Proton Transfer Can Govern Regioselectivity Assisted by Iron Catalysis

HIGHLIGHTS
Highly ortho-selective halogenations of anilines and carbazoles
Lewis acids being able to accelerate EAS reactions
Proton shift found to be crucial for the regioselectivity
Practical iron sulfonate catalysis being scaled up to 100 g

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Proton Transfer Can Govern Regioselectivity Assisted by Iron Catalysis

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SUMMARY
Ortho-selective aromatic C-H functionalization is frequently used in organic synthesis and chemical/pharmaceutical industries. However, this reaction relies heavily on the use of directing groups suffering from limited substrate scope and extra steps to put on and remove the directing/protecting groups. Herein we present the previously neglected concept that enables good to nearly complete selective ortho position. Proton transfer was utilized to tune the electron density on the aryl ring and determine the positional selectivity of electrophilic substitution. Consistently with deuteration experiments and DFT studies, this work demonstrates that acid-promoted proton transfer directs accelerated ortho-selective halogenation of NH/OH contained aromatic amines/phenols with excellent selectivity (>40 examples; up to 98:2 ortho/para selectivity). The application potential of this Fe-catalyzed method is demonstrated by the convenient synthesis of three alkaloids and tizanidine. This report raises the possibility that proton transfer could serve as the basis of developing new selective C-H functionalization reactions.

INTRODUCTION
Undoubtedly, chemical structure determines reactivity. In addition, understanding how to activate substrate molecules benignly is fundamental in bioorganic chemistry, organic chemistry, and catalysis (Rudroff et al., 2018; Roduner, 2014; Bauer and Knölker, 2015). Electrophilic aromatic substitution reaction (S_EAr) is perhaps the most widely used reaction for aromatic C-H functionalization but often suffers from the production of mixture of positional isomers (Figure 1A) (Taylor, 1990). With catalysts and the directing group (DG), functionalization reactions.

Herein, we describe the use of proton transfer assisted by iron(III) sulfonates under heating conditions as the general and convenient approach to ortho-halogenation of aromatic amines and phenols. Proton transfer occurs ubiquitously as the basic step in many biological and chemical transformations (Migliore et al., 2014; Markle et al., 2018). Moreover, proton transfer/shift commonly features in aromatic compounds such as phenols or aromatic amines (Bai et al., 2019; Chen and Sun, 2017). Specifically, proton transfer/shift is more often recognized as a kind of isomerization useful in organic synthesis. As a basic step, the influence of proton transfer/formal proton shift in aromatic substitution reactions has never been carefully investigated. In this work, proton transfer as a powerful strategy is developed to be involved into determining selectivity, accelerating aromatic substitution reactions, and generating active intermediates favorable for ortho-halogenation of aryl amines and phenols (Figure 1C). This finding is notable providing a straightforward method to access valuable natural products and drug intermediates (Figure 1D). The application of this method is demonstrated by the convenient synthesis of tizanidine with up to 97% ortho-selectivity and scale-up to 100-g scale. This catalytic process involving proton shift/isomerization is backed by theoretical
and NMR studies and showcased the utility of Lewis acid altering the aromatic ring electronics and promoting ortho-halogenation.

**RESULTS AND DISCUSSION**

We take S$_2$Ar reactions of N-H anilines as the model to explore the synthetic value of proton transfer strategy. It is well known that the advanced mechanism in chemistry textbooks involves the electrophilic attack and formation of a resonance-stabilized carbocation, and formation of the arenium ion is considered as the rate-determining step followed by deprotonation to restore aromaticity (Figure 2A). On the other hand, in the presence of Lewis acid or under heating conditions, partial dearomatization reactions might happen, including 1,3- or 1,5-proton shift via enamine isomerization procedures (prototropic equilibria of anilines) (Ma et al., 2017). Consequently, is it possible that higher electron density for para (species I) or ortho (species II) position could be achieved following such kind of isomerization? Is it possible to achieve higher reactivity for aromatic substitution under acidic conditions (e.g., Lewis acid)? Theoretically, the deprotonated anionic species III should be more nucleophilic compared with the neutral anilines. In contrary to the established notion of organic chemistry, this means in the presence of LA, more active species might be formed. Critically, proton shift in NH anilines needs to be first investigated.

Deuteration is an exchange reaction of proton with deuterium and is a straightforward method to test proton shift/transfer reactions. Initially, the deuteration reactions of N-Me aniline were carried out in the mixture of SOCl$_2$/D$_2$O or Fe(OTs)$_3$/D$_2$O, which are useful methods to generate D$^+$ in situ. To our delight, for both reactions ortho- and para-deuterations were observed (40%–66% D ratios), which is consistent with electrophilic aromatic substitution-type reactivity for ortho- and para-sites (Scheme 1). When SOCl$_2$ or Fe(OTs)$_3$ was absent, no C-H deuteration was observed. Then, when N,N-dimethyl aniline is used, lower deuteration ratios (17%–33%) were obtained. This implies that the presence of N-H proton is involved for the promotion of H/D exchange process (reactions A/B versus C/D). Considering that N-H/D shift should occur rapidly, it is highly possible that deuteration could be promoted due to the proton transfer
of N-D to the aryl ring. To prove this assumption, N-D-N-Me aniline (ca. 72% D by ¹H NMR) was prepared and treated under heating conditions in the presence of Fe(OTs)₃. Ortho-deuteration was observed (15% D), with trace of D-labeling at the para-position. Hence, we can make the claim that, in the presence of acids, proton shift could occur selectively between the N-H and C-H at ortho/para-positions.

At elevated temperature, quantitative D-labeling at ortho- and para-position was achieved for 2-phenyl aniline (Scheme 1F). Nevertheless, catalytic amounts of Lewis acid Fe(OTs)₃ (5 mol%) in D₂O could be used for the preparation of anilines with moderate D ratios at ortho- and para-positions. This is the first time such kind of Fe-promoted deuteration of sp²C-H bond is noticed, which might be useful for the synthesis of deuterated drugs. In fact, such kind of proton shift in anilines is observed in gas phase chromatography studies (Raczyńska, et al., 2011), even though it is not well explored for the purpose of organic synthesis, such as deuteration or halogenation of sp²C-H bonds.

Halogenation is a type of important reaction in electrophilic aromatic substitutions (SₐAr) for preparation of aryl halides (Galabov et al., 2016; Anbarasan et al., 2011). Specifically, SₐAr reactions of anilines/phenols are usually described in textbooks through resonance formalism to explain regioselectivity control,

**Figure 2. Analysis of the Positional Selectivity: Electron Resonance versus Proton Shift**

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which leads to mixture of ortho- and para-substituted products. Notably, we were taught to avoid the
use of Lewis acids in \( \text{SEAr} \) reaction for anilines due to LA-nitrogen interaction lowering the electron den-
sity on the aromatic ring. It was curious to see if the presence of LA could promote the \( \text{SEAr} \) halogenation
of aromatic amines/phenols. For this purpose, carbazole was chosen as the model substrate, since it has
\( C_2 \)-symmetry with a 1:1 ratio of ortho:para carbon sites, acquiescent to positional selectivity studies.
Specifically, we investigated the bromination of carbazole with N-bromosuccinimide (NBS) as the convenient
and stable electrophilic bromide source. The reaction favored para-bromination without catalyst either at
room temperature or 90°C (o/p = 3/97, 23/77; Table 1, entries 1, 3). Screening of various transition metal
catalysts revealed that the use of palladium(II) or iron(III) triflates resulted in the formation of
ortho-brominated isomer as the major product (Table S1, entries 2–6). Here, it is noteworthy to mention
that other Lewis acids such as CuCl\(_2\) and FeCl\(_3\) have been applied for selective para-halogenation of an-
ilines (Urones et al., 2013; Jin et al., 2011; Mostafa et al., 2017). Among the solvents screened, the use of
nonpolar solvent is beneficial and the highest o/p ratio of 97/3 was obtained in benzene in the presence
of 2 mol% of Fe(OTf)\(_3\) (90% yield; Table 1, entry 4). Heating the reaction (>60°C) in the presence of
Fe(OTf)\(_3\) is necessary for ortho-selectivity, whereas para-bromination occurred at room temperature
(o/p = 3/97; Table 1, entry 2). Notably, in the presence of 2 mol% of Fe(OTf)\(_3\), the expected acceleration
effect was observed and quantitative yield of ortho product was obtained in 45 s, which is much higher in
the absence of catalyst (99% versus 42% yields; Table 1, entries 3 versus 4). Scaling up to 50 g of carba-
zole is also successful, with the efficiency retained (see the Supplemental Information). Such kind of pro-
motion effect using Fe(III)-Lewis acid is striking and contrary to the description in chemistry textbook
where the use of Lewis acid is claimed unsuitable for \( \text{SEAr} \) reactions of anilines. Overall, the use of LA
not only accelerated halogenation of aniline but also led to high ortho-selectivity control when using
appropriate sulfonate anion of iron salts.

The attempt of bromination reaction of N-methylaniline using NBS in the absence of Fe(OTf)\(_3\) catalyst af-
forded poor selectivity (o/m/p = 32/23/45) at 90°C. In contrast, when using catalyst Fe(OTf)\(_3\), ortho-bromi-
nation was favored giving o/p as 66:34 with the meta-product not detected. Moreover, we considered that
sulfonate anion has an effect in directing the ortho preference. Here, the sulfonates might be crucial for
activation of the ortho positions. Specifically, the LA-assisted 1,n-shift of proton might make the ortho-po-
position more nucleophilic leading to higher reactivity and ortho-selectivity. Accordingly, a plausible reaction
mechanism for ortho-halogenation of N-H aryl amines is proposed (Figure 3). From the experimental re-
results, it is apparent that heating is required for Fe(OTf)\(_3\) to promote ortho-bromination to occur. This sug-
gests that there is an energy barrier to overcome, which might correspond to isomerization of aryl amines.
Formal 1,5-H shift via Fe-sulfonate promoted proton transfer might lead to species II, which is responsible
for ortho-substitution. In fact, formal 1,n-H shift of N-H aniline derivatives is known and used to generate
new resonance species for addition reaction (Bai et al., 2019). However, to the best of our knowledge,
this strategy has never been applied for \( \text{SEAr} \) reactions.

To rationalize such proposal and understand the origin of the regioselectivity, we used 1,8-di-deuterated
carbazole with carbazole in competing reactions for kinetic isotope effect (KIE) study. The results gave an
intermolecular KIE value of 1.0 implying that C-H bond cleavage is not involved in the rate-determining

| Entry | T (°C) | x (mol%) | t (s) | Conv. (1a, %) | 2a/3a* |
|-------|--------|----------|------|--------------|--------|
| 1     | 25     | –        | 300  | 18           | 3/97   |
| 2     | 25     | 2        | 300  | 15           | 5/95   |
| 3     | 90     | –        | 45   | 42           | 23/77  |
| 4     | 90     | 2        | 45   | 99           | 97/3   |

Table 1. Fe(III)-Catalyzed Selective Bromination of Carbazole
Reaction conditions: 1a (0.20 mmol), NBS (1.1 equiv.), benzene (10 mL).
*Yields and o/p ratios determined by GC using n-hexadecane as an internal standard.
step (Scheme 2). This result suggests that a mechanism similar to the classic SEAr is involved. Control experiments using N-chlorocarbazole revealed that intermolecular halogenation is involved rather than intramolecular halogen migration, which is also consistent with SEAr mechanism (see the Supplemental Information).

With respect to regioselectivity control using iron sulfonates, experiments showed that the presence of N-H in substrates is crucial for ortho-selectivity. Specifically, when N-methylcarbazole is used as substrate, para-selectivity was obtained under the optimal conditions (o/p = 5/95; see the Supplemental Information). Furthermore, the system was investigated by UV-vis and NMR spectroscopy. Monitoring the reaction under optimized conditions by UV-vis gave rise to a new signal, which corresponds to the distorted carbazole with lower planar aromaticity. In the $^1$H NMR experiments, the interaction of NBS with carbazole caused the N-H signal to shift downfield by 0.2 ppm, which corresponds to hydrogen bonding interactions. In addition, the experiments using Al(OTf)$_3$ and NBS showed interaction to affect the methylene protons of NBS. For metal-carbazole interaction, a downfield shift of the N-H signal in $^1$H NMR spectrum was only observed under heating conditions (>60°C), suggesting metal-N coordination (see the Supplemental Information).

