled out the mechanism proposed by Biju and co-workers for the final SNAr step of the reaction; they proposed a sequential mechanism involving a stabilised negatively charged aryl group intermediate,[17] whereas our results indicate that the SNAr step (**Za**→**7a**) actually proceeds through a concerted mechanism via the transition-state **TS4**. In this transition-state structure, the carbon atom undergoing the nucleophilic substitution is tetracoordinated and adopts a $sp^3$-like hybridisation, as shown by bond lengths and angles measurements as well as natural bond orbital (NBO) analyses (Figure 3, see also the Supporting Information). During this concerted process, the hybridisation of the phenyl carbon atom thus evolves as follows: $sp^2$ (in **Za**)→ $sp^3$-like (in **TS4**)→$sp^2$ (in **7a**). This work uncovers a new plausible mechanistic pathway for the nucleophilic aromatic substitution,[24] which we propose to name “concerted nucleophilic aromatic substitution”.

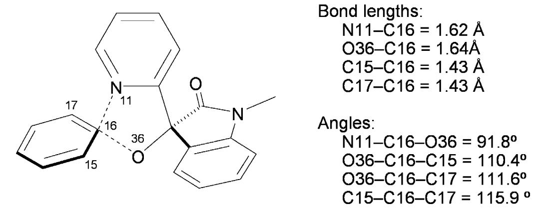


Figure 3. Structure of the transition-state **TS4** obtained by DFT calculations (B3LYP-6-311++G** level of theory); see the Supporting Information for details.

The possibly concurrent formation of the dimeric compound **5** from **3** was examined and found to be irreversible under the reaction conditions with an activation energy of 7.70 kcal mol$^{-1}$ (Figure 4). This result nicely corroborates the previous experimental observation of **5** by HRMS (see above) when the pyridylidene **3** is generated from the reaction of pyridine and benzyne (**1**) in the absence of any other reaction partner. However, when the pyridylidene **3** is similarly generated in the presence of the electrophilic *N*-methyl isatin (**6a**), the formation of **5** is kinetically disfavoured when compared to the formation of **7a**, via **TS3**, **Za** and **TS4**, requiring only 2.01 kcal mol$^{-1}$ of activation energy. In agreement with these theoretical calculations, the HRMS analysis of the reaction mixture leading to **7a** showed, after 15 min at room temperature, an intense signal at *m*/*z*: 317.1282 corresponding to the molecular ion [**7a**+H] ($C_{20}H_{17}N_2O_2^+$, theoretical *m*/*z*: 317.1285) and no detectable amount of the dimer **5**.

The reaction of the carbene **3** with **6a** through the described nucleophilic addition/concerted SNAr sequence uncovers a new generic type of reactivity of carbenes with carbonyl compounds. Some stable carbenes are known to react with aldehydes to give the corresponding epoxide by a nucleophilic addition/nucleophilic addition sequence (formal [2+1] cycloaddition).[25] This reaction pathway was examined for the formation of the epoxide **8a** from the zwitterionic adduct **Za** (Figure 5). It was found that,

