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Bismuth(III)-Catalyzed Dehydrative Etherification and Thioetherification of Phenolic Hydroxy Groups

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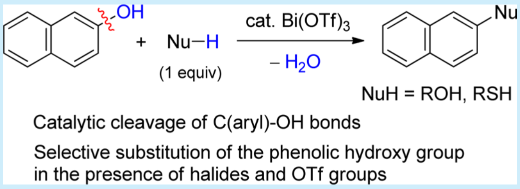
S *Supporting Information*

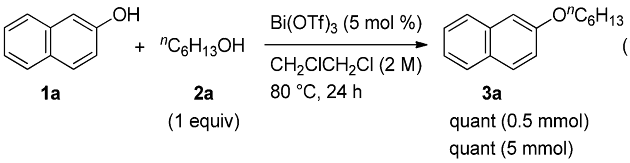
ABSTRACT: Use of a bismuth catalyst allowed efficient dehydrative substitution of phenolic hydroxy groups with alcohols and thiols to form C−O and C−S bonds. The reaction required equimolar amounts of two readily available substrates that generated H_2O as the only byproduct. The relatively mild reaction conditions were compatible with the functional groups selected, and provided excellent chemoselectivity.



Alkyl naphthyl ethers constitute important structural units in perfumes, cosmetics, and flavoring compounds, such as yara yara (Nerolin I), bromelia (Nerolin II), and fragrol (Nerolin Fragnol).[1] They also serve as versatile synthetic building blocks of drug candidates. For example, 2-methoxynaphthalene is an important intermediate for the production of naproxen and nabumetone, widely used as nonsteroidal anti-inflammatory drugs.[2] Because of their usefulness in fine chemical synthesis, alkyl aryl ethers have been investigated as synthetic targets. The most common approach for their preparation known as Williamson's synthesis, involves the treatment of preactivated phenol derivatives with alkylating reagents containing good leaving groups such as halides, tosylates (OTs), or triflates (OTf) under basic conditions.[3] Unfortunately, these organic halides and pseudohalides result in the formation of undesirable acidic byproducts and are usually more expensive compared with the corresponding alcohols.[4] Representative alternative preparative methods include S_NAr reactions with electron-deficient aromatics, and reactions with Mitsunobu type reagents or benzyne intermediates.[5] Although these methods are widely used, they require multiple steps to prepare the starting materials and generate stoichiometric byproducts. Therefore, effort has been devoted to the development of highly efficient dehydrative etherification of phenols with alcohols as an environmentally benign process. Classical reactions require stoichiometric amounts of strong Brønsted acids, such as hydrochloric acid, sulfuric acid, or fluorosulfonic acid, to activate the hydroxy groups because they are inherently poor leaving groups.[6] These methods are very useful, but possess drawbacks such as limited substrate scope and low functional group compatibility (i.e., they tend to produce undesirable products when hydroxy and halide functional groups exist in their backbones). In addition, the use of strong acid or harsh conditions limits their application in the syntheses of complex molecules.

During a study designed to develop new and efficient catalytic processes, unexpected dehydrative coupling of 2-naphthols with alcohols occurred selectively to form new C−O bonds in the presence of a catalytic amount of a bismuth complex. This observation prompted a detailed examination of this unique reaction because (1) the reaction proceeded efficiently with phenols and alcohols, even at a 1:1 ratio, and (2) bismuth salts are readily available, possess low toxicity despite being the heavy metal, and have been used as environmentally benign reagents and catalysts during the past few years.[7] The present study describes a highly selective, operationally simple catalytic substitution reaction enabling the direct use of phenols and alcohols as substrates and the production of water as the only byproduct.

Conditions were optimized for the reaction of 2-naphthol **1a** with a stoichiometric amount of 1-hexanol **2a**. After a screening of reaction conditions, we found the 2-(hexyloxy)naphthalene **3a** was obtained quantitatively in the presence of 5 mol % of $Bi(OTf)_3$ in 1,2-dichloroethane at 80 °C (eq 1). It is worth mentioning that the reaction occurred as well on a 5 mmol scale (0.72 g of **1a** with 0.51 g of **2a**) as on a 0.5 mmol scale under these reaction conditions (eq 1). Several other transition metal complexes, such as $Sc(OTf)_3$, $FeCl_3$, $Fe(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, and $In(OTf)_3$, showed catalytic activity, although none of which were superior to $Bi(OTf)_3$.[8,9] Other bismuth complexes, including $Bi(OAc)_3$, $BiCl_3$, and $BiBr_3$, were ineffective and resulted in recovery of most of the **1a** and **2a** used.[8] When TfOH was used as a catalyst, the yield decreased