Furthermore, DFT calculations were used to understand the plausibility of 1,3 and 1,5-H shift of carbazole and the reason behind the acceleration of the reaction rate with Fe(III) Lewis acids. In the proposed species II formed via 1,5-H shift, the para-position exists as methylene group and the favored selectivity to ortho-bromination might be attributed partially to the suppression of para-substitution reaction due to such kind of para-site blocking by proton. In DFT calculations, carbazole was chosen as substrate owing to the observed superior ortho-selectivity, whereas Fe(OMe)$_3$ was chosen as catalyst instead of Fe(OTf)$_3$ for computational efficiency. As shown in the potential energy surface (PES) of Figure 4, two carbazole molecules gather at the Fe(III) metal center by Fe-N coordination interaction (Fe-N bond distances are 2.24 and 2.41 Å) and hydrogen bonding between pyrrole NH group and OMe- group of sulfonate. As noticed during the reaction, the coordination of CZ to Fe(OMe)$_3$ would change the metal center d-d transition and thus change the color of solution. Besides, under heating conditions with the distortion of carbazole planar structure, the lone pair electrons of N atom is partially localized allowing for Fe(III)-N coordination (Chen et al., 1971).

Such combination process is exothermic with estimated interaction energy, around −16.0 kcal/mol. Then, the upper carbazole (CZ1) easily devotes the N-H proton to the para-position of the lower carbazole (CZ2) via TS1 by overcoming a barrier, around 27.6 kcal/mol. To conquer such a barrier a temperature of nearly 400 K is necessary, which is in line with the experimental conditions. A protonated 6H-CZ2 in MS1 is produced and would preferentially be brominated at the ortho-position by NBS subsequently. For comparison, the reaction profile for pyrrole proton transfer from CZ1 to the ortho-site of CZ2 was also shown in

**Figure 3. Proposed Mechanism for Ortho-Bromination Using Fe(OTf)$_3$ and NBS**

**Scheme 2. KIE Study**
Figure 4 (path via TS2). From TS2 plot, CZ1 would transfer its pyrrole proton to the α-C (or α’-C) of CZ2 after the N-H bond of CZ2 breaks. The produced MS2 is thermodynamically unstable and would favorably evolve into MS3 in which a protonated 1H-CZ2 is formed. The rate-determining step of this process needs a very high energy barrier, around 49.5 kcal/mol. The calculated results indicate that the para-site of CZ2 would be favorably protonated by intermolecular proton transfer reaction via TS1 in the presence of Fe(OMe)₃ and leave the ortho-site for subsequent bromination by NBS. All these combined interactions support the observed high ortho-bromination selectivity. The natural populations analyses on the deprotonated CZ1 coordinated to Fe(III) in both MS1 and MS3 shows that the ortho-site is more negative than the para-site. This is beneficial to the subsequent bromination at the ortho-position by NBS. Specifically, the deprotonation at para-position will render the aryl ring anionic and thus allow for accelerated electrophilic attack of Br/Cl atoms at the ortho-position.

Meanwhile, we believe that few weak interactions are involved including N-H...O=C hydrogen bonding and X...O=S halogen bonding (Cavallo et al., 2016; Beale et al., 2013) accompanied with metal...C=O interaction to make the halogen source close to the ortho-position. These cumulative effects with proton-transfer isomerization accelerate the reaction at the ortho-position significantly (45 s, 97% yield; Table 1, entry 4).

Halogenated anilines are important synthetic intermediates. For the chlorination of N-Me-aniline using different transition metal salts, iron sulfonates were found suitable catalyst. Specifically, when Fe(OTs)₃
Carbazoles are important molecules with their structural motif featuring in many bioactive and optically relevant compounds, and recently their selective catalytic transformation has attracted significant interests (Hirota et al., 2012; Ishikura et al., 2013; Uoyama et al., 2012; Ryan et al., 2018; Creutz et al., 2012). To further elucidate the synthetic utility of such proton-transfer substitution strategy (Hirota et al., 2012; Ishikura et al., 2013; Uoyama et al., 2012; Ryan et al., 2018; Creutz et al., 2012), (5 mol%) was used as the catalyst in the presence of chlorination reagent tri-chloroisocyanuric acid (5, 0.35 equiv.), high ortho-selectivity (α/ω = 90/10) was obtained for the desired 2-chloro-N-methylaniline 6a (78% yield; Scheme 3). In the absence of catalyst, bromination of N-methylaniline using NBS afforded no selectivity (α/ω = 32/23/45) at 90°C. When using Fe(OTs)₃, ortho-bromination became the major pathway giving α/ω as 66.34 with meta-product not detected. Under similar conditions, good to excellent ortho-selectivities were achieved for the substrates studied and the corresponding mono-chlorinated products were obtained in good to excellent yields (6b-m; 58%–90%). Unprecedented high regioselectivity (97%) was observed for the production of halogenated diaryl amine 6i with 90% isolated yield. Notably, the reaction of aniline proceeded smoothly giving o-chloroaniline in 58% isolated yield.

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To further demonstrate the application potential of this methodology, we choose to investigate total synthesis of natural products bearing carbazole moiety. First, we tested the versatile transformation of brominated carbazole 2a, and the corresponding 1-substituted products bearing -NH₂, -CHO, -OMe, and -Ph were conveniently obtained in good yields (Scheme 5).

Then, we applied this method for the synthesis of carbazole-type alkaloids, for which traditional methods suffer from complicated and/or inefficient multi-step procedures (Scheme 6). For example, starting from 1-bromo-6-methylcarbazole (2l), Clausenal was synthesized in 39% total yield in three steps: Fe-catalyzed ortho-bromination to 11; Cu-catalyzed methoxylation to 12, and oxidation by 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to Clausenal (Scheme 6A). This is in contrast to a recent report using iridium-based procedure for the synthesis of Clausenal through five steps with the total yield as 3% (Liyu and Sperry, 2017).

Meanwhile, total synthesis of natural product 1,8-dimethoxy-4-formylcarbazole 15 from carbazole 1a was achieved in four steps with 33% total yield. Specifically, selective ortho-bromination of carbazole gave 1,8-dibromocarbazole 2c in 64% yield (Scheme 6B). After methoxylation, 1,8-dimethoxycarbazole 13 was

**Scheme 4. Fe(OTf)₃-Catalyzed ortho-Halogenation of Carbazoles**

- Reaction conditions: 1 (0.20 mmol), NBS (1.1 equiv.), Fe(OTf)₃ (2 mol%), toluene (10 mL), 1–6 h in the absence of light, 90 °C; isolated yields.  
- Reaction conditions: 1 (0.20 mmol), NCS (1.1 equiv.), Fe(OTf)₃ (10 mol%), toluene (10 mL), in dark, 110 °C; isolated yields.
obtained in 82% yield. Bromination-formylation sequence gave the final product 15. Meanwhile, Mukolidine was synthesized in three steps from 3-methylcarbazole 2l in 52% total yield via 100-g scale Fe-catalyzed bromination reaction (Scheme 6 C) (Schuster et al., 2014). Moreover, the method was also applied for the synthesis of tizanidine intermediate 6n giving the product in 73% yield with an o/p ratio of 95:5 (Scheme 6 D) (Xu et al., 2005).

At last, the ortho-chlorination of phenols was also tested using this new methodology. To our delight, it is found that almost complete ortho-selectivity was achieved for phenol under optimal conditions (96:4 ortho/para ratio, 85% yield). In sharp contrast, without catalyst complicated products with oxidation side products were obtained. Hence, the substrate scope of phenols was investigated under the same conditions. All the substrates, including ortho-MeO phenol gave the desired products in good to excellent selectivity (64%–92% yields; Scheme 7).

Scheme 5. Selective ortho-Functionalization of Anilines

*Reaction conditions: 2a (0.5 mmol). (i) Phenylboronic acid (1.1 eq), K$_2$CO$_3$ (4 equiv.), PdCl$_2$(PPh$_3$)$_2$ (5 mol%), toluene/H$_2$O/EtOH, 95 °C, 16 h. (ii) NaH, nBuLi, -78 °C, DMF. (iii) CuBr (2 equiv.), sodium methanolate (20 equiv.), DMF/MeOH, 120 °C, 3 h. (iv) CuI (0.2 equiv.), aqueous ammonia (5 equiv.), 2-carboxylic acid-quinoline-N-oxide (0.4 equiv.), K$_2$CO$_3$, DMSO, 80 °C, 24 h.

Scheme 6. Synthesis of Bio-active Natural Compounds
Conclusions

In conclusion, we have revisited aromatic substitution of anilines and discovered proton shift process catalyzed by iron sulfonate catalysts favoring ortho substitution. We have developed a general site-selective deuteration and halogenation of aryl amines. Various non-N-protected anilines and carbazole-type heteroaryls were directly transformed to halogenated products in good to excellent selectivities and yields (>40 examples; 58%–90% yields). The practical application is demonstrated on 100-g scale reaction and convenient synthesis of alkaloids, and tizanidine intermediates. Ortho-halogenation of phenols was also achieved. Overall, this method is complementary to the traditional S$_{E}$Ar limited to para-halogenations.

Mechanistic studies suggest that the ortho-regioselectivity promotion is likely controlled by 1,n-proton shift via Fe-N coordination. This strategy involving 1,n-proton shift in the presence of Lewis acids would serve the basis for other types of selective C-H functionalizations.

Limitations of the Study

This study systematically exploited proton shift process catalyzed by iron sulfonate catalysts for selective ortho substitutions. The methodology has wide range of substrates applicability, although this report is proof of concept for ortho-halogenations of aryl amines and phenols. Further studies are needed to apply 1,n-proton shift strategy in the presence of Lewis acids for other types of reactions.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.101214.

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AUTHOR CONTRIBUTIONS

Y.L. and C.X. conceived, directed, and secured funding for the project. Y.L., L.F., and X.J. performed the experiments, analyzed the data, and prepared the supporting information. H.-F.W. performed DFT calculations. Y.L., D.Z., C.X., and H.-F.W. wrote the paper.
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DECLARATION OF INTERESTS

The authors declare no competing interests.

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REFERENCES

Anbarasan, P., Schareina, T., and Beller, M. (2011). Recent developments and perspectives in palladium-catalyzed cyanation of aryl halides: synthesis of benzonitriles. Chem. Soc. Rev. 40, 5049–5067.

Bai, J.-F., Yasumoto, K., Kano, T., and Maruoka, K. (2019). Asymmetric synthesis of chiral 1,4-enynes through organocatalytic alkenylation of propargyl alcohols with trialkenylboroxines. Angew. Chem. Int. Ed. 58, 8898–8901.

Bauer, I., and Knöcker, H.-J. (2015). Iron catalysis in organic synthesis. Chem. Rev. 115, 3170–3387.

Beale, T.M., Chudzinski, M.G., Sarwar, M.G., and Taylor, M.S. (2013). Halogen bonding in solution: thermodynamics and applications. Chem. Soc. Rev. 42, 1667–1680.

Bedford, R.B., Hadlow, M.F., Mitchell, C.J., and Webster, R.L. (2011). Mild C–H halogenation of anilides and the isolation of an unusual palladium(II)-palladium(II) species. Angew. Chem. Int. Ed. 50, 5524–5527.

Cavallo, G., Metrangolo, P., Milani, R., Pilati, T., Primagi, A., Resinati, G., and Terraneo, G. (2016). The halogen bond. Chem. Rev. 116, 2476–2601.

Chen, M., and Sun, J. (2017). Catalytic asymmetric N-alkylation of indoles and carbazoles through 1,4-conjugate addition of aza-para-quinone methides. Angew. Chem. Int. Ed. 56, 4583–4587.

Chen, H.J., Hakka, L.E., Hinman, R.L., Kresge, A.J., and Whipple, E.B. (1971). Basic strength of carbazole. Estimate of the nitrogen basicity of pyrrole and indole. J. Am. Chem. Soc. 93, 5102–5107.

Creutz, S.E., Lotito, K.J., Fu, G.C., and Peters, J.C. (2012). Photoinduced Ullmann C–N coupling: demonstrating the viability of a radical pathway. Science 338, 647–651.

