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Demand-Based Thiolate Anion Generation under Virtually Neutral Conditions: Influence of Steric and Electronic Factors on Chemo- and Regioselective Cleavage of Aryl Alkyl Ethers†

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Thiolate anions have been generated in a "demand-based" fashion under virtually neutral conditions for chemoselective deprotection of aryl alkyl ethers. Solvents play the critical role in making the reaction effective and should have high values of ϵ (>30), molecular polarizabilities (>10), and DN (>27) and low values of AN (<14). However, it is the combined effect of all of these physical properties that make a particular solvent effective. The reaction rates of cleavage of various aryl alkyl ethers are dependent on the steric crowding around the *O*-alkyl carbon and follow the order propargyl ≈ allyl ≈ benzyl > methyl > ethyl. Electron-withdrawing substituents increase the rate of ether cleavage reaction. The influence of the steric and electronic factors have been successfully exploited for selective deprotection of aryl alkyl ethers during inter- and intramolecular competitions.

Introduction

The cleavage of aryl alkyl ethers is a versatile transformation in organic synthesis in light of its importance for the deprotection of phenols, particularly keeping in view the ease of the generation of aryl alkyl ethers,[1] and its involvement in the manufacture of a number of pharmaceuticals, drugs, and other fine chemicals. The various approaches for the coveted transformation are (i) nucleophilic,[2] (ii) reductive,[3] and (iii) photo/electrochemical[4] cleavages. However, these are not applicable to compounds having additional functionalities sensitive to these reactions. Thus there have been continuous efforts to develop new reagents for chemoselective deprotection of aryl alkyl ethers. Since the introduction by Feutrill and Mirrington,[5] alkaline thiolates have been the commonly employed reagents for this purpose.[6] Hwu et al.[7] later introduced sodium trimethylsilanethiolate (Me_3SiSNa) for aryl alkyl ether cleavage. Despite the widespread popularity of thiolates as effective nucleophiles for cleavage of aryl alkyl ethers, only a limited number of examples are reported highlighting the scope of these reagents for regioselective demethylation.[8] In all of these protocols, the effective thiolate reagents are generated/required in stoichiometric amounts or more, and in some cases the reactions are carried out in carcinogenic hexamethylphosphoramide (HMPA). The use of stoichiometric amounts of thiolates is often associated with the nucleophilic displacement of nitro[9] and halogen[10] groups. Furthermore, thiolate anions are strong reducing

† Dedicated to Prof. D. V. S. Jain on the occasion of his 69th birthday.

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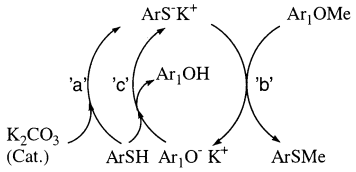

FIGURE 1. Catalytic cycle for demand-based in situ thiolate anion generation for aryl alkyl ether cleavage.

agents[11] as a result of RS^- to RS• transformation. Thus, the chances of involvement of the radical processes are always high when the reactions are carried out using stoichiometric amounts of thiolate anions with substrates having nitro[7b,c] and α,β-unsaturated carbonyl[12] groups, leading to the reduction of these groups. The propensity of the thiolate anions for Michael additions to α,β-unsaturated carbonyl groups[13] add further complexicity to the issue of chemoselectivity for substrates bearing such functionalities. Other major disadvantages of these protocols are the (i) need to use expensive and difficult to handle bases (e.g., LiH, NaH, and MeLi), (ii) extra efforts needed to make the metal hydride bases oil-free, (iii) manipulations involved in using the low boiling thiols, (iv) use of excess (1.5−8 equiv) of thiols, (v) longer reaction time (3.4−24 h), and (vi) use of stringent reaction conditions such as the requirement of heating in a sealed tube.

Results and Discussion

We presumed that the potential problems of the use of stoichiometric amounts of the thiolate anions would be circumvented by devising a protocol in which the thiolate anions would be generated in situ in "demand-based" fashion (Figure 1). The use of catalytic amounts of a base would initially generate ArS^- by acid−base reaction. Nucleophilic attack by the in situ generated ArS^- on the alkyl group of the ether should generate the aryloxide anion, which in turn would undergo proton exchange with the excess thiol, present in the reaction mixture, due to the better charge dispersal of thiolate anions compared to that of the aryloxide anions in polar aprotic solvents.[14] In preliminary communications we reported that the uses of PhSH in the presence of catalytic amounts of K_2CO_3 in NMP constitute efficient protocols for in situ generation of PhS^- to deprotect aryl methyl ethers,[15] alkyl esters,[16] and aryl esters.[17] We describe herein the scope and limitations of the methods of demand-based thiolate anion generation for chemo- and regioselective cleavage of aryl alkyl ethers.

The efficiency of the demand-based thiolate anion generation should be dependent upon the (i) initial proton exchange between the thiol and the base (present in catalytic amount) (path a), (ii) nucleophilic attack by the thiolate anion on the *O*-alkyl carbon (path b), and (iii) proton exchange between the liberated aryloxide anion and the thiol to regenerate the thiolate anion (path c). Thus, the effectiveness of path a should depend on the basicity of the catalyst. Path b and path c should be influenced by the specific solvent−anion interaction; the major factors involved in this regard are the (i) dielectric constant (ϵ), (ii) donor number (DN), acceptor number (AN),[18] and (iii) molecular polarizability of the solvent. The higher the values of ϵ, DN, and the molecular polarizability of a solvent the better will be its interaction with the cation, resulting in the generation of the naked thiolate anion from ArS^-M^+, facilitating path b. The thiolate anion should exhibit its nucleophilicity more effectively in a solvent with low AN. As the dispersion interactions (or mutual polarizabilities) are indicated by the molecular polarizabilities of the solvents, path c should become more effective for solvents with higher molecular polarizabilities.

To find out the best operative condition for aryl methyl ether cleavage, 2-methoxynaphthalene (**1a**) was subjected to the treatment with PhSH in the presence of catalytic amounts of K_2CO_3 under various conditions (Table 1).

The reaction is best carried out in dry 1-methyl-2-pyrrolidinone (NMP) under reflux for 15−30 min. The reaction temperature has no detrimental effects on the products or the unreacted starting materials. Other solvents such as *N*,*N*-dimethylacetamide (DMA), *N*,*N*-diethylformamide (DEF), *N*,*N*-diethylacetamide (DEA), HMPA, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), and 1,3-dimethyl-2-imidazolidinone (DMEU) provided good to excellent results. The effectiveness of these solvents could be explained as efficient ionization of PhS^-M^+ due to the combined effects of high values of ϵ (29.6−37.8), molecular polarizabilities (18.8−9.65), and DN (38.8−27.3) and low values of AN (10.6−13.6) of these solvents. Probably the lower molecular polarizability of DMA (9.65) compared to that of NMP (10.3) affects the proton exchange in path c and makes it inferior (compare the result of entry 13 with those of entries 1 and 2, Table 1). The poor results obtained with other polar solvents with comparable/higher values of ϵ such as *N*,*N*-dimethylformamide DMF (36.7), dimethyl sulfoxide (DMSO) (48.9), and formamide (109.5) may be accounted for the low molecular polarizabilities (7.91, 7.97, and 4.219, respectively) of these solvents, making the proton exchange step (path c) sluggish. Further, the high AN value (39.8) of formamide measures its electrophilic behavior, suggesting the hydrogen bonding capability of formamide with anionic species (e.g., the AN values of protic polar solvents such as MeOH, EtOH, and PrOH, known for their hydrogen bond formation abilities with anions, are 41.3, 37.1 and 33.5, respectively).[18] The zero/negative values of activity coefficients of the halide anions in formamide are evidences of hydrogen bond