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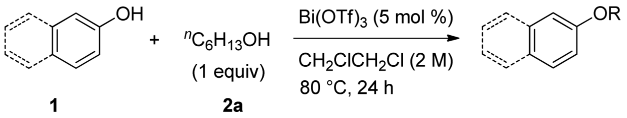
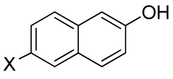
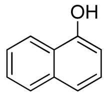
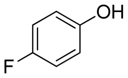
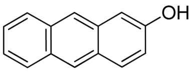
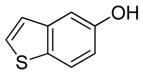
to 66% and the undefined byproducts, such as di(2-naphthyl) ether and BINOL, were formed.[10]

Using the optimized reaction conditions, the scope of phenols was investigated for dehydrative etherification with 1-hexanol **2a** as a model reaction (Table 1). 2-Naphthols **1b**, **1c**, and **1d** possessing electron-neutral, -donating, and -withdrawing substituents on the naphthyl ring all reacted to form the corresponding 2-(hexyloxy)naphthalenes **3b**, **3c**, and **3d** in good-to-excellent yields (entries 1−3). 1-Naphthol **1e** was also a suitable substrate and afforded 1-(hexyloxy)naphthalene **3e** albeit in slightly lower yield compared with the reaction of **1a** (entry 4 vs eq 1). In contrast, the use of phenol derivatives, such as **1f** as substrates resulted in a decrease in yield to less than 30% (entry 5). Notably, dehydrative etherification was not restricted to naphthols but could be achieved using 2-anthracenol **1g** and 5-hydroxybenzothiophene **1h** as substrates, although slight excess of 1-hexanol **2a** was required to obtain the adducts in high yields (entries 6 and 7).

Table 1. Bismuth(III)-Catalyzed Dehydrative Etherification of Phenols 1 with 1-Hexanol 2a

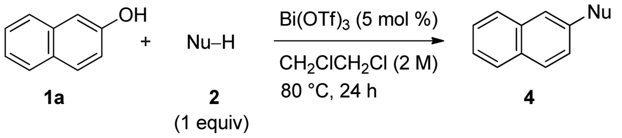


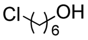
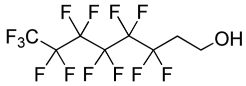
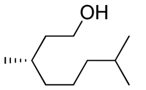
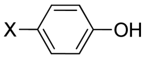
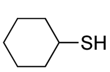
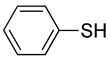
Entry	phenolic alcohol			product	Yield (%)[a]
1		X = Et	**1b**	**3b**	quant
2		NPh$_2$	**1c**	**3c**	53
3		Br	**1d**	**3d**	82
4			**1e**	**3e**	86
5			**1f**	**3f**	29[b]
6			**1g**	**3g**	74 (99[b])
7			**1h**	**3h**	52 (84[b])

[a] Isolated yields. [b] At 115 °C.

Next, several nucleophiles were subjected to the optimized reaction conditions (Table 2). Reaction with alcohols containing a linear alkyl chain **2b** gave the corresponding ether **4b** in quantitative yield (entry 1). A chloro group was well-tolerated under the present reaction conditions (entry 2). A perfluorinated alkyl chain was also introduced to furnish the corresponding ether **4d** in excellent yield (entry 3). In addition, the branched alcohol **2e** derived from (−)-*β*-citronellol could be employed as a substrate to furnish **4e** with complete retention of stereochemistry (entry 4). Unfortunately, phenol derivatives were less reactive and afforded the corresponding naphthyl ethers **4f** and **4g** in moderate-to-low yields (entries 5 and 6). The reaction occurred at the alcoholic oxygen not on the aromatic ring probably due to the steric hindrance. Thiols could be applied to the present dehydrative carbon-hetero bond formation to furnish the corresponding naphthyl thioether **4h** in 94% yield (entry 7). Note that naphthyl thioether **4h** was obtained selectively without forming 2-(hexyloxy)naphthalene **3a**, clearly indicating that substitution of the phenolic hydroxy group occurred with the current catalyst system.[11] Although the reaction did not proceed using sterically hindered secondary alcohols, such as 2-propanol and cyclohexanol, the substrate cyclohexanethiol **2i** furnished the cyclohexyl naphthyl thioether **4i** in 95% yield (entry 8). Thiophenol **2j** was also applicable to give the corresponding thioether **4j** in 94% yield (entry 9).