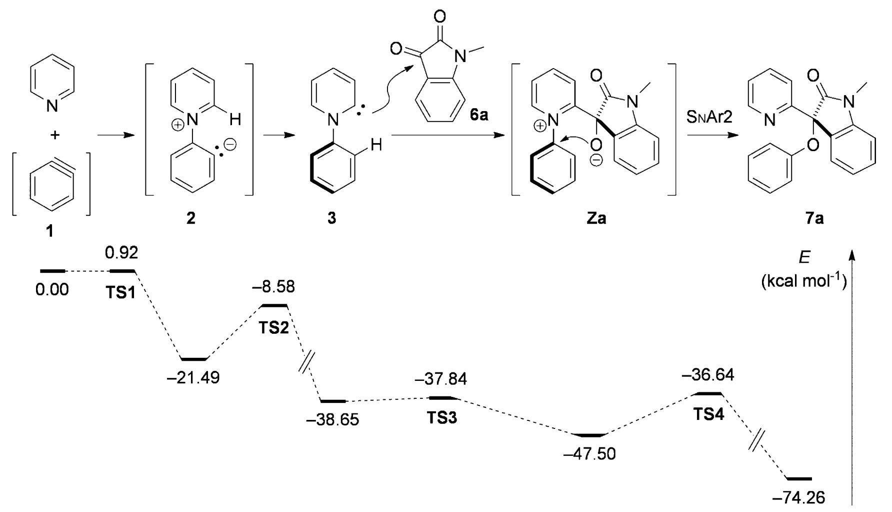


Figure 2. Detailed mechanism and energy profile for the formation of **7a**. The energy profile was obtained by DFT calculations (B3LYP-6-311++G** level of theory); see text and Supporting Information for details.

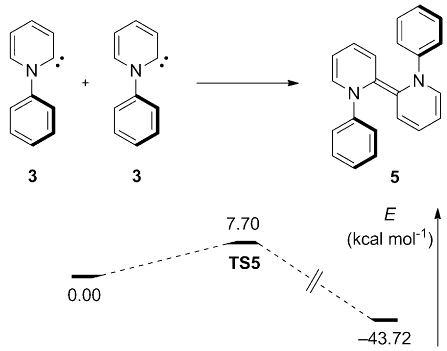


Figure 4. Energy profile for the dimerisation reaction of **3**. The reaction energy profile was obtained for **7a** by DFT calculations (B3LYP-6-311++G** level of theory); see text and Supporting Information for details.

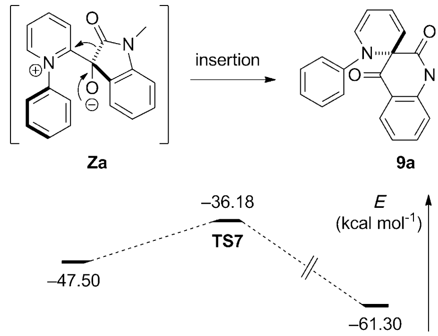


Figure 6. Energy profile for the formation of the insertion product **9a**. The reaction energy profile was obtained for **7a** by DFT calculations (B3LYP-6-311++G** level of theory); see text and Supporting Information for details.

under its most stable conformation, the negatively charged oxygen atom of intermediate **Za** is prone to undergo a reversible nucleophilic addition to the pyridinium ion affording the epoxide product **8a**. Analysis of the calculated energy values have shown that the formation of the epoxide product **8a** was possible and, although largely thermodynamically disfavoured, could kinetically compete with the formation of **7a** (**TS6** leading to the epoxide product **8a** is just 1.0 kcal mol$^{-1}$ higher than **TS4** leading to **7a**). Additionally, this part of the theoretical study pointed out the existence of a nonproductive stabilised conformation of **Za** ($E = -49.41$ kcal mol$^{-1}$ in Figure 5) for the title reaction.

Recently, Bielawski and co-workers revealed that *N,N'*-diamidocarbenes react with 1,2-dicarbonyl compounds to give the corresponding carbene insertion product into the C(O)–C(O) bond.[26] The same reactivity with the pyridylidene **3** and the isatin derivative **6a** would afford the product **9a**, and this pathway was also examined (Figure 6). It was found that the zwitterionic adduct **Za** may reversibly evolve to the product **9a** with an activation energy **TS7** slightly higher than the one of **TS4**. However, the product **9a** was found to be about 13 kcal mol$^{-1}$ less stable than the actually observed thermodynamic product **7a**. Although the epoxide **8a** and the insertion product **9a** have not been isolated, their reversible formation might be at the origin of the relatively long reaction times observed experimentally for the formation of the thermodynamic product **7a**. More generally, the overall thermodynamic control of the reaction suggests that the reactivity of *N*-phenyl pyridylidenes in the described C–H functionalisation/bis-arylation reaction might be generalised.