Engle, K.M., Mei, T.-S., Wasa, M., and Yu, J.-Q. (2011). Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. Acc. Chem. Res. 45, 788–802.

Galabov, B., Nabrantova, D., Schleyer, P.R., and Schaefer, H.F. (2016). Electrophilic aromatic substitution: new insights into an old class of reactions. Acc. Chem. Res. 49, 1191–1199.

Hirota, T., Lee, J.K., St.John, P.C., Sawa, M., Iwaisako, K., Noguchi, T., Pongswakul, P.Y., Sonntag, T., Welsh, D.K., Brenner, D.A., et al. (2012). Identification of small molecule activators of cryptochrome. Science 337, 1094–1097.

Ishikura, M., Abe, T., Choshi, T., and Hibino, S. (2013). Simple indole alkaloids and those with a non-rearranged monoterpenoid unit. Nat. Prod. Rep. 30, 694–752.

Jin, H., Huang, Z., Kuang, C., and Wang, X. (2011). Iron-catalyzed bromination of aryl azides by N-bromosuccinimide: efficient method for the synthesis of brominated aryl azides. Chin. Chem. Lett. 22, 310–313.

Li, J., and Sperry, J. (2017). Synthesis of putative clausenal from carbazole using sequential C–H borylations. Tetrahedron Lett. 58, 1699–1701.

Ma, G., Liu, G., Shen, S., Chai, Y., Yue, L., Zhao, S., and Pan, Y. (2017). Competitive bencyl cation transfer and proton transfer: collision-induced mass spectrometric fragmentation of protonated N,N-dibenzylaniline. J. Mass Spectrom. 52, 197–203.

Makle, T.F., Darcy, J.W., and Mayer, J.M. (2018). A new strategy to efficiently cleave and form C–H bonds using proton-coupled electron transfer. Sci. Adv. 4, eaat5776.

Migliore, A., Polizzi, N.F., Therien, M.J., and Beratan, D.N. (2014). Biochemistry and theory of electron oxidation and one-electron reduction for (hetero)arenes. Nat. Catal. 1, 107–115.

Taylor, R. (1990). Electrophilic Aromatic Substitution (John Wiley & Sons).

Uoyama, H., Goushi, K., Shizu, K., Nomura, H., and Adachi, C. (2012). Highly efficient organic light-emitting diodes from delayed fluorescence. Nature 492, 234–238.

Urones, B., Martinez, A.M., Rodriguez, N., Arrayás, R.G., and Carretero, J.C. (2013). Copper-catalyzed ortho-halogenation of protected anilines. Chem. Commun. 49, 11044–11046.

Wan, X., Ma, Z., Li, B., Zhang, K., Cao, S., Zhang, S., and Shi, Z. (2014). Highly selective C–H functionalization/halogenation of anilinamide. J. Am. Chem. Soc. 136, 7416–7417.

Wang, L., and Ackermann, L. (2014). Ruthenium-catalyzed ortho-C–H halogenations of benzamides. Chem. Commun. 50, 1083–1085.

Wencel-Delord, J., and Glorius, F. (2013). C–H bond activation enables the rapid construction and late-stage diversification of functional molecules. Nat. Chem. 5, 369–375.

Xiong, X., and Yeung, Y.Y. (2016). Highly ortho-selective chlorination of anilines using a secondary ammonium salt organocatalyst. Angew. Chem. Int. Ed. 55, 16101–16105.

Xu, J., Shen, Y., Xiang, L., and Deng, Y. (2005). Synthesis of tiazanine hydrochloride. Chin. J. Pharm. 36, 593–596.
Supplemental Information

Proton Transfer Can Govern
Regioselectivity Assisted by Iron Catalysis

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Supplemental Figures for NMR spectrums:

Figure S1. $^1$H NMR spectrum of 2a, related to Scheme 4

![1H NMR spectrum of 2a](image1)

Figure S2. $^{13}$C NMR spectrum of 2a, related to Scheme 4

![13C NMR spectrum of 2a](image2)
Figure S3. $^1$H NMR spectrum of 2b, related to Scheme 4

Figure S4. $^{13}$C NMR spectrum of 2b, related to Scheme 4
Figure S5. $^1$H NMR spectrum of 2c, related to Scheme 4

Figure S6. $^{13}$C NMR spectrum of 2c, related to Scheme 4
Figure S7. $^1$H NMR spectrum of 2d, related to Scheme 4

Figure S8. $^{13}$C NMR spectrum of 2d, related to Scheme 4
**Figure S9.** $^1$H NMR spectrum of 2e, related to Scheme 4

![H NMR spectrum of 2e](image)

**Figure S10.** $^{13}$C NMR spectrum of 2e, related to Scheme 4

![13C NMR spectrum of 2e](image)
Figure S11. $^1$H NMR spectrum of 2f, related to Scheme 4

Figure S12. $^{13}$C NMR spectrum of 2f, related to Scheme 4
Figure S13. $^1$H NMR spectrum of 2g, related to Scheme 4
Figure S14. $^{13}$C NMR spectrum of 2g, related to Scheme 4

Figure S15. $^1$H NMR spectrum of 2h, related to Scheme 4
**Figure S16.** $^{13}$C NMR spectrum of 2h, related to Scheme 4

**Figure S17.** $^1$H NMR spectrum of 2i, related to Scheme 4
Figure S18. $^{13}$C NMR spectrum of 2i, related to Scheme 4

Figure S19. $^1$H NMR spectrum of 2j, related to Scheme 4
Figure S20. $^{13}$C NMR spectrum of 2j, related to Scheme 4

Figure S21. $^1$H NMR spectrum of 2k, related to Scheme 4
Figure S22. $^{13}$C NMR spectrum of $2k$, related to Scheme 4

Figure S23. $^1$H NMR spectrum of $2l$, related to Scheme 4
Figure S24. $^{13}$C NMR spectrum of 2l, related to Scheme 4

Figure S25. $^1$H NMR spectrum of 2m, related to Scheme 4
Figure S26. $^{13}$C NMR spectrum of 2m, related to Scheme 4

Figure S27. $^1$H NMR spectrum of 2n, related to Scheme 4
Figure S28. $^{13}$C NMR spectrum of 2n, related to Scheme 4

Figure S29. $^1$H NMR spectrum of 2o, related to Scheme 4
Figure S30. $^{13}$C NMR spectrum of 2o, related to Scheme 4

Figure S31. $^1$H NMR spectrum of 2p, related to Scheme 4
Figure S32. $^{13}$C NMR spectrum of 2p, related to Scheme 4

Figure S33. $^1$H NMR spectrum of 2q, related to Scheme 4
Figure S34. $^{13}$C NMR spectrum of 2q, related to Scheme 4

Figure S35. $^1$H NMR spectrum of 2r, related to Scheme 4
Figure S36. $^{13}$C NMR spectrum of 2r, related to Scheme 4
Figure S37. $^1$H NMR spectrum of 2s, related to Scheme 4

Figure S38. $^{13}$C NMR spectrum of 2s, related to Scheme 4
Figure S39. $^1$H NMR spectrum of 2t, related to Scheme 4

Figure S40. $^{13}$C NMR spectrum of 2t, related to Scheme 4
Figure S41. $^1$H NMR spectrum of 2u, related to Scheme 4

Figure S42. $^{13}$C NMR spectrum of 2u, related to Scheme 4
Figure S43. $^1$H NMR spectrum of 2v, related to Scheme 4

Figure S44. $^{13}$C NMR spectrum of 2v, related to Scheme 4
Figure S45. $^1$H NMR spectrum of 2w, related to Scheme 4

Figure S46. $^{13}$C NMR spectrum of 2w, related to Scheme 4
Figure S47. $^1$H NMR spectrum of 2x, related to Scheme 4

Figure S48. $^{13}$C NMR spectrum of 2x, related to Scheme 4
Figure S49. $^1$H NMR spectrum of 2y, related to Scheme 4

Figure S50. $^{13}$C NMR spectrum of 2y, related to Scheme 4
Figure S51. $^1$H NMR spectrum of $2z$, related to Scheme 4

Figure S52. $^{13}$C NMR spectrum of $2z$, related to Scheme 4
Figure S53. $^1$H NMR spectrum of 2aa, related to Scheme 4

Figure S54. $^{13}$C NMR spectrum of 2aa, related to Scheme 4
Figure S55. $^1$H NMR spectrum of 2ab, related to Scheme 4

Figure S56. $^{13}$C NMR spectrum of 2ab, related to Scheme 4
Figure S57. $^1$H NMR spectrum of 2ac, related to Scheme 4

Figure S58. $^{13}$C NMR spectrum of 2ac, related to Scheme 4
Figure S59. $^1$H NMR spectrum of 2ad, related to Scheme 4

Figure S60. $^{13}$C NMR spectrum of 2ad, related to Scheme 4
Figure S61. $^1$H NMR spectrum of 2ae, related to Scheme 4

Figure S62. $^{13}$C NMR spectrum of 2ae, related to Scheme 4
Figure S63. $^1$H NMR spectrum of 2af, related to Scheme 4

Figure S64. $^{13}$C NMR spectrum of 2af, related to Scheme 4
Figure S65. $^1$H NMR spectrum of 2ag, related to Scheme 4

Figure S66. $^{13}$C NMR spectrum of 2ag, related to Scheme 4
Figure S67. $^1$H NMR spectrum of 6a, related to Scheme 3

Figure S68. $^{13}$C NMR spectrum of 6a, related to Scheme 3
Figure S69. $^1$H NMR spectrum of 6b, related to Scheme 3

Figure S70. $^{13}$C NMR spectrum of 6b, related to Scheme 3
Figure S71. $^1$H NMR spectrum of 6c, related to Scheme 3

Figure S72. $^{13}$C NMR spectrum of 6c, related to Scheme 3
Figure S73. $^1$H NMR spectrum of 6d, related to Scheme 3

Figure S74. $^{13}$C NMR spectrum of 6d, related to Scheme 3
Figure S75. $^1$H NMR spectrum of 6e, related to Scheme 3

Figure S76. $^{13}$C NMR spectrum of 6e, related to Scheme 3
Figure S77. $^1$H NMR spectrum of 6f, related to Scheme 3

Figure S78. $^{13}$C NMR spectrum of 6f, related to Scheme 3
Figure S79. $^1$H NMR spectrum of 6g, related to Scheme 3

Figure S80. $^{13}$C NMR spectrum of 6g, related to Scheme 3
Figure S81. $^1$H NMR spectrum of 6j, related to Scheme 3

Figure S82. $^{13}$C NMR spectrum of 6j, related to Scheme 3
Figure S83. $^1$H NMR spectrum of 6i, related to Scheme 3

Figure S84. $^{13}$C NMR spectrum of 6i, related to Scheme 3
Figure S85. $^1$H NMR spectrum of 6h, related to Scheme 3

Figure S86. $^{13}$C NMR spectrum of 6h, related to Scheme 3
Figure S87. $^1$H NMR spectrum of 6k, related to Scheme 3

Figure S88. $^{13}$C NMR spectrum of 6k, related to Scheme 3
Figure S89. $^1$H NMR spectrum of 6l, related to Scheme 3

Figure S90. $^{13}$C NMR spectrum of 6l, related to Scheme 3
Figure S91. $^1$H NMR spectrum of 6m, related to Scheme 3

Figure S92. $^{13}$C NMR spectrum of 6m, related to Scheme 3
Figure S93. $^1$H NMR spectrum of 6n, related to Scheme 6

Figure S94. $^{13}$C NMR spectrum of 6n, related to Scheme 6
Figure S95. $^1$H NMR spectrum of 7, related to Scheme 5

Figure S96. $^{13}$C NMR spectrum of 7, related to Scheme 5
Figure S97. $^1$H NMR spectrum of 8, related to Scheme 5

Figure S98. $^{13}$C NMR spectrum of 8, related to Scheme 5
Figure S99. $^1$H NMR spectrum of 9, related to Scheme 5

Figure S100. $^{13}$C NMR spectrum of 9, related to Scheme 5
Figure S101. $^1$H NMR spectrum of 10, related to Scheme 5

Figure S102. $^{13}$C NMR spectrum of 10, related to Scheme 5
Figure S103. $^1$H NMR spectrum of 11, related to Scheme 6

