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# Design and application of intramolecular arylogous nitroaldol condensation to access 2-aryl-benzofuran and -indole derivatives and formal synthesis of saprisartan†

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This study presents the design and application of intramolecular arylogous nitroaldol (Henry) condensation. A transition metal-free, base-mediated reaction of *ortho*-heteroatom-substituted aryl aldehydes/ketones and 2-nitrobenzyl (pseudo)halides has been developed to access a wide range of 2-(2-nitroaryl) benzofuran/2-(2-nitroaryl)indole derivatives in high yields. The reaction appears to proceed through *O*-/*N*-benzylation and intramolecular arylogous nitroaldol condensation. The application potential of the presented strategy has been demonstrated in the formal synthesis of anti-hypertensive agent saprisartan through the efficient synthesis of an advanced key intermediate, which has been accomplished in a ten-fold high overall yield by using resourceful, inexpensive and less-toxic reagents compared to the known methods.

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Benzofurans and indoles are important and privileged heterocycles because of their diverse biological activities and relevance in drug development. 2-Arylbenzofuran and 2-arylindole derivatives have attracted significant interest as biologically valuable compounds and pharmaceutical agents.<sup>1</sup> Their potential to target a wide range of diseases and conditions continue to make them promising candidates for future drug development. In particular, 2-(2-arylamino)benzofuran/indole derivatives have received considerable attention in medicinal chemistry and drug discovery research programs. For example, saprisartan, an approved drug belonging to the sartan family that is devoid of the diphenyl moiety, functions as an angiotensin II receptor antagonist and helps to treat anti-hypertensive symptoms as well as heart failure.<sup>2</sup> Compound A displays strong bladder relaxant effects, as well as high bladder (*versus* aorta) selectivity.<sup>3a,b</sup> Furthermore, 2-(2-nitroaryl)benzofuran derivatives serve as key starting materials for the synthesis of targeted products that have exhibited light emitting properties.<sup>3c,d</sup> Paullones possess excellent inhibitory profiles against cyclin dependent kinases (CDKs) and glycogen synthase kinase 3 (GSK3) (Fig. 1).<sup>4</sup> The vinylogy principle has emerged as one of the important tools in organic chemistry enabling the synthesis of complex and structurally varied molecules including natural products and pharmaceutical

compounds.<sup>5</sup> It continues to drive advancements in materials science, drug discovery, and other areas of chemical research. On the other hand, 2-aryl-benzofurans/indoles are a class of compounds that have gained significant attention in the field of organic/medicinal chemistry. In continuation of our research efforts in vinylogous transformations<sup>6</sup> and considering their importance as potential building blocks, we envisaged to develop arylogous nitroaldol condensation<sup>7</sup> to access 2-(2-nitroaryl) benzofuran and 2-(2-nitroaryl)indole derivatives where the nitro group can serve as a synthetic handle.

To the best of our knowledge, transition metal catalysts are generally employed to access 2-(2-nitroaryl)benzofurans/2-(2-nitroaryl)indoles. Palladium-catalyzed cross-coupling reactions of 2-substituted benzofurans/indoles and 2-halonitroarenes were employed to obtain the aforementioned derivatives (Scheme 1a).<sup>8</sup> Pd-catalyzed decarboxylative/desulfative cross-coupling reactions of the respective benzofuran carboxylic acids and 2-nitrobenzoic acid/2-nitrobenzenesulfonyl chloride were also reported to access 2-(2-nitroaryl)benzofurans (Scheme 1b).<sup>9</sup> In 2018, Patil and coworkers reported the synthesis of 2-(2-

