

A Simple and Regioselective Carbon-Oxygen Bond Cleavage Using Niobium(V)

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Abstract: A simple and convenient method for the differentiation of alkoxy groups on aromatic rings is described. Niobium(V) is found to possess a strong Lewis acid property to transform alkyl arylethers smoothly to the corresponding phenols in high yields. The excellent regioselectivity was also observed in dialkoxy benzene derivatives under mild conditions.

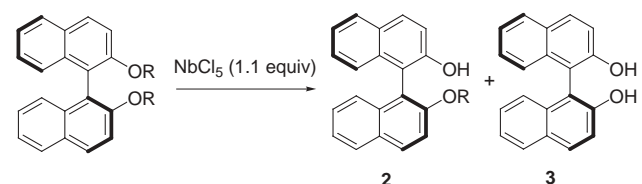
Key words: dealkylation, Friedel–Crafts acylation, niobium

Since niobium(III) has been reported as an efficient reductant to produce 1,2-dianion from alkynes by Pedersen¹ and Utimoto and co-workers,² independently, the development of its utility in organic synthesis have been attractive area. On the other hand, high valence niobium acts as a Lewis acid and its application to carbon-carbon bond forming reactions has been investigated.^{3–9} We are also interested in the character of its strong acidity and of its development and utilization in organic synthesis. In this article, we report our recent results concerning regioselective carbon-oxygen bond cleavage of alkyl arylethers and regioselective Friedel–Crafts acylation promoted by niobium(V).

Since Nb(V) has been known to possess strong oxophilicity to promote Lewis acid-mediated reactions such as Diels–Alder reaction,³ allylation of aldehydes⁴ and imines,⁵ dealkylative acylation,⁶ sulfur transfer⁷ and others,^{8,9} we have planned to apply the utility of Nb(V) in deprotection of alkyl group of aryl ethers. First of all, mono demethylation of binaphthol-dimethylether **1a** was examined in dichloroethane and we were pleased to find that the reaction proceeded smoothly as a spot-to-spot and gave the corresponding mono deprotected compound **2a**¹⁰ in an excellent yield, which was a useful chiral intermediate for elaboration of various chiral ligands (Table 1, entry 1). Toluene was also useful to give the compound in an excellent yield as a sole product (entry 2).¹¹ The reaction was quite selective to give the **2a**, exclusively, even though a 2 mol equivalent of NbCl₅ was used. We assume that the ligand exchange between chlorine and oxygen affords niobium(V) aryloxy complex which does not exhibit enough Lewis acidity due to bidentate ability of **2a**. Diethyl ether **1b** was also employed under milder conditions to give **2b** quantitatively (entries 3 and 4). Furthermore, dibenzyl ether **1c** was quite reactive to give **2c** in

87% together with **3** (8%) even at –78 °C (entry 5).¹² These results suggest that acceleration of the reaction depends strongly on the stability of a carbocation intermediate and indicate the rate determining step would be C–O bond cleavage.

Table 1 Selective Mono Dealkylation of **1**



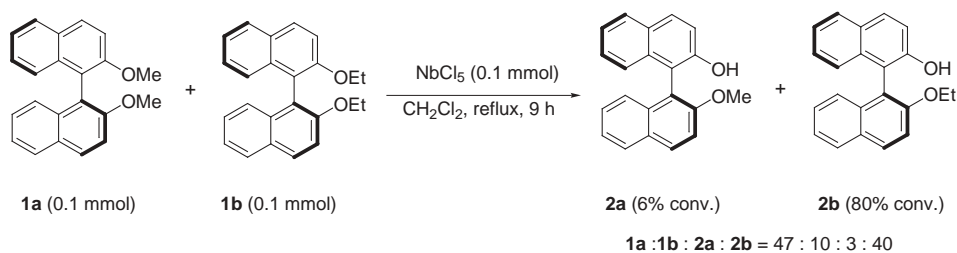
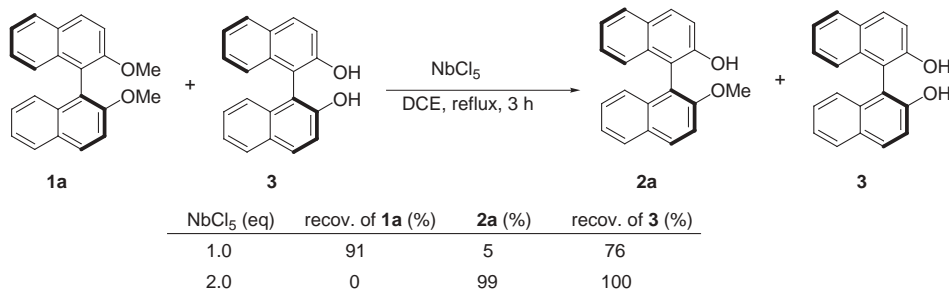
Entry	R	Conditions	Yield	
			2 (%)	3 (%)
1	1a : R = Me	DCE, ^a reflux, 3.5 h	2a : >99	Trace
2	1a : R = Me	Toluene, reflux, 3.5 h	2a : 99	1
3	1b : R = Et	DCE, reflux, 0.5 h	2b : 91	Trace
4	1b : R = Et	CH ₂ Cl ₂ , reflux, 7 h	2b : quant.	0
5	1c : R = Bn	Toluene, –78 °C, 3 h	2c : 87 ^b	8

^a DCE: 1,2-dichloroethane.

