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NBS-Initiated Electrophilic Phenoxyetherification of Olefins

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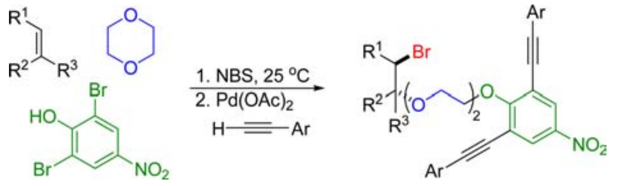
ABSTRACT



A one-pot electrophilic phenoxyetherification using an olefin, a cyclic ether, a phenol, and *N*-bromosuccinimide has been developed. This type of multicomponent reaction (MCR) is useful in the synthesis of building blocks that are potentially applicable to self-assembly complex construction.

To synthesize target compounds with great efficiency and atom economy, many highly effective and powerful synthetic tools have been developed in modern green chemistry.[1] Among these, multicomponent reactions (MCRs) have been considered as the “cream of the crop”, by generating structural complexity in a single step from three or more reactants generally and reliably.[2] Although successes had been reported on MCRs, developing new reactions is still of significant importance.[3] Partly due to the common incompatibility of electrophiles with the other components, electrophilic MCRs have been relatively less reported.[4]

In the course of our endeavor to develop electrophilic MCR utilizing *N*-bromosuccinimide (NBS) as the brominating initiator, we have disclosed a number of electrophilic cascades using various nucleophilic partners.[5] In these studies, it was found that a nucleophile that contains an acidic proton is necessary to achieve high reaction yield. The acidic proton may be used to activate the halogen source NBS. Herein, we report the use of electron-deficient phenol as the nucleophilic partner in this type of MCR. The resulting products **B**, which contain a ether linkage and a functionalized phenoxy unit, can be further manipulated to give building blocks (e.g., **C**) that are potentially useful for self-assembly complex construction (vida infra) (Scheme 1).

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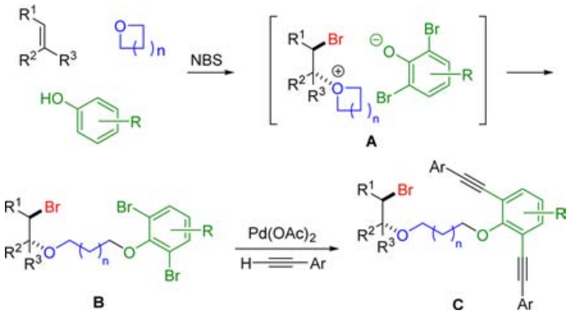
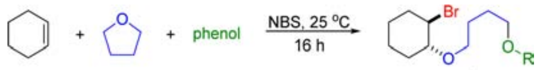
Scheme 1. NBS-Promoted Electrophilic Cascades



In our preliminary study on the MCR using cyclohexene, tetrahydrofuran (THF), and NBS as the components, it was found that phenol and nitrophenols were brominated and the desired adducts were achieved in moderate to good yields (Table 1, entries 1–4). Other electron-deficient phenols were also examined, and moderate to good yields were obtained in general (Table 1, entries 5–9).[6] However, for the highly electron-deficient pentafluorophenol (Table 1, entry 6), low yield was observed which may be partly attributed to the low nucleophilicity of the counter phenoxy anion that results in the low **A** → **B** conversion efficiency (Scheme 1).

