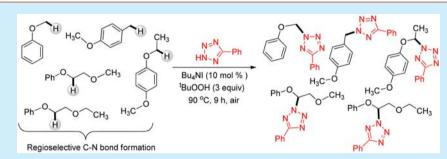


Bu₄NI Catalyzed C–N Bond Formation via Cross-Dehydrogenative Coupling of Aryl Ethers (C_{sp3}–H) and Tetrazoles (N–H)

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Supporting Information



ABSTRACT: Intermolecular C–N bond formations via cross-dehydrogenative coupling (CDC) of aryl ethers and tetrazoles have been developed under a metal-free condition. In the presence of catalytic amount of tetrabutylammonium iodide (TBAI) and aqueous TBHP, aryl ethers coupled efficiently with tetrazoles to afford hemiaminal ethers. This strategy showed high level of regioselectivity for substrates possessing multiple sp³ C–H bonds adjacent to the ethereal oxygen.

rom the viewpoint of academic and industrial research, development of an "ideal synthetic procedure" for the synthesis of complex molecules from simple starting materials via C-H bond functionalization is of paramount interest to synthetic chemists.¹ From this perspective, the step and atom economical strategy, i.e., cross-dehydrogenative coupling (CDC) has played a vital role in the construction of C-C and C-X (heteroatom) bonds, utilizing sp, sp², and sp³ C-H bonds.² CDC protocols involving simple solvents provide potential methods for the construction of a variety of functionalized molecules.³ As a part of our ongoing research on C-H bond functionalization, we have contributed a number of CDC protocols involving common solvents such as alkylbenzenes, cyclic ethers, cycloalkanes, and ethyl acetate with various coupling partners, most of which have ultimately led to the formation of C-C, C-O, and C-S bonds via C_{sp3} -H functionalization.⁴ Due to the inertness of C_{sp3} -H bonds adjacent to oxygen in aryl ethers, their functionalization has been unexplored, barring one report for the functionalization of aryl ethers with saccharins.⁵

Hemiaminal ethers are prevalent structural motifs in biologically active materials and natural products.⁶ For example, hemiaminal ether framework containing zalcitabine^{7a} is a potential anti-HIV agent, tegafur^{7b} is an anticancer agent, natural product aspidophylline^{7c,d} is known to reverse drug resistance in KB cells, and 5-fluorouridine^{7e} is an anticancer agent. However, nitrogenous heterocycle tetrazole is an admired functionality with a wide range of applications in organic^{8a} and medicinal chemistry.^{8b,c} For example, biphenyl tetrazoles are key intermediates for the preparation of sartan drugs, pemirolast is an antiallergic drug, and azosemide is a diuretic.^{8d–f} Therefore, developing protocols for the construction of structurally diverse hemiaminal ethers by linking arylether with tetrazole will be of significant interest. So far hemiaminal ethers have been synthesized via (i) metal-catalyzed hydroamination of enol ethers,⁹ (ii) amidation of cyclic ethers induced by a nitrene precursor of either *N*-sulfonylimino- λ^3 -iodane or chloramine-T,¹⁰ (iii) α -amination of ethers with hypervalent sulfonylimino- λ^3 -bromane,¹¹ and (iv) cross-dehydrogenative couplings between cyclic ethers and various nitrogen nucleophiles using either transition metal or metal-free conditions.¹² In addition, some other C–N bond forming reactions are also reported under a metal-free condition following CDC approach.¹³ In this Letter, we report an oxidative C–N bond formation involving sp³ C–H bond of aryl ethers (adjacent to oxygen) with aryl tetrazoles in the presence of a catalytic quantity of TBAI and oxidant TBHP.