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TABLE 1. Effect of Solvent, Temperature, and Time on Cleavage of 2-Methoxynaphthalene (1a) by PhSH[a]

entry	solvent	temp (°C)[b]	time (h)	yield (%)[c−e]
1	NMP	202	0.5	97
2	NMP	202	0.25	81
3	NMP	80	1	0
4	DMPU	146/44 mm	0.5	94
5	DMEU	106/17 mm	0.5	96
6	HMPA	235	0.5	90
7	HMPA	80	1	0
8	formamide	210	1	0
9	DMF	153	1	35[f]
10	DMF	153	7	67
11	DEF	176	0.5	65[g]
12	DMSO	189	1	49
13	DMA	166	1	62.5[h]
14	DEA	182	0.5	88[i]
15	morpholine	130	1	0[j]
16	MeCN	80	9	0
17	sulfolane	285	0.5	30
18	phenyl ether	259	1	0
19	PhMe	110	1	0
20	PhMe-HMPA	110	1	0[k]
21	PhMe-NMP	110	1	0[l]

[a] The ether (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 5 mol % of K_2CO_3 in the respective solvent under heating at a bath temp of 210 °C (except for entries 3, 7, 9−11, 13, 15, 16, and 19−21, for which the corresponding figures in column 3 refer to the respective reaction temperatures). [b] Bp of the respective solvents (except for entries 3 and 7). [c] Isolated yield of 2-naphthol. [d] The ^{1}H NMR spectra of the products were in full agreement with the literature.[25] [e] The unreacted ether could be recovered. [f] A 15% yield was obtained in carrying out the reaction with a bath temp of 210 °C for 0.5 h. [g] A 66% yield was obtained in carrying out the reaction with a bath temp of 210 °C for 0.5 h. [h] A 23% yield was obtained in carrying out the reaction with a bath temp of 210 °C for 0.5 h. [i] Comparable yield was obtained in carrying out the reaction with a bath temp of 210 °C for 0.5 h. [j] No appreciable amount of the product was obtained in carrying out the reaction with a bath temp of 210 °C for 0.5 h. [k] HMPA was used in 5 mol %. [l] NMP was used in 5 mol %.

TABLE 2. Effect of Various Bases on Cleavage of 1a by PhSH in NMP[a]

entry	base[b]	time (h)	yield (%)[b−d]
1	None	12	0
2	Li_2CO_3	1	14
3	Na_2CO_3	1	71
4	K_2CO_3	0.5	97
5	Cs_2CO_3	0.5	90
6	$MgCO_3$	1	0
7	$CaCO_3$	1	0
8	$BaCO_3$	1	10
9	$SrCO_3$	1	0
10	$ZnCO_3$	1	0
11	$NaHCO_3$	0.5	90
12	$KHCO_3$	0.5	87.5
13	$LiOH·H_2O$	0.5	82
14	NaOH	0.5	90
15	KOH	0.5	88
16	$CsOH·H_2O$	0.5	82
17	LiH	0.5	85
18	NaH	0.5	70
19	KH	0.5	90
20	CaH_2	0.5	87.5
21	$LiNH_2$	0.5	93
22	$NaNH_2$	0.5	86
23	^{t}BuOK	1	62.5

[a] The ether (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 5 mol % of the base in NMP under heating at a bath temp of 210 °C. [b] Isolated yield of 2-naphthol. [c] The unreacted ether could be recovered. [d] The ^{1}H NMR spectra of the products were in full agreement with the literature.[25]

formation between the solvent and the anions.[14] Thiolate anions, being more polarizable than the halide anions, should be more prone to hydrogen bond formation with formamide. Therefore, use of formamide as solvent should reduce the nucleophilicity of the thiolate anion, via hydrogen bond formation, making path b (Figure 1) slower and thereby resulting in poor yields. Probably the low DN (14.8) of sulfolane makes it less effective in the ionization of ArS^-M^+ to liberate the effective nucleophile (ArS^-) and is responsible for the poor results obtained in this solvent. The low DN (14.1), high AN (19.3), and low molecular polarizability (4.45) of MeCN make it ineffective despite its comparable value of ϵ (37.5). The lack of any appreciable amount of ether cleavage in weakly polar solvents such as morpholine, phenyl ether, and PhMe further emphasize the role of the solvents in controlling path b and path c (Figure 1). Although the temperature plays an important role (compare the results of entries 1−3 and 7, Table 1), it is not the decisive factor as revealed by the results obtained in the use of high boiling polar solvents such as formamide, DMSO, and sulfolane and weekly polar solvent such as phenyl ether (entries 8, 12, 17, and 18, Table 1).

To find out the effect of the base, **1a** was treated with PhSH in the presence of various catalysts in NMP (Table 2). The ether cleavage proceeds smoothly with alkali metal carbonates, bicarbonates, hydroxides, and hydrides, but the alkaline earth metal carbonates do not offer any appreciable catalytic effects. The weak basicity of the alkaline earth metal carbonates, making the initial proton exchange with PhSH (path a) ineffective, may be the reasons for the poor results obtained with these salts (compare the result of entry 20 with those of entries 6−10, Table 2). The inferior result obtained in using ^{t}BuOK as the catalyst (entry 23, Table 2) could be due to the reduced nucleophilicity of PhS^- as a result of hydrogen bond formation between PhS^- and the liberated ^{t}BuOH. The presence of the catalyst is essential, as no ether cleavage was observed in its absence (entry 1, Table 2).

The detection/isolation (see Experimental Section) of thioanisole in the reaction of **1a** with PhSH in the presence of K_2CO_3 (5 mol %) supports the proposal of nucleophilic attack by the in situ generated PhS^- on the methoxyl carbon (path b, Figure 1). The lack of detection/isolation of appreciable amounts of Ph_2S_2 ruled out the possibility of demethylation involving single electron transfer (SET) from the PhS^-.[11a,19]

The effect of the thiol was evaluated by carrying out the reaction of **1a** with various thiols in the presence of K_2CO_3 (5 mol %) in NMP (Table 3). Although the arene thiolate anions bearing the Me, OMe, and NH_2 substitution at C-4 are expected to be better nucleophiles, the inferior results obtained may be due to the weak acidic properties of these thiols compared to that of PhSH affecting path a (compare the result of entry 1 with those of entries 2 and 3 in Table 3 and the result of entry 2, Table 1 with that of entry 4, Table 3). The ineffectiveness of 4-NO_2-C_6H_4SH is due to the decreased nucleophilicity of the corresponding thiolate anion (entry 7, Table 3). No

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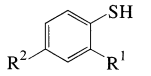
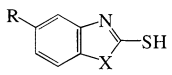
TABLE 3. Effect of Various Thiols on Cleavage of 1a in the Presence of K_2CO_3 (5 mol %) in NMP[a]

entry	thiol	time (h)	yield (%)[b,c,d,e]
			
1	$R^1 = R^2 = H$	0.5	97
2	$R^1 = H$; $R^2 = Me$	0.5	78
3	$R^1 = H$; $R^2 = OMe$	0.5	37
4	$R^1 = H$; $R^2 = NH_2$	0.25	67
5	$R^1 = NH_2$; $R^2 = H$	0.25	94 (Nil)
6	$R^1 = NH_2$; $R^2 = H$	0.75	Nil[f]
7	$R^1 = H$; $R^2 = NO_2$	0.5	Nil
			