Table 1. Electrophilic Phenoxyetherification of Cyclohexene



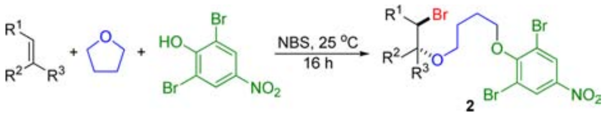
1

entry[a]	phenol	product, R	yield[e] (%)
1[b]	C_6H_5OH	**1a**, 2,4,6-$Br_3C_6H_2$	42
2	2,4,6-$Br_3C_6H_2OH$	**1a**, 2,4,6-$Br_3C_6H_2$	42
3[c]	4-$NO_2C_6H_4OH$	**1b**, 2,6-Br_2-4-$NO_2C_6H_2$	85
4[c]	2-$NO_2C_6H_4OH$	**1c**, 4,6-Br_2-2-$NO_2C_6H_2$	45
5	2,6-Br_2-4-$NO_2C_6H_2OH$	**1b**, 2,6-Br_2-4-$NO_2C_6H_2$	96
6	C_6F_6OH	**1d**, C_6F_6	18
7	3,5-$(CF_3)_2C_6H_3OH$	**1e**, 3,5-$(CF_3)_2C_6H_3$	50
8[c]	4-$CF_3C_6H_4OH$	**1f**, 2,6-Br_2-4-$CF_3C_6H_2$	44
9[c]	4-$CF_3OC_6H_4OH$	**1g**, 2,6-Br_2-4-$CF_3OC_6H_2$	42
10[c]	4-*t*BuC_6H_4OH	no reaction	
11[c]	4-$CH_3C_6H_4OH$	no reaction	
12	2,6-Br_2-4-$CH_3C_6H_2OH$	no reaction	
13[d]	2,6-Br_2-4-$NO_2C_6H_2OH$	**1b**, 2,6-Br_2-4-$NO_2C_6H_2$	95

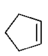
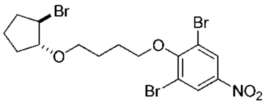
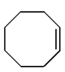
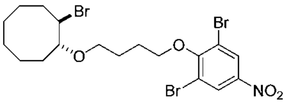
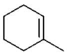
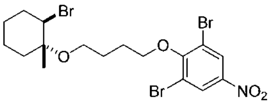
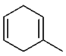
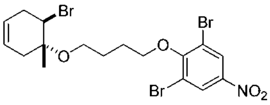
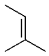
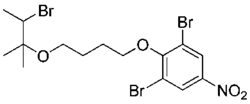
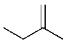
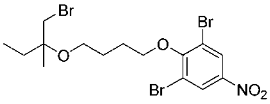
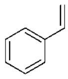
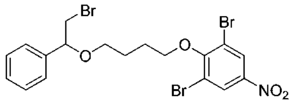
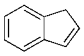
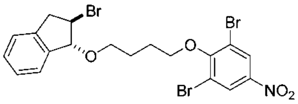
[a] Reactions were carried out with cyclohexene (0.6 mmol), phenol (0.5 mmol), and NBS (0.6 mmol) in THF (4.0 mL) at 25 °C for 16 h. [b] Using 4.5 equiv of NBS. [c] Using 3.5 equiv of NBS. [d] The reaction was conducted on a 5 mmol scale. [e] Isolated yields.

Some relatively electron-rich phenols, including 4-methyl-, 4-*tert*-butyl-, and 2,6-dibromo-4-methylphenols, were subjected to the reaction, and no desired product was detected (Table 1, entries 10–12). This result is consistent with our previous observation in which the acidic proton plays a crucial role in the MCR, potentially acting as the NBS activator.[5,7] Finally, the reaction was readily scalable with equal reaction efficiency (Table 1, entry 13).

Table 2. Electrophilic Phenoxyetherification Using Various Olefins



2

entry[a]	substrate	product		yield (%)[b]
1			**2a**	64
2			**2b**	71
3			**2c**	88
4			**2d**	90
5			**2e**	85
6			**2f**	97
7			**2g**	89
8			**2h**	82

[a] Reactions were carried out with cyclohexene (0.6 mmol), phenol (0.5 mmol), and NBS (0.6 mmol) in THF (4.0 mL) at 25 °C for 16 h. [b] Isolated yields.

Having proven the feasibility of this multicomponent reaction, various olefinic substrates were then subjected to investigation (Table 2).[8] In general, the reactions proceeded smoothly with good to excellent yields. Furthermore, high chemoselectivities were observed, as the more electron-rich olefinic position react more readily (Table 2,

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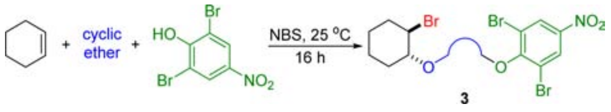
(6) The pK_a values of the phenols are summarized in the Supporting Information (Table S1).

