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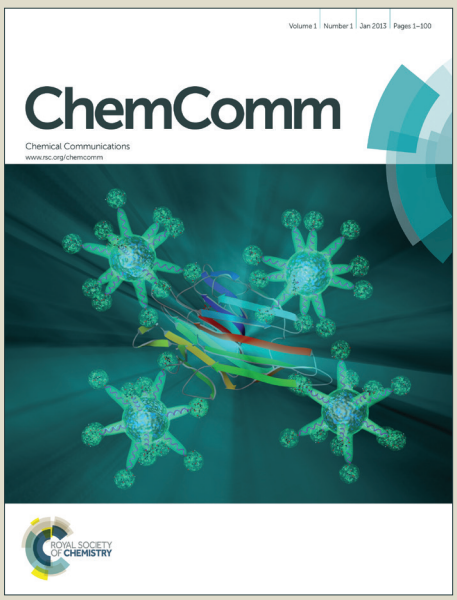

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Chemoselective Arylation of Phenols with Bromo-nitroarenes: Synthesis of Nitro-biaryl-ols and Their Conversion into Benzofurans and Carbazoles

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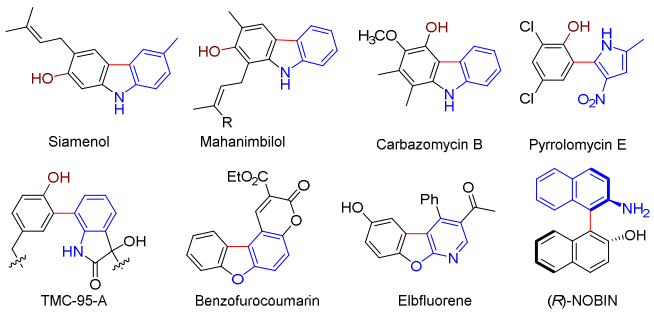
A series of electron withdrawing or donating group substituted phenols were chemoselectively arylated with variously substituted bromo-nitroarenes using KO^{t}Bu at room temperature *via* S_NAr pathway. Synthesis of natural alkaloids (carbazoles), dibenzofurans, and biaryl-indole has been achieved from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

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

Fig 1. Biologically Active Carbazoles and Dibenzofurans

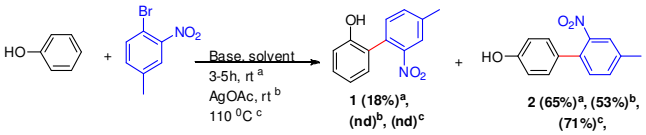


Similarly, pyrrolomycin E, TMC-95-A, benzofurocoumarin, elbfluorene and NOBIN biaryls possessing 2-OH, 2'-NO_2/ NH_2 groups are being used as anticancer agents or ligands.[4]

In this context, a mild method will be highly desirable to access diversely substituted nitro-biaryl-ols. Mild reaction conditions are required for the selective transformations that could tolerate sensitive groups such as Br, NH_2, CHO, OH, etc., which are most advantageous because of their easy transformation at later stage 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 the protection of phenolic group. Direct arylation of phenol remains unexplored and 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 acidic functionality is essential for the binding of Pd-catalyst with aryl iodide in the benign methodology. Daugulis and co-workers reported transition metal free arylation of phenols at 135 ^oC.[7] Nonetheless, these methodologies showed limited substrate scope due to specific binding of the catalyst with acid/ amide functionalities or require harsh reaction conditions.

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 alkaloids 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. Synthesis of biaryl indole was also accomplished from synthesized nitro-biaryl-ol.

