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COMMUNICATION

Dearomatization-Scission-Aromatization of Anilines: En route to Synthesis of 3,3-Disubstituted Oxindoles with Wide Heteroatom Nucleophiles

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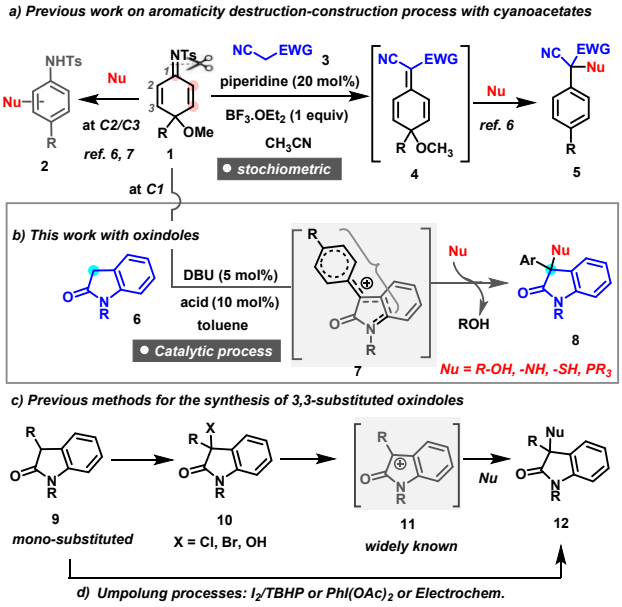
Herein, we report a catalytic, redox-neutral method for the difunctionalization of oxindoles using ketimines derived from anilines and heteronucleophiles. The reaction proceeds through dearomatization-aromatization strategy via tetra-substituted alkene intermediate stabilized by extended resonance, facilitating the selective formation of 3,3-disubstituted oxindoles with wide chemical space in good to high yields.

Functionalization of anilines is an attractive synthetic strategy for the synthesis of substituted aromatic compounds, and developed significant advancement in fundamental discoveries in C-C and C-X bond formation and cross-coupling reactions via aryldiazonium salts[1] and arylammonium salts.[2] In addition, dearomatization of aromatic compounds has been emerged as fundamental chemical transformation for synthesizing multi-functional aromatic compounds through the aromaticity destruction–reconstruction process.[3-5] In this line, substituted anilines was also employed to offer *ortho*- or *meta*- substituted anilines **2** by exploiting the reactivity of conjugated alkene (C-2 or C-3 of ketamine **1**) systems (Scheme 1a, left).[5] The seminal report came from Fan group, reported first time for aromatic carbon-nitrogen bond functionalization through a Knoevenagel-type condensation with active nitriles **3**, followed by nucleophilic addition for the construction of cyano-substituted quaternary centres (**5**) in the presence of stoichiometric $BF_3.OEt_2$ (Scheme 1a, right).[6,7] Given the importance of oxindole and its derivatives in many of natural products and bioactive molecules,[8] we sought to use an oxindole nucleophile to generate 3,3-disubstituted oxindoles **8** (Scheme 1b). Considering the existing methods, which are often constrained by the requirement of pre-functionalized C3-mono-substituted starting materials **9**. Exploiting the conventional nucleophilic



Scheme 1 Context and importance of this work

reactivity of oxindoles **9** with halogen followed by nucleophilic substitution gave 3,3-disubstituted oxindoles **12** in two steps via carbocationic intermediate **11** (Scheme 1c).[9,10] Umpolung processes were also developed for the direct synthesis of **12** following electrochemistry or in the presence of oxidizing agents (Scheme 1d).[11] Overall these reported methods required multiple steps, or pre-C3-functionalized oxindoles **9** for further transformation. Furthermore, use of transition-metals or strong oxidants and subsequent generation of waste adding the complexity to the existing methods.[9-11] In this report, we disclosed a catalytic, redox-neutral process for the synthesis of 3,3-disubstituted oxindoles **8** via resonance-stabilized cationic intermediate **7**, directly from oxindoles **6** via geminal dual C-H functionalization with an arenes and wide arrays of heteronucleophiles (Scheme 1b).

