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Ni-Catalyzed Reduction of Inert C−O Bonds: A New Strategy for Using Aryl Ethers as Easily Removable Directing Groups

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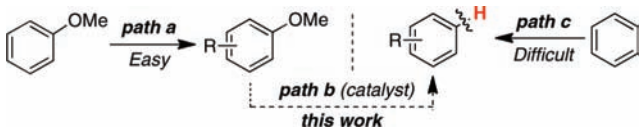
Abstract: An efficient Ni-catalyzed protocol for the reductive cleavage of inert C−O bonds has been developed. The method is characterized by its simplicity and wide scope, thereby allowing the use of aryl ethers as *easily removable directing groups* in organic synthesis.

The pivotal role of aryl ethers as synthetic intermediates has attracted the attention of chemists for decades. The utility of methyl aryl ethers is mainly attributed to their ability to act as directing groups, thus maximizing the reactivity and selectivity of a wide variety of transformations such as *ortho*-metalation,[1] electrophilic aromatic substitution,[2] or Friedel−Crafts-type reactions,[3] among others (Scheme 1, path a).[4] Despite the attractiveness of directing groups in organic synthesis, however, their selective cleavage still constitutes a tremendous challenge.[5] Ideally, *catalytic techniques* that could readily replace the C−O bond of readily available methyl aryl ethers by hydrogen[6] would be highly desirable (Scheme 1, path b), thus constituting a powerful alternative for arene functionalization as electronically unbiased arenes often lead to unselective chemical processes (Scheme 1, path c).[7]

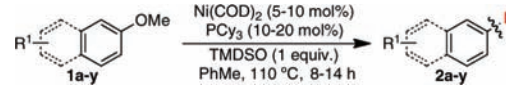
Scheme 1



Prompted by the seminal work of Wenkert,[8] recent studies have demonstrated the formidable potential of aryl ethers in catalytic C−C and C−N bond-forming reactions.[9] Despite the advances realized, these methods are still at their infancy compared with the use of aryl halides as substrates. As part of our program aimed at activating inert molecules,[10] we present herein the first catalytic reductive cleavage of inert C−O bonds as a means to use aryl methyl ethers as *removable directing groups.*[11,12] This method is characterized by its simplicity, wide preparative scope, and the availability of the substrates employed. Remarkably, this study does not require the use of toxic halogenated or tin-based compounds, thus representing an additional bonus when compared with related dehalogenation or Stille-reduction protocols, respectively.[13]

We began our investigations by examining the reactivity of 2-methoxynaphthalene (**1a**) with several hydride sources using nickel catalysts.[14] After extensive experimentation, we found that the use of PCy_3 as the ligand and tetramethyldisiloxane (TMDSO) as the hydride source was critical for obtaining the desired arenes in good yields.[15] Control experiments in which the metal was omitted resulted in no product formation.[15] Notably, the nature of the aryl ether employed had a pronounced influence on the reaction outcome. Indeed, the use of ethoxy, acetoxy, mesylate, tosylate, or pivalate groups gave lower conversions to products, thus indicating the subtleties of our catalyst system.[15] At present we do not have an explanation for this marked difference in reactivity.

Table 1. Ni-Catalyzed Reductive Cleavage of Aryl Methyl Ethers[a,b]



entry	product	yield(%)[b]	entry	product	yield(%)[b]
1	R=H	99	14		75
2	R=TMS	86			
3	R=Ph	89			
4	R=CO_2Me	88			
5	R=	99			
6	R=	91	15		81
7		71			
8	R=	96	16	R=H	56[c]
			17	R=CF_3	78[c]
9		99	18		73[c]
10		62[c]	19	R=TIPS	55[c]
11		86[c,d]	20	R=	76[c]
12		82	21	R=H	76[c]
			22	R=1-Indolyl	78[c]
			23	R=Ph	99[c]
			24	R=N(Me)Ph	72[c]
13		78[c,e]	25	R=	74[c]

[a] ArOMe (0.5 mmol), $Ni(COD)_2$ (5 mol %), PCy_3 (10 mol %), TMDSO (0.5 mmol), PhMe (1 mL) at 110 °C. [b] Isolated yields, average of two runs. [c] $Ni(COD)_2$ (10 mol %). [d] TMDSO (1.0 mmol). [e] TMDSO (0.23 mmol).