Figure S104. $^{13}$C NMR spectrum of 11, related to Scheme 6
Figure S105. $^1$H NMR spectrum of 12, related to Scheme 6

Figure S106. $^{13}$C NMR spectrum of 12, related to Scheme 6
Figure S107. $^1$H NMR spectrum of 13, related to Scheme 6

Figure S108. $^{13}$C NMR spectrum of 13, related to Scheme 6
Figure S109. $^1$H NMR spectrum of 14, related to Scheme 6

Figure S110. $^{13}$C NMR spectrum of 14, related to Scheme 6
Figure S111. $^1$H NMR spectrum of 15, related to Scheme 6

Figure S112. $^{13}$C NMR spectrum of 15, related to Scheme 6
Figure S113. $^1$H NMR spectrum of 16, related to Scheme 6
Figure S114. $^{13}$C NMR spectrum of 16, related to Scheme 6

Figure S115. $^1$H NMR spectrum of 8D-2a, related to Scheme 2
Figure S116. $^{13}$C NMR spectrum of 8D-2a, related to Scheme 2
**Transparent Methods**

**General information**
Air- and moisture-sensitive syntheses were performed under argon atmosphere. Fe(OTf)<sub>3</sub> was purchased from Alfa, and Fe(OTs)<sub>3</sub> was purchased from Energy Chemical. Other chemicals were purchased from Adamas, Aldrich, TCI, Alfa etc. Unless otherwise noted, all commercial reagents were used without further purification. And the NMR spectroscopy was in full accordance with the data in the literature. The products of halogenation were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS and HRMS spectroscopy. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Zhongke Niujin WNMR-I 400 (400 MHz). Chemical shift δ (ppm) was given relative to solvent: references for CDCl<sub>3</sub> were 7.26 ppm (<sup>1</sup>H NMR) and 77.0 ppm (<sup>13</sup>C NMR), and for d-DMSO were 2.50 ppm (<sup>1</sup>H NMR) and 39.60 ppm (<sup>13</sup>C NMR), and for d-toluene were 2.08, 6.97, 7.01, 7.09 ppm (<sup>1</sup>H NMR), and for d-benzene were 7.16 ppm (<sup>1</sup>H NMR), <sup>13</sup>C NMR spectra were acquired on a broad band decoupled mode. And for the <sup>13</sup>C NMR spectra of the <sup>13</sup>C-labelled compounds, the coupling was not analyzed due to complexity. Multiplets were assigned as s (singlet), d (doublet), dd (doublet doublet), and m (multiplet) etc. EI (Electron impact) mass spectra were recorded on a GCMS-QP2010 SE spectrometer (70 eV). ESI (electrospray ionization) high resolution mass spectra were recorded on an Agilent Technologies 6530 TOF LC/MS. UV-vis spectra were recorded on an Agilent 8454 spectrophotometer. All measurements were carried out at room temperature unless otherwise stated.

**Computational methods**  （Fox et al., 2013）
All calculations were performed by Gaussian 09 D.01 using the range-separated hybrid WB97XD functional including dispersion correction. The dispersion correction has been proved to be critical in describing the regioselectivity of Fe-catalyzed reactions. For geometry optimizations, we used double-zeta polarized basis set 6-31g(d) for H, C, N, O, F atoms and Lanl2dz for Fe and S atom (WB97XD/B1). Frequency calculations at the same level were calculated to verify either local minima or transition states and to estimate the thermal corrections Gibbs free energy at 298K. Then, single-point energies of the optimized structures was calculated with a larger triple-zeta basis set 6-311+G(d,p) (WB97XD/B2) for non-metallic atoms and Lanl2dz for Fe and S.

**Screening of the reaction conditions**
Table S1: Investigation of different catalysts for ortho-bromination of 1a, related to Table 1**
Table S2: Investigation of different solvents for ortho-bromination of 1a, related to Table 1

| Entry | Catalyst   | x  | solvent     | Yield (2a, %) | Sel. (2a, %) |
|-------|------------|----|-------------|---------------|--------------|
| 1     | Fe(OTf)₃  | 10 | toluene     | 69            | 81           |
| 2     | Fe(OTf)₃  | 10 | DCE         | 20            | 28           |
| 3     | Fe(OTf)₃  | 10 | CH₂CN       | 4             | 4            |
| 4     | Fe(OTf)₃  | 10 | 1,4-Dioxane | 9             | 11           |
| 5     | Fe(OTf)₃  | 10 | DMF         | 1             | 1            |
| 6     | Fe(OTf)₃  | 10 | THF         | 7             | 8            |

**Scheme S1: Ortho-halogenation Reaction of Carbazoles, related to Scheme 4**

To a solution of the carbazole (0.2 mmol), catalyst Fe(OTf)₃ (0.004 mmol, 2 mol%) in toluene (10 mL) was added NBS (0.22 mmol, 1.1 equiv) at 90 °C in the absence of light. The mixture was stirred at 90 °C for 1h - 6 h. The solution was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluted with ethyl acetate/ hexane 1:20 to 1:2) to yield the corresponding ortho-bromination product.
toluene (10 mL) was added NCS (0.22 mmol, 1.1 equiv.) at 110 °C in the absence of light. The mixture was stirred at 110 °C for 6 - 12 h. The solution was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluted with ethyl acetate/ hexane 1:20 to 1:2) to yield the corresponding ortho-chlorination product.

**Scheme S2: Ortho-chlorination Reaction of N-Methylaniline, related to Scheme 3**

![Ortho-chlorination Reaction of N-Methylaniline](image)

To a solution of the N-Methylaniline (0.2 mmol, 1.0 equiv.), catalyst Fe(OTf)₃ (0.01 mmol, 0.05 equiv.) in toluene (4 mL) was added TCCA (0.07 mmol, 0.35 equiv.) at 90 °C in the absence of light. The mixture was stirred at 90 °C for 12 - 24 h. The solution was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluted with ethyl acetate/ hexane 1:20 to 1:2) to yield the corresponding ortho-chlorination product.

**Table S3: Optimization of Ortho-bromination Reaction of Phenol, related to Scheme 7**

| Entry | Catalyst      | T (°C) | Conv(%, %) | Yield (%, %) | o / p |
|-------|---------------|-------|------------|--------------|------|
| 1     | /             | 90    | 52         | 16           | 62 / 38 |
| 2     | Fe(OTf)₃      | 90    | 99         | 85           | 96 / 4  |

*Reaction conditions: 17 (0.20 mmol), NBS (1.1 equiv.), toluene (10.0 mL), in the absence of light at 90°C. Yields and o/p ratios determined by GC using n-hexadecane as an internal standard.

**Scheme S3: Ortho-bromination Reaction of Phenol, related to Scheme 7**

![Ortho-bromination Reaction of Phenol](image)

To a solution of the Phenol (0.2 mmol), catalyst Fe(OTf)₃ (0.01 mmol, 5 mol%) in toluene (10 mL) was added NBS (0.22 mmol, 1.1 equiv) at 90 °C in the absence of light. The mixture was stirred at 90 °C for 1 min - 2 h. The solution was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluted with ethyl acetate/ hexane 1:20 to 1:2) to yield the corresponding ortho-bromination product.
Preparations of target product 7-10

To a dry 25 mL round bottom flask equipped with a stir bar were added 2a (0.5 mmol, 1.0 equiv.), 4-chlorophenylboronic acid (0.55 mmol, 1.1 equiv.), K$_2$CO$_3$ (2.0 mmol, 4.0 equiv.), and PdCl$_2$(PPh$_3$)$_2$ (0.025 mmol, 0.05 equiv.). Toluene (6 mL), 4 mL of H$_2$O, and 2 mL of EtOH were added, and the resulting mixture was heated to 95 °C. After 16 hours, the reaction mixture was cooled, and the mixture was diluted with 25 mL of saturated aqueous NH$_4$Cl and 25 mL of CH$_2$Cl$_2$. The resulting biphasic solution was separated. The organic phase was washed 1 × 25 mL of water and 1 × 25 mL of saturated aqueous NaHCO$_3$. The organic phase was dried over Na$_2$SO$_4$ and decanted. The filtrate was concentrated in vacuo to afford an oil.

To a suspension of sodium hydride (1.3 mmol) in dry THF (8 mL), compound 2a (0.5 mmol) was added and stirred at 0 °C under nitrogen for 40 min before the temperature was lowered to -78 °C. To the mixture, a solution of n-butyl lithium (4 mL of a 1.7 M solution in hexane, 6.8 mmol) was added dropwise by a syringe over 3 min. The mixture was then allowed to reach rt over 1 h before being cooled again to -78 °C. Dry DMF (1 mL, 13 mmol) was introduced into the reaction mixture via a syringe and the mixture was allowed to reach rt. The mixture was stirred for additional 1.5 h at rt before it was poured into a 1 M H$_3$PO$_4$ solution (40 mL) which afforded a fine precipitate. The precipitate was filtered through a bed of celite and the product was extracted in hot pyridine (20 mL). The solution was diluted with water (20 mL) to induce precipitation which was then suction filtered. The solid material was repeatedly washed with diethyl ether and the yellowish impurity was completely removed.

DMF (6 mL), CuI (95%, 0.48 mmol), and 2a (0.5 mmol) were added to a solution of metallic sodium (9.3 mmol) in absolute MeOH (1.5 mL). The reaction mixture was refluxed (oil bath temperature ) 120 °C) for 3 h under an argon atmosphere. After the reaction, EtOAc (20 mL) was added to the reaction mixture and the insoluble materials were filtered through Celite and washed with EtOAc. The filtrate was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was chromatographed on a column of silica gel using 10:1 n-hexane/EtOAc to give 1-methoxy-9H-carbazole.

Catalyst recycling

Initially, to a solution of the carbazole (0.2 mmol, 1.0 equiv.), catalyst Fe(OTf)$_3$ (0.004 mmol, 0.02 equiv.) in toluene (10 mL) was added NBS (0.22 mmol, 1.1 equiv.) at 90 °C in the absence of light. The mixture was stirred at 90 °C for 1 h affording ortho-brominated product 83% yield and 90% selectivity. The first round recycling was performed by allowing reaction mixture to cool to room temperature and additional carbazole (0.2 mmol, 1.0 equiv.), NBS (0.22 mmol, 1.1 equiv.) were added to the reaction and stirred at 90 °C for 1 h providing product in 80% yield 89% selectivity. The second and third rounds were performed in a similar fashion giving product yields in 79% and 75%, and selectivities in 79% and 75%, respectively.
Table S4: Catalyst recycling, related to Scheme 4

| Catalyst recycling | Yield, (2a %) | 2a/(2a+3a) |
|--------------------|--------------|------------|
| 0 round            | 83           | 90%        |
| First round        | 80           | 89%        |
| Second round       | 79           | 87%        |
| Third round        | 75           | 80%        |

Scheme S4: Reaction scale-up, related to Scheme 4

To a solution of the 1a (300 mmol, 1.0 equiv.), catalyst Fe(OTf)_3 (6.0 mmol, 0.02 equiv.) in toluene (200 mL) was added 330 mmol NBS (divided into five portions, once of addition every 60 minutes) at 90 °C in the absence of light. The mixture was stirred at 90 °C for 1 h. 42.6 g of 2a was obtained through recrystallization.

Scheme S5: The total synthesis of natural compounds., related to Scheme 6
Preparations of target product 11-16

1,8-dibromo-3-methyl-9H-carbazole (11)
To a solution of 2i (0.2 mmol, 1.0 equiv.), catalyst Fe(OTf)$_3$ (0.004 mmol, 0.02 equiv.) in toluene (10 mL) was added NBS (0.22 mmol, 1.1 equiv.) at 90 °C in the absence of light. The mixture was stirred at 90 °C for 2 h. The solution was diluted with water (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na$_2$SO$_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluted with ethyl acetate/ hexane 1:20 to 1:2) to yield the corresponding ortho-bromination product.

1,8-dimethoxy-3-methyl-9H-carbazole (12) (Tamariz et al., 2017)
DMF (8 mL), Cul (95%, 1.0 mmol), and 11 (0.5 mmol) were added to mixture of metallic sodium (18.6 mmol) in absolute MeOH (3.0 mL). The reaction mixture was refluxed (oil bath temperature) 120 °C for 3 h under an argon atmosphere. After the reaction, EtOAc (40 mL) was added to the reaction mixture and the insoluble materials were filtered through Celite and washed with EtOAc. The filtrate was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was chromatographed on a column of silica gel using 10:1 n-hexane/EtOAc to give 1,8-dimethoxy-3-methyl-9H-carbazole.