Recently, we reported a redox-neutral condition for the generation of all carbon quaternary centres on oxindoles using two distinct arenes.[12] Here, we sought to explore with two

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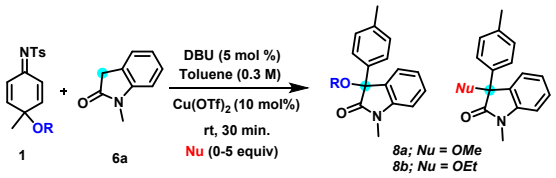
Table 1 Optimization of the reaction condition[a]

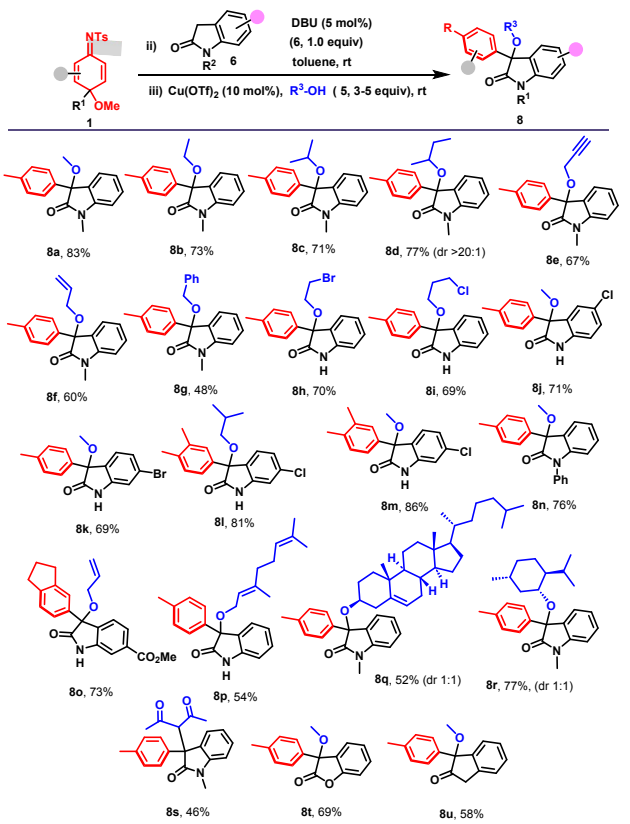


entry		Nu = R'OH	Inter- (% yield)	Intra-
1	R = Me (1a)	*Without Nucleophile*	8a, 70%	-
2		*Nu = MeOH (5 equiv)*	-	8a, 83%
3		*Nu = EtOH (5 equiv)*	8a, 10%	8b, 73%
4		*Nu = EtOH (5 equiv), 50 °C*	-	-[b]
5	R = Et (1b)	*Without Nucleophile*	8b, 60%	-
6		*Nu = EtOH (5 equiv)*	-	8b, 70%
7		*Nu = MeOH (5 equiv)*	8b, 15%	8a, 65%
8	R = *t*-Bu (1c)	*Without Nucleophile*	8c, 0%	-
9		*Nu = MeOH (5 equiv)*	-	8a, 64%
10		*Nu = EtOH (5 equiv)*	-	8b, 63%

[a]General conditions: **1** (0.2 mmol, 1.0 equiv.), **6a** (0.2 mmol, 1.0 equiv.) in toluene (0.3 M). Isolated yields were noted.