8	R = H; X = S	0.25	16
9	R = H; X = NH	0.25	Nil
10	R = Me; X = NH	0.25	Nil
11		0.25	22
			
12	R = Ph	0.25	38
13	R = 2-Furyl	0.25	Nil
14	R = Me	0.5	14

[a] The ether (2.5 mmol) was treated with 1 equiv of the thiol (except entry 6) in the presence of 5 mol % of K_2CO_3 in NMP under heating at a bath temp of 210 °C. [b] Isolated yield of 2-naphthol. [c] The unreacted ether could be recovered. [d] The ^1H NMR spectra of the products were in full agreement with the literature.[25] [e] The figure in parentheses (entry 5) corresponds to the yield when the reaction was carried out at 100 °C for 1 h. [f] The reaction was carried with 5 mol % of the thiol.

displacement of the nitro group, as a result of suicidal nucleophilic attack, could be observed. No product corresponding to the reduction of the nitro group, arising out of SET from the thiolate anion, could be detected, which further confirms that SET process is unimportant for thiolate anion generated in demand-based fashion. However, the presence of the nitro group would have made electron transfer from 4-NO_2-$C_6H_4S^-$ difficult[4b] and may partly be accounted for the lack of formation of the corresponding reduced product. The better results obtained with 2-NH_2-C_6H_4SH may be due to the increased nucleophilicity of the corresponding thiolate anion as a result of the field effect involving the anionic site and the lone pair electron of the 2-NH_2 group (entry 5, Table 3). The poor results obtained with the benzimidazoles, benzthiazole, and thiazoline may be due to poor nucleophilicity of the corresponding thiolate anion as a result of resonance stabilization (entries 8−11, Table 3). In case of thioalkanes, lack of proton exchange, due to their weak acidic character, with ArO^- makes them ineffective (entries 12−14, Table 3). The ineffectiveness of the use of catalytic quantities of thiol (entry 6, Table 3) in the cleavage of ether further justifies that the deprotection does not take place via SET from the thiolate anion[11a,19]

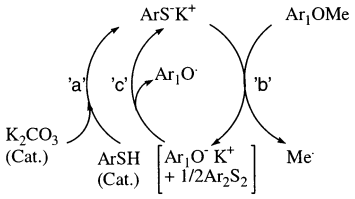


FIGURE 2. Single electron-transfer route for aryl alkyl ether cleavage.

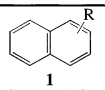
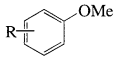
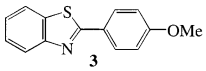
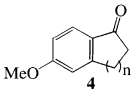
(path b, Figure 2) as in such an occasion the disulfide produced would have undergone reduction by the aryloxide anion (path c, Figure 2),[20] due to the lability of the S−S bond, to regenerate the thiolate anion making the ether cleavage feasible with catalytic amount of thiol.

To establish this protocol as a generalized method for aryl alkyl ether cleavage various aryl alkyl ethers were subjected to the treatment with PhSH (method A) and 2-NH_2-C_6H_4SH (method B) in the presence of K_2CO_3 (5 mol %) in NMP (Table 4). In many occasions method B was found to be superior to method A as revealed by the increase in product yields and/or shorter reaction times (entries 1, 3, 10, 12, 13, 17, and 26, Table 4). The use of 2-NH_2-C_6H_4SH (method B) offers the additional advantages that the byproducts[21] are easily separated from the phenolic products in the final acidification step of the workup (see Experimental Section). Benzyl ethers are relatively more facile to be cleaved than the corresponding methyl ethers, which in turn are more reactive than the ethyl ethers (compare entries 1−3 and 6−8, Table 4). Substrates containing electron-withdrawing groups (entries 13, 15−17, 19 and 21, Table 4) react at a faster rate, as is reflected by the shorter reaction time or higher yield (compare entry 9 and the footnote of entry 17, Table 4) in accord with the earlier observations.[8j,22] Electron-donating groups retard the reaction rates (entries 10, 24, and 25, Table 4). The excellent results obtained for substrate with 2-NH_2 substituent (entry 9, Table 4) may be explained as a result of hydrogen-bond assisted nucleophilic attack at the *ortho O*-Me group.[8i] The reactions with 2-chloroanisole, 4-chloroanisole, and 4-nitroanisoles (entries 11−13, Table 4) need special attention because use of stoichiometric amounts of thiolates are associated with the replacement of the nitro group and halogen rather than the usual ether cleavage. Chemoselective ether cleavage is not possible by the use of Me_3SiSNa, as it converts *p*-nitrophenol to *p*-amino phenol, as a result of concomitant reduction of the nitro group,[7b] and nitrile to thioamides.[23] Methoxystilbene (entry 18, Table 4) and ethers containing α,β-unsaturated carbonyl groups (entries 20−22, Table 4) are efficiently cleaved without competitive addition to the styrenoid double bond[24] or Michael addition.[13]

The difference in the rates of reaction of **2f** and **2g** (entries 14 and 15, Table 4) led us to study the effect of

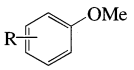
(20) Phenolate ions are known to give stable radicals. Altwicker, E. R. *Chem. Rev.* **1967**, *67*, 475.
(21) Apart from ArSR, arising out of the nucleophilic attack by the thiolate anion on the aryl alkyl ether, ArSSAr is generated from the unreacted thiol and the alkali during the workup.
(22) Hansson, C.; Wickberg, B. *Synthesis* **1976**, 191.
(23) Lin, P.-Y.; Ku, W.-S.; Shiao, M.-J. *Synthesis* **1992**, 1219.
(24) (a) Katrizky, I.; Takahashi, I.; Marson, C. M. *J. Org. Chem.* **1986**, *51*, 4914. (b) Beily, M.; Zamboni, R. *J. Org. Chem.* **1989**, *54*, 2642.

TABLE 4. Chemoselective Deprotection of Aryl Alkyl Ethers by Catalytically in Situ Generated ArS^{-a-d}

entry	ether	Method A time (min)	Method A yield (%)	Method B time (min)	Method B yield (%)
	 **1**				
1	**1a**: R = 2-OMe	30	97[e]	15	94
2	**1b**: R = 2-OEt	30	60		
3	**1c**: R = 2-OCH_2Ph	15	76[f]	15	90
4	**1d**: R = 2-$OCH_2CH{=}CH_2$			15	75
5	**1e**: R = 2-$OCH_2C{\equiv}CH$			15	72
6	**1f**: R = 1-OMe	30	97[g]		
7	**1g**: R = 1-OEt	30	58		
8	**1h**: R = 1- OCH_2Ph	15	80		
	 **2**				
9	**2a**: R = 2-NH_2	30	80		
10	**2b**: R = 4-Me	60	40	15	90
11	**2c**: R = 2-Cl	30	65		
12	**2d**: R = 4-Cl	30	70	15	89
13	**2e**: R = 4-NO_2	15	70	15	79
14	**2f**: R = 3-CHO	30	85		
15	**2g**: R = 4-CHO	15	90	15	82
16	**2h**: R = 4-COMe	15	85	15	71
17	**2i**: R = 4-CN	15	65[h]	15	89
18	**2j**: R = 4-CH=CHPh (*E*)	30	80		
19	**2k**: R = 4-COCOPh	15	87		
20	**2l**: R = 4-CH=CHCOPh (*E*)	30	90[i]	15	80[i]
21	**2m**: R = 4-COCH=CHPh (*E*)	15	85[j]	15	72[j]
22	**2n**: R = 4-CH=CHCOMe (*E*)	30	73		
23	**2o**: R = 4-CONHPh	120	94[k,l]		
24	**2p**: R = 4-NHCOPh	120	32[l]		
25	**2q**: R = 4-NH_2	120	25		
26	**2r**: R = H	30	80[m]	15	80
	 **3**				
27				15	90[n]
	 **4**				
28	**4a**: n = 1	30	75		
29	**4b**: n = 2	30	90		

