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Chemoselective arylation of phenols with bromo-nitroarenes: synthesis of nitro-biaryl-ols and their conversion into benzofurans and carbazoles†

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A series of electron withdrawing or donating group substituted phenols were chemoselectively arylated with various substituted bromo-nitroarenes using KO^{t}Bu at room temperature *via* an S_NAr pathway. The synthesis of natural alkaloids (carbazoles), dibenzofurans, and a biaryl-indole was achieved from the synthesized nitro-biaryl-ols.

Intermolecular cross-coupling reactions for the construction of carbon–carbon bonds are an interesting area in synthetic chemistry. The direct functionalization of C–H bonds avoids the use of pre-functionalized coupling partners, leading to more atom economical and environment-friendly processes.[1] Biaryls, particularly containing nitro/amino and hydroxyl functionalities, are of paramount importance for materials and medicines and are also precursors for natural products.[2] Alkaloids with OH and NH_2/NO_2 groups (*e.g.* siamenol, mahanimbine, mahanimbilol, and carbazomycin B) have numerous biological functions such as antiviral, antifungal, cytotoxic, anti-malarial, anti-HIV agents and antibiotics (Fig. 1).[3]

Similarly, pyrrolomycin E, TMC-95-A, benzofurocoumarin, elbfluorene and NOBIN biaryls possessing 2-OH or 2′-NO_2/NH_2 groups have been used as anticancer agents or ligands.[4]

In this context, a mild method is highly desirable for accessing diversely substituted nitro-biaryl-ols. Mild reaction conditions are required for selective transformations that can tolerate sensitive groups such as Br, NH_2, CHO, OH, *etc.*, which are advantageous because of their easy transformations at later stages for the synthesis of functionalized biaryls such as mahanimbine and TMC-95-A.[3b,4b] Although various methods have been reported for the arylation of phenol making use of transition metal catalysts,[5] most of the methods require protection of the phenolic group. The direct arylation of phenol has attracted considerable interest. Zhou *et al.* discovered a palladium catalyzed *para* arylation of phenol using aryl iodide in water.[6] In order to combine aryl iodides with phenols, the presence of an acidic functionality is essential for the binding of the Pd-catalyst with aryl iodide in benign methodologies. Daugulis and co-workers reported a transition metal free arylation of phenols at 135 °C.[7] Nonetheless, these methodologies showed limited substrate scope due to specific binding of the catalyst with the acid/amide functionalities, or they require harsh reaction conditions.

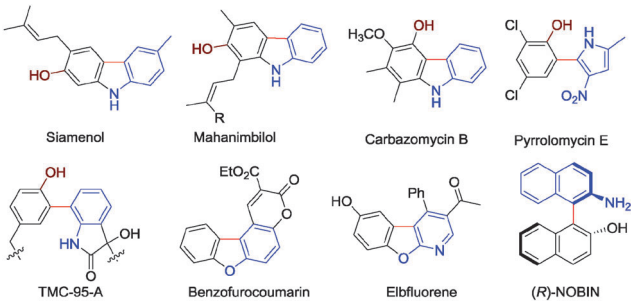

Fig. 1 Biologically active carbazoles and dibenzofurans.

In continuation of our work on carbon–carbon and carbon–heteroatom coupling reactions,[8] herein, we present a transition metal free mild method for the synthesis of nitro-biaryl-ols which tolerates a variety of functional groups. The synthesized nitro-biaryl-ols were employed for the synthesis of natural alkaloid clausine V and related carbazole analogues. Moreover, dibenzofurans can also be obtained from *para*-substituted phenols and 2-nitrobromobenzene in one pot by the formation of C–C and C–O bonds. The synthesis of a biaryl indole was also accomplished from the synthesized nitro-biaryl-ol.

