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Synthesis of Biaryls via Benzylic C−C Bond Cleavage of Styrenes and Benzyl Alcohols

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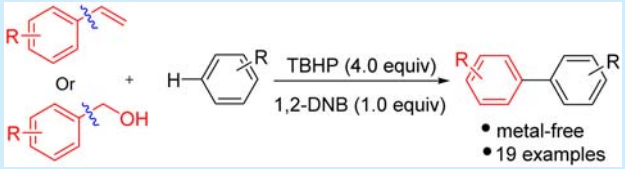
Supporting Information

ABSTRACT: A metal-free oxidative coupling of styrenes and benzyl alcohols with arenes has been developed for the synthesis of biaryls. The reaction features a conspicuous benzylic C−C bond cleavage of styrenes and benzyl alcohols. The reaction with both substrates proceeds through a common aldehydic intermediate formed through oxidative C−C bond cleavage of alkene and oxidation of benzyl alcohols. The reaction proceeds efficiently over a broad range of substrates with excellent functional group tolerance.



Unarguably, the biaryl motif has a pervasive presence in a plethora of bioactive molecules, natural products, pharmaceuticals, and functional materials.[1] Their constant demand has led to development of copious synthetic methods which includes many famous name reactions like Negishi,[2] Suzuki,[3] Stille,[4] Ullman,[5] Hiyama,[6] and Kumada[7] coupling (Figure 1). Broadly speaking, the aryl−aryl bond-forming

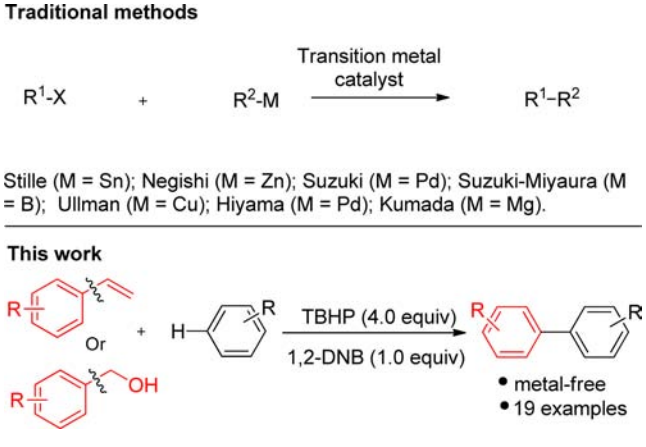


Figure 1. Approaches for the synthesis of biaryls.

strategies employ (1) transition-metal-catalyzed coupling,[8] which involves prefunctionalization of both the coupling partners, (2) direct arylation of the aryl C−H bond[9] or oxidative coupling of arenes[10] requiring prefunctionalization of only one coupling partner, or (3) dehydrogenative cross-coupling[11] circumventing the need of prefunctionalization, which has recently emerged at a breathtaking pace. The problem with most of these strategies is that they involve the use of metal catalysts with very few methods known to access biaryl structures without the use of metals.[12] This area is rapidly evolving with newer methods for their construction from different functionalities as the core objective. Having a closer look at the literature, we found that most of these methods use aryl halides, arylmetal, or C−H functionalization of arenes. Therefore, development of a direct method for biaryl synthesis from two different C−H bonds under metal-free conditions is of great interest and a challenge to synthetic organic chemists. We are particularly interested in exploring the potential of transition-metal-free systems, which might provide an alternative approach for the construction of biaryls.

Although several coupling partners have been used for the synthesis of biaryls, to the best of our knowledge, the direct use of ubiquitously present terminal alkenes as a substrate has no precedence. To address this challenge and pursue our research program toward development of new oxidative coupling protocols,[13] we here report a new strategy amenable to a wide variety of terminal styrenes for the synthesis of biaryls. Furthermore, the method could easily be extended to various benzyl alcohols, which also to our knowledge have never been used as substrates for the synthesis of biaryls. The method presents a first benzylic C−C bond cleavage of styrenes and benzyl alcohols. Furthermore, it is metal-free and proceeds efficiently over a broad range of substrates.