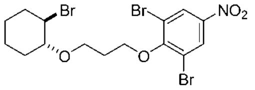
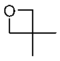
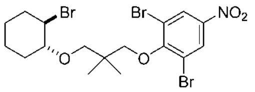
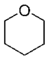
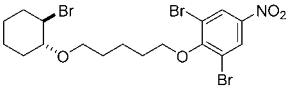
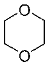
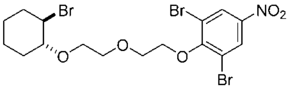
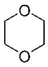
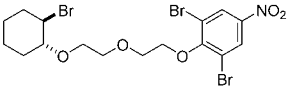
(7) We had also suspected that the cyclic ether might be preopened by the phenols before the bromoetherification of olefin. Nonetheless, we attempted to mix 2,6-dibromo-4-nitrophenol and NBS in THF for 16 h at 25 °C in which no THF ring-opening product was observed.

entry 4). In the cases of trisubstituted cyclic (**2c** and **2d**), acyclic (**2e** and **2f**), and benzylic (**2g** and **2h**) olefins, excellent regioselectivities were achieved wherein only the Markovnikov-type products were found.

The scope of this phenoxyetherification disclosed herein appears to be quite broad in regard to not only the olefinic component but also the cyclic ether partner. We carried out the reaction using cyclohexene, 2,6-dibromo-4-nitrophenol, and NBS in a variety of cyclic ethers (Table 3).

Table 3. Electrophilic Phenoxyetherification Using Various Cyclic Ethers



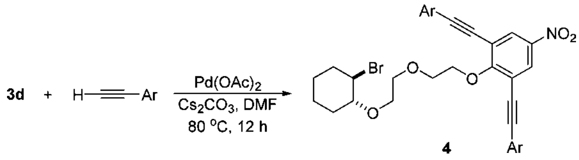
entry[a]	cyclic ether	product		yield (%)[c]
1			**3a**	78
2			**3b**	87
3			**3c**	88
4			**3d**	95
5[b]			**3d**	94

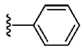
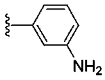
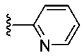
[a] Reactions were carried out with cyclohexene (0.6 mmol), phenol (0.5 mmol), and NBS (0.6 mmol) in THF (4.0 mL) at 25 °C for 16 h. [b] The reaction was conducted on a 5 mmol scale. [c] Isolated yields.

Treatment of the substrates in oxetane gave the desired product **3a** in 78% yield, whereas adduct **3b** was isolated in 87% yield when 3,3-dimethyloxetane was used (Table 3, entries 1 and 2). Besides four- and five-membered-ring cyclic ethers, a six-membered-ring tetrahydropyran was also found to be effective in the reaction, giving **3c** in 88% yield (Table 3, entry 3). Interestingly, polyether adduct **3d** was isolated (95%) when 1,4-dioxane was used in the reaction (Table 3, entries 4 and 5).

It is noteworthy that the resulting compounds could serve as the fundamental units of metal complexation ligands. For instance, compound **3d** can be converted to **4** simply by double-Sonogashira coupling reactions (Table 4). In particular, Fujita[9] reported the application of this type of compounds to the synthesis of self-assembly spherical complexes potentially applicable to the construction of high-density data-storage materials. Those complexes consist of metals and multistep-synthesized ligands obtained from coupling between 2,6-dibromophenoxy motif and 4-ethynylpyridine.

Table 4. Sonogashira Coupling of **3d** with Arylacetylene



entry[a]	product	Ar	isolated yield (%)
1	**4a**		92
2	**4b**		85
3	**4c**		87

[a] Reactions were carried out with **3d** (0.2 mmol), arylacetylene (0.6 mmol), Pd(OAc)$_2$ (0.02 mmol), and Cs$_2$CO$_3$ (0.3 mmol) in DMF (2.5 mL) at 80 °C for 12 h.

