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Frustrated Lewis Pair Mediated C-O or C-H Bond Activation of Ethers†

Michael H. Holthausen,† Tayseer Mahdi,† Christoph Schlepphorst, Lindsay J. Hounjet, Jan J. Weigand* and Douglas W. Stephan*†h

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Protocols for the FLP-mediated transformation of ethers are presented. Distinct reaction pathways involving either C–O or C–H bond activation occur depending on the application of oxophilic B(C6F5)3 or hydridophilic tritylium ion as the Lewis acid.

The recent renaissance of main-group chemistry has been driven by the discovery that main-group compounds can be used in transformations that are typically the purview of transition metal complexes.1 In this context, frustrated Lewis pairs (FLPs), which are sterically encumbered Lewis acids and bases, have garnered considerable interest due to their propensity to bind and activate a plethora of small molecules.2

A variety of O-based substrates including CO2, CO, aldehydes, ketones, isocyanates, enones and yrones have been shown to react stoichiometrically with intermolecular P/B FLPs resulting in cooperative addition to the C–O multiple bonds.2 Similarly, intramolecular P/B FLPs have been shown to bind carbonyl fragments of ketones and aldehydes.2 The reactions of endiienes with intermolecular P/B were shown to result in a 1,4 addition product while the corresponding reaction of intramolecular FLPs results in cyclization to give a an acetal derivative.3 Furthermore, such FLP combinations have also been shown to deprotonate alcohols yielding phosphonium-alkoxyborates.4 While the (Et3O)B(C6F5)3 adduct has been shown to act as an FLP activating H2,5 P/B FLPs react with THF to effect C–O bond cleavage affording the ring opening of THF.6 Such FLP ring-openings have also been applied to a number of other ethers including dioxane, thioxane, and lactides.7 Gagné and coworkers have exploited related C–O bond cleavage and ring-opening reactions, using the Lewis acid B(C6F5)3 in the presence of silanes, to catalytically deoxygenate carbohydrates.8

Reactions of a variety of FLPs with cyclic ethers, in particular THF, are well documented.5,7 The ring-opening of THF was first described by Wittig and Rücker in 1950,9 who showed C–O bond scission by combination of the anion [Ph3C]– and THF(BPH) affording [Ph3C(CH2)3OBPh3]. Subsequent reports have shown similar THF ring-opening by phosphine / ZrCl4(THF)4 as well as other transition metal Lewis acids based on U,11 Sm,12 Ti13 Zr14 and Mn complexes,15 as well as other main group systems, like Al Lewis acids16 and Te nucleophiles.17 Nonetheless, reactions of acyclic ethers with combinations of Lewis acids and bases have drawn less attention.

In the present manuscript, we describe the stoichiometric reactions of differing FLPs with ethers. We demonstrate that judicious choice of the components of the FLP altered the chemistry observed. Selective routes to C–O bond activation and unprecedented avenues to alpha-C–H bond activation in these substrates are described.

The intermolecular FLP, t-Bu3P and B(C6F5)3 reacts with an equivalent of dibenzylether, (PhCH2)2O to effect heterolytic C–O bond cleavage yielding the salt (1) isolated in 86% yield (Scheme 1). The 1H NMR spectrum reveals two distinct methylene resonances, a singlet at 4.30 ppm assignable to a benzyl-oxo-borate anion and a doublet at 3.71 ppm with two-bond PH coupling of 13 Hz attributable to the benzyl-phosphonium moiety. Collectively, the heteronuclear NMR spectroscopy, elemental analysis and X-ray crystallography are consistent with the formulation of 1 as [t-Bu3PCH2Ph][PhCH2OB(C6F5)3]. The new B–O and P–C bond distances of 1.457(4) and 1.896(3) Å in 1 are typical (Figure 1).

Figure 1. POV-ray depiction of 1. C: black, P: orange, O: red, F: pink, B: yellow-green, Hydrogen atoms have been omitted for clarity.

