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Exploring Tandem Ruthenium-Catalyzed Hydrogen Transfer and S_NAr Chemistry

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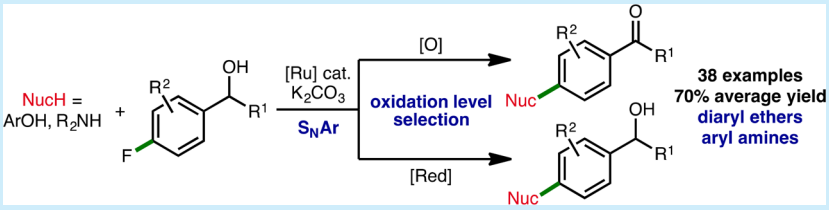
Supporting Information

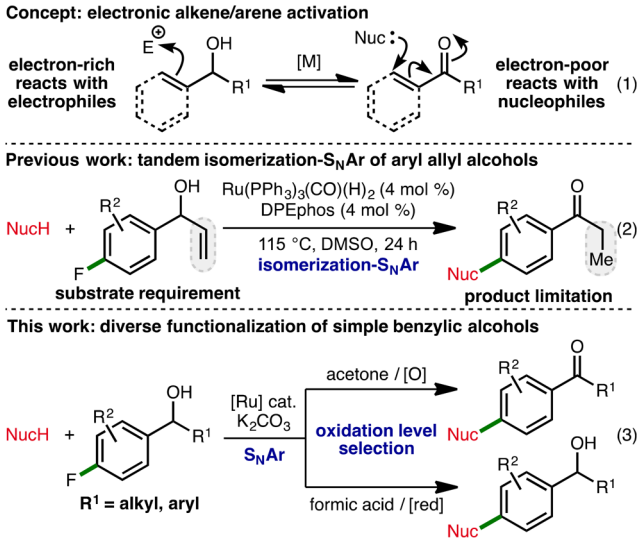


ABSTRACT: A hydrogen-transfer strategy for the catalytic functionalization of benzylic alcohols via electronic arene activation, accessing a diverse range of bespoke diaryl ethers and aryl amines in excellent isolated yields (38 examples, 70% average yield), is reported. Taking advantage of the hydrogen-transfer approach, the oxidation level of the functionalized products can be selected by judicious choice of simple and inexpensive additives.

The carbonyl functional group is one of the most prevalent and versatile in chemistry.[1] However, in some cases, carbonyl compounds suffer from poor stability (e.g., air oxidation of aldehydes to carboxylic acids; enolization leading to deleterious side reactions and erosion of enantiopurity) and limited commercial availability. In comparison, alcohols are typically widely available, inexpensive, and relatively inert toward air, moisture, and light, making them highly attractive starting materials for synthesis. Furthermore, the alcohol functional group is ubiquitous in pharmaceuticals, agrochemicals, dyes, fragrances, polymers, functional materials, and catalysts. As such, the development of novel methods that directly functionalize alcohols, diversifying their reactivity profile, is an important pursuit.

Hydrogen transfer is a powerful approach that can be employed to access the diverse reactivity of carbonyl compounds from alcohol starting materials.[2] Dehydrogenation of secondary alcohol substrates accesses ketones that can react with both nucleophiles and electrophiles (via enolization) in a variety of important reactions including C−C or C−N bond formation.[3,4] Dehydrogenation of allylic and benzylic alcohols dramatically alters the properties and reactivity of the olefin and arene, respectively, via electronic activation (Scheme 1, eq 1).[5] In 2013, Williams and co-workers developed a ruthenium-catalyzed transfer hydrogenation/isomerization of aryl allyl alcohols, generating acetophenones that are activated toward nucleophilic aromatic substitution (S_NAr) (Scheme 1, eq 2).[6] This redox-neutral approach requires a sacrificial olefin hydrogen acceptor within the substrate, significantly limiting its broader application in organic synthesis. Taking inspiration from these reports, we envisaged developing a more general strategy for catalytic arene functionalization via electronic activation of simple benzylic alcohols through the use of inexpensive additives that serve as oxidants or reductants. This approach would remove the strict requirement for highly