Table 2. Bismuth(III)-Catalyzed Dehydrative Etherification and Thioetherification of 2-Naphthol 1a

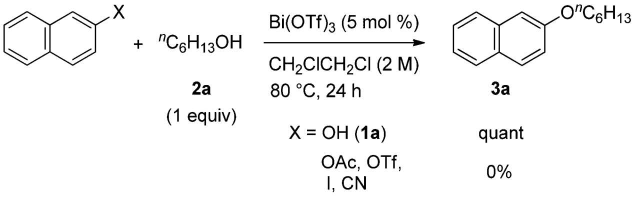


Entry	Nu–H (**2**)			product (**4**)	Yield (%)[a]
1	$^{n}C_8H_{17}OH$		**2b**	**4b**	quant
2			**2c**	**4c**	96
3			**2d**	**4d**	quant
4			**2e**	**4e**	quant
5		X = MeO	**2f**	**4f**	55[b]
6		= H	**2g**	**4g**	31
7	$^{n}C_6H_{13}SH$		**2h**	**4h**	94
8			**2i**	**4i**	95
9			**2j**	**4j**	94

[a] Isolated yields. [b] **2f** (2 equiv).

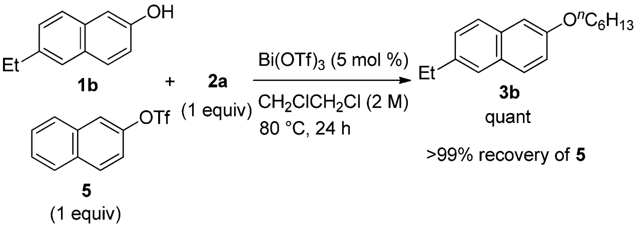
To obtain insight into the reaction mechanism, the effect of the leaving group of the naphthalene derivatives was investigated (Scheme 1). Interestingly, other oxygen-based leaving groups, including acetate (OAc) and trifluoromethanesulfonate (OTf), which often act as good leaving groups in various transition metal-catalyzed cross-coupling reactions, did not work.[12] In addition, halides and cyano groups did not afford the corresponding substituted product **3a**, even though they are better leaving groups compared with hydroxy groups. This unique chemoselectivity enables selective substitution of the phenolic hydroxy group in the presence of other "good" leaving groups. For example, treatment of 2-naphthol **1b** with 1-hexanol **2a** in the presence of the corresponding triflate **5** gave **3b** quantitatively along with the recovery of intact **5** (Scheme

Scheme 1. Effect of the Leaving Group



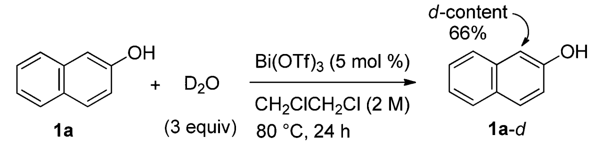
2). This result confirms that leaving group ability is in the order OH > OTf with the current bismuth catalyst system.

Scheme 2. Selective Substitution of the Phenolic Hydroxy Group



To gain understanding into the reaction mechanism, 2-naphthol **1a** was treated with 3 equiv of D_2O in the presence of the bismuth catalyst (Scheme 3). A total of 66% of the deuterium atoms was incorporated exclusively into the 1-position to afford the deuterium incorporated naphthol **1a**-*d* quantitatively.[13] Incorporation of deuterium was not observed when **1a** was reacted with D_2O in the absence of $Bi(OTf)_3$. Since $Bi(OTf)_3$ is known to generate TfOH in the presence of H_2O, this result indicated that the present reaction proceeded via selective protonation by TfOD at the 1-position.[10,14]