The corresponding reaction of cyclohexyl-vinyl ether with the P/B FLP gives the salt (2) which was isolated in 80% yield. The formation of the phosphonium cation [t-Bu3PH]+ was confirmed by the diagnostic doublet in the 1H NMR spectrum at 5.05 ppm (JPH = 427 Hz). Furthermore, the 11B NMR spectrum showed a sharp singlet at −3.45 ppm. These data, together with the resonances in the 19F NMR spectrum, support the presence of the [C6H4OB(C6F5)3]– anion and thus the formulation of 2 as [t-Bu3PH][C6H4OB(C6F5)3] with the concurrent loss of acetylene (Scheme 1). The analogous product [t-Bu3PH] [p-C6H4FOB(C6F5)3] (3) was obtained in 88% isolated yield from
the reaction of 4-fluorophenyl tert-butyl ether with t-Bu3P and B(C6F5)3 (Scheme 1). In this case, the reaction proceeds with the liberation of isobutylene (see SI).

The formation of compounds 1-3 are thought to proceed by initial coordination of the ether to the oxophilic Lewis acid B(C6F5)3. This is followed by subsequent nucleophilic attack of the Lewis base at the α-carbon leading to alkylation of P or alternatively deprotonation of the β-carbon atom (Scheme 1). In either case this is accompanied by the heterolytic cleavage of a C–O bond.

\[
\begin{align*}
\text{Ph}_2\text{O} & \xrightarrow{\text{t-Bu}_3\text{P} / \text{B(C}_6\text{F}_5)_3} \text{[t-Bu}_3\text{PCH}_2\text{Ph]} \\
\text{Cy}_2\text{O} & \xrightarrow{\text{t-Bu}_3\text{P} / \text{B(C}_6\text{F}_5)_3} \text{[t-Bu}_3\text{PH]} \\
\text{O} & \xrightarrow{\text{t-Bu}_3\text{P} / \text{B(C}_6\text{F}_5)_3} \text{[t-Bu}_3\text{PH]} \\
\end{align*}
\]

Scheme 1. Reaction of ethers with the FLP t-Bu3P/B(C6F5)3.

We were interested in probing the impact of less oxophilic Lewis acids on the reactivity of FLPs with ethers. To that end, we first considered the combination of the Lewis acid [Ph3C][X] (X = OSO2CF3 or B(C6F5)3) and the Lewis base t-Bu3PH. Initial combination of these reagents gave the salt [t-Bu3PH- (C6H5)3CPh3][X] 4 which was isolated in almost quantitative yield (96% for X = OSO2CF3).

While the NMR data for 4 is consistent with the formulation of a phosphonium ion featuring a cyclohexadienyl substituent (see SI), this was further confirmed by X-ray crystallography (Figure 2). The cyclohexadienyl-moiety of 4 is evidenced by the short C6–C7 and C4–C3 bond distances of 1.332(3) Å and 1.329(3) Å, the C1–C2 bond length of 1.364(3) Å and the sum of angles at C1 of 359.9(6)°. The P–C bond distance of 1.837(2) Å is shorter than the P–C bonds in phosphonium ions of the type [R$_3$PCH$_2$]$_n^+$ (av. 1.876(4) Å, see SI) consistent with the diminished steric crowding. It is noteworthy that the corresponding reactions of R$_3$PH (R = Ph, Cy) led to the formation of cations of type R$_3$PPhCH$_2$P$_n^+$ (see SI), illustrating the impact of steric demand of the phosphine. These latter species are unreactive with ethers. Analogues of 4 have been spectroscopically observed, however, to the best of our knowledge, compound 4 represents the first structurally characterized cyclohexadienyl-phosphonium cation.[19]

Despite the formation of this phosphonium-cyclohexadienyl cation in 4, this species behaves as an FLP which reacts with a range of ethers (Scheme 2).

\[
\begin{align*}
\text{t-Bu}_3\text{PH} & + \text{[Ph}_3\text{C][X]} \\
\end{align*}
\]

Scheme 2. Isomerization of FLP 4 to 4': equilibrium dissociation of 4 to [Ph3C][X] and t-Bu3PH and phosphonium ions 5-10 obtained in the reaction of FLP 4 with (thio)ethers. X = OSO2CF3 or B(C6F5)3. a Yield determined by integration of all resonances in the $^1$H and $^{31}$P NMR spectra of the reaction mixture. b Isolated yield. c Obtained as the free phosphine.