distinct functionalities; one arene, derived from ketamine/aniline and other one with hetero-atom nucleophiles. In continuation of our previous work, we examined the reaction with *N*-tosylketimine **1a** and *N*-methyloxindole **6a**; and sequential addition of catalytic DBU (5 mol%) and $Cu(OTf)_2$ (20 mol%) in the absence of external nucleophile. A methoxy addition product **8a** was obtained in 70% yield at room temperature, which was expected to come from the substrate, 4-methoxy ketamine **1a** (Table 1, entry 1). Yield of **8a** could be improved in the presence of excess MeOH (entry 2). While studying the scope for hetero-nucleophiles, using ketimines (**1**) and oxindoles (**6a**) in the presence of other nucleophilic solvents, we encountered a mixture of inter- and intramolecular substitution products via an intermediate (**7**), likely involving both internal (OR) and external (solvent) nucleophilic attack (Table 1). For example, a reaction was done with **1a** in the presence of EtOH (5 equiv.) under the identical reaction sequence. The desired product **8b** was obtained in 73% yield along with methoxy adduct in 10% yield (entry 3). Identical condition at elevated temperature resulted the complex reaction. Thus, to circumvent the formation of side product, which originates from substrates itself, we studied different ketimines **1a-1c** and tested in the presence of different nucleophilic solvents (Table 1, entries 1-10). 4-Ethoxy ketamine **1b** resulted the corresponding ethoxy product **8b** in the absence or presence of ethanol (60% and 70%, respectively; entries 5 and 6). However, in the presence of external solvent methanol, **8a** was formed along with **8b** (entry 7). As *tert*-BuOH is hindered and thus could be less nucleophilic, we sought to use *p*-(*t*-BuO) ketamine **1c** for the above transformation. As anticipated, the corresponding product **8c** was not formed via nucleophilic addition of the intramolecular tertiary butoxy group of **1c** (entry 8). Pleasingly, ketamine **1c** afforded **8a** and **8b** exclusively in the presence of external nucleophiles, MeOH or EtOH, respectively. Despite, there was no formation of *t*-BuOH addition adduct **8c** with ketamine **1c**, we opted to move further for the substrate

Table 2 Substrate scope with alcohols[a]



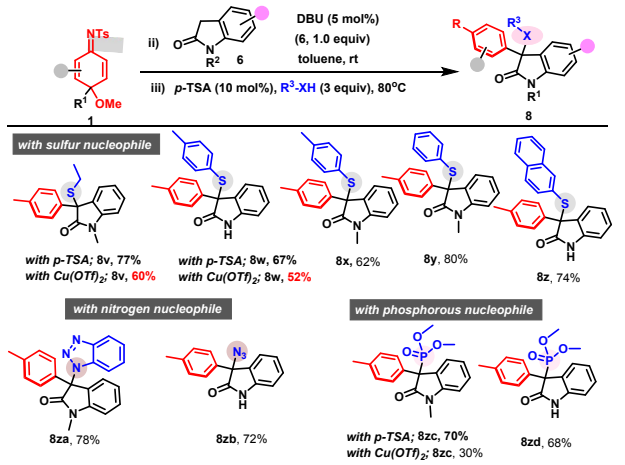
[a]Isolated yields were noted.

scope with the substrate **1a** owing to comparatively better chemical yields and atom-economy outcome.