Scheme 3. Control Experiment



Among the results obtained above, we focused on the following three observations to discuss the reaction mechanism. (1) Selective C−S bond formation occurred without production of a C−O bond in the reaction of 2-naphthol **1a** with thiols (Table 2, entries 7 and 8), indicating that alcohols and thiols acted as nucleophiles and cleaved the phenolic hydroxy group in the presence of the bismuth catalyst. (2) Substituted 2-naphthols underwent selective etherifications exclusively at the ipso carbon of the phenolic hydroxy group, irrespective of the electronic nature of the substituent (Table 1, entries 1−3). (3) Common leaving groups, including halide and cyano groups,[15] remained intact, and only naphthalene derivatives with hydroxy groups were suitable substrates (Scheme 1). This observation ruled out the possibility of the present reaction proceeding via an S_NAr reaction mechanism. Since the phenolic anions are good σ-donor ligands, they could bind to the bismuth catalyst and induce bismuth-assisted cleavage of the hydroxy group. The lack of homocoupling of alcohols under the current reaction conditions also supports bismuth-assisted selective elimination of the phenolic hydroxy group.

Taking these observation into consideration, a possible mechanism is depicted in Figure 1, which exemplifies the reaction of 2-naphthol. Initially, ligand exchange of $Bi(OTf)_3$ with 2-naphthol generated intermediate **A** along with elimination of TfOH. Subsequent protonation of **A** with TfOH formed the oxocarbenium ion intermediate **B**,[10] which was trapped by nucleophiles leading to **C**. At this stage, nucleophiles selectively attacked the most electronically deficient oxocarbenium carbon. Finally, the elimination of the hydroxy group assisted by the bismuth complex furnished the corresponding coupling product followed by regeneration of the bismuth catalyst.[16]

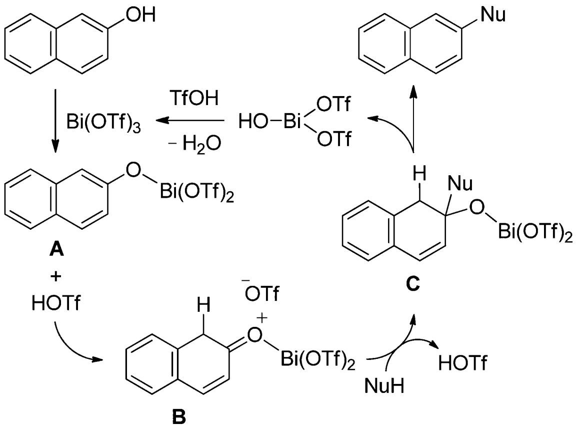
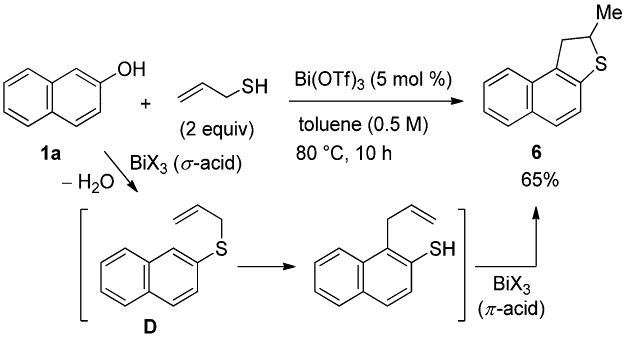


Figure 1. Proposed reaction mechanism.

Because $Bi(OTf)_3$ is known to serve as both an σ- and π-acid catalyst,[7,16,17] the cascade reaction was likely initiated by the dehydroetherification that takes advantage of the dual activation mode. Treatment of 2-naphthol **1a** with allyl thiol in the presence of $Bi(OTf)_3$ provided 1,2-dihydro-2-methylnaphtho-[2,1-*b*]thiophene **6** in 65% yield (Scheme 4). The reaction sequence involves not only the dehydrative etherification of **1a** to generate allyl 2-naphthyl ether **D**, but also subsequent thio-Claisen rearrangement followed by the cycloisomerization leading to **6**. A catalytic amount of $Bi(OTf)_3$ was also confirmed to promote thio-Claisen rearrangement and cyclization of allyl 2-naphthyl thioether **D**, which was prepared by the Williamson ether method, probably as a π-acid.[18,19]

Scheme 4. Bismuth(III)-Catalyzed Cascade Reaction Initiated by Dehydrative Thioetherification of 1a



In conclusion, a novel straightforward bismuth-catalyzed dehydrative substitution of phenolic hydroxy groups with alcohols and thiols has been developed. Neither severe reaction conditions nor an excess of substrates are required in the current catalytic system, which offer a practical and environmentally friendly route to a wide variety of aryl ethers. Although catalytic cleavage of C(aryl)−OH bonds has been reported recently using a late transition metal catalyst,[11] its replacement by an inexpensive, air-stable, and environmentally friendly bismuth catalyst that offers practical production possibilities is an important development. Thus, we believe the present system opens up new perspectives for advances in the dehydrative nucleophilic substitution system. Further investigation on the highly efficient bismuth-catalyzed transformations as well as applications of the resulting aryl ethers are currently in progress.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(4) The use of halides, which are usually derived from alcohols, limits efficiency for overall yields and step economy. See: De La Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: New York, 1976.