Optimization of the reaction conditions was carried out using phenol and 1-bromo-4-methyl-2-nitrobenzene as coupling partners, Scheme 1 (see also ESI,† Table S1, page S3, for the detailed optimization of reaction conditions). After screening various bases and solvents, we found that KO^{t}Bu in DMSO at room temperature gave nitro-biaryl-ol **1** and 2′-nitro-biaryl-4-ol **2** in good yields with high regioselectivity. The addition of silver acetate as an additive to the reaction mixture provided **2** exclusively, albeit in a low yield

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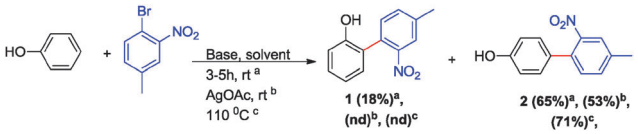
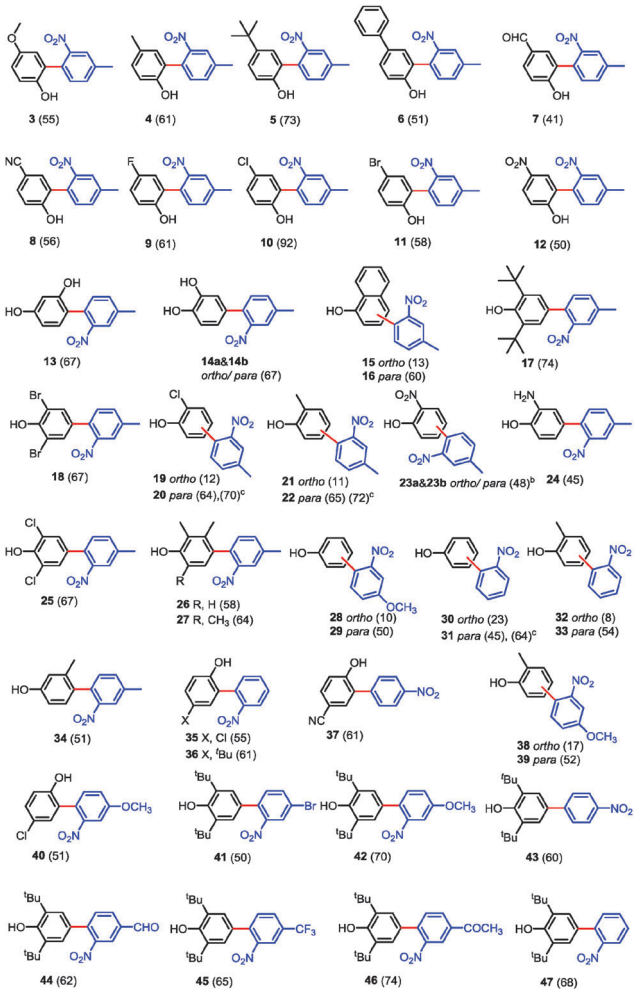


Scheme 1 Optimization of the synthesis of nitro-biaryl-ols. [a] The reaction was carried out using 1.0 mmol of bromo-nitrobenzene, 1.2 mmol of phenol, and 2.5 mmol of KO^{t}Bu in DMSO (4 mL) at RT. [b] AgOAc (1.2 mmol) was added. [c] The temperature was raised up to 110 °C for 2 h.

of 53% (see ESI,† Table S1, entry 13).[7] Interestingly, the reaction at a higher temperature (110 °C) gave 2′-nitro-biaryl-4-ol **2** exclusively in 2 h (see ESI,† Table S1, entry 14).

The scope and limitations of this method were further studied and the results are summarized in Table 1. *para*-Substituted phenols underwent coupling reactions successfully, and yielded nitro-biaryl-ols (**3–12**) in 41–92% yields. Nitro-biaryl-ols with OCH_3 (**3**), CH_3 (**4**) *tert*-butyl (**5**), phenyl (**6**) and other sensitive functional groups such as CHO (**7**), CN (**8**), F (**9**), Cl (**10**), Br (**11**) and NO_2 (**12**) were obtained under the optimized reaction conditions. Functional groups such as CHO, CN, Cl, and Br could then be further transformed into other functionalities.