Scheme **1**. Optimization for the Synthesis of Nitro-biaryl-ols



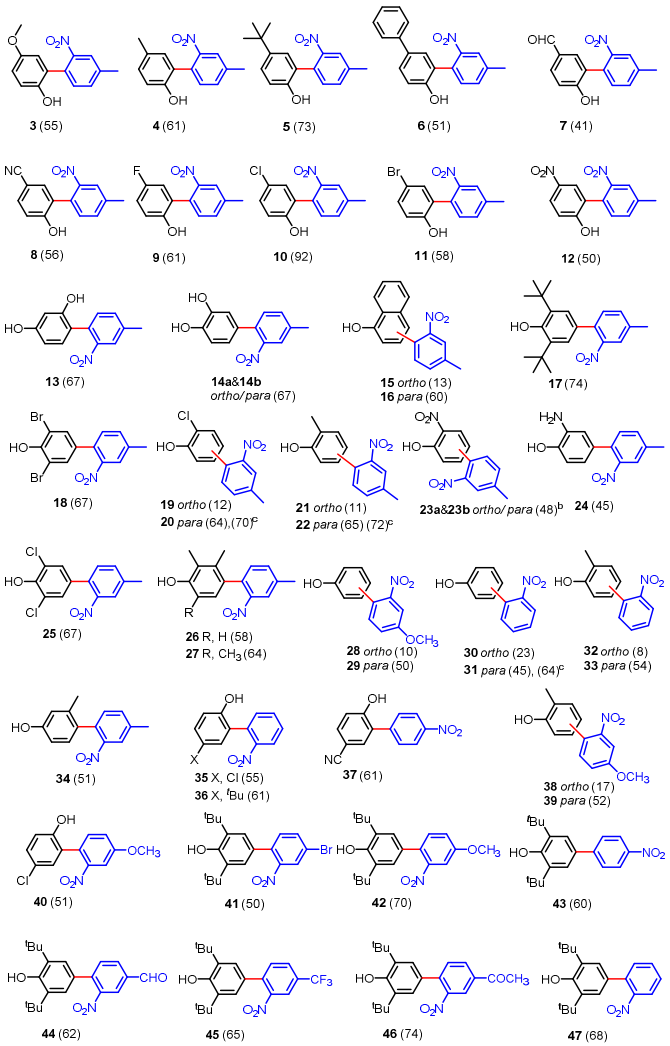
[a]Reaction was carried out using 1.0 mmol of bromo-nitrobenzene, 1.2 mmol of phenol, and 2.5 mmol of KO^{t}Bu in DMSO (4 mL) at RT. [b] AgOAc (1.2 mmol) was added. [c] Temperature was raised up to 110 ^oC for 2h.

Optimization of reaction conditions was carried out using phenol and 1-bromo-4-methyl-2-nitrobenzene as coupling partners, Scheme 1 (please also see SI Table S1, page S3, for detailed optimization of

reaction conditions). After screening of 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 yield with high regioselectivity. The addition of silver acetate as an additive to the reaction mixture provided **2** exclusively, albeit in low 53% yield (see SI, table S1, entry 13).[7] Interestingly, reaction at high temperature (110 ^{o}C) gave 2'-nitro-biaryl-4-ol **2** exclusively in 2 h (see SI, Table S1, entry 14).

The scope and limitation of this method was further studied and results are summarized in Table 1. *para*-Substituted phenols underwent coupling reaction 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 sensitive functional groups such as CHO (**7**), CN (**8**), F (**9**), Cl (**10**), Br (**11**) and NO_2 (**12**) were obtained under optimized reaction conditions. Functional groups CHO, CN, Cl, and Br could be further transformed into other functionalities.

Table 1. Synthesized 2'- and 4'-nitro-biaryl-ols[a]



[a]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] *ortho* & *para* Isomers were not separated. [c] Reaction was heated at 110 ^{o}C.

The reaction with 2-iodo-phenol was noticed to be sluggish and isolation of corresponding iodo-nitro-biaryl-ol was unsuccessful.

Next, nitro-biaryl-diols **13** and **14** were obtained from resorcinol and catechol. Resorcinol gave a single regioisomer **13** with 67% yield whereas catechol gave a mixture of two regioisomers **14a** and **14b** in 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 overall 73% yield with 18:82 ratio, respectively. 2,6-Disubstituted phenols were then subjected to arylation reaction which gave 74% yield of 2'-nitro-biaryl-4-ol **17**, on the other hand 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 mixture 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 reaction at 110 ^{o}C. *meta*-Substituted phenol gave only one regiosomer **34** with 51% yield. Highly substituted 2,3,6-trimethyl and 2,3-dimethyl substituted phenols have also been coupled with bromo-nitrobenzene and yielded 2'-nitro-biaryl-4-ols **26** and **27**.