1,8-dimethoxy-9H-carbazole (13) (Sperry et al., 2017)
DMF (8 mL), CuI (95%, 1.0 mmol), and 2e (0.5 mmol) were added to the mixture of metallic sodium (18.6 mmol) in absolute MeOH (3.0 mL). The reaction mixture was refluxed (oil bath temperature) 120 °C for 3 h under an argon atmosphere. After the reaction, EtOAc (40 mL) was added to the reaction mixture and the insoluble materials were filtered through Celite and washed with EtOAc. The filtrate was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was chromatographed on a column of silica gel using 10:1 n-hexane/EtOAc to give 13.

4-bromo-1,8-dimethoxy-9H-carbazole (14)
To a solution of the 13 (0.5 mmol, 1.0 equiv.), NBS (0.55 mmol, 1.1 equiv.) in DMF (10 mL) (0.22 mmol, 1.1 equiv.) at 25 °C in the absence of light. The mixture was stirred at 25 °C for 10 h. The solution was diluted with water (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na$_2$SO$_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluted with ethyl acetate/ hexane 1:20 to 1:2) to yield the corresponding 14.

1,8-dimethoxy-9H-carbazole-4-carbaldehyde (15)
To a suspension of sodium hydride (1.3 mmol) in dry THF (8 mL), compound 14 (0.5 mmol) was added and stirred at 0 °C under nitrogen for 40 min before the temperature was lowered to -78 °C. To the mixture a solution of $n$-butyl lithium (4 mL of a 1.7 M solution in hexane, 6.8 mmol) was added dropwise by a syringe over 3 min. The mixture was then allowed to reach rt over 1 h before being cooled again to -78 °C. Dry DMF (1 mL, 13 mmol) was introduced into the reaction mixture via a syringe and the mixture was allowed to reach rt. The mixture was stirred for additional 1.5 h at rt before it was poured into a 1 M H$_3$PO$_4$ solution (40 mL) which afforded a fine precipitate. The precipitate was filtered through a bed of celite and the product was extracted in hot pyridine (20 mL).
The solution was diluted with water (20 mL) to induce precipitation which was then suction filtered. The solid material was repeatedly washed with diethyl ether and the yellowish impurity was completely removed.

1-methoxy-6-methyl-9H-carbazole (16) (Tamariz et al., 2011)
DMF (6 mL), CuI (95%, 0.48 mmol), and 2I (0.5 mmol) were added to a solution of metallic sodium (9.3 mmol) in absolute MeOH (1.5 mL). The reaction mixture was refluxed (oil bath temperature) 120 °C for 3 h under an argon atmosphere. After the reaction, EtOAc (20 mL) was added to the reaction mixture and the insoluble materials were filtered through Celite and washed with EtOAc. The filtrate was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was chromatographed on a column of silica gel using 10:1 n-hexane/EtOAc to give 16.

Schenme S5 : Control experiments, related to Table 1

Schenme S6 : KIE study, related to Scheme 2
Preparations of target product 18
1-bromo-8-deuterium-9H-carbazole (18)

To a solution of the 1,8-2D-1a (0.2 mmol, 1.0 equiv.), catalyst Fe(OTf)$_3$ (0.004 mmol, 0.02 equiv.) in benzene (10 mL) was added NBS (0.22 mmol, 1.1 equiv.) in the absence of light at 90 °C. The mixture was stirred at 90 °C for 1 h. The solution was diluted with water (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na$_2$SO$_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel to yield the corresponding ortho-bromination product.

UV-Vis for Carbazole study

Figure S117: UV-vis spectra of 1a; Both spectra were measured in toluene, related to Figure 1, 2, 3, 4,

Control NMR experiment
Figure S118: Carbazole in d-benzene and Carbazole + NBS in d-benzene, related to Figure 1, 2, 3, 4.

Figure S119: NBS + Al(OTf)\textsubscript{3} in d-toluene 25 °C and NBS + Al(OTf)\textsubscript{3} in d-toluene 60 °C, related to Figure 1, 2, 3, 4.
Figure S120: NBS + Al(OTf)$_3$ in d-toluene 25 °C and NBS + Al(OTf)$_3$ in d-toluene 60 °C, related to Figure 1, 2, 3, 4

Characterization data for products

1-bromo-9H-carbazole (2a) (Cho et al., 2017)
White solid; Yield = 75%, o/p = 90/10; $^1$H NMR (400 MHz, d-DMSO) δ 11.49 (s, 1H), 8.15 (d, $J = 7.6$ Hz, 2H), 7.63 (d, $J = 7.6$ Hz, 2H), 7.49 - 7.43 (m, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 7.16 - 7.12 (m, 1H). $^{13}$C NMR (101 MHz, d-DMSO) δ 140.3, 138.6, 128.3, 126.8, 124.7, 123.0, 121.1, 120.4, 120.0, 119.8, 112.1, 104.0.

1-chloro-9H-carbazole (2b) (Kronberg et al., 2011)
White solid; Yield = 57%, o/p = 75/25; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.30 (s, 1H), 8.08 (d, $J = 7.8$ Hz, 1H), 7.98 (d, $J = 7.8$ Hz, 1H), 7.54 - 7.39 (m, 3H), 7.30 - 7.26 (m, 1H), 7.19 (t, $J = 7.8$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 139.3, 136.7, 126.6, 125.1, 124.8, 123.5, 120.8, 120.2, 120.1, 118.8, 116.0, 111.1.

1,8-dibromo-9H-carbazole (2c) (Thummel et al., 2008)
White solid; Yield = 75%, o/p = 89/11; $^1$H NMR (400 MHz, d-DMSO) δ 11.19 (s, 1H), 8.23-8.20 (m, 2H), 7.84 - 7.56 (m, 2H), 7.33 - 7.07 (m, 2H). $^{13}$C NMR (101 MHz, d-DMSO) δ 138.8, 129.8, 125.2, 121.6, 120.5, 104.6.

1-bromo-8-chloro-9H-carbazole (2d)

White solid; Yield = 74%, o/p = 88/12; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.37 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.12 - 7.13 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 137.9, 136.3, 128.7, 125.8, 125.1, 124.7, 121.2, 120.9, 119.8, 119.3, 116.5, 104.5. HRMS (ESI) calcd for C$_{12}$H$_7$BrClN m/z [M + H]$^+$: 279.9523; found: 279.9521.

1-bromo-8-phenyl-9H-carbazole (2e)

White solid; Yield = 70%, o/p = 85/15; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.46 (s, 1H), 8.08 - 8.06 (m, 2H), 7.75 (d, J = 7.3 Hz, 2H), 7.67 - 7.57 (m, 3H), 7.52 (d, J = 7.4 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.19 - 7.14 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.7, 137.1, 136.7, 129.5, 128.3, 127.8, 126.6, 125.6, 124.9, 124.1, 120.8, 120.7, 120.0, 119.5, 104.3. HRMS (ESI) calcd for C$_{18}$H$_{12}$BrCINH m/z [M + H]$^+$: 322.0226; found: 322.0231.

1-chloro-8-phenyl-9H-carbazole (2f)

White solid; Yield = 67%, o/p = 80/20; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.36 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.1 Hz, 2H), 7.52 - 7.48 (m, 2H), 7.44 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.7, 137.1, 136.7, 129.5, 128.3, 127.8, 126.6, 125.6, 124.0, 120.7, 120.4, 119.9, 118.9, 116.1. HRMS (ESI) calcd for C$_{18}$H$_{12}$ClCINH m/z [M + H]$^+$: 278.0731; found: 278.0737.

1-bromo-2-methyl-9H-carbazole (2g) (Bumwoo et al., 2016)

White solid; Yield = 83%, o/p = 92/8; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.26 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.55 - 7.40 (m, 2H), 7.34 - 7.23 (m, 1H), 7.15 (d, J = 7.7 Hz, 1H), 2.61 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 139.1, 138.8, 134.7, 126.0, 124.0, 122.3, 122.1, 120.5, 119.9, 118.8, 110.9, 106.2, 22.4.

1-chloro-2-methyl-9H-carbazole (2h)

White solid; Yield = 75%, o/p = 88/12; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.18 (s, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.44 (s, 2H), 7.10 (d, J = 7.8 Hz, 1H), 2.56 (s, 3H). $^{13}$C NMR (101 MHz,
CDCl$_3$ $\delta$ 139.3, 137.3, 132.9, 125.9, 123.9, 122.8, 122.2, 120.5, 120.0, 118.2, 115.9, 111.0, 19.1. HRMS (ESI) calcd for C$_{13}$H$_{10}$ClN m/z [M + H]$^+$: 216.0575; found: 216.0576.

1-bromo-2-methoxy-9H-carbazole (2i)
White solid; Yield = 73%, o/p = 85/15; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.15 (s, 1H), 7.95 (d, $J$ = 7.7 Hz, 1H), 7.89 (d, $J$ = 8.5 Hz, 1H), 7.45 - 7.33 (m, 2H), 7.28 - 7.17 (m, 1H), 6.84 (d, $J$ = 8.5 Hz, 1H), 3.98 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 154.5, 139.9, 139.4, 125.4, 123.9, 120.1, 120.1, 119.6, 118.6, 110.8, 104.9, 92.7, 57.0. HRMS (ESI) calcd for C$_{13}$H$_{10}$BrNO m/z [M + H]$^+$: 276.0019; found: 276.0029.

1-chloro-2-methoxy-9H-carbazole (2j)
White solid; Yield = 75%, o/p = 87/13; $^1$H NMR (400 MHz, d-DMSO) $\delta$ 11.41 (s, 1H), 8.05 - 7.98 (m, 2H), 7.56 (d, $J$ = 6.1 Hz, 1H), 7.42 - 7.38 (m, 1H), 7.21 - 7.18 (m, 1H), 7.02 - 6.96 (m, 1H), 3.95 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 153.6, 139.7, 138.5, 125.4, 123.7, 120.0, 119.9, 118.8, 118.7, 110.9, 105.1, 103.7, 56.9. HRMS (ESI) calcd for C$_{13}$H$_{10}$ClNO m/z [M + H]$^+$: 232.0524; found: 232.0527.

1-bromo-2-phenyl-9H-carbazole (2k)
Gray solid; Yield = 75%, o/p = 88/12; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.39 (s, 1H), 8.11 (d, $J$ = 8 Hz, 1H), 8.05 (t, $J$ = 8 Hz, 1H), 7.62 - 7.57 (m, 2H), 7.52 - 7.46 (m, 5H), 7.35 - 7.32 (m, 1H), 7.28 (s, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.1, 139.4, 139.3, 138.8, 129.8, 128.8, 127.9, 127.4, 126.4, 123.7, 123.3, 122.5, 120.8, 120.1, 119.0, 111.0. HRMS (ESI) calcd for C$_{13}$H$_{12}$BrN m/z [M + H]$^+$: 322.0226; found: 322.0231.

1-bromo-6-methyl-9H-carbazole (2l) (Driver et al., 2009)
White solid; Yield = 78%, o/p = 91/9; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.17 (s, 1H), 7.97 (d, $J$ = 7.8 Hz, 1H), 7.85 (s, 1H), 7.55 (d, $J$ = 7.7 Hz, 1H), 7.39 (d, $J$ = 8.2 Hz, 1H), 7.28 (d, $J$ = 8.2 Hz, 1H), 7.10 (t, $J$ = 7.7 Hz, 1H), 2.54 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 138.4, 137.3, 129.5, 127.9, 127.8, 124.50, 123.8, 120.7, 120.3, 119.2, 110.7, 104.1, 21.5.

1-chloro-6-methyl-9H-carbazole (2m)
White solid; Yield = 70%, o/p = 82/18; $^1$H NMR (400 MHz, d-DMSO) $\delta$ 11.40 (s, 1H), 8.06 - 7.99 (m, 2H), 7.57 (d, $J$ = 6.6 Hz, 1H), 7.41 - 7.37 (m, 1H), 7.21 - 7.16 (m, 1H), 7.02 - 6.99 (m, 1H), 3.96 (s, 3H). $^{13}$C NMR (101 MHz, d-DMSO) $\delta$ 153.6, 140.8, 138.8, 125.6, 123.3, 120.3, 119.7, 119.6, 118.6,
111.7, 105.2, 103.1, 57.1. HRMS (ESI) calcd for C_{13}H_{10}ClNH m/z [M + H]^+: 216.0575; found: 216.0579.