We began by exploring appropriate reaction conditions for benzylic C−C bond cleavage of styrenes and coupling with benzene. Preliminary results showed that the reaction of styrene and benzene in the presence of *tert*-butyl hydroperoxide (TBHP, 4 equiv) at 150 °C gave the corresponding product in trace amount (Table 1, entry 1). We further contemplated using a co-oxidant like molecular iodine to improve reaction yields but did not obtain any desired product whatsoever (Table 1, entry 2). Upon use of benzoic acid as an additive there was a slight improvement in reaction yields (Table 1, entry 3). However, the use of other additives such as triflic acid,

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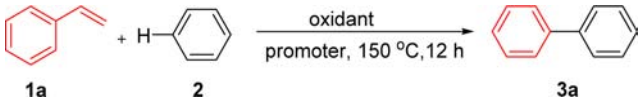
Table 1. Optimization of the Reaction Conditions[a]



1a 2 3a

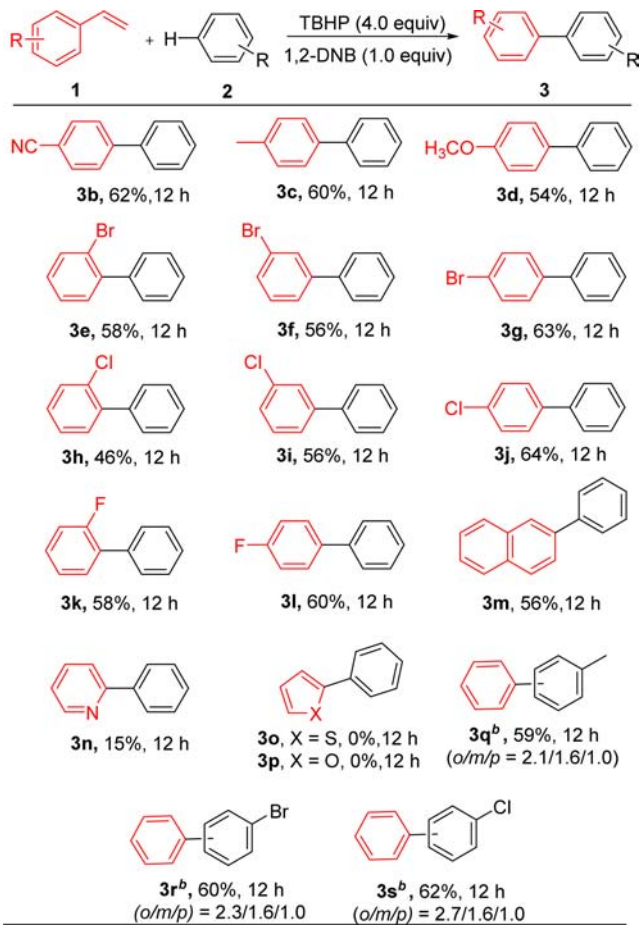
entry	oxidant	promoter (equiv)	yields (%)
1	TBHP (4.0)		trace
2	TBHP (4.0)	I_2 (1.0)	
3	TBHP (4.0)	benzoic acid (1.0)	11
4	TBHP (4.0)	TfOH (1.0)	
5	TBHP (4.0)	TFA (1.0)	
6	TBHP (4.0)	PTSA (1.0)	
7	TBHP (4.0)	4-nitrobenzoic acid (1.0)	30
8	TBHP (4.0)	nitrobenzene (1.0)	19
9	TBHP (4.0)	1,2-dinitrobenzene (1.0)	64
10	TBHP (4.0)	1,2-dinitrobenzene (2.0)	63
11	TBP (4.0)	1,2-dinitrobenzene (1.0)	45
12	CuHP (4.0)	1,2-dinitrobenzene (1.0)	10
13	*m*-CPBA (4.0)	1,2-dinitrobenzene (1.0)	trace
14	H_2O_2 (4.0)	1,2-dinitrobenzene (1.0)	trace

[a]Reaction conditions: **1a** (0.5 mmol), oxidant, and promoter in benzene (1.5 mL) for 12 h at 150 °C.

trifluoroacetic acid (TFA), and *p*-toluenesulfonic acid (PTSA) did not result in any product formation (Table 1, entries 4−6). Remarkably, the use of *p*-nitrobenzoic acid as an additive increased the reaction yields to 30% (Table 1, entry 7). We know that nitrobenzene compounds are used as oxidants in modern industrial chemistry;[14] thus, we envisioned their use an additive instead of *p*-nitrobenzoic acid. The use of nitrobenzene in combination with TBHP (1:4 ratio) led to a drop of yields to 19% (Table 1, entry 8) but nevertheless implied that acid as an additive is probably not playing any role in the reaction. We suspected the reaction proceeds through aldehdye as an intermediate, and recently, a report appeared where they used 1,2- dinitrobenzene to facilitate decarbonylative arylation.[15] To our delight, the use of 1,2-dinitrobenzene led to an overwhelming improvement in the reaction yields to 64% (Table 1, entry 9). A further increase in the amount of 1,2-dinitrobenzene to 2.0 equiv made no significant improvement in reaction yields (Table 1, entry 10). We also screened other oxidants such as hydrogen peroxide (H_2O_2), *m*-chloroperbenzoic acid (*m*-CPBA), cumene hydroperoxide (CuHP), and *tert*-butyl peroxide (TBP). A significant drop in yields was observed with these oxidants, showing that use of TBHP in combination with 1,2-DNB is the condition of choice (Table 1, entries 11−14) .