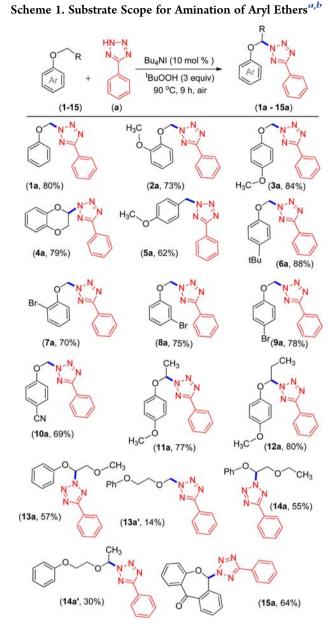
Initially, the oxidative CDC between anisole (1) $C-H(sp^3)$ and N-H of phenyl tetrazole (a) under various catalytic conditions was examined. 5-Phenyl-2*H*-tetrazole (a) when treated with anisole (1) in the presence of Bu₄NI (20 mol %) and TBHP in decane (3 equiv) at 90 °C expected CDC product (1a) was obtained in 30% yield (Table S1, entry 1, Supporting Information, SI). Gratifyingly, by switching to aqueous TBHP (70% in water) (3 equiv) in lieu of TBHP in decane (5–6 M) significant improvement in the yield (82%) of (1a) was observed (Table S1, entry 2, SI). Keeping all the parameters constant but decreasing the quantity of catalyst Bu₄NI from 20 to 10 mol %, yields are (1a) marginally reduced to (80%) (Table S1, entry 3, SI). However, incomplete consumption of the starting material

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was observed even after 10 h by further decreasing the quantity of catalyst Bu₄NI from 10 to 5 mol % (Table S1, entry 4, SI). Furthermore, no significant enhancement in the yield was observed by either increasing the oxidant quantity to 4 equiv or the reaction temperature to 100 °C (Table S1, entries 5–6, SI). Again, by reducing the amount of oxidant (2 equiv) or temperature (80 °C) the yield of (1a) decreased to 41% and 47%, respectively (Table S1, entries 7–8, SI). Substituting TBHP with other oxidants such as aqueous H_2O_2 , $K_2S_2O_8$, di-tert-butyl peroxide (DTBP), benzoylperoxide, tert-butyl peroxybenzoate (TBPB), and DIB used was completely unproductive (Table S1, entries 9-14, SI). A genre of quaternary ammonium salts such as Bu₄NF, Bu₄NCl, and Bu₄NBr when tested all were found to be ineffective for this transformation (Table S1, entries 15–17, SI). Other halogen species, viz. KI and I2 when used instead of Bu4NI, afforded, respectively, 18% and 10% yields (Table S1, entries 18–19, SI). A cooperative combination of oxidant (TBHP) and catalyst (TBAI) is essential for the success of this strategy, as the reaction failed in the absence of any one of them (Table S1, entries 20–21, SI). Solvent optimization was not required as the aryl ethers used were all liquids or low melting solids, which served the dual role of a reactant and the reaction medium. After a series of optimization reactions (Table S1) it was found that the coupling is best achieved using anisole (1) (250 μ L) and tetrazole (a) (0.5 mmol) at 90 °C for 9 h (Table S1, entry 3, SI).

A variety of substituted aryl ethers were coupled with 5phenyl-2*H*-tetrazole (a) to test the versatility of this coupling strategy (Scheme 1). The reaction of 1,2-dimethoxybenzene (2) and 1,4-dimethoxybenzene (3) with 5-phenyl-2H-tetrazole (a) proceeded smoothly, providing their hemiaminal products (2a) and (3a) in 73% and 84% yields, respectively. The lesser yield of product obtained for 1,2-dimethoxybenzene (2) compared to 1,4-dimethoxybenzene (3) is possibly due to steric hindrance of the other ortho-methoxy group in the former. The main attribute of these reactions is the exclusive formation of mono (CDC) products (2a) and (3a) with the other methoxy group remaining intact. Substrate 2,3-dihydro-1,4-benzodioxine (4) having two symmetrical methylene groups α to oxygen reacted with tetrazole (a) to form mono hemi aminal product (4a) in 79% yield. For substrate possessing a methoxy and a methyl group as in (5) the methyl C_{sp3} -H participated in CDC reaction with tetrazole (a) giving product (5a), while the methoxy group remained intact. This suggests aryl methyl group is more susceptible to CDC reaction than the aryl methoxy group, a coupling pattern similar to previous results. 4^{4} , 14 4-tert-Butyl anisole (6) gave the coupled product (6a) in excellent yield (88%) originating from C_{sp3} -H of the methoxy group rather than the three methyl groups in tertbutyl anisole (6). Methoxy arenes possessing a bromo substituent, irrespective of its position ortho (7), meta (8) or para (9), underwent CDC reactions with tetrazole (a) giving desired coupled products (7a), (8a), and (9a) in 70%, 75%, and 78% yields, respectively. A slightly lower yield of product obtained for ortho-bromo substituted substrate (7) compared to meta (8) and para (9) analogues could be due the steric factor in the former. Smooth coupling was observed for aryl ether having strong electron withdrawing substituent such as p-CN (10) giving product (10a) in 69% yield. The present metal-free single electron oxidant system (TBHP/TBAI), efficiently promoted C_{sp3} –H activation α to oxygen. When several such C_{sp3} –Hs are present their coupling with other partner is of challenge, particularly in achieving the desired regioselectivity.