In our previous related studies, it is believed that the counter nucleophiles, sulfonamides[5b,c] and carboxylic acids,[5d] are responsible for the activation of NBS. In the present study, we had also suspected that the same activation mode appeared in this phenoxyetherification reaction which is the sole origin of reactivity. However, pentafluorophenol that is more acidic than 2,6-dibromo-4-nitrophenol did not return with higher reaction yield (Table 1, entry 6). A NMR study on the mixture of NBS and 2,6-dibromo-4-nitrophenol was performed in order to get further insight. A new proton signal (8.47 ppm), which is more downfield than that of the aromatic proton of 2,6-dibromo-4-nitrophenol (8.45 ppm), appeared when mixing NBS and 2,6-dibromo-4-nitrophenol. The NBS proton signal (2.81 ppm) diminished accompanied by the generation of succinimide (2.61 ppm). These chemical shifts resemble the species 2,4,6-tribromophenol and 2,4,4,6-tetrabromo-2,5-cyclohexadienone.[10] In addition, upon mixing NBS with 2,6-dibromo-4-nitrophenol, the solution changed from colorless to bright orange, which is identical to the color of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (Figure 1). Based on these results, we believe that 2,4,6-tribromo-4-nitro-2,5-cyclohexadienone (**5**) might be generated in situ

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(8) Representative procedure: to a solution of olefin (0.6 mmol) in cyclic ether (1 mL) were added phenol (0.5 mmol) and *N*-bromosuccinimide (107 mg, 0.6 mmol) at 0 °C. The reaction was shielded from light and then stirred at 25 °C for 16 h. The solvent was then removed under reduced pressure, and the residue was purified by flash column chromatography (*n*-hexane/EtOAc 20:1) to yield the corresponding product.

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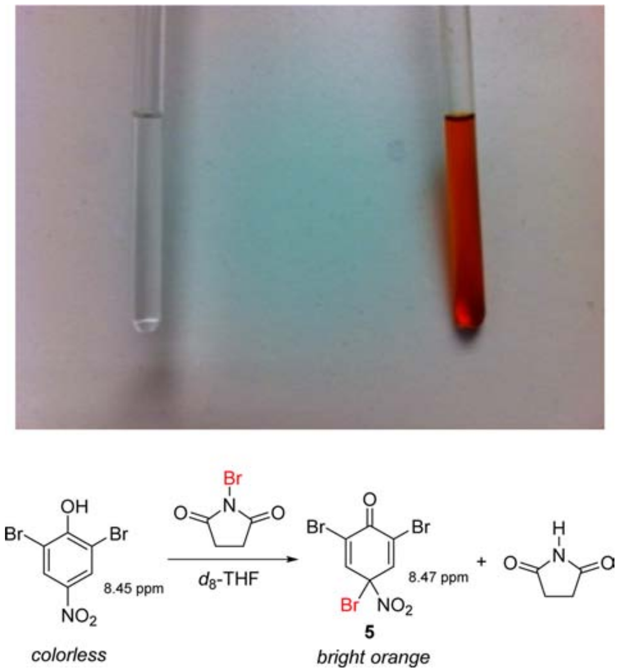

Figure 1. Color change when NBS is mixed with 2,6-dibromo-4-nitrophenol.

and acts as the active halogenating source. On the other hand, no sharp color change upon mixing pentafluorophenol with NBS.[11] This can also explain why the more electron-deficient aromatic systems, which should be less reactive toward the generation of the para-brominated species, gave lower reaction efficiency.

In summary, we have developed a general and efficient electrophilic phenoxyetherification using an olefin, a cyclic ether, a phenol, and NBS. The olefin and cyclic ether partners can be flexibly varied to produce different kinds of phenoxy ether derivatives. Furthermore, the coupling protocol allows the facile ligand preparations. Hence, the resulting products are potentially useful structural motifs in material chemistry.

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Supporting Information Available. Experimental details and ^{1}H and ^{13}C NMR spectral data for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The details appear in the Supporting Information (Figure S1).

The authors declare no competing financial interest.