Remarkably, the product **7a** was overall obtained from an unprecedented three-component reaction[27] featuring a carbene intermediate, resulting in a net C–H functionalisation/bis-arylation sequence. The transformation was further exemplified with a series of isatin derivatives **6b–i**, which afforded the expected indolinones **7b–i** in comparable yields with **7a** (Scheme 5). The introduction of a 4-amino group on pyrid-2-ylidenes was predicted to increase their stabilisation,[7c] and expectedly, 4-(dimethylamino)pyridine reacted with benzyne (**1**) and the isatin derivative **6f**, affording the corresponding product **7j** in 52% yield.[17]

## Conclusion

The results reported here show that free *N*-(phenyl)pyrid-2-ylidenes can be generated from pyridines and benzyne via a pyridine–benyne zwitterionic adduct that evolves by an intramolecular proton shift. These rare carbenes can covalently add to isatin derivatives and rearrange in a unique manner, resulting in an original bis-arylation reaction involving a formal pyridine C–H bond functionalisation. The overall transformation is a three-component reaction featuring a carbene intermediate. The mechanism was examined in detail, including a deuterium labelling experiment and a comprehensive theoretical study, which uncovered a new plausible mechanistic pathway for the nucleophilic aromatic substitution. Under the three-component reaction conditions, the pyridyli-

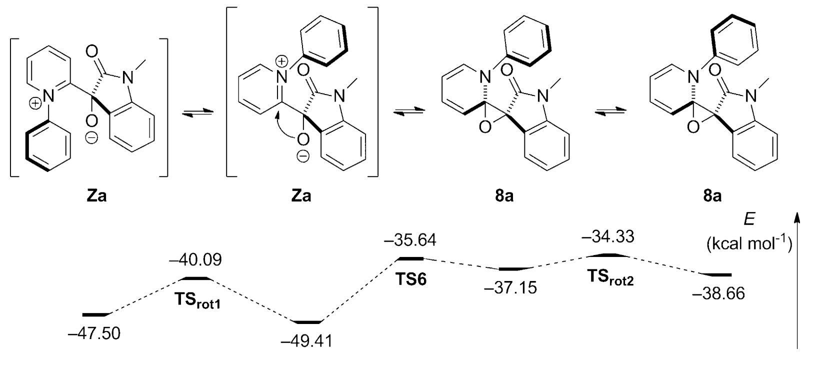
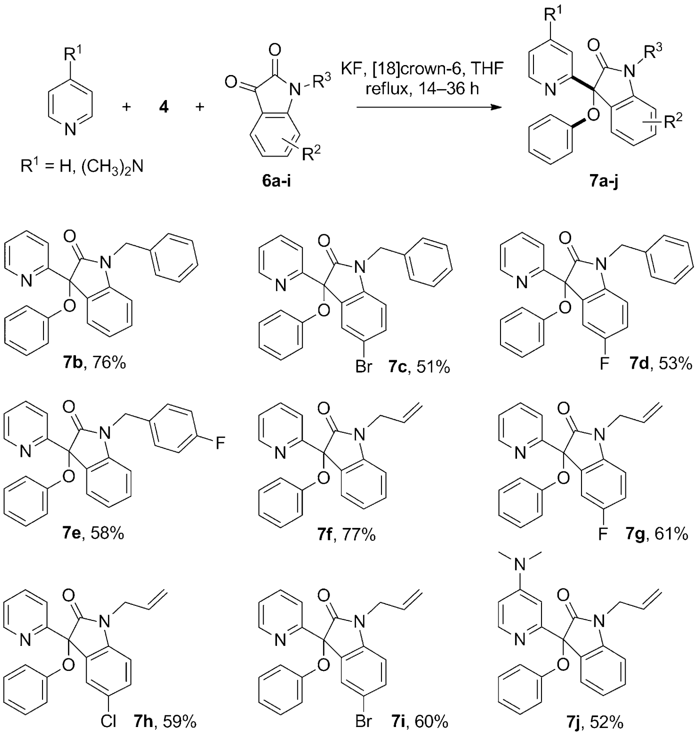


Figure 5. Detailed mechanism and energy profile for the formation of the epoxide **8a**. The energy profile was obtained by DFT calculations (B3LYP-6-311++G** level of theory); see text and Supporting Information for details.