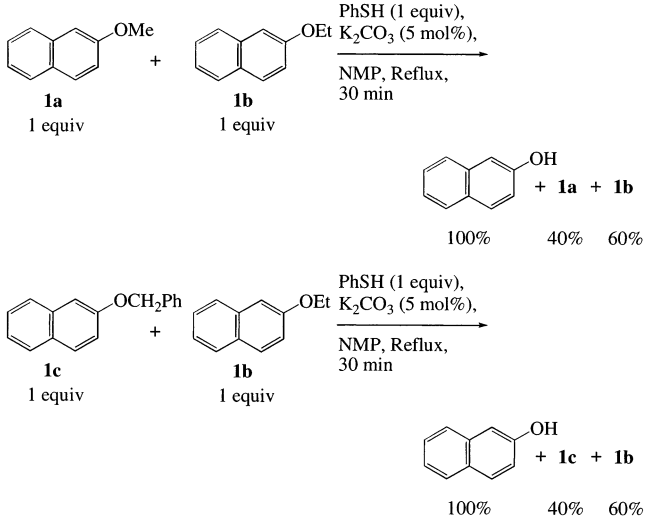
[a] Method A: the ether (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 5 mol % of K_2CO_3 in NMP under heating at a bath temp of 210 °C. Method B: the ether (2.5 mmol) was treated with 1 equiv of 2-H_2N-C_6H_4SH in the presence of 5 mol % of K_2CO_3 in NMP under heating at a bath temp of 210 °C. [b] Isolated yield of the corresponding phenol. [c] The ^1H NMR spectra of the products were in full agreement with the literature.[25] [d] The unreacted ether could be recovered. [e] A 20% yield was obtained in carrying out the reaction for 10 min. [f] A 50% yield was obtained in carrying out the reaction for 10 min. [g] A 56% yield was obtained in carrying out the reaction for 15 min. [h] A 90% yield was obtained in carrying out the reaction for 30 min. [i] The mp and spectral data (IR and MS) of the products were in full agreement with the literature.[26] [j] The mp and spectral data (IR, UV, and MS) of the products were in full agreement with the literature.[27] [k] A 53% yield was obtained in carrying out the reaction for 30 min. [l] The mp and spectral data (^1H and ^{13}C NMR) of the products were in full agreement with the literature.[28] [m] A 60% yield was obtained in carrying out the reaction for 15 min. [n] The mp and spectral data (^1H and ^{13}C NMR) of the products were in full agreement with the literature.[29]

TABLE 5. Effect of Hammett Substituent Constant (σ) on Methyl Ether Cleavage of Anisole Derivatives by PhSH in the Presence of K_2CO_3 in NMP[a]

entry	ether	σ[b]	yield (%)[c-e]
	 **2**		
1	**2e**: R = 4-NO_2	0.81	68
2	**2i**: R = 4-CN	0.71	60
3	**2h**: R = 4-COMe	0.47	85
4	**2g**: R = 4-CHO	0.47	90
5	**2f**: R = 3-CHO	0.41	70
6	**2d**: R = 4-Cl	0.24	50
7	**2p**: R = 4-NHCOPh	0.078	12[f]
8	**2b**: R = 4-Me	−0.14	10
9	**2q**: R = 4-NH_2	−0.57	<5

[a] The ether (2.5 mmol) was treated with 1 equiv of PhSH in the presence of 5 mol % of K_2CO_3 in NMP under heating at a bath temp of 210 °C for 10 min. [b] Carey, F.; Sandberg, R. J. *Advanced Organic Chemsitry, Part A*, 3rd ed.; Plenum: New York, 1990. Gonzalez, A. G.; Jorge, J. D.; Dorto, H. L. *Tetrahedron Lett.* **1981**, *37*, 2585. [c] Isolated yield of the corresponding phenol. [d] The ^1H NMR spectra of the products were in full agreement with the literature.[25] [e] The unreacted ether could be recovered. [f] The mp and spectral data (^1H and ^{13}C NMR) of the products were in full agreement with the literature.[28]

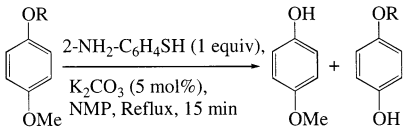
SCHEME 1



the Hammett substituent constant (σ). Thus substituted anisoles (**2**) were treated with PhSH in the presence of K_2CO_3 (5 mol %) in NMP under reflux for 10 min (Table 5). The yields of the corresponding phenolic products clearly establish the correlation between the reaction rate and σ. The inferior results obtained in the cases of **2e** and **2i** (compared to what might have been expected with respect to the higher σ values) may be due to the slower rate of proton exchange in path c (Figure 1).

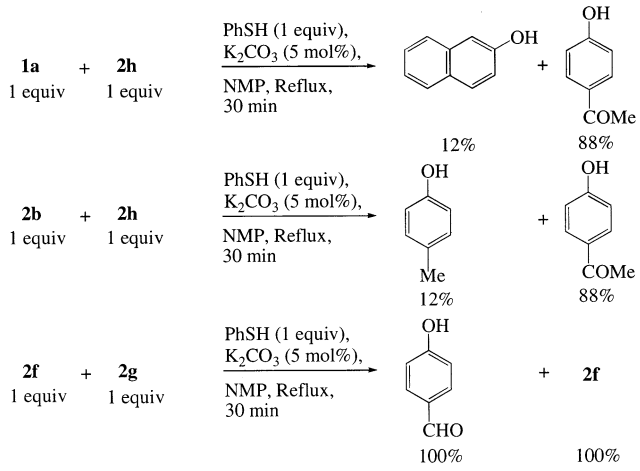
The difference in the rates of deprotection of methyl, ethyl, and benzyl ethers prompted us to exploit the steric effect for selective ether cleavage. In a intermolecular competition study, the treatment of equimolar amounts of **1a** and **1b** following method A resulted in a 3:2 selectivity in favor of methyl ether cleavage (Scheme 1). Similar treatment of **1b** and **1c** resulted in the selective deprotection of a benzyl ether in a ratio of ~3:2 over an ethyl ether.

SCHEME 2



a: R = Et	Nil	90%
b: R = $H_2CCH{=}CH_2$	78%	Nil
c: R = $H_2CC{\equiv}CH$	80%	Nil
d: R = H_2CPh	75%	Nil

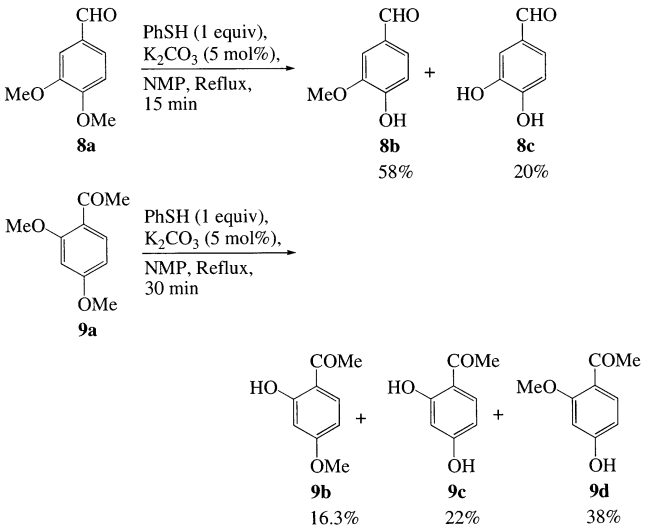
SCHEME 3



Being encouraged by the results of the intermolecular competitions of ether cleavage, we subjected various 4-alkoxyanisoles (**5**) to the treatment following method B (Scheme 2). Excellent regioselectivity was observed wherein a methyl ether was selectively deprotected in the presence of a, ethyl ether, and benzyl, allyl, and propargyl ethers were selectively deprotected in preference to a methyl ether.