Reacting 4 with THF or THF-d$_8$ yielded the 2-tetrahydrofuranyl-substituted phosphonium ions 5 or 5-d$_8$ in quantitative yield. An additional competition reaction containing THF and THF-d$_8$ indicates that the dissociation of FLP 4 to Ph3C$^+$ and t-Bu3PH is the rate determining step in the reaction sequence with ethers (see SI for additional information). Subsequently, abstraction of hydride by [Ph3C][X] from the α-carbon atom of the respective ether generates a transient oxonium ion which is intercepted by [t-Bu3PH]$^+$. The FLP 4 slowly isomerizes in solution to compound 4’ (see SI for details on the mechanism of the isomerization and full characterization of 4’). Reacting 4 with...
varying amounts of Et₂O showed that large ether concentrations favour the C−H bond activation pathway. The respective phosphonium ion salt 6 was obtained almost quantitatively when 20 equivalents of Et₂O were employed. Although BnO and tetrahydropryan derivatives were successfully converted to compounds 7-9, however, these reactions were accompanied by the formation of considerable amounts of 4’. Finally, tetrahydrothiophene, diethyl sulphide and N-methylidiphenylamine were converted to phosphonium ion salts 10-12 in moderate yields showing that the scope of this synthetic protocol also includes thioethers and amines.

It was of interest to investigate if this method is suitable for the preparation of functionalized phosphines. Thus mixtures containing the OSO₂CF₂-salts of 5-7 were prepared and treated with t-BuOK (Scheme 3). This resulted in deprotonation of the phosphonium ions and afforded the respective phosphines 11-15 which could be isolated by distillation in satisfying yields on a multi-gram scale.

![Scheme 3. Synthetic route to phosphines 13-15.](image)

**Conclusions**

In conclusion, we have uncovered distinct reaction pathways for the FLP-mediated transformation of ethers. Oxophilic B(C₆F₅)₃ reacts via coordination to the oxygen donor and initiates reaction sequences which involve heterolytic C−O bond cleavage. In contrast, the FLP system 4, which is based on a hydrophilic tritylum ion, reacts with ethers via hydride abstraction and instalement of a phosphoniumyl-substituent on an α-carbon atom. This reaction constitutes a rare example of FLP-mediated C−H bond activation.[20] While previous studies have illustrated the ability of FLPs to effect both ether C−O and aromatic[20a] or allylic[20a] C−H activations, the present results are the first to demonstrate that judicious selection of the Lewis acid / base composition of an FLP provides an avenue for selective reactivity of one class of substrates. We are currently exploring the impact of varying the Lewis acid in the reactivity of FLPs with other substrates and on catalysis.

**Notes and references**


E-mail: dstephane@chem.utoronto.ca

1[1] Chemistry Department, Faculty of Science, King Abdulaziz University (KAU), Jeddah 21589, Saudi Arabia.
2[2] Institut für Anorganische und Analytische Chemie, Westfälische Wilhelms-Universität Münster, Corrensstraße 30, 48149 Münster (Germany)
3[3] Institut für Anorganische Koordinationschemie, TU Dresden, 01062 Dresden (Germany), Fax (+49) 351-883-31216, E-mail: ian.wie gand@tu-dresden.de
4[4] Note: Electronic Supplementary Information (ESI) available: Synthetic and spectroscopic details are deposited Crystallographic data have been deposited in the Cambridge database: see DOI:10.1039/b000000x/c.
5[5] CCDC 991775–991782 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
6[6] Department of Chemistry, 80 St. George Street, University of Toronto, Toronto, Ontario, Canada, M5S 3H6.
Graphical TOC

Lewis Acid Mediated

C-O Bond Activation

B(CF₃)₃ + R₃P

[Ph₃C][SO₂CF₃] + R₃P

C-H Bond Activation