Scheme 1. Concept, Previous Work, And Outline of the Hydrogen Transfer−S_NAr Strategy



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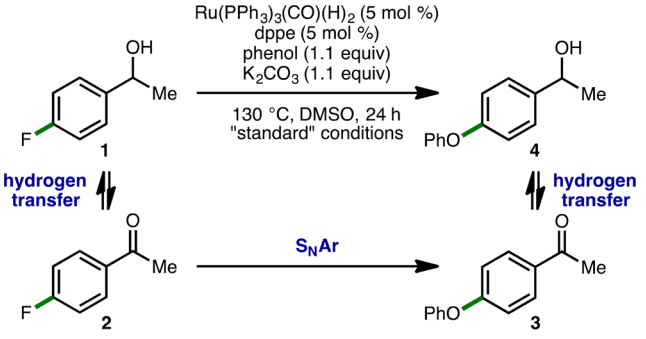
specialized aryl allyl alcohol substrates, significantly expanding the potential synthetic applications of the method. Furthermore, taking advantage of the hydrogen transfer approach, it was anticipated that the oxidation level of the functionalized products could be selected as desired by addition of an external oxidant or reductant, generating a diverse array of bespoke ketone and alcohol products, respectively (Scheme 1, eq 3). Herein, we report the successful implementation of this strategy and describe the diverse catalytic functionalization of simple benzylic alcohols via electronic arene activation.

To test our hypothesis, we selected 1-(4-fluorophenyl)ethan-1-ol **1** as the model substrate and phenol (1.1 equiv) as the nucleophile. Cognizant of the potentially challenging reduction of electron-rich acetophenones via metal-catalyzed hydrogen transfer,[7] the formation of mixtures containing benzylic alcohols **1** and **4** and acetophenones **2** and **3** was anticipated (Table 1). Therefore, the initial target was to achieve full conversion of **1** to a mixture of phenoxy-substituted arenes **3** and **4**, with a view to altering the product composition to favor acetophenone **3** or benzylic alcohol **4** via the addition of oxidants or reductants, respectively. After extensive optimization,[8] it was found that $Ru(PPh_3)_3(CO)(H)_2$ (5 mol %), 1,2-bis(diphenylphosphino)ethane (dppe) (5 mol %), and K_2CO_3 (1.1 equiv) in bench grade DMSO ([**1**] = 1 M) at 130 °C for 24 h, resulted in full consumption of **1** and formation of **3** and **4** in 62% and 28% NMR yield, respectively (entry 1). The observed net loss of hydrogen is attributed to the challenging hydrogenation of electron-rich acetophenone **3**, resulting in H_2 expulsion (i.e., acceptorless dehydrogenation)[4] into the headspace of the reaction vessel. No reaction occurs in the absence of ruthenium catalyst (entry 2), with 23% remaining starting material observed in the absence of dppe as ligand (entry 3). Variation of the ligand (entries 4 and 5), base (entries 6 and 7), and solvent (entry 8) all had a deleterious effect on conversion to **3** and **4**, as did reducing the concentration (entry 9), reaction temperature (entry 10), and catalyst loading (entry 11). The product distribution could be readily tailored by the addition of simple, inexpensive additives. Acetone (5 equiv) and formic acid (5 equiv), selected due to their low cost and ease of separation, permitted access to acetophenone **3** and benzylic alcohol **4** in 79% (entry 12) and 80% (entry 13) isolated yield, respectively.