^b NbCl₅ (1.5 equiv) was employed.

In order to confirm these speculations, the mixture of **1a** and **1b** (1:1) were reacted with NbCl₅ (1.0 equiv) under similar conditions (Scheme 1). As expected, **1b** reacted much faster than **1a** to give **2b** in 80% conversion and 94% of unreacted **1a** was observed in ¹H NMR analysis. This result clearly shows high selectivity in differentiation of the alkyl groups (Me vs. Et). Furthermore, no trace amount of BINOL (**3**) was detected during the reaction indicating poor reactivity of the possible intermediate, niobium phenoxide(V), for further deprotection due to lack of Lewis acid property.

We next investigated the effect of the Lewis base as an additive (Scheme 2). The treatment of **1a** with BINOL **3** (1 equiv) in the presence of NbCl₅(V) (1 equiv) resulted in the recovery of **1a** in 91% with BINOL (100%) and in only 5% of **2a** was isolated. On the other hand, **2a** and **3** were isolated in quantitative yield, respectively, in case of

**Scheme 1** Differentiation of alkyl groups in Nb(V)-mediated reaction**Scheme 2**

2 equiv of NbCl₅ was used. These results indicate that the rapid formation of Nb complex with BINOL decrease Lewis acidity and the additional ligand-free Nb(V) promotes the deprotection. However it is unclear the generated methyl chloride does affect as an electrophile or not, niobium phenoxide no longer exhibit enough nucleophilicity.

Encouraged by these results, we next turned our attention to the differentiation of two neighboring alkoxy groups on the benzene ring (**4a–f**). As expected, Nb(V) acts as a quite selective agent for deprotection of **4a** to give methoxy phenol **5a**, which was isolated as mesylate **6a** in 93% yield because of its high volatility. Major product **6a** would be given via nucleophilic addition of chloride into the less hindered methyl group. Moreover, 2,3-diethoxytoluene **4b** was also smoothly transformed into the corresponding phenol **6b**, exclusively (entry 2). On the other hand, the regioisomers such as **4c** and **4d** were transformed into **6** and **7** without any selectivity because of the ineffective steric repulsion between a methyl group and Nb atom (entries 3 and 4). Other 3-substituent such as a methoxycarbonyl group was quite effective to differenti-

ate the 1,2-dimethoxy groups to give the corresponding phenol **7e** in 90%, exclusively (entry 5). In this case, regioselectivity would be strongly dependent on the neighboring carbonyl group, which would be expected to react with the more hindered methyl group, predominantly (entry 1 vs 5). These results are summarized in Table 2.

As additional interesting character of Nb(V) was we found it to be quite an effective promoter for Friedel–Crafts reaction in the presence of acyl halide. For example, **4a** was predominantly converted into the corresponding 4-acylated product **8a** without any C–O bond cleavage or O-acylation.⁶ This reaction showed that Nb(V) complexes to an acyl halide much faster than to an ether, as outlined in Scheme 3. Moreover, the addition of BzCl after formation of Nb-phenoxide intermediate failed in neither C- nor O-acylations. These results show the Nb–O bond does not possess enough nucleophilicity and its character of electron withdrawing property prevents the following C-acylation. Although the regioselectivity on C–O bond cleavage is still unclear, further investigation is currently in progress.