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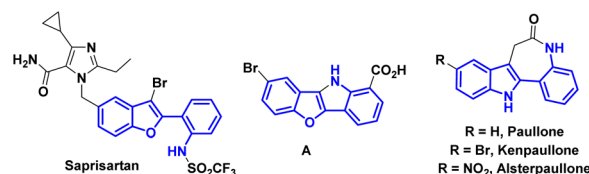
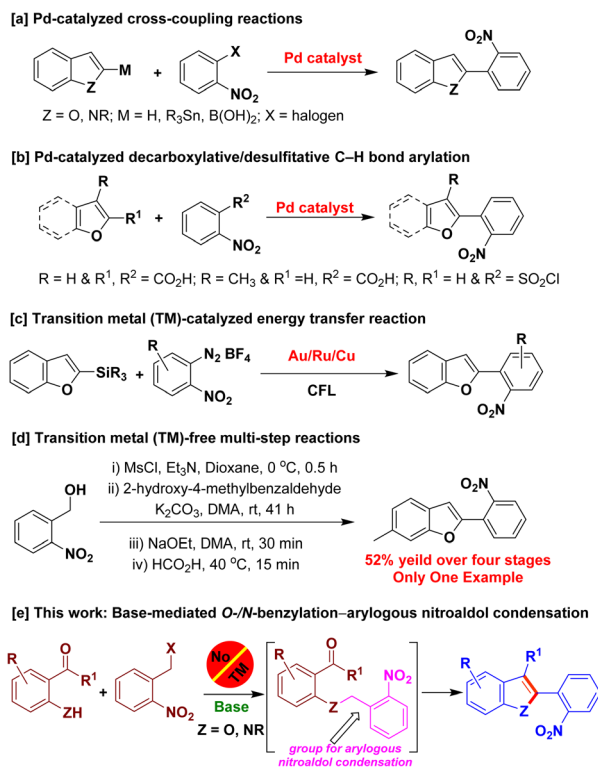
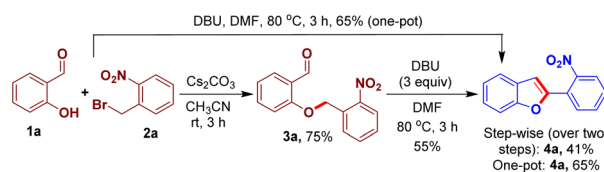


Fig. 1 Bioactive molecules containing 2-arylamino benzofuran and indole cores.





Scheme 1 Construction of 2-(2-nitroaryl)benzofuran/indole derivatives and this work.



Scheme 2 Step-wise and one-pot synthesis of 2-(2-nitrophenyl)benzofuran 4a.

nitroaryl)benzofurans using desilylative C(sp<sup>2</sup>)-C(sp<sup>2</sup>) cross-coupling reaction of 2-benzofuranylsilane with 2-nitrophenyldiazonium salts, catalyzed by Au–Ru–Cu/photoredox system (Scheme 1c).<sup>10</sup> Transition metal-free base-mediated reactions were also reported for the synthesis of a derivative of 2-(2-nitroaryl)benzofuran in four stages (Scheme 1d).<sup>11</sup> Although, these methods are elegant, they suffer from the use of expensive transition metal catalysts, lengthy synthetic steps and use of not-readily-accessible metalated/substituted benzofuran/indole derivatives as starting materials. Herein, we report the development of a base-mediated intramolecular arylogous nitroaldol condensation to construct the benzofuran/indole nuclei enabling the synthesis of 2-(2-nitroaryl)benzofuran and 2-(2-nitroaryl)indole derivatives using commercially available, inexpensive and less-toxic starting materials/reagents obviating transition metals (Scheme 1e).

We designed an easily accessible *O*-alkylated intermediate **3a** integrating the arylogous nitroaldol donor moiety and

Table 1 Optimization study<sup>a</sup>

Entry	Base	X in 2	Solvent	Temp. °C	% yield of 4a <sup>b</sup>
1	DBU	Br	DMF	80	65
2	DABCO	Br	DMF	80	21
3	K <sub>2</sub> CO <sub>3</sub>	Br	DMF	80	38
4	Cs <sub>2</sub> CO <sub>3</sub>	Br	DMF	80	46
5	KO <sup>t</sup> Bu	Br	DMF	80	55
6	DBU	Br	DMF	120	58
7	DBU	Br	DMSO	80	45
8	<b>DBU</b>	<b>Br</b>	<b>Toluene</b>	<b>80</b>	<b>85</b>
9	DBU	Cl	Toluene	80	53
10	DBU	OMs	Toluene	80	80
11	DBU	OTs	Toluene	80	76