Scheme 5. Generalisation of the three-component route to indolinones **7** via the temporary intramolecular generation of *N*-phenyl-pyrid-2-ylidenes.

dene adds to the ketone group of the isatin derivative to produce a zwitterionic adduct amenable to an intramolecular aryl transfer reaction by concerted nucleophilic aromatic substitution. This new mechanistic perspective for nucleophilic aromatic substitution reactions has been coined “concerted nucleophilic aromatic substitution”, and further studies are ongoing in our laboratory to ascertain this mechanism. The peculiar reactivity of the pyridylidenes reported herein was compared to possibly competitive known reactions of stable carbenes with carbonyl compounds, and the reaction was found to be under thermodynamical control. This work unlocks new research directions on the chemistry of pyridylidenes and related nitrogen-stabilised carbenes, and opens up new perspectives in organic synthesis.

## Experimental Section

**General procedure for the preparation of 7a–j**: A sealable oven-dried tubular reaction vessel equipped with a magnetic stirring bar was charged with the isatin derivative **6** (0.2 mmol), potassium fluoride (0.4 mmol) and [18]crown-6 (0.4 mmol), and subjected to a high vacuum for 30 min. The mixture was then placed under an argon atmosphere, and anhydrous THF (2 mL) was added. To this solution was added pyridine (0.2 mmol), followed by the aryne precursor 2-(trimethylsilyl)phenyl triflate (**4**, 0.4 mmol), and the resulting reaction mixture was stirred magnetically and heated at 70 °C (oil bath) until the starting material **6** was no longer detectable by TLC analysis (ca. 16 h). The reaction mixture was then diluted with ethyl acetate and hydrolyzed with water. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the crude product. Flash chromatography of this material on silica gel afforded the pure product **7**.

*Compound **7a** (representative)*: By following the general procedure, the reaction of *N*-methyl isatin (**6a**, 100 mg, 0.62 mmol), KF (70 mg, 1.20 mmol), [18]crown-6 (317 mg, 1.20 mmol), pyridine (49 μL, 0.61 mmol) and 2-(trimethylsilyl)phenyl triflate (**4**, 291 μL, 1.20 mmol) in THF (6.0 mL) for 16 h afforded the pure product **7a** as a light-beige solid (123 mg, 64 %). $R_f$ (EtOAc/PE: 1:2) = 0.29; M.p. 119 °C (recrystallised from $CH_2Cl_2$/hexane); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 174.1$ (C), 158.9 (C), 155.1 (C), 149.2 (CH), 144.4 (C), 137.0 (CH), 130.2 (CH), 129.1 (CH), 128.6 (C), 125.4 (CH), 123.6 (CH), 123.1 (CH), 123.0 (CH), 121.0 (CH), 120.7 (CH), 108.8 (CH), 86.1 (C), 26.5 ppm ($CH_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 8.46$ (ddd, $J = 4.8$, 1.7, 0.8 Hz, 1 H), 8.14 (ddd, $J =$ 8.0, 1.1, 0.8 Hz, 1 H), 7.82 (ddd, $J = 8.0$, 8.0, 1.7 Hz, 1 H), 7.30 (ddd, $J =$ 7.8, 7.8, 1.3 Hz, 1 H), 7.23–7.18 (m, 2 H), 7.14–7.08 (m, 2 H), 7.01 (ddd, $J = 7.8$, 7.8, 0.8 Hz, 1 H), 6.95 (tt, $J = 7.2$, 1.4, 1 H), 6.88–6.82 (m, 3 H), 3.24 ppm (s, 3 H); HRMS (ESI+): *m*/*z*: calcd for $C_{20}H_{17}N_2O_2^+$: 317.1285 $[M+H]^+$; found: 317.1283; recrystallisation of **7a** from $CH_2Cl_2$/hexane afforded crystalline colourless prisms suitable for X-ray diffraction analysis.[18]

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