With the optimized conditions in hand, the substrate scope of the reaction was expanded to various styrenes. The terminal alkene bearing electron-withdrawing or -donating substituents were successfully transformed into the desired biaryl products (Scheme 1). The reactions with styrenes such as 4-cyano-, 4-methyl-, and 4-methoxystyrene proceeded smoothly to afford corresponding products (**3b−d**) in good yields. Furthermore, the substrate scope was also extended to various halogenated styrenes, which can offer the possibility of further functionalization. The reaction proceeded efficiently over a range of substituted styrenes such as *o*-, *m*-, and *p*-bromo- (**3e−g**), *o*-, *m*-, and *p*-chloro- (**3h−j**), and *o*- and *p*-fluorostyrenes (**3k−l**) to give the corresponding biaryls in good yields. Steric hindrance had no impact on the reaction yields, as reaction with various *ortho*-substituted styrenes proceeded efficiently to

Scheme 1. Substrate Scope with Different Styrenes and Arenes[a]



[a]Reaction conditions: **1** (0.5 mmol), TBHP (4.0 equiv), and 1,2-dinitrobenzene (1,2-DNB) (1 equiv) in arene (1.5 mL) for 12 h at 150 °C. [b]The regioselectivity (*o*/*m*/*p*) ratio of isomers was determined by GC and ^{1}H NMR data.

give the corresponding biaryls. The bicyclic styrene 2-vinylnapthalene could also be easily transformed into the corresponding product (**3m**) in 56% yields. We extended the reaction to heterocyclic styrenes such as 2-vinylpyridine, thiophene, and furan. The reaction of 2-vinylpyridine gave the corresponding biaryl (**3n**) in low yields, whereas 2-vinylthiophene and furan degraded to give a complex mixture of inseparable byproducts. The scope of the reaction was also extended to the cross coupling of terminal alkenes with different arenes, which could essentially lead to the formation of a mixture of *o*-, *m*-, and *p*-substituted products. Thus, the reaction of styrene with toluene, bromo-, and chlorobenzene afforded corresponding biaryls **3q** (*o*/*m*/*p* = 2.1/1.6/1.0), **3r** (*o*/*m*/*p* = 2.3/1.6/1.0), and **3s** (*o*/*m*/*p* = 2.7/1.6/1.0), respectively, in good yields. Notably, in all cases the *ortho*-functionalized isomers were predominant along with *p*- and *m*-substituted minor products. We also tried the reaction of pyridine with styrene only to find no product formation. These results demonstrate the versatility and tolerability of the present methodology to a wide range of substituted styrenes and arenes.

From our previous work, we know TBHP can prompt oxidative C−C cleavage of styrene to in situ generate aldehyde. Thus, based on our previous work[13b] and a recent report on

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oxidative decarbonylative coupling of aromatic aldehydes,[15] we assume that reaction possibly proceeds via aldehyde as an intermediate (Figure 2). The reaction probably initiates with

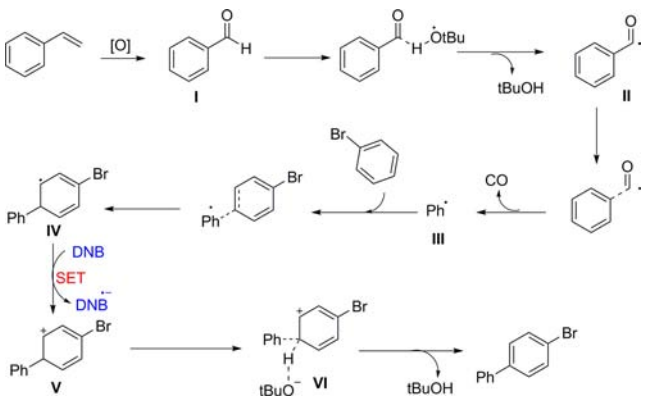
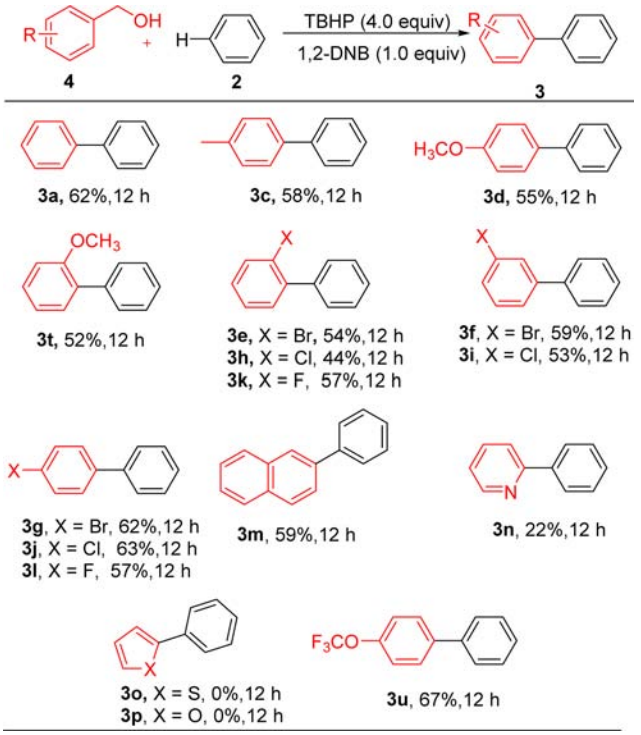