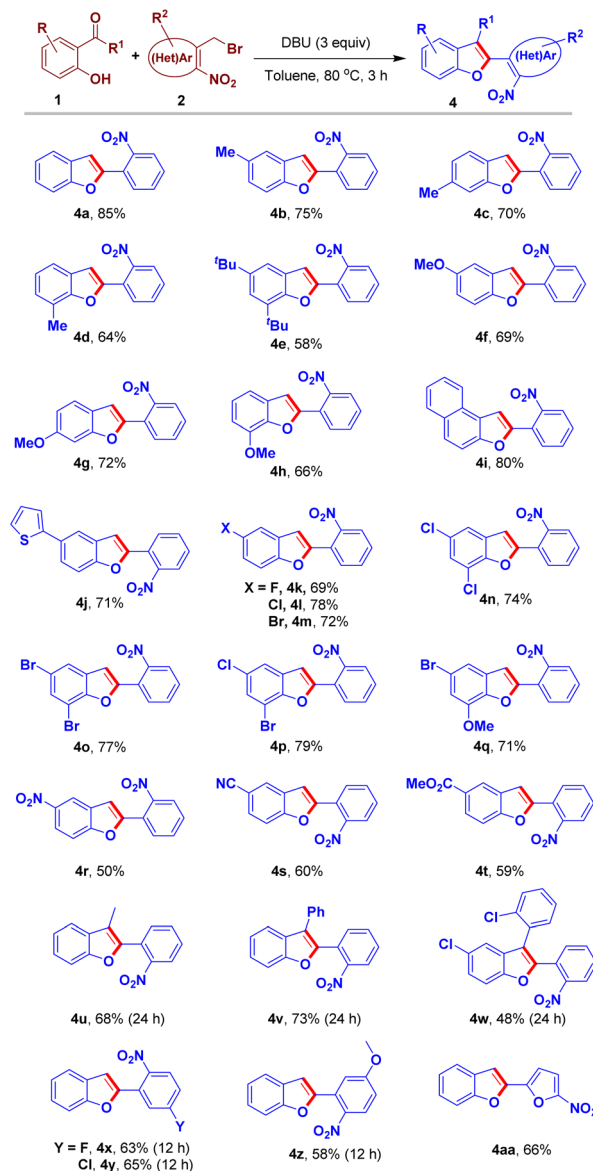
<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), base (1.5 mmol), solvent (4 mL). <sup>b</sup> Isolated yields.

electrophilic carbonyl moiety to validate our idea. Salicylaldehyde **1a** and 1-(bromomethyl)-2-nitrobenzene **2a** were used to generate the intended intermediate **3a**. Following our approach, compound **3a** was treated with base DBU in *N,N*-dimethylformamide for 3 h at 80 °C. We observed the formation of 2-(2-nitrophenyl)benzofuran **4a** in 55% yield. Subsequently, benzofuran **4a** was produced in a higher yield of 65% using a one-pot process starting from the reaction of **1a** and **2a** (Scheme 2).

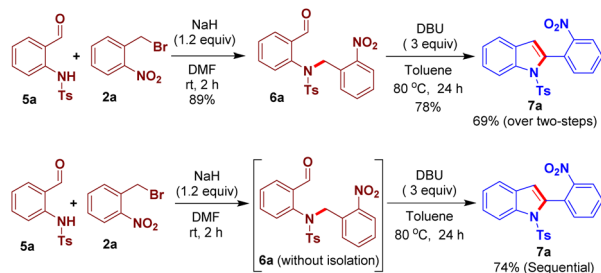
Then, we conducted an optimization study of the one-pot reaction by varying bases, solvents, and reaction conditions in order to obtain **4a** in better yields. The use of bases such as DABCO, K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub> and KO<sup>t</sup>Bu provided inferior results (Table 1, entries 2–5). Increasing the reaction temperature was not useful (Table 1, entry 6). To our delight, while screening the solvents, toluene was found to be the best solvent to give **4a** in a very good yield (Table 1, entries 7 and 8). Then, we tested different leaving groups such as chloro, OMs and OTs in place of Br group in **2** and isolated **4a** in slightly lower yields (Table 1, entries 9–11).