Using the optimized conditions for the dehydrogenative S_NAr process (Table 1, entry 12), various aryl alcohols can be employed as the nucleophile, accessing a range of substituted diaryl ether products in excellent yields (products **3** and **5**–**12**, 70–86% yield) (Scheme 2).[9] Within the aryl alcohol, 4-Me, 3-Me, and 2-Me substitution were tolerated in addition to electron-donating substituents (4-OMe). The use of 4-chlorophenol and 4-bromophenol as the nucleophile was successful, incorporating an additional functional handle into

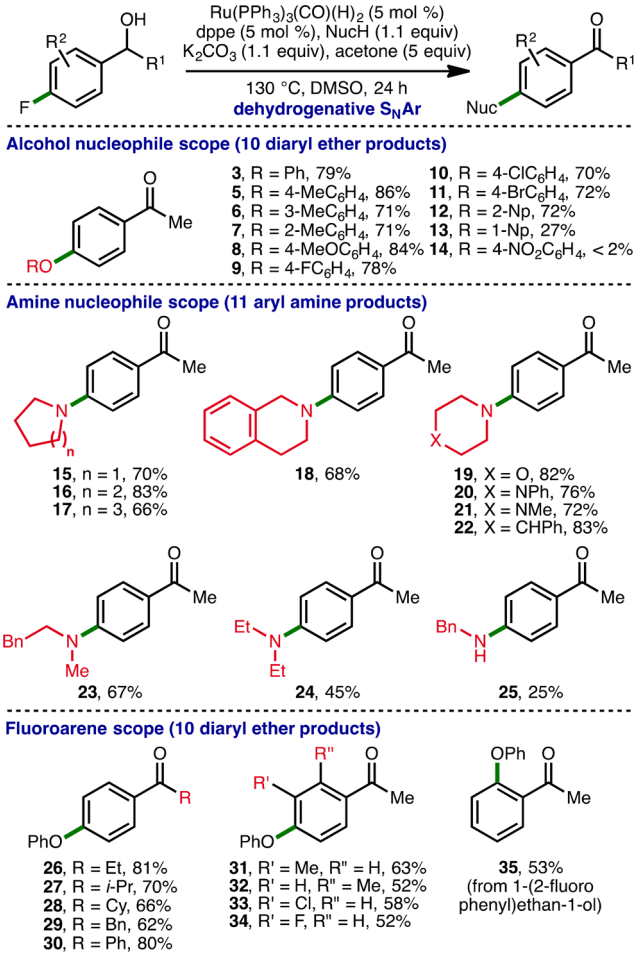
Table 1. Optimization of Hydrogen Transfer–S_NAr Protocol[a]



entry	variation from "standard" conditions	yield (**1**, **2**, **3**, **4**)[b] (%)
1	none	0, 1, 62, 28
2	no $Ru(PPh_3)_3(CO)(H)_2$	98, 0, 0, 0
3	no dppe	23, 2, 38, 25
4	Xantphos instead of dppe	7, 1, 35, 33
5	DPEphos instead of dppe	7, 2, 37, 40
6	Cs_2CO_3 instead of K_2CO_3	2, 2, 44, 34
7	Et_3N instead of K_2CO_3	43, 26, 10, 3
8	DMF instead of DMSO	38, 0, 30, 23
9	[**1**] = 0.5 M instead of 1 M	2, 2, 45, 37
10	115 °C instead of 130 °C	10, 3, 47, 39
11	2.5 mol % catalyst and ligand instead of 5 mol %	63, 1, 25, 7
12	**acetone (5 equiv) as additive**	**0, 0, 81 (79), 5**
13[c]	**formic acid (5 equiv) as additive**	**0, 0, 9, 82 (80)**

[a]Reactions performed using 0.4 mmol of alcohol **1** and bench-grade DMSO. [**1**] = 1 M. [b]Yield as determined by ^1H NMR analysis of crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Formic acid was added after 24 h followed by further reaction in DMSO at 130 °C for 24 h.

Scheme 2. Scope of Dehydrogenative S_NAr Protocol[a]



[a]Reactions performed using 0.4 mmol of alcohol starting material. All yields are isolated yields after chromatographic purification.