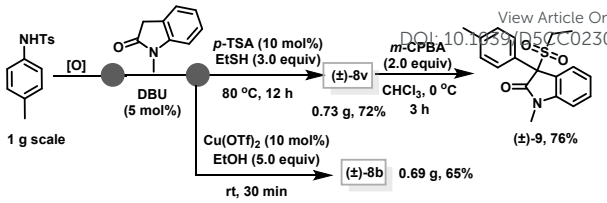
As shown in Table 2, the substrate scope was first investigated using *p*-methoxy ketimine **1a** and N-methyloxindole **6a** in the presence of various linear and branched alcohols; such as methanol, ethanol, isopropanol, secondary butanols, afforded the corresponding 3,3-disubstituted oxindoles **8a-8d** in 71-83% yields. Functionalized alcohols, such as allyl alcohol, propargyl alcohol, 2-bromoethanol, 3-chloropropanol, and benzyl alcohol were well tolerated under the optimum conditions with free-NH, N-methyl oxindoles (**8e-8i**). Subsequently, ketamine and oxindole derivatives were examined to give corresponding products (**8j-8o**) in 69-86% yields. The reaction scope was further studied with natural and structurally complex alcohols, such as menthol, cholesterol, and geraniol, afforded the corresponding products **8p-8r** in yields ranging from 52-77% yields with a diastereomeric ratio (dr) of 1:1 in the cases of **8q** and **8r**. Carbon nucleophile, acetylacetone gave the functionalized oxindole **8s** with addition at C3 position in 46% yield. Scope of the reaction was also investigated with 2-coumaranone and 2-indanone, successfully afforded corresponding aryl-methoxylated products **8s** and **8t** in methanol in 69% and 58% yields, respectively.

Expanding the scope of hetero-nucleophiles, sulphur and nitrogen were investigated (Table 3). C3-sulfonated products **8v** and **8w** were obtained in 60% and 52% yields with ethane thiol and *p*-

Table 3 Substrate scope with thiols, phosphorous and nitrogen nucleophiles[a]



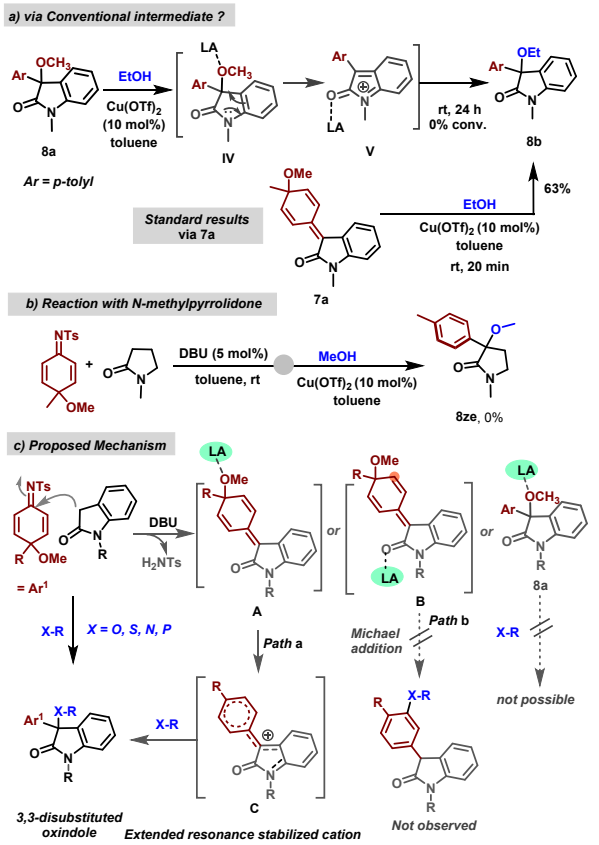
[a]Gram-scale synthesis and further transformation



Scheme 2 Gram-scale synthesis and further transformation

tolyl thiophenol under the standard reaction conditions using DBU (5 mol%) and $Cu(OTf)_2$ (10 mol%) catalytic sequence. Further optimization led to improved yields for **8v** and **8w** to 77% and 67%, respectively with *p*-TSA (10 mol%) at 80 °C instead of $Cu(OTf)_2$ at room temperature (Table 3). Having improved yields with slightly modified conditions, rest of substrate scope was examined with *p*-TSA, resulted **8x-8z** in 62-80% yields. Benzotriazole and azide afforded the corresponding C3-nitrogen substituted oxindoles **8za** and **8zb** in 78% and 72% yields, respectively. Then, phosphorated 3,3-disubstituted oxindoles **8zc** and **8zd** were synthesized for the first time using trimethylphosphite in 70% and 68% yields, respectively. Notably, initial conditions using $Cu(OTf)_2$ gave only 30% yield for **8zc**. The practicality and robustness of present process were further demonstrated through a gram-scale reactions using *N*-tosylaniline with ethanol and ethane thiol under standard conditions. The method remained effective at a 1.0-gram scale, afforded 3,3-aryl/heteronuclophile-substituted oxindoles **8b** and **8v** in 65% and 72% yields, respectively. C3-sulfenyl product **8v** was further demonstrated to convert into sulfonyl oxindole **9** in 76% yield using *m*-CPBA at 0 °C (Scheme 2).