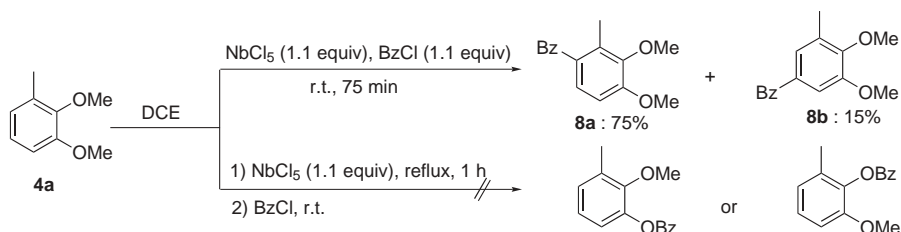
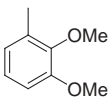
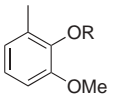
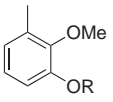
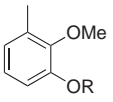
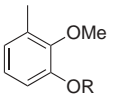
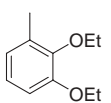
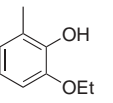
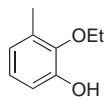
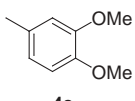
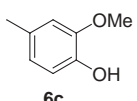
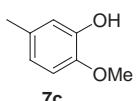
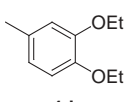
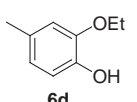
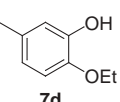
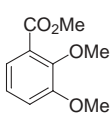
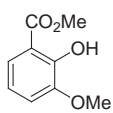
**Scheme 3**

Table 2 Mono Deprotection of Dialkoxy Benzenes

Entry	Substrate	Conditions	Yield (%)
1	 4a	1) NbCl ₅ (1.1 equiv), DCE, r.t., 37 h 2) MsCl, Et ₃ N	 5a : R = H  6a : R = Ms (93%)  5b : R = H  7a : R = Ms (7%)
2	 4b	NbCl ₅ (1.1 equiv), DCE, r.t., 7 h	 6b : 83%  7b : trace
3	 4c	NbCl ₅ (1.1 equiv), DCE, reflux, 70 min	 6c  7c 82% (7c : 7c = 52 : 48)
4	 4d	NbCl ₅ (1.1 equiv), DCE, r.t., 7 h	 6d  7d 93% (6d : 7d = 50 : 50)
5	 4e	NbCl ₅ (1.1 equiv), DCE, reflux, 1 h	 7e : 90%

In conclusion, we have succeeded in regioselective deprotection of aryl alkylethers mediated by NbCl₅. Furthermore, this methodology can be quite useful for the differentiation of neighboring alkoxy groups on aromatic rings. Further investigation on the synthetic utility of niobium complexes is in progress.

References

- Roskamp, E. J.; Peredsen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551.
- Kataoka, Y.; Miyai, J.; Tezuka, M.; Takai, K.; Ohshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 369.
- Howarth, J.; Gillespie, K. *Tetrahedron Lett.* **1996**, *37*, 6011.
- Andrade, C. K. Z.; Azevedo, N. R. *Tetrahedron Lett.* **2001**, *42*, 6473.
- Andrade, C. K. Z.; Oliveira, G. R. *Tetrahedron Lett.* **2002**, *43*, 1935.
- Guo, Q.; Miyaji, T.; Hara, R.; Shen, B.; Takahashi, T. *Tetrahedron* **2002**, *58*, 7327.
- Ortiz, A.; Quintero, L.; Hernández, H.; Maldonado, S.; Mensoza, G.; Bernès, S. *Tetrahedron Lett.* **2003**, *44*, 1129.
- Maeta, H.; Nagasawa, T.; Handa, Y.; Takei, T.; Osamura, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *36*, 899.
- Yamamoto, M.; Nakazawa, M.; Kishikawa, K.; Kohmoto, S. *Chem. Commun.* **1996**, 2353.
- An example for the synthesis of mono-alkylethers of BINOL have been reported, see: Takahashi, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3125.
- Other Lewis acid agents, such as TiCl₄, AlCl₃, TaCl₅ and MoCl₅ (1.1 equiv) with **1a** under similar conditions (PhMe, reflux), were quite ineffective to be resulted in the recovery of **1a** with >95% yield even after 5 h. In case of WCl₆ (1.1 equiv, toluene, reflux, 9 h), **2a** was obtained in only 18% yield together with **3** (18%) and **1a** (60%). BBr₃ with **1a** (CH₂Cl₂ at -78 °C) was also subjected and gave **2a** (90%) with **3** (9%). In other substrates, NbCl₅ is found to be more selective reagent than BBr₃ in C–O bond cleavage, unpublished results.
- Typical Experimental Procedure for the Synthesis of 2a (Table 1, Entry 1):** To a mixture of **1a** (30 mg, 0.1 mmol) and NbCl₅ (31 mg, 0.11 mmol) under an argon atmosphere, dichloroethane (1.0 mL) was added and the suspension was stirred for 3.5 h under reflux condition. The reaction mixture was quenched by 10% aq K₂CO₃ (1.0 mL) and extracted with CH₂Cl₂ (5.0 mL × 3). The resulting organic layer was washed with brine and dried over Na₂SO₄, and subsequent flash column chromatography (hexane:EtOAc = 8:1) gave the desired product **2a** as a white amorphous (29.6 mg, 0.1 mmol, 100%).