The results in Table 5 clearly reveal the effects of electronic factor on the rates of ether cleavage. To exploit the influence of electronic factor for selective ether cleavage, equimolar mixtures of **1a** and **2h**, **2b** and **2h**, and **2f** and **2g** were separately subjected to the treatment following method A (Scheme 3). Excellent selectivities were observed wherein **2h** underwent *O*-demethylation preferential to that of **1a** in a ratio of ~8:1. The electronic effect of the Me and COMe substituents led to the selective *O*-Me cleavage of **2h** over that of **2b** in a ratio of ~8:1. Interestingly, the difference in the electronic effect of the 3-CHO and 4-CHO substituents enabled us to achieve complete selective demethylation of **2g**. To find out whether the difference of the electronic effect of the 3-CHO and 4-CHO substituents could be utilized for regioselective demethylation in intramolecular competion, 3,4-dimethoxybenzaldehyde (**8a**) was subjected to the ether cleavage following method A (Scheme 4). The monodemethylation product **8b** (58%) was obtained along with the complete demethylation product **8c** (20%) accounting for an overall selectivity of 78:20 for the deprotection of the *O*-Me *para* to the CHO group over the *O*-Me *meta* to the CHO group (see Experimental Section). The cleavage of the *O*-Me *meta* to the CHO group may be the result of OH-directed deprotection[8i] of **8b**.

SCHEME 4



The phenolic product obtained by the treatment of 2,4-dimethoxyacetophenone (**9a**) following method A, after chromatographic separation, afforded three components in 16.3% (eluent 5% EtOAc−PhH), 22% (eluent 10% EtOAc−PhH), and 38% (eluent 20% EtOAc−PhH) yields (Scheme 4). The second fraction was identified to be the completely demethylated product **9c** (see Experimental Section). The first and third fractions absorbed at 1633 and 1649 cm^{-1}, respectively, in the IR. The ^1H NMR of the first fraction showed a OH signal at δ 12.76 representing a hydrogen bonded OH. Accordingly these two fractions were assigned the structures **9b** and **9d**, respectively. Confirmation of the structures of **9b** and **9d** were obtained through comparison of their spectral data (IR and ^1H NMR) with those of 2-hydroxy-4-methoxyacetophenone and 4-hydroxy-2-methoxyacetophenone, respectively. Further support has been obtained from the analyses of the ^{13}C NMR spectra of the first and third fractions wherein the COMe carbons absorbed at δ 26.19 and 31.80, respectively.[30] The reaction of **9a** reveals that the *O*-Me *para* to COMe is selectively deprotected in a ratio of 3:2 over the *O*-Me *ortho* to COMe. The slower rate of reaction at the *O*-Me *ortho* to COMe may be due to the electrostatic repulsion of the oxygen lone pair electrons of the carbonyl group toward the approach of the PhS^-.

The results of entries 23 and 24, Table 4 showed that the amide substituents, CONHPh and NHCOPh, have different deactivating effects on demethylation of the corresponding substituted anisoles. These observations

(25) Pouchart, C. J.; Jacqlynn, B. *The Aldrich Library of ^{13}C and ^1H FT NMR Spectra*; Aldrich Chemical Co. Inc., Milwaukee, 1993; Vol. II, ed. I.

(26) Hseih, H.-K.; Lee, T.-H.; Wang, J.-P.; Wang, J.-J.; Lin, C.-N. *Pharma. Res.* **1998**, *15*, 39.

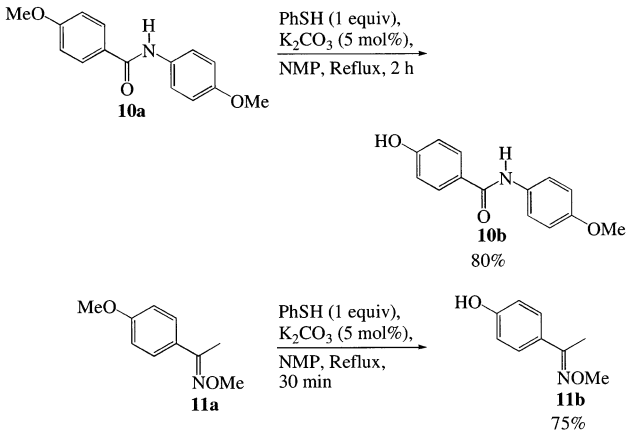
(27) Cirovic, M. M. *Properties of Organic Compounds*, POC-personal ed., version 5.1; CRC Press Inc.: Boca Raton, FL, 1996.

(28) Suezawa, H.; Yuzuri, T.; Hiroto, M.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 328.

(29) Isikdag, I.; Ucucu, U. *Chem. Abstr.* **1990**, *113*, 184199c.

(30) The COMe carbons of 4-methoxyacetophenone and 2-methoxyacetophenone absorb at δ 26.92 and 32.42, respectively.

SCHEME 5



encouraged us to exploit the deactivation effect of amide substituents for regioselective ether cleavage during intramolecular competitions (Scheme 5). *N*-(4-Methoxyphenyl)-4-methoxybenzamide (**10a**), on treatment following method A, resulted in complete regioselective demethylation as only one phenolic compound was isolated (80%). The product showed the lone OMe signal at δ 3.75 in the ^{1}H NMR spectrum and was assigned the structure **10b** on comparison with the ^{1}H NMR spectrum of **10a**[31] and taking into consideration the chemical shift values of the *O*-Me protons in **2o** (δ 4.28) and **2p** (δ 4.22).

The oxime ether **11a**, when subjected to reaction following method A, exhibited excellent selectivity (Scheme 5) and afforded the monodemethylation product (75%) with the *O*-Me protons appearing at δ 3.89 in the ^{1}H NMR. The product was assigned the structure **11b**,[32] by comparing its ^{1}H NMR data with those of **11a** and 4-methoxyacetophenoneoxime.[33] Therefore, selective deprotection of the phenolic *O*-Me takes place in the presence of the oxime *O*-Me. The result also exemplifies excellent chemoselectivity that no competitive nucleophilic addition to the C═N takes place.

The phenolic product obtained from the reaction (method A) of **12a** (Scheme 6), after chromatographic separation, afforded two fractions eluting with 5% EtOAc−PhH and 20% EtOAc−PhH in 63% and 20% yields, respectively (see Experimental Section). The ^{1}H NMR spectrum of the first fraction showed two sets of singlets at δ 3.67 and 3.70 and δ 9.27 and 9.53 corresponding to the *O*-Me and phenolic *O*-H protons, respectively. The GC−MS spectra of this fraction revealed it to be the mono demethylation product(s). The relative intensities of the two sets of singlets in the ^{1}H NMR spectra suggest the mono demethylation products to be in a ratio of 68:32 corresponding to **12b**[34] and **12c**, respectively. The second fraction was found to be the completely demethylated product **12d**[35] as determined by ^{1}H NMR and MS. Thus an overall regioselective deprotection of the methyl ether having 4-CO substituent could be achieved.

Conclusions

In summary, the work embodied in this article introduces the concept of demand-based thiolate anion generation for chemoselective aryl alkyl ether cleavage under virtually neutral conditions. The solvent plays critical roles and should have high values of ϵ (>30), molecular polarizabilities (>10), and DN (>27) and low values of AN (<14) in making the reaction effective. The steric factors around the alkoxy carbon significantly influence the rate of the ether cleavage reactions. The reaction rates of cleavage of various aryl alkyl ethers follow the order propargyl ≈ allyl ≈ benzyl > methyl > ethyl. The presence of electron-withdrawing groups accelerate the rates of the ether cleavage reactions. A correlation between the reaction rate and σ has been established. The influence of the steric and electronic factors have been successfully exploited for regioselective ether cleavage during inter- and intramolecular competitions.