**1,6-dibromo-9H-carbazole (2n)**

Yellow solid; Yield = 63%, o/p = 75/25; 'H NMR (400 MHz, d-DMSO) δ 11.64 (s, 1H), 8.41 (s, 2H), 8.21 (dd, J = 7.8 Hz, 1H), 7.66 (dd, J = 7.7 Hz, 1H), 7.54 - 7.59 (m, 2H), 7.33 - 7.01 (m, 2H). ^13^C NMR (101 MHz, d-DMSO) δ 139.0, 138.9, 129.2, 129.1, 125.0, 123.8, 123.6, 120.9, 120.6, 114.1, 111.9, 104.1. HRMS (ESI) calcd for C_{13}H_{12}Br_{2}N m/z [M + H]^+: 323.9018; found: 323.9016.

**1-bromo-6-methoxy-9H-carbazole (2o)**

White solid; Yield = 70%, o/p = 81/19; 'H NMR (400 MHz, CDCl₃) δ 8.09 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.63 - 7.62 (m, 1H), 7.47 - 7.43 (m, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.28 - 7.26 (m, 1H), 7.14 - 7.11 (m, 1H), 3.98 (s, 3H). ^13^C NMR (101 MHz, CDCl₃) δ 144.9, 139.1, 130.8, 126.3, 123.3, 123.1, 122.4, 119.5, 110.8, 107.3, 106.7, 55.8. HRMS (ESI) calcd for C_{13}H_{13}BrNO m/z [M + H]^+: 276.0019; found: 276.0029.

**1-bromo-6-phenyl-9H-carbazole (2p)**

White solid; Yield = 73%, o/p = 86/14; 'H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 8.26 (s, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.70 - 7.72 (m, 3H), 7.61 - 7.45 (m, 4H), 7.37 (t, J = 7.4 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H). ^13^C NMR (101 MHz, CDCl₃) δ 141.8, 138.5, 133.7, 128.8, 128.2, 127.3, 126.7, 126.2, 124.7, 124.2, 122.2, 120.7, 119.4, 119.3, 111.3, 104.2. HRMS (ESI) calcd for C_{13}H_{12}BrNOH m/z [M + H]^+: 322.0226; found: 322.0231.

**1-bromo-6-iodo-9H-carbazole (2q)**

White solid; Yield = 66%, o/p = 80/20; 'H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 8.26 (s, 1H), 7.94 (d, J = 7.4 Hz, 1H), 7.72 (d, J = 6.9 Hz, 1H), 7.61 (d, J = 7.3 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H). ^13^C NMR (101 MHz, CDCl₃) δ 138.1, 134.8, 129.7, 128.7, 127.2, 126.1, 123.2, 121.0, 119.5, 113.0, 104.2, 82.7. HRMS (ESI) calcd for C_{13}H_{12}IBr m/z [M + H]^+: 371.8879; found: 371.8872.

**1-bromo-3,6-dichloro-9H-carbazole (2r)**

White solid; Yield = 78%; 'H NMR (400 MHz, CDCl₃) δ 8.25 (s, 1H), 7.94 (s, 1H), 7.89 (s, 1H), 7.59 (s, 1H), 7.47 - 7.40 (m, 2H). ^13^C NMR (101 MHz, CDCl₃) δ 137.8, 137.1, 128.3, 127.4, 125.9, 125.5, 124.0, 123.9, 120.7, 119.3, 112.3, 104.3. HRMS (ESI) calcd for C_{13}H_{12}BrCl₂ m/z [M + H]^+: 573.
313.9133; found: 313.9136.

1,3,6-trichloro-9H-carbazole (2s) (Pielichowski et al., 2004)
White solid; Yield = 78%; \(^1^H\) NMR (400 MHz, d-DMSO) \(\delta \) 11.93 (s, 1H), 8.45 (d, \(J = 11.8\) Hz, 2H), 7.68 (s, 1H), 7.62 - 7.52 (m, 2H). \(^1^C\) NMR (101 MHz, d-DMSO) \(\delta \) 139.5, 136.4, 130.0, 127.8, 125.1, 124.2, 123.9, 116.9, 114.2, 112.3, 110.9.

1,3,6-tribromo-9H-carbazole (2t) (Pielichowski et al., 2004)
Gray solid; Yield = 80%; \(^1^H\) NMR (400 MHz, d-DMSO) \(\delta \) 11.84 (s, 1H), 8.50 (s, 2H), 7.83 (s, 1H), 7.60 - 7.55 (m, 2H). \(^1^C\) NMR (101 MHz, d-DMSO) \(\delta \) 139.4, 138.0, 130.5, 130.0, 124.9, 124.3, 124.0, 123.3, 114.3, 112.3, 111.3, 105.0. HRMS (ESI) calcd for \(\text{C}_{12}\text{H}_{7}\text{Br}_3\text{N}\) m/z [M + H]^+: 401.8123; found: 401.8129.

3,6-dibromo-1-chloro-9H-carbazole (2u)
White solid; Yield = 80%; \(^1^H\) NMR (400 MHz, d-DMSO) \(\delta \) 11.91 (s, 1H), 8.30 (d, \(J = 9.1\) Hz, 2H), 7.60 - 7.55 (m, 2H). \(^1^C\) NMR (101 MHz, d-DMSO) \(\delta \) 139.4, 136.3, 127.4, 125.4, 124.6, 124.5, 123.7, 123.4, 121.2, 119.9, 116.6, 113.7. HRMS (ESI) calcd for \(\text{C}_{12}\text{H}_{12}\text{Br}_2\text{ClNH}\) m/z [M + H]^+: 357.8628; found: 357.8630.

1-bromo-3,6-diiodo-9H-carbazole (2v)
White solid; Yield = 80%; \(^1^H\) NMR (400 MHz, d-DMSO) \(\delta \) 11.78 (s, 1H), 8.62 (s, 2H), 7.91 (s, 1H), 7.74 (d, \(J = 6.9\) Hz, 1H), 7.42 (d, \(J = 8.3\) Hz, 1H). \(^1^C\) NMR (101 MHz, d-DMSO) \(\delta \) 139.5, 138.0, 135.6, 135.4, 130.2, 129.1, 125.5, 124.5, 114.6, 105.2, 83.4, 82.2. HRMS (ESI) calcd for \(\text{C}_{12}\text{H}_{13}\text{BrI}_2\text{NH}\) m/z [M + H]^+: 497.7846; found: 497.7851.

1-chloro-3,6-diiodo-9H-carbazole (2w)
Brown solid; Yield = 83%; \(^1^H\) NMR (400 MHz, CDCl_3) \(\delta \) 8.29 (s, 1H), 8.24 (s, 1H), 8.13 (s, 1H), 7.73 - 7.63 (m, 2H), 7.23 (d, \(J = 8.5\) Hz, 1H). \(^1^C\) NMR (101 MHz, CDCl_3) \(\delta \) 138.3, 136.0, 135.5, 133.3, 129.8, 127.8, 125.7, 125.3, 124.6, 118.8, 117.0, 113.1. HRMS (ESI) calcd for \(\text{C}_{13}\text{H}_6\text{ClI}_2\text{NH}\) m/z [M + H]^+: 453.8351; found: 453.8355.

1-bromo-3,6-diphenyl-9H-carbazole (2x)
Yellow solid; Yield = 75%; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.30 (s, 1H), 8.25 (s, 2H), 7.84 (s, 1H), 7.74 - 7.69 (m, 5H), 7.55 - 7.48 (m, 5H), 7.39 (d, J = 7.2 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.7, 140.9, 139.0, 138.0, 134.7, 133.6, 128.9, 128.9, 127.3, 127.0, 126.7, 126.3, 125.1, 124.4, 119.5, 118.0, 111.3, 104.5. HRMS (ESI) calcd for C$_{23}$H$_{16}$BrN m/z [M + H]$^+$: 398.0539; found: 398.0543.

1-bromo-3,6-di-tert-butyl-9H-carbazole (2y) (Ema et al., 2016)
White solid; Yield = 67%; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.30 (s, 1H), 8.25 (s, 2H), 7.84 (s, 1H), 7.74 - 7.69 (m, 5H), 7.55 - 7.48 (m, 5H), 7.39 (d, J = 7.2 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.7, 140.9, 139.0, 138.0, 134.7, 133.6, 128.9, 128.9, 127.3, 127.0, 126.7, 126.3, 125.1, 124.4, 119.5, 118.0, 111.3, 104.5. HRMS (ESI) calcd for C$_{23}$H$_{16}$BrN m/z [M + H]$^+$: 398.0539; found: 398.0543.

3,6-di-tert-butyl-1-chloro-9H-carbazole (2z)
Brown solid; Yield = 85%; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.30 (s, 1H), 8.25 (s, 2H), 7.84 (s, 1H), 7.74 - 7.69 (m, 5H), 7.55 - 7.48 (m, 5H), 7.39 (d, J = 7.2 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.7, 140.9, 139.0, 138.0, 134.7, 133.6, 128.9, 128.9, 127.3, 127.0, 126.7, 126.3, 125.1, 124.4, 119.5, 118.0, 111.3, 104.5. HRMS (ESI) calcd for C$_{23}$H$_{16}$ClN m/z [M + H]$^+$: 314.1670; found: 314.1672.

1,2,7-tribromo-9H-carbazole (2aa)
White solid; Yield = 68%, α/ρ = 82/18; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.30 (s, 1H), 8.25 (s, 2H), 7.84 (s, 1H), 7.74 - 7.69 (m, 5H), 7.55 - 7.48 (m, 5H), 7.39 (d, J = 7.2 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 139.9, 139.3, 124.7, 123.8, 122.5, 122.4, 121.9, 121.4, 120.3, 120.0, 114.2, 106.9.

1-chloro-2,7-dimethoxy-9H-carbazole (2ab)
White solid; Yield = 55%, α/ρ = 71/29; $^1$H NMR (400 MHz, d-DMSO) δ 11.24 (s, 1H), 7.90 (t, J = 7.9 Hz, 2H), 7.02 (s, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 3H). $^{13}$C NMR (101 MHz, d-DMSO) δ 158.6, 152.7, 142.1, 138.7, 132.7, 138.7, 121.1, 118.8, 118.6, 118.0, 108.5, 105.2, 103.1, 95.7, 57.1, 55.7. HRMS (ESI) calcd for C$_{14}$H$_{12}$ClNO$_2$H m/z [M + H]$^+$: 262.0629; found: 262.0631.

1-bromo-4-(oxiran-2-ylmethoxy)-9H-carbazole (2ac)
White solid; Yield = 66%, α/ρ = 78/22; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.36 (s, 1H), 8.34 (s, 1H), 7.55 - 7.41 (m, 3H), 7.35 - 7.31 (m, 1H), 6.57 (d, J = 8.5 Hz, 1H), 4.50 - 4.47 (m, 1H), 4.23 - 4.19 (m, 1H), 3.59 (s, 1H), 3.06 - 3.04 (m, 1H), 2.94 - 2.92 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.2, 139.0,
HRMS (ESI) calcd for C_{15}H_{12}BrNO_{2}H m/z [M + H]^+; 318.0124; found: 318.0125.

8-bromo-7H-benzo[c]carbazole (2ad) (Lee et al., 2015)
White solid; Yield = 58%, o/p = 71/29; ¹H NMR (400 MHz, CDCl₃) δ 8.71 (d, J = 8.3 Hz, 1H), 8.59 (s, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.75 - 7.70 (m, 1H), 7.65 - 7.56 (m, 2H), 7.54 - 7.50 (m, 1H), 7.28 - 7.24 (m, 1H).
³¹C NMR (101 MHz, CDCl₃) δ 137.0, 136.9, 129.9, 129.4, 129.3, 128.2, 127.1, 126.5, 125.2, 123.4, 123.1, 121.3, 121.1, 116.0, 112.6, 104.7.