Having a set of optimization conditions, the substrate scope of the sequential *O*-alkylation–intramolecular arylogous nitroaldol condensation was explored as illustrated in the Scheme 3. Various substitutions on the salicylaldehyde partner were examined. The reaction of methyl-substituted-salicylaldehydes and **2a** furnished the respective benzofurans **4b–4d** in good yields. Noteworthy to mention we could obtain 6-methyl-2-(2-nitrophenyl)benzofuran **4c** in 70% yield in one step using commercially available starting materials (Scheme 3) whereas the same was reported to have been synthesized in four stages with a low overall yield (Scheme 1d).<sup>11</sup> 5,7-Di-*tert*-butyl-2-(2-nitrophenyl)benzofuran **4e** was obtained in 58% yield from the reaction of 3,5-di-*tert*-butylsalicylaldehyde **1e** and **2a**. The reaction of methoxy-substituted-salicylaldehydes and **2a** provided the corresponding benzofuran derivatives **4f–4h** in



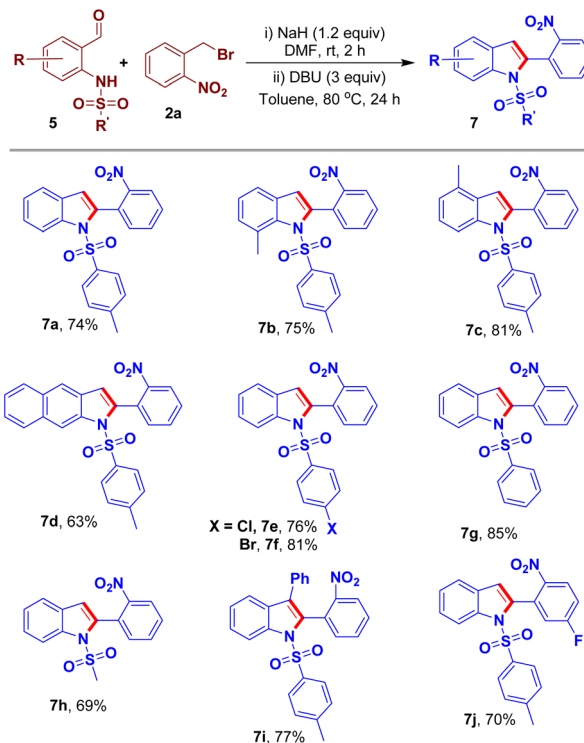


Scheme 3 Scope of the one-pot reaction to access 2-(2-nitroaryl)benzofuran derivatives 4a–4aa.



Scheme 4 Step-wise and sequential reactions of *N*-benzylation followed by intramolecular arylogous nitroaldol condensation for the synthesis of 7a.

good yields. Naphthofuran derivative **4i** was obtained in 80% yield from the reaction of 2-hydroxy-1-naphthaldehyde and **2a**. The reaction of 2-hydroxy-5-(thiophen-2-yl)benzaldehyde **1j** and



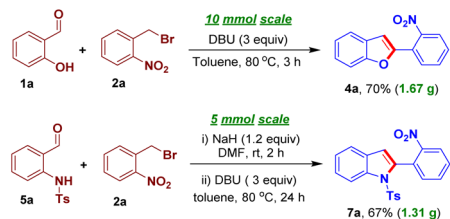
Scheme 5 Scope of the sequential transformation to access 2-(2-nitrophenyl)indole derivatives 7a–7j.

**2a** furnished the respective benzofuran **4j** in 71% yield. Later, the sequential process of **2a** and salicylaldehydes bearing halogen groups was examined. Accordingly, halogen-substituted-benzofuran derivatives **4k–4m** were obtained in moderate to good yields. Furthermore, we used dihalogen-substituted-salicylaldehydes that furnished the respective benzofuran products **4n–4p** in high yields. Salicylaldehyde bearing halogen and electron releasing group (ERG) was employed in this protocol to obtain the respective benzofuran derivative **4q** in 71% yield. Strong electron-withdrawing groups (EWGs) such as nitro, nitrile and ester groups on salicylaldehyde were well tolerated and afforded the corresponding benzofuran derivatives **4r–4t** in moderate to good yields. Furthermore, in place of aldehyde group we tested keto groups in the reaction partner **1**. Accordingly, acetophenone and substituted benzophenones were engaged in this transformation furnishing the corresponding 2,3-disubstituted-benzofuran derivatives **4u**, **4v** and **4w** in 68%, 73% and 48% yields, respectively.