To get some insight on reaction mechanism, we sought of a possible intermediate **8a**, which was often received as a minor by-product (Table 1). Based on literature precedence,[3] an isolated methoxy product **8a** was treated with ethanol in the presence of catalytic $Cu(OTf)_2$ (Scheme 3a). Notably, there was no reaction (0% conversion), even after 24 hours at room temperature and turns to be a complex mixture while heating. In contrast, under identical conditions, intermediate **7a** underwent rapid transformation, yielding the corresponding product **8b** in 63% within just 20 minutes. This observation suggests that reaction doesn't proceed via conventional **8a** intermediate. Further to understand the importance of aromatic ring fused to lactam ring, a reaction was conducted N-methylpyrrolidone (Scheme 3b). Reaction didn't work under standard catalytic as well stoichiometric conditions, confirming the extended resonance stabilized cation (*vide infra,* intermediate C in Scheme 3c) is essential for the above transformations. Based on these observation, a plausible reaction mechanism has been proposed. The first step involves DBU-catalyzed de-aminative Knövenagel-type condensation, leading to the formation of intermediate **A** or **B** with the elimination of $TsNH_2$ (Scheme 3). In the subsequent acid-catalyzed step, two possible modes of activation can be considered; activation through the amidic C=O (path **b**) or the *p*-methoxy group (path **a**). If activation occurs via the amidic carbonyl in the presence of $Cu(OTf)_2$ or *p*-TSA, the resulting dienone intermediate would act as a strong Michael acceptor. However, this pathway would likely lead to other aromatized products, which were not observed in the reaction. Therefore, activation via pathway **B** can be ruled out. Instead, pathway **A**, involving activation of the *p*-methoxy group by $Cu(OTf)_2$ or *p*-TSA, could lead to an extended resonance-stabilized cation **C**



Scheme 3 Mechanistic Study and plausible pathways for germinal dual C-H functionalization

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with a 6- or 8-π electron system. Subsequent nucleophilic addition at the most stabilized carbocationic C3-position would lead to the formation of 3,3-disubstituted oxindoles. Whereas, possible reaction path through **8a** can be completely ruled out as we didn't observe any reaction (Scheme 3).

In conclusion, a redox-neutral strategy has been developed for the geminal dual C–H functionalization of oxindoles via sequential base/acid catalysis. This three-component modular approach enables the synthesis of 3,3-disubstituted oxindoles using aniline and a variety of structurally diverse hetero O, S, N, and P nucleophiles. The reaction follows dearomatization-functionalization-aromatization sequence, proceeding through an extended resonance-stabilized carbocation.

PJ carried out experiments and Characterization. SH and SS supported some of the experiments. RK designed and conceptualized the scheme. All authors have given approval to the final version of the manuscript**.** Financial support from SERB, New Delhi, grant no- CRG/2023/003756 are highly acknowledged. PJ and SH thank UGC and CSIR, respectively, for providing fellowship. The authors acknowledge SAIF, CSIR-CDRI for providing analytical support. CDRI communication number XXXX.

Conflicts of interest

"There are no conflicts to declare".

Data availability

All experimental procedures, characterization data and NMR spectra for all compounds can be found in the ESI.†

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Data Availability Statement

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All experimental procedures, characterization data and NMR spectra for all compounds can be found in the ESI.†