6-bromo-5H-benzofuro[3,2-c]carbazole (2ae)
White solid; Yield = 65%, o/p = 77/23; ¹H NMR (400 MHz, d-DMSO) δ 11.89 (s, 1H), 8.47 (s, 1H), 8.35 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.59 - 7.38 (m, 4H).
³¹C NMR (101 MHz, d-DMSO) δ 155.91, 149.91, 139.91, 138.50, 126.75, 126.45, 124.33, 123.88, 122.34, 120.84, 120.47, 116.76, 112.54, 112.11, 108.94, 99.36. HRMS (ESI) calcd for C_{18}H_{10}BrNO_{2}H m/z [M + H]^+; 336.0019; found: 336.0020.

methyl 2-(1-bromo-6-chloro-9H-carbazol-2-yl)propanoate (2af)
White solid; Yield = 75%, o/p = 90/10; ¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 7.90 (s, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.35 (s, 2H), 7.15 (d, J = 7.2 Hz, 1H), 4.38 - 4.33 (m, 1H), 3.69 (s, 3H), 1.57 (s, 3H).
³¹C NMR (101 MHz, CDCl₃) δ 174.43, 139.13, 139.03, 137.52, 126.41, 125.51, 124.65, 122.44, 120.33, 119.60, 119.37, 111.95, 105.97, 52.21, 44.29, 18.12. HRMS (ESI) calcd for C_{16}H_{13}BrClNO_{2}H m/z [M + H]^+; 365.9891; found: 365.9897.

propyl 2-(1-bromo-6-chloro-9H-carbazol-2-yl)propanoate (2ag)
White solid; Yield = 74%, o/p = 90/10; ¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1H), 7.97 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.40 (s, 2H), 7.20 (d, J = 8.4 Hz, 1H), 4.40 - 4.35 (m, 1H), 4.07 (t, J = 6.6 Hz, 2H), 1.58 (d, J = 6.4 Hz, 5H), 0.85 (t, J = 7.2 Hz, 3H).
³¹C NMR (101 MHz, CDCl₃) δ 174.05, 139.21, 137.88, 137.58, 126.47, 125.65, 124.84, 122.26, 120.43, 119.59, 119.54, 111.98, 106.12, 66.57, 44.45, 21.90, 18.12, 10.26. HRMS (ESI) calcd for C_{16}H_{17}BrClNO_{2}Na m/z [M + Na]^+; 416.0023; found: 416.0028.
2-chloro-N-methylaniline (6a) (Zhu et al., 2015)
Colorless oil; Yield = 78%, o/p = 85/15; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 (d, $J = 8.3$ Hz, 1H), 7.27 - 7.18 (m, 1H), 6.72 - 6.68 (m, 2H), 4.40 (br, 1H), 2.96 (d, $J = 5.0$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 145.0, 129.0, 127.9, 119.1, 117.0, 110.6, 30.4.

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\text{N-allyl-2-chloroaniline (6f) (Wang et al., 2016)}
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Colorless oil; Yield = 85%, o/p = 91/9; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 - 7.29 (m, 4H), 7.12 - 7.02 (m, 1H), 6.66 - 6.63 (m, 2H), 4.75 (br, 1H), 4.43 - 4.40 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 143.9, 138.8, 129.1, 128.8, 127.8, 127.3, 117.5, 111.5, 47.9.

2-chloro-N-ethylaniline (6b) (Zh0u et al., 2016)
Colorless oil; Yield = 77%, o/p = 85/15; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26 - 7.24 (m, 1H), 7.16 - 7.09 (m, 1H), 6.67 - 6.54 (m, 2H), 4.19 (br, 1H), 3.23 - 3.18 (m, 2H), 1.33 - 1.22 (m, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 144.2, 129.1, 127.8, 118.9, 116.9, 111.1, 38.2, 14.7.

N-butyl-2-chloroaniline (6c) (Shankarling et al., 2013)
Colorless oil; Yield = 75%, o/p = 84/16; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.20 (d, $J = 6.4$ Hz, 1H), 7.11 - 7.07 (m, 1H), 6.62 - 6.50 (m, 2H), 4.21 (br, 1H), 3.11 (t, $J = 6.4$ Hz, 2H), 1.65 - 1.58 (m, 2H), 1.44 - 1.39 (m, 2H), 0.93 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 144.3, 129.1, 127.7, 119.0, 116.8, 111.1, 43.4, 31.4, 20.3, 13.9.

2-chloro-N-cyclohexylaniline (6d) (Cai et al., 2017)
Light yellow oil; Yield = 82%, o/p = 88/12; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.23 - 7.20 (m, 1H), 7.11 - 7.06 (m, 1H), 6.65 (d, $J = 8.4$ Hz, 1H), 6.58 - 6.53 (m, 1H), 4.20 (br, 1H), 3.28 (s, 1H), 2.03 (d, $J = 10.8$ Hz, 2H), 1.77 - 1.74(m, 2H), 1.65 - 1.62m, 1H), 1.41 - 1.32(m 2H), 1.26 - 1.18(m 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 143.2, 129.3, 127.7, 119.0, 116.5, 111.7, 51.4, 33.2, 25.9, 24.9.

2-chloro-N-dodecylaniline (6e)
Light yellow oil; Yield = 65%, o/p = 75/25; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 - 7.26 (m, 1H), 7.21 - 7.17(m, 1H), 6.72 - 6.60(m, 2H), 4.31 (br, 1H), 3.23 - 3.20 (m, 2H), 1.72 - 1.33 (m, 20H), 0.95 (t, $J = 6.4$Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 144.2, 129.0, 127.7, 118.9, 116.8, 111.1, 43.7, 31.9, 29.7, 29.6, 29.4, 29.2, 27.1, 22.7, 14.1. HRMS (ESI) calcd for C$_{18}$H$_{30}$ClN: m/z [M + H]$^+$: 296.2140; found: 296.2144.

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\text{V-allyl-2-chloroaniline (6f) (Wang et al., 2016)}
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3-((2-chlorophenyl)amino)propanenitrile (6g) (Zargarian et al., 2016)
White solid; Yield = 75%, o/p = 86/14; 1H NMR (400 MHz, CDCl3) δ 7.38 - 7.31 (m, 1H), 7.22 (t, J = 7.6 Hz, 1H), 6.78 - 6.68 (m, 2H), 4.68 (br, 1H), 3.67 - 3.61 (m, 2H), 2.75 - 2.69 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 142.2, 129.65, 127.9, 119.8, 118.5, 117.8, 110.9, 39.5, 18.1.

2-chloro-N-phenylaniline (6j) (Rossi et al., 2009)
Light yellow oil; Yield = 70%, o/p = 83/17; 1H NMR (400 MHz, CDCl3) δ 7.41 - 7.30 (m, 4H), 7.22 - 7.14 (m, 3H), 7.09 (t, J = 7.3 Hz, 1H), 6.85 (t, J = 7.6 Hz, 1H), 6.16 (br, 1H). 13C NMR (101 MHz, CDCl3) δ 141.6, 140.4, 129.8, 129.5, 127.5, 122.7, 121.6, 120.4, 120.3, 115.7.

1-chloro-N-phenynaphthalen-2-amine (6i) (Falvey et al., 2005)
Brown oil; Yield = 90%, o/p = 95/17; 1H NMR (400 MHz, CDCl3) δ 8.10 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.30 (t, J = 7.6 Hz, 3H), 7.14 (d, J = 8.0 Hz, 2H), 7.03 (t, J = 7.1 Hz, 1H), 6.37 (br, 1H). 13C NMR (101 MHz, CDCl3) δ 141.7, 137.9, 131.9, 129.5, 129.4, 128.1, 127.5, 127.4, 123.7, 122.9, 122.9, 120.3, 117.3, 115.1.

9-chloro-3,4-dihydro-1H-benzo[b]azepin-5(2H)-one (6h) (Mori et al., 1997)
White solid; Yield = 76%, o/p = 88/12; 1H NMR (400 MHz, CDCl3) δ 7.61 (d, J = 7.6 Hz, 1H), 7.37 - 7.35 (m, 1H), 6.73 (t, J = 7.9 Hz, 1H), 5.40 (s, 1H), 3.33 - 3.29 (m, 2H), 2.82 (t, J = 7.2 Hz, 2H), 2.26 - 2.19 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 201.9, 149.1, 132.1, 128.3, 126.6, 121.3, 118.3, 47.7, 41.0, 31.9.

2-chloro-N-methyl-4-(trifluoromethyl)aniline (6k) (Roth et al., 2003)
Light yellow oil; Yield = 90%; 1H NMR (400 MHz, CDCl3) δ 7.54 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 4.72 (s, 1H), 2.99 (d, J = 5.2 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 147.3, 126.1, 125.6, 125.2, 118.4, 109.5, 30.1.

3-chloro-4-(methylamino)benzonitrile (6l) (Jeganmohan et al., 2013)
Light yellow oil; Yield = 88%; Yield = 88%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.50 (d, $J$ = 1.6 Hz, 1H), 7.43 (d, $J$ = 8.4 Hz, 1H), 6.61 (d, $J$ = 8.4 Hz, 1H), 4.91 (br, 1H), 2.96 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 148.1, 132.5, 132.3, 119.1, 118.5, 109.9, 98.8, 29.9.

2-chloroaniline (6m) (Sun et al., 2018)
Light yellow oil; Yield = 58%, o/p = 70/30; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 (d, $J$ = 7.9 Hz, 1H), 7.14 - 7.10 (m, 1H), 6.82 - 6.80 (m, 1H), 6.77 - 6.73 (m, 1H), 4.09 (s, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 142.9, 129.4, 127.6, 119.3, 119.0, 115.9.

5-chlorobenzo[c][1,2,5]thiadiazol-4-amine (6n) (Deng et al., 2005)
Light yellow oil; Yield = 80%, o/p = 95/5; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.47 (d, $J$ = 9.2 Hz, 1H), 7.30 (d, $J$ = 9.2 Hz, 1H), 5.02 (br, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.2, 147.3, 135.1, 131.9, 112.1, 109.0.

1-phenyl-9H-carbazole (7) (Unsworth et al., 2015)
White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.36 (s, 1H), 8.19 - 8.14 (m, 2H), 7.76 (d, $J$ = 7.6 Hz, 2H), 7.62 (t, $J$ = 7.2 Hz, 2H), 7.52 - 7.45 (m, 4H), 7.41 - 7.38 (m, 1H), 7.34 - 7.30 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 139.5, 139.1, 137.3, 129.3, 128.4, 127.6, 126.0, 125.8, 125.1, 123.7, 123.6, 120.5, 119.9, 119.6, 119.5, 110.7.

9H-carbazole-1-carbaldehyde (8) (Brimble et al., 2016)
Red solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 10.28 (s, 1H), 10.18 (s, 1H), 8.30 (d, $J$ = 7.7 Hz, 1H), 8.10 (d, $J$ = 7.8 Hz, 1H), 7.80 (d, $J$ = 7.4 Hz, 1H), 7.75 - 7.48 (m, 2H), 7.35 - 7.30 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 193.5, 140.0, 138.1, 131.3, 126.9, 126.8, 124.7, 121.9, 120.5, 119.5, 118.8, 111.5.