Figure 2. Plausible mechanism.

oxidative C−C bond cleavage of styrene catalyzed by TBHP affording benzaldehyde (**I**) as an intermediate, which is followed by a hydrogen atom abstraction by *tert*-butoxy radical to give acyl radical (**II**). The acyl radical (**II**) then subsequently undergoes decarbonylation to provide phenyl radical (**III**), which on addition of bromobenzene leads to the formation of phenylcyclohexadienyl radical (**IV**). The next step involves crucial transfer of an electron (SET) from phenylcyclohexadienyl radical (**IV**) to 1,2-dinitrobenzene because of persistent radical effect to afford phenyl cyclohexadienyl cation (**V**) and $DNB^{\bullet -}$.[15,16] Consequently, the phenyl cyclohexadienyl cation undergoes deprotonation by *tert*-butoxide anion to give the desired biaryls.

Owing to stability, availability, low toxicity, and cost of alcohols, considerable attention has been diverted toward their use as starting materials for the synthesis of amides,[17] nitriles,[18] acetals,[19] esters,[20] lactams,[21] and benzazoles.[22] As the coupling of terminal alkenes with arenes presumably proceeds through aldehyde as an intermediate, we turned our attention toward using benzyl alcohol as a coupling partner for the synthesis of biaryls. To the best of our knowledge, this is the first synthesis of biaryls from benzyl alcohols, which provides a more economical and distinctive path to their synthesis. To support our assumption, we carried out the reaction of benzyl alcohol and benzene in the presence of TBHP. As expected, the reaction under optimized conditions gave the desired biaryl (**3a**) in 62% yields (Scheme 2). The optimized conditions were applicable to 4-methyl-, 4-methoxy-, and 2-methoxybenzyl alcohol to give the corresponding products (**3c-d**) and (**3t**) in 58, 55, and 52% yields, respectively. Furthermore, halo-substituted benzyl alcohols, viz. *o*-, *m*-, and *p*-bromo-, *o*-, *m*-, and *p*-chloro-, and *o*- and *p*-fluorobenzyl alcohols were also successfully transformed into their corresponding biaryl products in good yields. Moreover, a bicyclic alcohol like naphthalen-2-ylmethanol (**3m**) could also be easily transformed into the corresponding biaryl in 59% yields. We also examined the cross coupling of heterocyclic alcohols like pyridin-2-ylmethanol, thiophene-2-ylmethanol, and furan-2-ylmethanol with benzene. The reaction followed suit as with styrenes; while pyridin-2-ylmethanol was successfully transformed to the corresponding product (**3n**), the thiophene-2-ylmethanol and furan-2-ylmethanol failed to undergo coupling and gave a mixture of degraded products. In addition, the 4-

Scheme 2. Substrate Scope with Different Alcohols[a]



[a]Reaction conditions: **4** (0.5 mmol), TBHP (4 equiv), and 1,2-dinitrobenzene (1 equiv) in benzene (1.5 mL) for 12 h at 150 °C.

(trifluoromethoxy)benzyl alcohol was successfully transformed into the corresponding biaryl (**3u**) in 67% yield.

In summary, we have developed an efficient strategy for oxidative coupling of styrenes and benzyl alcohols with arenes to access biaryls through a new metal-free approach. The reaction features a first of its kind benzylic C−C bond cleavage of styrenes and benzyl alcohols. The reaction with both styrenes and benzyl alcohols proceeds through an aldehydic intermediate generated through oxidative C−C bond cleavage of terminal alkene and oxidation of alcohols, respectively. The aldehydic intermediate undergoes subsequent decarbonylation and arylation to give biaryls. The strategy presents metal-free reaction conditions and proceeds efficiently over a broad range of substrates with excellent functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02578.

Experimental procedures, characterization data, and ^{1}H NMR, ^{13}C NMR, and GC spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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