We also examined the scope of *ortho*-nitrobenzyl/heteroarylmethyl bromides through a reaction of the respective substrate **2b–2e** and salicylaldehyde **1a** affording the corresponding benzofuran derivatives **4x–4aa** in a good yields (Scheme 3).

Subsequently, we became interested to implement the optimized reaction conditions to develop an *N*-benzylation-intramolecular nitroaldol condensation process in order to obtain 2-(2-nitrophenyl)indole **7a**, in one-pot, from the reaction of *N*-(2-formylphenyl)-4-methylbenzenesulfonamide **5a** and **2a**.

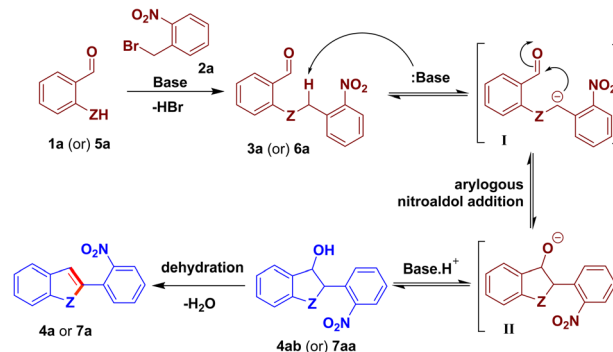




Scheme 6 Gram-scale syntheses of the compounds 4a and 7a.

However, the desired **7a** product was isolated in lower yields, under the optimized conditions and even after screening different bases and solvents (see the ESI† for more details). An *N*-benzylated compound **6a** was then prepared from the reaction of **5a** and **2a**. Delightfully, the intramolecular arylogous Henry condensation reaction of **6a**, in the presence of DBU in toluene, afforded the desired indole derivative **7a** in 78% yield with 69% yield over two-steps. Consequently, we carried out a sequential reaction of **5a** and **2a**, without the isolation of *N*-benzyl intermediate **6a**, that efficiently produced **7a** in 74% yield (Scheme 4).

By selecting the competitive reaction conditions, the scope of the sequential *N*-benzylation and arylogous nitroaldol condensation was investigated. Initially, we focused on the substitutions on benzene ring of 2-(*N*-tosylamido)benzaldehyde **5**. Accordingly, the reactions of methyl-substituted **5** and **2a** were performed to generate the corresponding 2-aryl-substituted-indole derivatives **7b–c** in good yields. Benzo-fused indole derivative **7d** was synthesized in 63% yield from the reaction of *ortho*-tosylamidonaphthaldehyde **5d** and **2a**. We also prepared the starting materials **5** having different *N*-sulfonylaryl groups and subsequently subjected them to the *N*-benzylation–intramolecular arylogous nitroaldol condensation process to provide the corresponding 2-(2-nitrophenyl)indole derivatives **7e–7g** in good yields. The reaction of *N*-(2-formylphenyl)methanesulfonamide **5h**, bearing an *N*-sulfonylalkyl group, and **2a** gave the respective indole derivative **7h** in 69% yield. The reaction of ketone such as benzophenone **5j** and **2a** were performed to generate the corresponding 2,3-diaryl-substituted indole derivative **7i** in 77% yield. We also examined the scope of *ortho*-nitrobenzy bromide through a reaction of 2-

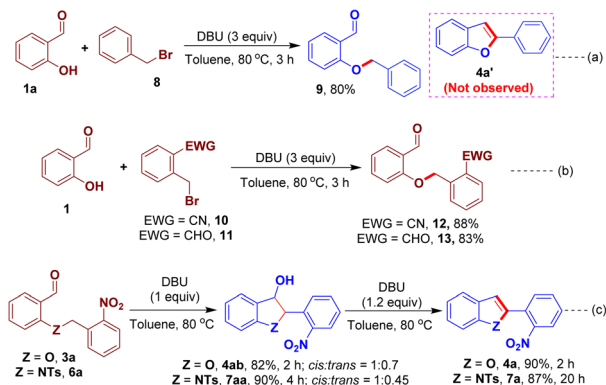


Scheme 8 Plausible mechanism.