Experimental Section

General Considerations. The ethers studied were either available commercially or prepared by standard procedures.[1,36] The solvents were distilled before use. DMA, DMPU, DMEU, DEF, DEA, HMPA, DMSO, sulfolane, formamide, PhSH, 4-Me-C_6H_4SH, 4-MeO-C_6H_4SH, 4-NH_2-C_6H_4SH, 2-NH_2-C_6H_4SH, $PhCH_2SH$, EtSH, 2-furylthiol, 2-mercaptobenzthiazole, 2-mercaptothiazoline, 2-mercaptobenzimidazole, 6-methyl-2-mercaptobenzimidazole, Cs_2CO_3, $CsOH·H_2O$, LiH, KH, $NaNH_2$, ^{t}BuOK, K_2CO_3, Na_2CO_3, Li_2CO_3, $MgCO_3$, $CaCO_3$, $BaCO_3$, $SrCO_3$, $ZnCO_3$, $KHCO_3$, $NaHCO_3$, KOH, NaOH, $LiOH·H_2O$, NaH, CaH_2, MeCN, morpholine, toluene, phenyl ether, DMF and NMP were available commercially. Melting points were taken in an open capillary and were uncorrected. Unless otherwise mentioned, chromatography was performed on silica gel (60−120) using a glass column (i.d. 1.5 cm).

Synthesis of Starting Materials and Reaction Products. The ^{1}H NMR and IR spectra of the following compounds were in complete agreement with those of the authentic samples: 1-naphthol, 2-naphthol, 4-nitrophenol, 4-methoxyphenol, 4-hydroxytoluene, 4-chlorophenol, 4-aminophenol, 2-aminophenol, 4-hydroxyacetophenone, 2-hydroxy-4-methoxyacetophenone, 2,4-dihydroxyacetophenone, 4-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-cyanophenol, 4-hydroxy-3-methoxybenzaldehyde, 6-hydroxy-1-tetralone, 5-hydroxy-1-indanone, *trans*-4-hydroxystilbene, 4-hydroxybenzylideneacetone, *trans*-4-hydroxychalcone, *trans*-4′-hydroxychalcone (available commercially), 2-(4-methoxyphenyl)benzothiazole (**3**)[37] 1-(4-methoxyphenyl)-2-phenylethanedione (**2k**),[38] and *N*-phenyl-4-methoxybenzamide (**2o**).[39] Physical data of the compounds, prepared following reported procedures, are given below.

3-Phenyl-1-(4-methoxyphenyl)-2-propene-1-one (2m): IR (KBr) 1655, 1602, 1572, and 1490 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.98 (d, J = 9 Hz, 2H), 7.37−7.72 (m, 7H), 8.06 (d, J = 9 Hz, 2H); λ_{max} 314.4 nm (log ϵ 4.55); MS (*m*/*z*) 238 (M^+), 135 (100), 103, 92 and 77. ***N*-(4-Methoxyphenyl)-benzamide (2p):** mp 153 °C (lit.[36] 154 °C); IR (KBr) 3225, 1640, and 1605, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.22 (s, 3H), 7.28 (d,

(31) The *O*-Me signals of **10a** absorb at δ 3.74 and 3.80, indicating that it is the activated *O*-Me that have undergone cleavage.

(32) Krueger, B. W.; Kysela, E.; Stetter, J.; Beckett, B.; Homeyer, B.; Stendel W. *Chem. Abstr.* **1984**, *101*, 23077k.

(33) The ^{1}H NMR chemical shift (δ) values of the phenolic and oxime *O*-Me protons of **11a** are 3.78 and 3.91, respectively.[42] The *O*-Me of 4-methoxyacetophenoneoxime absorbs at δ 3.80. The *O*-H protons of 4-methoxyacetophenoneoxime and **11a** appear at δ 9.43 and 6.21, respectively.

(34) Sipos, G.; Dobo, I.; Czukor, B. *Chem. Abstr.* **1963**, *59*, 5059h.

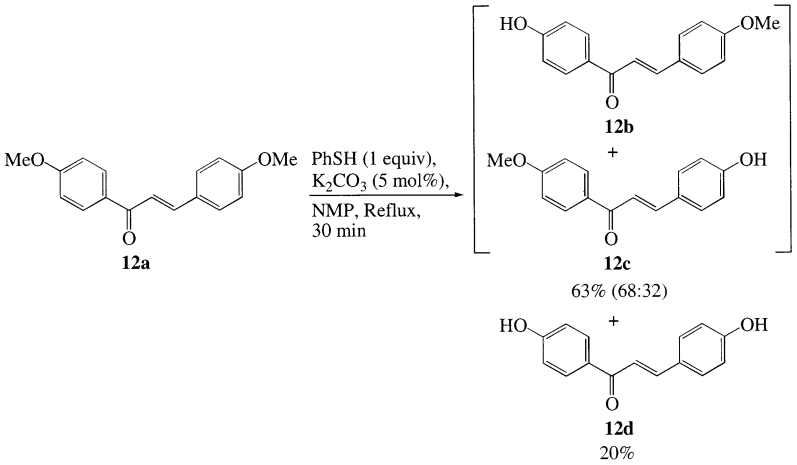
(35) Geisman, T. A.; Clinton, R. O. *J. Am. Chem, Soc.* **1946**, *68*, 697.

(36) Furniss, B. R.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longman: London, 1996.

(37) Mourtas, S.; Gatos, D.; Barlos, K. *Tetrahedron Lett.* **2001**, *42*, 2201.

(38) Ishibashi, H.; Matsuoka, K.; Ibeda, M. *Chem. Pharm. Bull.* **1991**, *39*, 1854.

SCHEME 6



J = 8 Hz, 2H), 7.62−7.92 (m, 5H), 8.15−8.28 (m, 3H). ***N*-(4-Methoxyphenyl)-4-methoxybenzamide (10a):** mp 200 °C (lit.[39] mp 200 °C); IR (KBr) 3326, 1646, and 1578, cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (s, 3H), 3.8 (s, 3H), 6.81−6.91 (q, 4H), 7.45 (d, J = 9 Hz, 2H), 7.59 (bs, 1H), 7.75 (d, J = 9 Hz, 2H); MS (m/z) 257 (M^+), 135 (100). **3-(4-Methoxyphenyl)-1-(4-methoxyphenyl)-2-propene-1-one (12a):** mp 102 °C (lit.[40] mp 100−102 °C); IR (KBr) 1655, 1647, 1593, and 1572 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (s, 3H), 3.98 (s, 3H), 7.01−7.09 (m, 4H), 7.52 (d, J = 16 Hz, 1H), 7.69 (d, J = 9 Hz, 2H), 7.87 (d, J = 16 Hz, 1H), 8.13 (d, J = 9 Hz, 2H); MS (m/z) 268 ($M,^+$ 100), 253, 237, 225, 161, 160, 135, 120, 108, 92, 77. **1-(4-Methoxyphenyl)ethanoneoxime:** mp 88 °C (lit.[36] mp 87 °C); IR (KBr) 3100−2800 and 1605 cm^{-1}; ^1H NMR (CCl_4) δ 2.23 (s, 3H), 3.80 (s, 3H), 6.80 (d, J = 9 Hz, 2H), 7.50 (d, J = 9 Hz, 2H), 9.43 (s, 1H).