Table 1 The synthesized 2′- and 4′-nitro-biaryl-ols[a]



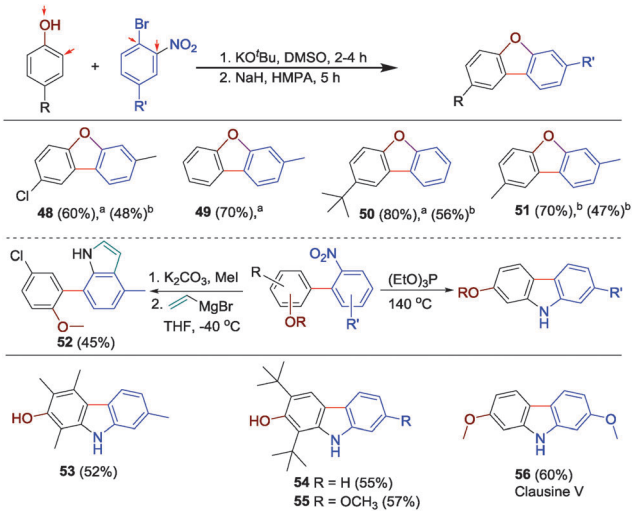
[a] The reactions were carried out using 1.0 mmol of bromo-nitrobenzene, 1.2 mmol of phenol, and 2.5 mmol of base in DMSO (4 mL). [b] The *ortho* and *para* isomers were not separated. [c] The reaction was heated at 110 °C.

Next, nitro-biaryl-diols **13** and **14** were obtained from resorcinol and catechol respectively. Resorcinol gave the single regioisomer **13** with a 67% yield, whereas catechol gave a mixture of two regioisomers **14a** and **14b** in an 8 : 2 ratio (67% yield). Further, α-naphthol was used in the coupling reaction giving a mixture of *ortho* and *para* regioisomers **15** and **16** in an overall yield of 73% with an 18 : 82 ratio, respectively. 2,6-Disubstituted phenols were then subjected to the arylation reaction which gave a 74% yield of 2′-nitro-biaryl-4-ol **17**. On the other hand, the electron withdrawing 2,6-di-chloro and bromo phenols gave 2′-nitro-biaryl-4-ols **18** and **25** in slightly lower yields. *ortho*-Methyl, chloro, and nitro substituted phenols afforded regioisomeric mixtures of *ortho* and *para*-nitro-biaryl-ols **19–23** at room temperature, whereas *ortho*-aminophenol gave only 2′-nitro-biaryl-4-ol **24**. Alternatively, 2′-nitro-biaryl-4-ols **20**, **22** and **31** (*vide supra*) were obtained exclusively by carrying out the reaction at 110 °C. A *meta*-substituted phenol gave only regioisomer **34** with a 51% yield. Highly substituted 2,3,6-trimethyl and 2,3-dimethyl substituted phenols were also coupled with bromo-nitrobenzene and yielded 2′-nitro-biaryl-4-ols **26** and **27**.

Next various bromo-nitroarenes were tested under the optimized reaction conditions. Simple 2-nitro and 4-nitro-bromobenzenes were successfully coupled with phenol derivatives leading to various substituted 2′-nitro-biaryl-4-ols **31**, **33**, and **47**, 2′-nitro-biaryl-2-ols **30**, **32**, and **35–37** and 4′-nitro-biaryl-4-ol **43**. Formation of the respective diaryl ethers was also observed along with nitro-biaryl-ols **30**, **31** and **36** (see ESI,† pages S19 and S21). *para*-Methoxybromonitrobenzene was noticed to be an equally efficient substrate as comparable yields of coupled nitro-biaryl-ols **28**, **29**, **38–40** and **42** were obtained. Bromo-nitrobenzenes with electron withdrawing substituents reacted sluggishly with phenol; however they coupled smoothly with electron rich 2,6-di-*tert*-butyl phenol. 2-Nitro-bromoarenes with Br, CHO, CF_3, and $COCH_3$ groups in *para* positions produced good yields of 2′-nitro-biaryl-4-ols **41**, and **44–46**, respectively.