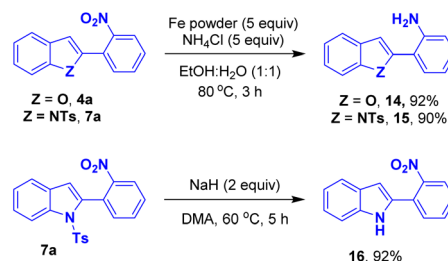
(bromomethyl)-4-fluoro-1-nitrobenzene **2b** and **5a** affording the respective indole derivative **7j** in 70% yield (Scheme 5).

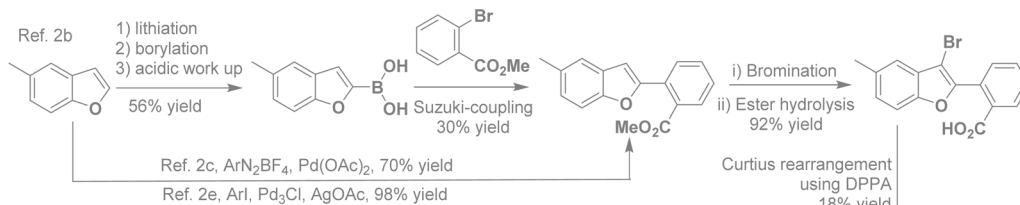
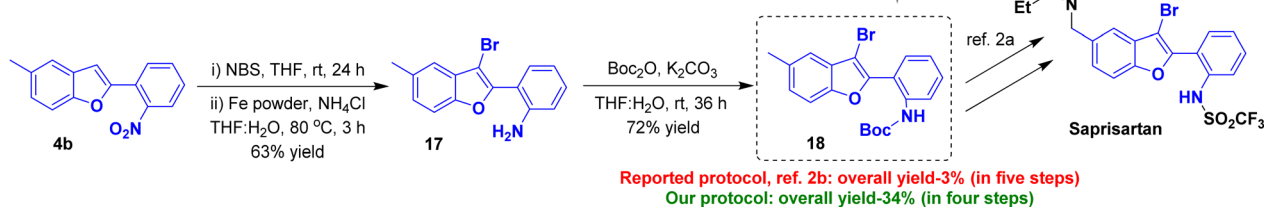
However, this transformation was not successful having an *N*-benzyl group in the place of sulfonyl group in **5** suggesting the requirement of a strong EWG that would enhance the acidity of the methylene group of the intermediate **6** to undergo intramolecular arylogous nitroaldol condensation. To establish the practicality of the present transformation, we conducted gram-scale reactions of **1a/5a** and **2a**, individually, under the optimized reaction conditions to successfully furnish the corresponding benzofuran/indole derivatives **4a/7a** in 70% and 67% yield, respectively (Scheme 6).

The mechanism of the present *O/N*-benzylation–intramolecular arylogous nitroaldol condensation process has been studied to know the requirement of nitro group and the involvement of the well-defined reaction intermediates. A reaction was performed using benzyl bromide **8**, instead of 1-(bromomethyl)-2-nitrobenzene **2a**, and salicylaldehyde; however, the corresponding benzofuran **4a'** was not observed and only *O*-alkylated product **9** was isolated in 80% yield (Scheme 7a). We then investigated alternative EWGs in place of NO<sub>2</sub> group in **2a**. Accordingly, the reactions of benzyl bromides **10/11** bearing nitrile (CN)/aldehyde (CHO) and salicylaldehyde were performed. In these reactions, the corresponding benzofuran derivatives were not observed while *O*-alkylated intermediates **12** and **13** were obtained in 88% and 83% of yield, respectively (Scheme 7b). These experiments suggest that a strong EWG such as nitro group is required that smoothly drive the later intramolecular arylogous condensation constructing the desired benzofuran derivative. We



Scheme 7 Control experiments.

Scheme 9 Post-synthetic transformations of benzofuran **4a** and indole **7a**.