Representative Procedure for Deprotection of Aryl Alkyl Ether. Method A. A mixture of **1a** (395.5 mg, 2.5 mmol), PhSH (0.27 g, 2.5 mmol), and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) in NMP (2.5 mL) was heated under reflux for 30 min under N_2. The cooled reaction mixture was made alkaline with 5% aqueous NaOH (25 mL) and extracted with Et_2O (3 × 15 mL) to separate any neutral component (GC−MS of these combined ethereal extracts showed the presence of PhSMe). The aqueous part was acidified in the cold (ice bath) with 6 N HCl and extracted with Et_2O (3 × 15 mL). The combined Et_2O extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under vacuo to afford a brown solid, which on passing through a column of silica gel (230−400, 1 g) and elution with 5% EtOAc−hexane (200 mL) afforded the product (349 mg, 97%), which was in full agreement with mp and spectral data (IR, ^1H NMR, and GC−MS) of an authentic sample of 2-naphthol. The reactions with the remaining substrates were carried out following this general procedure and in each occasion the mp and spectral data (IR, ^1H NMR, and MS) compared well with the literature.[25−29,36−40]

Method B. The treatment of **1a** (395.5 mg, 2.5 mmol) with 2-NH_2-C_6H_4SH (0.31 g, 2.5 mmol) and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) in NMP (2.5 mL) under reflux for 15 min under N_2 after usual workup afforded the product (338 mg, 94%), which was in full agreement with mp and spectral data (IR, ^1H NMR, and GC−MS) of an authentic sample of 2-naphthol. The reactions with the remaining substrates were carried out following this general procedure. In most of the cases the product could be isolated in pure form without the involvement of chromatographic separation, and in each occasion the mp and spectral data (IR, ^1H NMR, and MS) compared well with the literature.[25−29,36−40]

Cleavage of 2k. Treatment of **2k** (480 mg, 2 mmol) with PhSH (264 mg, 2.4 mmol) and K_2CO_3 (14 mg, 0.1 mmol, 5 mol %) in NMP (2.5 mL) under reflux for 10 min followed by usual workup afforded the acidic product, which on passing through a column of silica gel (15 g) and elution with 50% EtOAc−PhH afforded the phenolic product (385 mg, 85%): mp 128−130 °C (lit.[41] mp 129−130 °C); IR (KBr) 3400, 1675, 1650, 1600, and 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.84(d, J = 9 Hz, 2H), 7.21−8.01 (m including a doublet J = 9 Hz, 7H); λ_{max} 286.4 nm (log ϵ = 4.24).

Cleavage of 2l. Treatment of **2l** (714 mg, 3 mmol) with PhSH (396 mg, 3.6 mmol) and K_2CO_3 (21 mg, 0.15 mmol, 5 mol %) in NMP (2.5 mL) under reflux for 30 min followed by usual workup and recrystallization (PhH−EtOAc) afforded the product (600 mg, 90%), identical (mp, IR, and MS)[26] to an authentic sample of *trans*-4-hydroxychalcone: ^1H NMR ($CDCl_3$) δ 6.84 (d, J = 9 Hz, 2H), 7.31−7.61 (m, 7H), 7.89−8.08 (m, 2H); λ_{max} 334.6 nm (log ϵ 4.34).

Cleavage of 2m. Treatment of **2m** (714 mg, 3 mmol) with PhSH (396 mg, 3.6 mmol) and K_2CO_3 (21 mg, 0.15 mmol, 5 mol %) in NMP (2.5 mL) under reflux for 10 min followed by usual workup and recrystallization (EtOH) afforded the phenolic product (560 mg, 83%), identical (mp, IR, UV, and MS)[27] to an authentic sample of *trans*-4′-hydroxychalcone: ^1H NMR ($CDCl_3$) δ 6.99 (d, J = 9 Hz, 2H), 7.06−7.98 (m, 7H), 8.05 (d, J = 9 Hz, 2H).

Cleavage of 2n. Treatment of **2n** (528 mg, 3 mmol) with PhSH (396 mg, 3.6 mmol) and K_2CO_3 (21 mg, 0.15 mmol 5 mol %) in NMP (2.5 mL) under reflux for 30 min followed by usual workup and crystallization (PhH−EtOAc) afforded the phenolic product (350 mg, 73%), identical (mp) to an authentic sample of 4-hydroxybenzylidineacetone: IR (KBr) 3150, 1670, 1630, 1600, and 1515 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.31 (s, 3H), 6.59 (d, J = 15 Hz, 1H), 6.79 (d, J = 9 Hz, 2H), 7.53 (d, J = 15 Hz, 1H), 7.54 (d, J = 9 Hz, 1H), 10.04 (bs, 1H); MS (m/z) 162 (M^+), 147 (100), 119, 91; λ_{max} 315.4 nm (log ϵ 4.22).

Cleavage of 4a. Treatment of **4a** (324 mg, 2 mmol) with PhSH (264 mg, 2.4 mmol) and K_2CO_3 (14 mg, 0.1 mmol, 5 mol %) in NMP (2.5 mL) under reflux for 30 min followed by usual workup afforded the acidic product, which on passing through a column of silica gel (15 g) and elution with 10% EtOAc−PhH (200 mL) afforded the phenolic product (220 mg, 75%), identical (mp) to an authentic sample of 5-hydroxyindanone: IR (KBr) 3199, 1678, 1619, and 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (t, J = 5.5 Hz, 2H), 2.97 (t, J = 5.5 Hz, 2H), 7.00 (s, 1H), 7.04 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.26 (d, J = 8.2 Hz, 1H); MS (m/z) 148 ($M,^+$ 100), 120, 91; λ_{max} 317.2 nm (log ϵ 3.71).

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Cleavage of 4b. Treatment of **4b** (352 mg, 2 mmol) with PhSH (264 mg, 2.4 mmol) and K_2CO_3 (14 mg, 0.1 mmol, 5 mol %) in NMP (2.5 mL) under reflux for 30 min followed by usual workup afforded the acidic product, which on passing through a column of silica gel (15 g) and elution with 20% EtOAc−PhH (200 mL) afforded the product (290 mg, 90%), identical (mp) to an authentic sample of 6-hydroxytetralone: IR (KBr) 3350, 1665, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06−2.19 (m, 2H), 2.65 (t, J = 6.5 Hz, 2H), 2.91 (t, J = 5.5 Hz, 2H), 6.71 (s, 1H), 6.79 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H); λ_{max} 290.6 nm (log ϵ 3.64).

Regioselective Deprotection of Aryl Alkyl Ethers during Intermolecular Competitions. Selectivity of 1a vs 1b. Treatment of a mixture of **1a** (395 mg, 2.5 mmol) and **1b** (430 mg, 2.5 mmol) in dry NMP (5 mL) with PhSH (275 mg, 2.5 mmol) and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) under reflux for 30 min followed by usual workup afforded the phenolic product (360 mg, 100%), identical (mp, IR, and ^1H NMR) with an authentic sample of 2-naphthol. The recovered unreacted ether mixture was found to contain **1a** (40%, t_R 6.50 min) and **1b** (60%, t_R 8.05 min) by GC−MS (100 °C 2 min, 5 °C/min, 200 °C 5 min) confirming a 3:2 selectivity of cleavage of methyl ether over ethyl ether.

Selectivity of 1b vs 1c. Treatment of a mixture of **1b** (430 mg, 2.5 mmol) and **1c** (585 mg, 2.5 mmol) in dry NMP (5 mL) with PhSH (275 mg, 2.5 mmol) and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) under reflux for 30 min followed by usual workup afforded the phenolic product (360 mg, 100%), identical (mp, IR, and ^1H NMR) with an authentic sample of 2-naphthol. The recovered unreacted ether mixture was found to contain **1b** (40%, t_R 11.61 min) and **1c** (60%, t_R 15.18 min) by GC−MS (80 °C 2 min, 5 °C/min, 200 °C 5 min) confirming a 3:2 selectivity of cleavage of benzyl ether over ethyl ether.