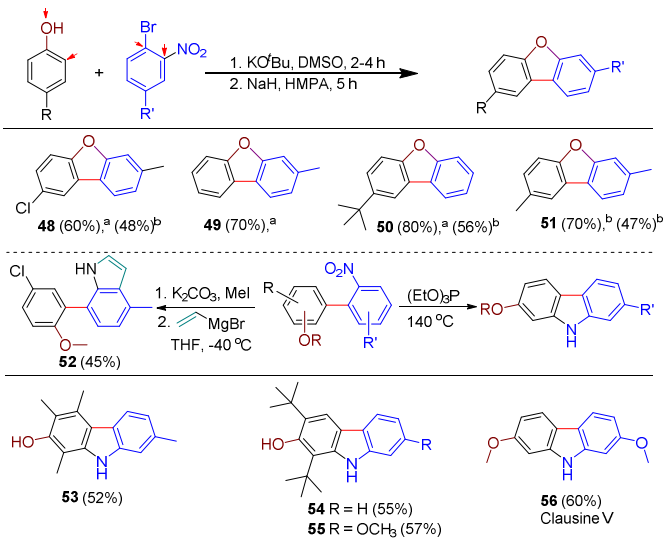
Next various bromo-nitroarenes were tested under optimized reaction conditions. Simple, 2-nitro and 4-nitro-bromobenzenes were successfully coupled with phenol derivatives leading to various substituted 2'-nitro-biaryl-4-ols **31, 33**, **47**, 2'-nitro-biaryl-2-ols **30, 32, 35-37** and 4'-nitro-biaryl-4-ol **43**. Formation of respective diaryl ethers were also observed along with nitro-biaryl-ols **30**, **31** and **36** (please see SI, page S19, S21). *para*-Methoxybromonitrobenzene was noticed to be 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 simple phenol; however, smoothly coupled with electron rich 2,6-di-*tert*-butyl phenol, 2-nitro-bromoarenes with Br, CHO, CF_3, and $COCH_3$ groups in para position produced good yields of 2'-nitro-biaryl-4-ols **41**, and **44-46**, respectively.

Structure of nitro-biaryl-ols **10**, **11** and 2'-nitro-biaryl-4-ols **27**, **33** were also established by single crystal X-ray studies (for crystal studies, see SI, pages S150-S169), which were crystallized in chiral space groups. Interestingly, Flack parameter value (0.08) for **10** is close to zero, which suggests that molecule crystallized in one of the enantiomeric form. Furthermore, optical rotation value [α] = 24.04±0.4 (c = 0.3, $CHCl_3$) of **10**, suggested an enantiomeric pure form in solution.

Next, synthesized 2'-nitro-biaryl-2-ols were utilized for the preparation of dibenzofurans (Scheme 2).[9] Synthesized nitro-biaryl-ols **10, 1, 36**, and **4** were readily converted into dibenzofurans **48, 49, 50,** and **51**, respectively, by using NaH base in HMPA under heating conditions. Moreover, synthesis of dibenzofurans can be accomplished in a single pot from *para* substituted phenols and nitrobromobenzene in slightly lower yields as compared to yields obtained from 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 ^{o}C leading to dibenzofurans. Previously, the synthesis of dibenzofurans was described by diazotization (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. Further, synthetic utility of prepared nitro-biaryl-ol **10** was demonstrated by synthesizing biaryl-indole **52**. For this transformation, first, OH group of nitro-biaryl-ol **10** was protected as methyl ether followed by the reaction of the nitro group with vinyl-magnesium bromide gave biaryl-indole **52** in 45% yield.

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

Scheme 2. Synthesis of Advanced Biaryl Heterocycles



[a] Yields were obtained from nitro-biaryl-ols. [b] Yields were obtained from pheonls and 2-bromonitrobenzens using one pot reaction.

Carbazoles are well known for their antioxidant functions (Figure 1). Here synthesis of fully CH_3-substituted phenol ring and two *tert*-butyl substituted carbazoles **54** and **55** have been achieved, which could be efficient antioxidants.[12] Also clausine V, **56** having anti-HIV property has been obtained in two steps from 2'-nitro-biaryl-4-ol **29**, first conversion of OH group as a methoxy 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 (please see SI, page S33).[13] The reaction seems following a traditional nucleophilic aromatic substitution S_NAr yet unexplored pathway.[14,15] Here, the addition of KO^{t}Bu to phenol generates a phenoxide ion, which subsequently converts into carbanion *via* resonance. The addition of carboanion to bromonitroarene, followed by proton abstraction and rearomatization led to desired nitro-biaryl-ols **1** and **2** (please see SI, Scheme S3, page 33).

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. Synthesized nitro-biaryl-ols have been converted into important class of biaryl heterocycles; dibenzofurans, and biaryl-indole, whereas 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 and is currently under investigation in our laboratory.

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Department of Chemistry, IISER Bhopal, Indore By-pass Road, Bhauri, Bhopal, Madhya Pradesh, India-462 066, E-mail: sangitkumar@iiserb.ac.in † Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

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