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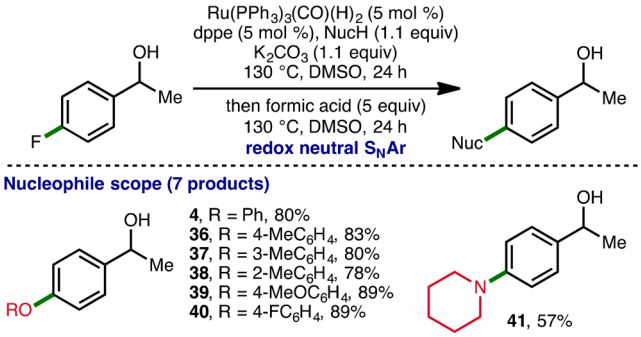
the products for subsequent elaboration via cross-coupling methods.[10] 2-Naphthol is a competent nucleophile in this process; however, aryl alcohols that are particularly sterically hindered (1-naphthol) or electron-poor (4-nitrophenol) do not readily react, with mostly starting materials returned.[11] A range of 5-, 6-, and 7-membered heterocyclic amines, including pyrrolidine, piperidine, morpholine, and azepane, can be employed as the nucleophile to afford various aryl amine products in high yields (products **15**–**22**, 66–83% yield).[12] Acyclic secondary amines *N*-methylphenethylamine and diethylamine afforded aryl amines **23** and **24** in 67% and 45% isolated yield,[13] respectively, with less nucleophilic benzylamine generating **25** in only 25% yield.[14] Furthermore, using phenol as nucleophile, a range of fluoroarene substrates undergo functionalization using the optimized reaction conditions, including sterically hindered secondary alcohols (R = *i*-Pr, Cy) and various trisubstituted arenes (products **26**–**34**, 52–81% yield). Finally, 1-(2-fluorophenyl)ethan-1-ol was employed in the dehydrogenative S_NAr protocol, accessing diaryl ether derivative **35** in 53% yield.[15]

Having successfully demonstrated the dehydrogenative S_NAr process for a variety of nucleophiles and fluoroarenes, we next investigated the scope of the formally redox neutral S_NAr approach,[3] employing formic acid as reducing agent (Scheme 3). Under the optimized reaction conditions (Table 1, entry

Scheme 3. Scope of Redox-Neutral S_NAr Protocol[a]

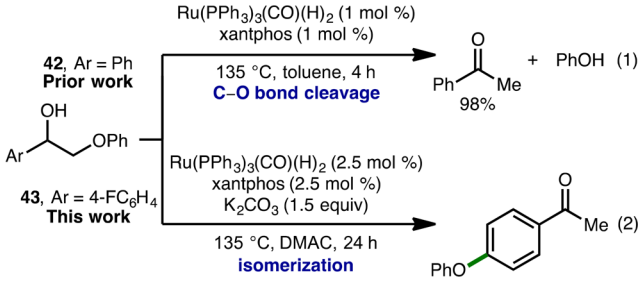


[a]Reactions performed using 0.4 mmol of alcohol starting material. All yields are isolated yields after chromatographic purification.

13), 1-(4-fluorophenyl)ethan-1-ol **1** couples with a representative selection of substituted aryl alcohol nucleophiles, accessing a range of diaryl ethers in excellent yields (products **4** and **36**–**40**, 78–89% yield). As observed in the dehydrogenative process, 4-Me, 3-Me, and 2-Me substitution is tolerated within the aryl alcohol in addition to electron-donating substituents (4-OMe). Considering that the reduction of electron-rich amino-substituted acetophenones is challenging via metal-catalyzed transfer hydrogenation processes,[6] it is noteworthy that piperidine can be employed as the nucleophile in this protocol, accessing **41** in 57% yield.