Selectivity of 1a vs 2h. Treatment of a mixture of **1a** (395 mg, 2.5 mmol) and **2h** (375.5 mg, 2.5 mmol) in dry NMP (5 mL) with PhSH (275 mg, 2.5 mmol) and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) under reflux for 30 min followed by usual workup afforded the crude product, which on passing through a column of silica gel (20 g) and elution with PhH (200 mL) afforded 2-naphthol (40 mg, 12%), identical (mp and ^1H NMR) with an authentic sample. Further elution with 5% EtOAc−PhH (200 mL) gave 4-hydroxyacetophenone (300 mg, 88%), identical (mp and ^1H NMR) with an authentic sample.

Selectivity of 2h vs 2m. Treatment of a mixture of **2h** (375.45 mg., 2.5 mmol) and **2b** (305.43 mg, 2.5 mmol) in dry NMP (5 mL) with PhSH (275 mg, 2.5 mmol) and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) under reflux for 30 min followed by usual workup afforded the phenolic product, which on passing through a column of silica gel (20 g) and elution with PhH (200 mL) afforded 4-methylphenol (33 mg, 12%), identical (^1H NMR) with an authentic sample. Further elution with 10% EtOAc−PhH (200 mL) gave 4-hydroxyacetophenone (300 mg, 88%), identical (mp and ^1H NMR) with an authentic sample.

Selectivity of 2f vs 2g. Treatment of a mixture of **2f** (340 mg, 2.5 mmol) and **2g** (340 mg, 2.5 mmol) in dry NMP (5 mL) with PhSH (275 mg, 2.5 mmol) and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) under reflux for 30 min followed by usual workup afforded the phenolic product, which on passing through a column of silica gel (20 g) and elution with PhH (200 mL) afforded 307 mg (100%) of 4-hydroxybenzaldehyde, identical (mp, IR, and ^1H NMR) to an authentic sample, indicating selective cleavage of **2g**.

Intramolecular Competitions. Cleavage of 8a. Treatment of **8a** (415.15 mg, 2.5 mmol) in dry NMP (5 mL) with PhSH (275 mg, 2.5 mmol) and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) under reflux for 15 min followed by usual workup afforded 380 mg of the phenolic product, which on passing through a column of silica gel (20 g) and elution with 5% EtOAc−PhH (200 mL) afforded 220 mg (58%) of the phenolic product **8b**, identical (mp, IR, and ^1H NMR[27]) to an authentic sample of 4-hydroxy-3-methoxybenzaldehyde. Further elution with 50% EtOAc−PhH (100 mL) afforded 70 mg (20%) of the dihydroxy compound **10c**, identical (mp, IR, and ^1H NMR[27]) to an authentic sample of 3,4-dihydroxybenzaldehyde.

Cleavage of 9a. Treatment of **9a** (200 mg, 1.1 mmol) in dry NMP (5 mL) with PhSH (121 mg, 1.1 mmol) and K_2CO_3 (7.5 mg, 0.05 mmol, 5 mol %) under reflux for 30 min followed by usual workup afforded 180 mg of the phenolic product, which on passing through a column of silica gel (15 g) and elution with 5% EtOAc−PhH (200 mL) afforded 30 mg (16.3%) of **9b**, ^{13}C NMR ($CDCl_3$) δ 26.12, 55.57, 100.78, 107.66, 113.88, 132.30, 165.25, 166.10, and 202.63, identical (mp, IR, ^1H NMR, and MS)[27] to an authentic sample of 2-hydroxy-4-methoxyacetophenone. Further elution with 10% EtOAc−PhH (200 mL) afforded 40 mg (22%) of the dihydroxy compound **9c**, identical (mp, IR, ^1H NMR, and MS)[27] to an authentic sample of 2,4-dihydroxyacetophenone. Further elution with 20% EtOAc−PhH (200 mL) afforded 70 mg (38%) of **9d**: mp 138 °C (lit.[27] 139 °C); IR (KBr) 3298, 1649, and 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.87 (s, 3H), 6.45−6.47 (m including a doublet, J = 9 Hz, 2H), 7.77 (d, J = 9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 31.80, 55.45, 98.95, 107.86, 120.36, 125.87, 132.97, 161.86 and 198.74; MS (m/z) 166 (M^+), 151 (100), 136, 121, 108 and 93.

Cleavage of 10a. Treatment of **10a** (642 mg, 2.5 mmol) in dry NMP (5 mL) with PhSH (275 mg, 2.5 mmol) and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) under reflux for 2 h followed by usual workup afforded the phenolic product, which on passing through a column of silica gel (20 g) and elution with 30% EtOAc in PhH (400 mL) afforded 480 mg (80%) of **10b**: mp 220−222 °C; IR (KBr) 3389, 3230, 1644, and 1603 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.75 (s, 3H), 6.78−6.84 (m, 4H), 7.54 (d, J = 9 Hz, 2H), 7.75 (d, J = 9 Hz, 2H), 8.68 (s, 1H), and 9.31 (s, 1H).

Cleavage of 11a. Treatment of **11a** (350 mg, 1.96 mmol) in dry NMP (5 mL) with PhSH (20 mg, 2 mmol) and K_2CO_3 (14 mg, 0.1 mmol, 5 mol %) under reflux for 30 min followed by usual workup afforded the phenolic product, which on passing through a column of silica gel (20 g) and elution with 10% EtOAc−PhH (200 mL) afforded 230 mg (75%) of **11b**: mp 64 °C; IR (KBr) 3400−3200, 1625, and 1605 cm^{-1}; ^1H NMR (CCl_4) δ 2.11 (s, 3H), 3.89 (s, 3H), 6.21 (s, 1H), 6.51 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H); MS (m/z) 165 (M^+), 119, 93 and 77.

Cleavage of 12a. Treatment of **12a** (670 mg, 2.5 mmol) in dry NMP (5 mL) with PhSH (275 mg, 2.5 mmol) and K_2CO_3 (17 mg, 0.125 mmol, 5 mol %) under reflux for 30 min followed by usual workup afforded the phenolic product, which on passing through a column of silica gel (20 g) and elution with 5% EtOAc−PhH (200 mL) afforded 400 mg (63%) of mono demethylation product: mp 185 °C;[34] IR (KBr) 3150, 1645 and 1601 cm^{-1}; MS (m/z) 254 (100, M^+); λ_{max} (MeCN) 350 nm (log ϵ 3.66). The ^1H NMR spectrum exhibited two singlets at δ 3.67 and 3.76 corresponding to *O*-Me protons and broad singlets at δ 9.27 and 3.53 corresponding to phenolic *O*-H protons. The relative intensities of these two sets of singlets revealed the phenolic product to be a mixture of **12b** and **12c** in a ratio of 68:32. Further elution with 20% EtOAc−PhH (200 mL) afforded 120 mg (20%) of complete demethylation product **12d**: mp 201 °C (lit.[40] mp 203.5 °C); IR (KBr) 3200, 1642, 1604 and 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90−6.97 (m, 4H), 7.40 (d, J = 16 Hz, 1H), 7.54 (d, J = 9 Hz, 2H), 7.76 (d, J = 16 Hz, 1H), 7.97 (d, J = 9 Hz, 2H), 9.44 (bs, 1H), 9.67 (bs, 1H); MS (m/z) 240 (M^+), 223, 206, 147, 121 (100); λ_{max} (MeCN) 336 nm (log ϵ 3.58).

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