To evaluate the regioselectivity some selected poly ethers having different substitution patterns were chosen. Substrates



^{*a*}Reaction conditions: 5-phenyl-2*H*-tetrazole (0.5 mmol), aryl ether (250 μ L), TBAI (10 mol %), and an aq TBHP (3 equiv) at 90 °C for 9 h. ^{*b*}Isolated yield.

(11) and (12) having two different C_{sp3} –Hs, α to oxygen, one methyl, and the other methylene, the coupling took place regioselectively at the methylene site rather than at the methyl group giving products (11a) and (12a), respectively (Scheme 1). The exclusive regioselectivity observed at the methylene side is due to the better stability of the resultant oxy radical/oxonium ion at this site compared to that of methyl side. This observation suggests the predominance of electronic over steric factors. The dominance of electronic over steric factor is again demonstrated with substrate (13) having two methylenes and a methyl group (Scheme 1). Here again, the major product (13a) obtained in 57% yield originates from the coupling of methylene C_{sp3} –H, α to oxygen toward the phenyl side. This is due to the better stability of the resultant oxy radical/oxonium ion over the other methylene C–H. The minor product (13a') obtained in 14%

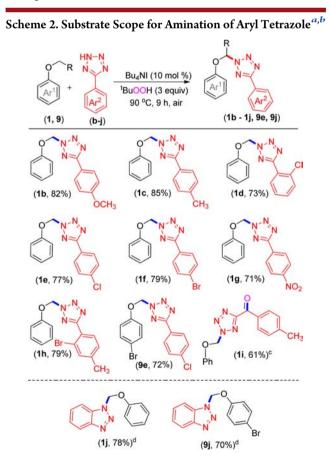
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yield is by the coupling of methyl C_{sp3} -H in (13), the intermediate of which is relatively less stable.

However, when the methyl group is replaced with an ethyl group, i.e., introduction of an extra methylene group as in (14), a marginal loss in regioselectivity was observed. The two products (14a) and (14a') were obtained, respectively, in 55 and 30% yields. Again, the higher percentage of product (14a) obtained is via the better stability of the resultant oxy radical α to oxygen toward phenyl side rather than at other two methylenes. Dibenz[b,e]oxepin (15), a pharmaceutically active compound having a methylene group α to oxygen, could be efficiently functionalized with tetrazole giving product (15a) in 64% yield. This CDC reaction when applied to the dimethyl acetal of acetophenone failed to undergo the desired coupling; rather it is deprotected to its parent keto compound.

Next the focus was on a substituent's variation in aryl tetrazoles to explore the scope of this coupling reaction. Phenyl ring of tetrazoles substituted with electron-donating groups such as *p*-OMe (**b**), *p*-CH₃ (**c**), and electron-withdrawing groups such as *o*-Cl (**d**), *p*-Cl (**e**), *p*-Br (**f**), and *p*-NO₂ (**g**) all coupled efficiently with anisole (**1**) to give their respective hemiaminal products (**1b**), (**1c**), (**1d**), (**1e**), (**1f**), and (**1g**) in the yields ranging from 71–85% (Scheme 2).