**Reported route for the key intermediate 18 (Ref. 2b, 2c & 2e)****Our route for the key intermediate 18**

Scheme 10 Formal synthesis of saprisartan.

also conducted some control experiments to further know the intermediates of the reaction. The *O*-*N*-alkylated intermediate **3a/6a** was reacted with one equivalent of DBU to furnish the 3-hydroxy-dihydrobenzofuran **4ab**/3-hydroxy-indoline **7aa** in 82% and 90% yield, respectively, albeit with low diastereoselectivities while favouring the *cis*-isomer as determined by 2D-NMR analysis (see ESI† for more details). The dihydro compounds **4ab/7aa** underwent dehydration reaction upon the treatment with 1.2 equiv. of DBU to give **4a/7a** in high yields (Scheme 7c).

A mechanism for the present *O*-*N*-benzylation followed by intramolecular arylogous nitroaldol condensation process is proposed based on the literature<sup>7d,e</sup> and control experiments. *O*-benzylation/*N*-benzylation of **1a/5a** with **2a** begins with a base-mediated reaction to give the intermediate **3a/6a**, which had also been isolated (see Schemes 2 and 4). Base abstracts the acidic proton present on the benzylic CH<sub>2</sub> group of **3a/6a**, activated by the nitro group through conjugation, to provide intermediate **I**. The ensuing intermediate **I** undergoes intramolecular arylogous nitroaldol addition reaction to provide 3-hydroxy-substituted dihydrobenzofuran/indoline intermediate **4ab/7aa**, which was also isolated (see Scheme 7). Base-mediated dehydration of **4ab/7aa** delivers 2-(2-nitrophenyl)-benzofuran/indole derivative **4a/7a** (Scheme 8).

A few post-synthetic transformations were performed using the representative benzofuran **4a** and indole **7a**. The nitro group of the compound **4a/7a** was reduced in presence of Fe/NH<sub>4</sub>Cl to provide the corresponding 2-(benzofuran-2-yl)aniline **14** and 2-(1-tosyl-1*H*-indol-2-yl)aniline **15** in 92% and 90% yield, respectively. The compound **7a** underwent detosylation to access the respective *NH*-indole derivative **16** in 92% yield<sup>12</sup> (Scheme 9).

We became interested to demonstrate the potential application of our method in the synthesis of an approved anti-hypertensive drug, saprisartan bearing substituted-benzofuran moiety. According to our one-pot *O*-alkylation-arylogous nitroaldol condensation we could obtain 5-methyl-2-(2-nitrophenyl) benzofuran **4b** from commercially available 5-methylsalicylaldehyde **1b** and **2a** (Scheme 3). The compound **4b** underwent an NBS-mediated bromination at C-3 position of

benzofuran followed by nitro reduction to yield the corresponding benzofuran derivative **17** in 63% yield over two steps. The compound **17** was treated with Boc anhydride, resulting in critical intermediate **18** in 72% yield. Compound **18** is an advanced key intermediate in the production of saprisartan, a medication approved to treat hypertension and heart failure. The known Pd-catalyzed method, starting from 5-methylbenzofuran, needed five consecutive steps to give compound **18** in only 3% overall yield.<sup>2b</sup> Furthermore, Noël and Wang, independently reported the palladium-catalyzed synthesis of an early intermediate of saprisartan, methyl 2-(5-methylbenzofuran-2-yl)benzoate.<sup>2c,e</sup> In sharp contrast, our strategy involving intramolecular arylogous nitroaldol condensation, using transition metal-free conditions, as a key step delivered the advanced intermediate **18** in four consecutive steps in a eleven-fold 34% overall yield (Scheme 10). Saprisartan can be synthesized from **18** using the reported literature, thus constituting the formal synthesis (see ESI† for details).

## Conclusions

In summary, we have demonstrated a convenient, facile and transition metal-free protocol for the synthesis of diverse range of 2-(2-nitroaryl)benzofuran/indole derivatives *via* *O*-*N*-alkylation followed by intramolecular arylogous nitroaldol condensation from the reaction of *ortho*-heteroatom-substituted aryl aldehydes/ketones and *ortho*-nitrobenzyl halides. Gram-scale reactions and post-synthetic modifications have been achieved proving the practicality of the developed method. Furthermore, the application of the developed protocol was successfully demonstrated in the synthesis of an advanced key intermediate and accomplished a formal synthesis of saprisartan.

## Data availability

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



## Conflicts of interest

There are no conflicts to declare.

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