Encouraged by these results, we set out to explore the scope of the Ni-catalyzed reductive cleavage of aryl methyl ethers (Table 1). Regardless of the substrates used, we found that silyl groups (entries 2 and 19), esters (entries 4, 9, 13, and 21−25), amides (entry 25), or acetals (entry 20) could all be tolerated. Equally striking is the fact that tertiary amines (entries 5 and 24) or nitrogen-containing heterocycles (entries 6, 8, 10, 15−20, and 22) do not interfere, indicating the low Lewis acidity of the operating catalyst. Interestingly, while the reduction of naphthalene derivatives invariably resulted in good yields of products (entries 1−13), the coupling of simple anisoles proved to be more difficult.[9g] We hypothesized that a suitable *ortho*-directing group might facilitate the C−O bond oxidative addition step within the catalytic cycle.[16] To our delight,

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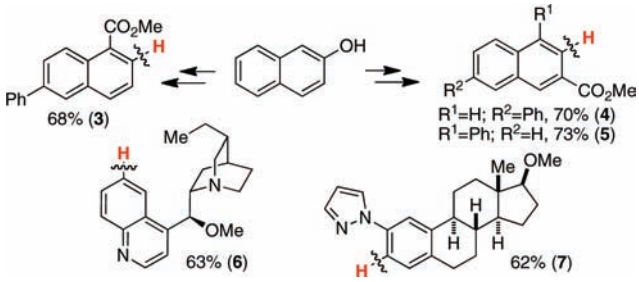
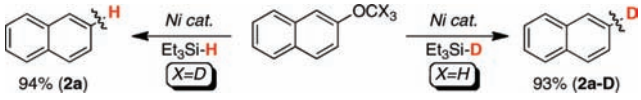
this was indeed the case, as pyridines (entry 15), oxazolines (entries 16−17), pyrazoles (entries 18−20), or esters (entries 21−25) could be efficiently coupled.[17] Remarkably, the presence of such groups in either *metha* or *para* position resulted in little conversion to products, indicating that electronic effects might not be the only factor coming into play.[15] On the basis of these results, we anticipated that high levels of site selectivity could be achieved based on subtle steric and electronic differences among multiple C−O bonds. Indeed, while exhaustive reduction was observed for simple substrates (entry 11), site selectivity was possible when using appropriate *ortho*-directing groups (entries 13 and 18), providing an additional handle for further manipulation. Similarly, sp^2 C−O bonds were selectively activated in the presence of multiple sp^3 C−O bonds (entries 12, 19, and 20); note, however, that activated benzylic C−O bonds[18] could also be coupled with equal efficiency (entry 14).[18,19]

Scheme 2. Synthetic Applicability



The usefulness of our methodology is nicely illustrated in Scheme 2. Thus, structurally related **3**−**5** could be selectively prepared from 2-naphthol.[15] We believe this demonstrates the flexibility in synthetic design when employing *temporary directing groups*. The preparation of **5** is particularly noteworthy; to the best of our knowledge, the Ni-catalyzed activation of inert C−O bonds with substrates containing two *ortho* substituents *has no precedent in the literature*. In view of the high ubiquity of aryl ethers in many pharmaceutically relevant molecules,[20] we envisioned that a late-stage, site-selective, C−O bond activation could be used as a manifold for natural product diversity. Gratifyingly, quinine and estradiol derivatives (**6** and **7**) could be obtained in 63 and 62% yield.

Scheme 3. Mechanistic Considerations



Next, we performed deuterium-labeling experiments to gather evidence about the reaction mechanism (Scheme 3). Interestingly, **2a** and **2a-D** were exclusively obtained when using $Et_3SiH(D)$,[21] thus ruling out a mechanistic scenario via β-hydride elimination from preformed arylnickel(II) alkoxy intermediates.[22] These results clearly indicate that our protocol can be used for *introducing deuterium atoms*[23] *in unbiased arene backbones from readily available precursors*. Although further mechanistic studies are needed, we tentatively propose a pathway consisting of C−O oxidative addition, σ-bond metathesis with the Si−H bond, and reductive elimination from a nickel(II) hydride intermediate.[24]

In summary, a highly efficient Ni-catalyzed reduction of aryl ethers has been developed. The ready availability of the substrates and the remarkable substrate scope observed make this method attractive to synthetic chemists. Further investigations into related processes and the identification of reactive intermediates are ongoing in our laboratories.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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