Further, structure of the product (1f) has been unequivocally conformed by X-ray crystallography as shown in Figure S1. No particular trends with the nature of the substituents and yield of their products obtained could be correlated. A disubstituted



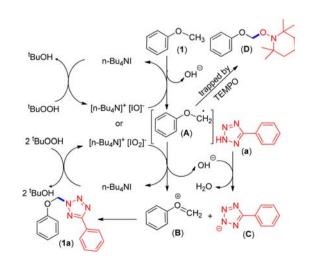
^{*a*}Reaction conditions: aryl tetrazole (0.5 mmol), anisole (250 μ L), TBAI (10 mol %), and aq TBHP (3 equiv) at 90 °C for 9 h. ^{*b*}Isolated yields. ^{*c*}S-[(4-methylphenyl)methyl]-2*H*-tetrazole was used as a starting material. ^{*d*}Aqueous TBHP (4 equiv) at 110 °C for 12 h.

substrate 5-(2-bromo-4-methylphenyl)-2H-tetrazole (h) reacted with anisole (1) under the optimized condition gave the expected product (1h) in 79% yield. p-Bromo anisole (9) underwent CDC reaction with 5-(4-chlorophenyl)-2H-tetrazole (e) furnishing hemiaminal product (9e) retaining both bromo and chloro functionalities. Interestingly, a benzylic tetrazole, viz. 5-[(4methylphenyl)]-2H-tetrazole (i), when reacted with anisole (1) gave hemiaminal product (1i) with concurrent oxidation at the benzylic position (Scheme 2). The use of other nucleophilic partner such as benzotrizole (j) in lieu of tetrazoles with anisole (1) and *p*-Br anisole (9) under the optimized condition gave only 43% yield of the coupled product (1j). However, by increasing the quantity of oxidant TBHP from three to four equivalents and the reaction temperature from 90 to 110 °C, yield improved up to (62%). Further improvement in the yield (78%) was observed when the reaction was allowed to proceed for 12 h. With this new optimized condition p-bromo anisole (9) gave its coupled product (9i) in 70% yield when reacted with benzotriazole (i).

To elucidate the mechanism of this coupling reactions some control experiments were carried out. The CDC reaction between aryl ether (1) and aryl tetrazole (a) was considerably hampered in the presence of a radical scavenger giving <8% yield of the product, indicating a radical nature of the reaction. Detection of trapped radical intermediate with TEMPO (D) supports the formation of phenoxymethyl radical (A). Replacement of TBAI with I2 or KI under otherwise identical conditions failed to produce the desired coupling product suggesting the noninvolvement of I_2 in the reaction. The oxidant TBHP is reported to oxidize the catalyst Bu₄N⁺I⁻ to either $[Bu_4N]^+[IO]^-$ or $[Bu_4N]^+[IO_2]^{-15}$ The formation $[IO]^-$ has been detected by ESI mass analysis of the reaction mixture.^{4a} This hypervalent species [Bu₄N]⁺[IO]⁻ initiates a homolytic cleavage at the C_{sp3} -H of methyl group α to oxygen giving intermediate (A). Further, a single electron transfer from intermediate (A) would give an oxonium ion intermediate (B). However, the phenyl-2H-tetrazole (a) is deprotonated by the hydroxide ion to give the anionic species (C). Finally, nucleophilic attack of species (C) on to α -carbon of the oxonium species (**B**) provided the hemiaminal product (**1a**) (Scheme 3). In conclusion, an efficient metal-free protocol for the oxidative C-N bond formation via cross-dehydrogenative coupling

Scheme 3. Proposed Mechanisms for Oxidative C–N Bond Formation

(CDC) involving aryl tetrazoles (N–H) and aryl ethers (C_{sp3} –



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H) has been developed. In this oxidative coupling aryl ethers served the dual role of solvent and reactant. Reaction displays a broad substrate scope with respect to both aryl ether and aryl tetrazole coupling partners. This strategy showed high level of regioselectivity for substrates possessing multiple C_{sp3} -H bonds adjacent to ethereal oxygen.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02749.

Experimental details, spectral and analytical data. (PDF) C14 H11 Br N4 O (CIF)

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Notes

The authors declare no competing financial interest.

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