The methods described thus far employ acetone and formic acid as oxidant and reductant, respectively. Despite the low cost of these additives and the ease of product isolation, an alternative approach with increased atom economy was sought.[16] In 2010, Bergman, Ellman, and co-workers described the catalytic C–O bond cleavage of 2-aryloxy-1-arylethanols (Scheme 4, eq 1),[17] which serve as model compounds for lignin depolymerization studies.[18] Inspired by these reports, we envisaged developing a one-pot isomerization of 2-aryloxy-1-

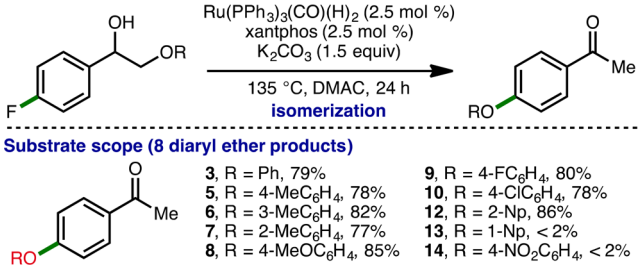
Scheme 4. Previous Work and Outline of the Isomerization Strategy



arylethanols to diaryl ethers, which proceeds via transfer hydrogenation to generate fluoroarenes that are electronically activated toward a subsequent S_NAr with aryl alcohols (Scheme 4, eq 2). To validate this approach, fluorinated 2-aryloxy-1-arylethanol **43** was employed as a model substrate. The reaction conditions developed by Bergman, Ellman, and co-workers were modified to facilitate a subsequent nucleophilic aromatic substitution step by switching to *N*,*N*-dimethylacetamide as solvent, adding K_2CO_3 (1.5 equiv) as base, increasing the reaction time to 24 h, and increasing the catalyst and ligand loading to 2.5 mol %.

Under these optimized reaction conditions,[8] various 2-aryloxy-1-arylethanols undergo isomerization, accessing a range of diaryl ether products in excellent yields (products **3**, **5**–**10**, and **12**-**14**, 77–86% yield) (Scheme 5). Within the aryl ether

Scheme 5. Scope of Isomerization Protocol[a]



[a]Reactions performed using 1.0 mmol of starting material. All yields are isolated yields after chromatographic purification.

moiety, 4-Me, 3-Me, and 2-Me substitution was tolerated in addition to electron-donating substituents (4-OMe). A 2-naphthyl ether substrate readily undergoes isomerization, giving **12** in 86% yield; however, introduction of a bulky 1-naphthyl ether moiety precluded C–O bond cleavage, with starting materials returned. Conversely, a 4-nitrophenyl ether substrate underwent C–O bond cleavage, but no S_NAr was observed due to the low nucleophilicity of 4-nitrophenol.

Finally, cognizant of the limited commercial availability of 2-aryloxy-1-arylethanols, we developed an alternative, telescoped synthesis of diaryl ether **3** that employs commodity epoxide **44** as the starting material. This one-pot transformation proceeds via an initial epoxide ring opening, followed by catalytic alcohol dehydrogenation/C–O bond cleavage and final S_NAr, accessing **3** in 59% isolated yield (Scheme 6).

In conclusion, we have developed a general approach for the catalytic functionalization of benzylic alcohols via electronic arene activation, accessing a diverse range of diaryl ethers and aryl amines in excellent isolated yields. Our method takes advantage of the hydrogen transfer approach to select the

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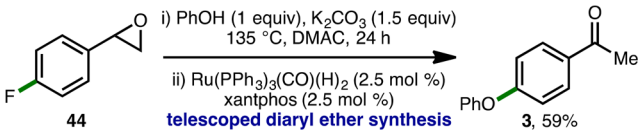
Scheme 6. One-Pot Diaryl Ether Synthesis from Epoxide



oxidation level of the functionalized products via the addition of simple, inexpensive additives. We have also developed a catalytic isomerization of 2-aryloxy-1-arylethanols and a telescoped synthesis of diaryl ethers directly from commodity epoxide starting materials. Ongoing studies are focused on further applications of hydrogen transfer in catalysis, and these results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03441.

Optimization data, experimental procedures, characterization of new compounds and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/10.17035/d.2017.0044059416.

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(11) Employing alkyl alcohols (e.g., benzyl alcohol or 1-decanol) as the nucleophile under optimized reaction conditions (or with NaH or KO*t*-Bu as base) results in the formation of complex mixtures of products. Employing thiophenol as the nucleophile results in catalyst deactivation, with starting materials returned.

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