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(8) Investigation of several transition-metal catalysts (5 mol%): $Sc(OTf)_3$, 40%; $[ReBr(CO)_3(thf)]_3$ (2.5 mol%), 12%; $FeCl_3$, 37%; $Cu(OTf)_2$, 72%; $AuCl_3$, 15%; $In(OTf)_3$, 36%; $BiCl_3$, 6%. The following catalysts did not afford **3a**: $Re_2(CO)_{10}$, $Sm(OTf)_3$, $Yb(OTf)_3$, $Fe(OTf)_3$, $RhCl(PPh_3)_3$, $Ir_4(CO)_{12}$, $BiBr_3$.

(9) Investigation of solvents: toluene, quant; *n*-octane, quant; 1,4-dioxane, 54%; MeCN, 0%; DMF, 0%; neat 90%.

(10) In the $Bi(OTf)_3$-catalyzed reaction, the catalytic role of the bismuth ion vs activity of TfOH formed by hydrolysis from residual water is still under debate. See: (a) Lambert, R. F.; Hinkle, R. J.; Ammann, S. E.; Lian, Y.; Liu, J.; Lewis, S. E.; Pike, R. D. *J. Org. Chem.* **2011**, *76*, 9269−9277. (b) Godeau, J.; Olivero, S.; Antoniotti, S.; Duñach, E. *Org. Lett.* **2011**, *13*, 3320−3323. (c) Ollevier, T.; Nadeau, E. *Org. Biomol. Chem.* **2007**, *5*, 3126−3134. When 5 mol% and 15 mol % of TfOH was used, **3a** was obtained in 66% and 68% yield, respectively, indicating a difference in behavior between TfOH and $Bi(OTf)_3$ for this transformation.

(11) Cross-coupling reactions involving the cleavage of C(aryl)−OH bonds in the presence of a nickel catalyst have been reported. See: (a) Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4566−4570. (b) Yu, D.-G.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7097−7100.

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(13) Theoretical percentage of deuterium incorporation would be 75%, when 3 equiv of D_2O was employed because one equiv of H_2O should be eliminated upon substitution of the hydroxy group of **1a** with D_2O.

(14) Acid scavengers, such as proton sponge and molecular sieves, completely inhibited the reaction of 2-naphthol **1a** with 1-hexanol **2a**. These proton scavengers may trap TfOH or decrease the Lewis acidity of $Bi(OTf)_3$.

(15) For reviews on C−CN bond cleavage, see: (a) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300−307. (b) Nakao, Y.; Hiyama, T. *Pure Appl. Chem.* **2008**, *80*, 1097−1107. For recent examples, see: (c) Nakai, K.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2013**, *15*, 856−859. (d) Tobisu, M.; Kinuta, H.; Kita, Y.; Rémond, E.; Chatani, N. *J. Am. Chem. Soc.* **2012**, *134*, 115−118. (e) Nakai, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 11066−11068.

(16) Kawai, N.; Abe, R.; Matsuda, M.; Uenishi, J. *J. Org. Chem.* **2011**, *76*, 2102−2114.

(17) For the unique σ- and π-activation by $Bi(OTf)_3$, see: Komeyama, K.; Takahashi, K.; Takaki, K. *Org. Lett.* **2008**, *10*, 5119−5122. See also ref 16.

(18) Treatment of 2-naphthyl thioether **D** with 5 mol% of $Bi(OTf)_3$ in toluene at 80 °C afforded naphtho[2,1-*b*]thiophene **6** in 76% yield. We have also confirmed that conversion of **D** to **6** did not take place in the absence of a $Bi(OTf)_3$ catalyst.

(19) For $Bi(OTf)_3$-catalyzed Claisen rearrangement of allyl naphthyl ethers, see: Ollevier, T.; Mwene-Mbeja, T. M. *Tetrahedron Lett.* **2006**, *47*, 4051.