1-methoxy-9H-carbazole (9) (Vranken et al., 2017)
White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.52 (s, 1H), 8.32-8.30 (m, 1H), 8.00 - 7.93 (m, 1H), 7.66 - 7.61 (m, 1H), 7.57 (d, $J$ = 8.0 Hz, 1H), 7.50 - 7.47 (m, 1H), 7.42 - 7.37 (m, 1H), 7.09 - 7.07 (m, 1H), 4.12 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 145.9, 139.5, 130.0, 125.9, 124.6, 123.9, 120.8, 119.9, 119.6, 113.1, 111.2, 106.2, 55.6.
9H-carbazol-1-amine (10) (Gale et al., 2009)

White solid; $^1$H NMR (400 MHz, d$_2$-DMSO) δ 10.81 (s, 1H), 8.03 (d, $J$ = 8.0 Hz, 1H), 7.52 (d, $J$ = 8.0 Hz, 1H), 7.37 (t, $J$ = 8.0 Hz, 2H), 7.13 (t, $J$ = 7.4 Hz, 1H), 6.94 (t, $J$ = 7.6 Hz, 1H), 6.68 (d, $J$ = 7.5 Hz, 1H), 5.19 (s, 2H). $^{13}$C NMR (101 MHz, d$_2$-DMSO) δ 139.5, 133.9, 129.2, 125.4, 123.7, 123.1, 120.6, 120.2, 118.7, 111.4, 109.7, 108.8.

\[ \text{9H-carbazol-1-amine (10)} \]

1,8-dibromo-3-methyl-9H-carbazole (11)

White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.19 (s, 1H), 7.92 - 7.89 (m, 1H), 7.72 (s, 1H), 7.57 (d, $J$ = 7.6 Hz, 1H), 7.42 (s, 1H), 7.13 - 7.09 (m, 1H), 2.50 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.0, 136.0, 131.1, 129.9, 128.5, 124.9, 124.7, 120.9, 119.8, 119.7, 104.4, 103.9, 21.2. HRMS (ESI) calcd for C$_{13}$H$_9$Br$_2$NH m/z [M + H]$^+$: 337.9175; found: 337.9178.

\[ \text{1,8-dibromo-3-methyl-9H-carbazole (11)} \]

1,8-dimethoxy-3-methyl-9H-carbazole (12) (Tamariz et al., 2017)

White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.42 (s, 1H), 7.64 (d, $J$ = 7.8 Hz, 1H), 7.47 (s, 1H), 7.14 (t, $J$ = 7.8 Hz, 1H), 6.89 (d, $J$ = 7.7 Hz, 1H), 6.74 (s, 1H), 4.01 (d, $J$ = 4.1 Hz, 6H), 2.55 (s, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 146.0, 145.6, 129.6, 124.7, 120.9, 119.4, 113.0, 112.7, 107.6, 105.6, 55.5, 21.9.

\[ \text{1,8-dimethoxy-3-methyl-9H-carbazole (12)} \]

1,8-dimethoxy-9H-carbazole (13) (Sperry et al., 2017)

White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.89 (s, 1H), 7.86 (d, $J$ = 7.9 Hz, 2H), 7.32 (t, $J$ = 7.8 Hz, 2H), 7.02 (d, $J$ = 7.8 Hz, 2H), 4.09 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 146.0, 129.6, 124.7, 119.7, 113.1, 105.8, 55.5.

\[ \text{1,8-dimethoxy-9H-carbazole (13)} \]

4-bromo-1,8-dimethoxy-9H-carbazole (14)

White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.69 (s, 1H), 8.35 (d, $J$ = 8.1 Hz, 1H), 7.32 (d, $J$ = 8.4 Hz, 1H), 7.26 (t, $J$ = 8.0 Hz, 1H), 6.98 (d, $J$ = 7.8 Hz, 1H), 6.76 (d, $J$ = 8.3 Hz, 1H), 4.05 (s, 3H), 4.01 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 145.6, 145.2, 130.6, 129.7, 124.2, 123.0, 122.8, 119.7, 114.8, 107.3, 106.5, 106.2, 55.8, 55.6. HRMS (ESI) calcd for C$_{14}$H$_{12}$BrNO$_2$H m/z [M + H]$^+$: 306.0124; found: 306.0134.

\[ \text{4-bromo-1,8-dimethoxy-9H-carbazole (14)} \]

1,8-dimethoxy-9H-carbazole-4-carbaldehyde (15)
White solid; mp 235 - 238 °C; 1H NMR (400 MHz, d-DMSO) δ 11.77 (s, 1H), 10.21 (s, 1H), 8.63 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 4.12 (s, 3H), 4.00 (s, 3H). 13C NMR (101 MHz, d-DMSO) δ 192.5, 151.8, 146.4, 131.9, 131.2, 130.4, 125.6, 123.7, 121.4, 119.7, 118.2, 107.3, 105.8, 56.5, 55.9 HRMS (ESI) calcd for C14H12BrNO2H m/z [M + H]+: 256.0968; found: 256.0973.

1-methoxy-6-methyl-9H-carbazole (16) (Tamariz et al., 2011)
White solid; 1H NMR (400 MHz, CDCl3) δ 8.21 (s, 1H), 7.90 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.29 (d, J = 4.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 4.05 (s, 3H), 2.57 (s, 3H).

13C NMR (101 MHz, CDCl3) δ 145.7, 137.4, 130.1, 128.7, 127.1, 124.2, 123.8, 119.9, 119.5, 112.8, 110.6, 105.7, 55.5, 21.4.

1-bromo-8-deuterium-9H-carbazole (18)
White solid; 1H NMR (400 MHz, CDCl3) δ 8.26 (s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.50-7.45 (m, 1H), 7.31-7.24 (m, 1H), 7.13 (t, J = 7.8 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 139.1, 128.0, 126.6, 126.5, 124.6, 123.7, 120.9, 120.6, 120.1, 119.3, 111.1, 104.1.

References

Chatterjee, T., Roh, G. B., Shoaib, M. A., Suhl, C. H., Kim, J. S., Cho, C. G. and Cho, E. J. (2017). Visible-Light-Induced Synthesis of Carbazoles by in Situ Formation of Photosensitizing Intermediate. Organic letters, 19, 1906 - 1909.

Svanfelt, J. and Kronberg, L. (2011). Synthesis of substituted diphenylamines and carbazoles: phototransformation products of diclofenac. Environmental Chemistry Letters, 9, 141 - 144.

Mudadu, M. S., Singh, A. N. and Thummel, R. P. (2008). Preparation and Study of 1,8-Di(pyrid-2′-yl)carbazoles. The Journal of organic chemistry, 73, 6513 - 6520.

Lee, S., Kwak, Y. and Bunwoo, P. A. R. K. U.S. (2016). Patent Application No. 15/093,400.

Stokes, B. J., Richert, K. J. and Driver, T. G. (2009). Examination of the Mechanism of Rh2(II)-Catalyzed Carbazole Formation Using Intramolecular Competition Experiments. The Journal of organic chemistry, 74, 6442 - 6451.

Bogdal, D.; Lukasiewicz, M. and Pielichowski, J. (2004). Halogenation of carbazole and other aromatic compounds with hydrohalic acids and hydrogen peroxide under microwave irradiation. Green Chemistry, 6, 110 - 113.

Maeda, C., Todaka, T., Ueda, T. and Ema, T. (2016). Color-Tunable Solid-State Fluorescence Emission from Carbazole-Based BODIPY. Chemistry—A European Journal, 22, 7508 - 7513.

Lee, B., Lee, S., Kim, D. and Lee, H. (2015) Preparation of carbazole compounds as organic electronic device materials. PCT Int. Appl., 2015108377.

Wang, D., Kuang, D., Zhang, F., Yang, C. and Zhu, X. (2015). Room-Temperature Copper-Catalyzed Arylation of Dimethylamine and Methylamine in Neat Water. Advanced Synthesis & Catalysis, Yuan, M. L., Xie, J. H., Zhu, S. F. and Zhou, Q. L. (2016). Deoxygenative Hydrogenation of Amides...
Catalyzed by a Well-Defined Iridium Pincer Complex. ACS Catalysis, 6, 3665 - 3669.

Lobo, H. R., Singh, B. S., Pinjari, D. V., Pandit, A. B. and Shankarling, G. S. (2013). Ultrasound-assisted intensification of bio-catalyzed synthesis of mono-N-alkyl aromatic amines. Biochemical engineering journal, 70, 29 - 34.

Li, Z. L. and Cai, C. (2017). Iron Catalyzed Oxidative C(sp³)-N Cross Coupling of Amides with C(sp³)-H via a Radical Process. ChemistrySelect, 2, 8076 - 8079.

Du, Z., Yan, Y., Fu, Y. and Wang, K. (2016). Palladium-Catalyzed Direct Amination of Allylic Alcohols in Aqueous Media. Asian Journal of Organic Chemistry, 5, 812 - 818.

Lapointe, S. and Zargarian, D. (2016). On the mechanism of Ni(II)-promoted Michael-type hydroamination of acrylonitrile and its substituted derivatives. Dalton Transactions, 45, 15800 - 15810.

Buden, M. E., Vaillard, V. A., Martin, S. E. and Rossi, R. A. (2009). Synthesis of Carbazoles by Intramolecular Arylation of Diarylamide Anions. The Journal of organic chemistry, 74, 4490 - 4498.

Kung, A. C. and Falvey, D. E. (2005). Photogenerated N-Methyl-N-1-naphthyl nitretrium Ion: Laser Flash Photolysis, Trapping Rates, and Product Study. The Journal of organic chemistry, 70, 3127 - 3132.

Kondo, K., Ogawa, H., Yamashita, H., Miyamoto, H., Tanaka, M., Nakaya, K. and Mori, T. (1997). 7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzo- pine (OPC-41061): A potent, orally active nonpeptide arginine vasopressin V2 receptor antagonist. Bioorganic & Medicinal Chemistry, 7, 1743 - 1754.

Stenkamp, D., Mueller, S. G. and Roth, G. J.(2003). Preparation of arylamides as melanin concentrating hormone (MCH) receptor antagonists.

Chinnagolla, R. K., Pimparkar, S. and Jeganmohan, M. (2013). Ruthenium-catalyzed intramolecular selective halogenation of O-methylbenzohydroximoyl halides: a new route to halogenated aromatic nitriles. Chemical Communications, 49, 3146 - 3148.

Jiang, H. Y., Zhang, S. S. and Sun, B. (2018). Highly Selective Hydrogenation with Ionic Liquid Stabilized Nickel Nanoparticles. Catalysis Letters, 148, 1336 - 1344.

Xu, J.; Shen, Y.; Xiang, L. and Deng, Y. (2005). Chin. J. Pharm. 36, 593 - 595.

James, M. J., Clubley, R. E., Palate, K. Y., Procter, T. J., Wyton, A. C., O’Brien, P. and Unsworth, W. P. (2015). Silver(I)-Catalyzed Dearomatization of Alkyne-Tethered Indoles: Divergent Synthesis of Spirocyclic Indolenines and Carbazoles. Organic letters, 17, 4372 - 4375.

Rennison, D., Gueret, S. M., Laita, O., Bland, R. J., Sutherland, I. A., Boddy, I. K. and Brimble, M. A. (2016). Substituted Carbazoles – A New Class of Anthelmintic Agent. Australian Journal of Chemistry, 69, 1268 - 1276.

Arredondo, V., Hiew, S. C., Gutman, E. S., Premachandra, I. D. U. A. and Van Vranken, D. L. (2017). Enantioselective Palladium-Catalyzed Carbene Insertion into the N–H Bonds of Aromatic Heterocycles. Angewandte Chemie International Edition, 56, 4156 - 4159.

Hiscock, J. R., Caltagirone, C., Light, M. E., Hursthouse, M. B. and Gale, P. A. (2009). Fluorescent carbazolylurea anion receptors. Organic & biomolecular chemistry, 7, 1781 - 1783.

Hernández-Benítez, R. I., Zarate-Zarate, D., Delgado, F. and Tamariz, J. (2017). Palladium-Catalyzed Synthesis of Diarylamines and 1- and 2-Oxygenated Carbazoles: Total Syntheses of Natural Alkaloids Clauraila A, Clausenal, Clausine P, and 7-Methoxy-O-methylmukonal. Synthesis, 49, 4357 - 4371.

Li, J. and Sperry, J. (2017). Synthesis of putative clausenal from carbazole using sequential C–H borylations. Tetrahedron letters, 58, 1699 - 1701.

Bautista, R., Bernal, P., Montiel, L. E., Delgado, F. and Tamariz, J. (2011). Total Synthesis of the Natural Carbazoles Glycozolicine, Mukoline, and Mukolidine, Starting from
4,5-Dimethyleneoxazolidin-2-ones. Synthesis, 06, 929 - 933.

Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, Cheeseman, G. E., M. A. Robb, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., J. Sonnenberg, L., Hada, M., Ehara, M., Toyota, K., Fukuda, Hasegawa, R., Ishida, J., Nakajima, M., Honda, T., Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, J. A., Jr. Peralta, J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Keith, T., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., J. Burant, C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, J. M., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R. L., Morokuma, K., Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, O., Foresman, J. B., Ortiz, J. V., Cioslowski, J., and Fox, D. J., Gaussian, Inc., (2013). Wallingford CT.