Structures of nitro-biaryl-ols **10**, **11** and 2′-nitro-biaryl-4-ols **27**, **33**, were established by single crystal X-ray studies (for the crystal studies, see ESI,† pages S152–S168). Nitro-biaryl-ols **10**, **11** were crystallized in chiral space groups structures of and interestingly, Flack parameter value (−0.08) for **10** is close to zero, which suggests that molecule crystallized in one of the enantiomeric form. Furthermore, the optical rotation value, $[\alpha] = 24.04 \pm 0.4$ ($c = 0.3$, $CHCl_3$), of **10**, suggests an enantiomeric pure form in solution.

Next, the synthesized 2′-nitro-biaryl-2-ols were utilized for the preparation of dibenzofurans (Scheme 2).[9] Nitro-biaryl-ols **10**, **1**, **36**, and **4** were readily converted into dibenzofurans **48**,



Scheme 2 The synthesis of advanced biaryl heterocycles. [a] The yields were obtained from nitro-biaryl-ols. [b] The yields were obtained from phenols and 2-bromonitrobenzenes using a one pot reaction.

49, **50**, and **51**, respectively, by using NaH base in HMPA under heating conditions. Moreover, the synthesis of dibenzofurans can be accomplished in a single pot from *para* substituted phenols and nitrobromobenzene in slightly lower yields compared to the yields obtained from the stepwise reactions. In a single pot reaction, *para*-substituted phenols were treated with *ortho*-nitrobromobenzenes in DMSO in the presence of KO^{t}Bu, after 4 h NaH and HMPA were added followed by heating at 80 °C, resulting in dibenzofurans. Previously, the synthesis of dibenzofurans was achieved by diazotization (the Pschorr reaction) and Pd-catalyzed dehydrogenative coupling of diarylethers.[10] Here dibenzofurans **48**, **50** and **51** were obtained in 47–56% yields in one pot from *para*-substituted phenols and bromo-nitroarenes. Furthermore, the synthetic utility of the prepared nitro-biaryl-ol **10** was demonstrated by synthesizing biaryl-indole **52**. For this transformation, first the OH group of nitro-biaryl-ol **10** was protected as a methyl ether, followed by the reaction of the nitro group with vinyl-magnesium bromide, which gave biaryl-indole **52** in a 45% yield.

Next 2′-nitro-biaryl-4-ols were converted into carbazoles. The heating of 2′-nitro-biaryl-4-ols **27**, **47**, **42**, and the protected form of **29** in EtO_3P at an elevated temperature provided good yields of carbazoles **53**, **54**, **55**, and **56**.[11]

Carbazoles are well known for their antioxidant functions (Fig. 1). Here the synthesis of a fully CH_3-substituted phenol ring, and two *tert*-butyl substituted carbazoles **54** and **55** was achieved, which could be efficient antioxidants.[12] Also clausine V, **56**, which has anti-HIV properties was obtained in two steps from 2′-nitro-biaryl-4-ol **29**, first conversion of the OH group to a methoxy group using CH_3I and K_2CO_3, followed by C–N coupling.

To understand the mechanistic part of the reaction, several control experiments were carried out (see ESI,† page S34).[13] The reaction seems to be following a traditional nucleophilic aromatic substitution (S_NAr), and also an unexplored pathway.[14,15] Here, the addition of KO^{t}Bu to phenol generates a phenoxide ion, which subsequently converts into a carbanion *via* resonance. The addition of the carbanion to bromonitroarene, followed by proton abstraction and rearomatization led to the desired nitro-biaryl-ols **1** and **2** (see ESI,† Scheme S3, page S34).

To sum up, a mild method has been developed for the construction of nitro-biaryl-ols and 2′-nitro-biaryl-4-ols which tolerates diverse functional groups. The synthesized nitro-biaryl-ols were converted into important classes of biaryl heterocycles, dibenzofurans and biaryl-indoles, whereas the 2′-nitro-biaryl-4-ols were converted into carbazoles. The developed methodology is mild and tolerates sensitive functionalities which could be useful for the preparation of highly functionalized biaryls such as siamenol, mahanimbine, and carbazomycin B alkaloids. This is currently under investigation in our laboratory.

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