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# Recent advances in ether dealkylation

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*Abbreviations*: Ac, acetyl; Alloc/Aloc, allyloxycarbonyl; BMIM, 1-*n*-butyl-3-imidazolium; Bn, benzyl; Boc, *t*-butyycarbonyl; BOM, benzyloxymethyl; Bz, benzoyl; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; CSI, chlorosulfonyl isocyanate; DAST, diethylaminosulfur trifluoride; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIB, (diacetoxyiodo)benzene; DMAC, dimethylacetamide; DMEU, *N*,*N*-dimethylpethylene urea; DMPU, *N*,*N*-dimethylpropylene urea; DMT, dimethoxytrityl; Dppp, 1,3-bis(diphenylphosphino) propane; EDG, electron-donating group; EWG, electron-withdrawing group; HMIMBr, 3-methylimidazolium bromo-hydrogenate; IL, ionic liquid; LAH, lithium aluminum hydride; LN, lithium naphthalide; LVT, low-valent titanium; MEM, 2-methoxyethyl; Mes, mesitylene; MMB, *m*-methoxybenzyl; MOM, methoxymethyl; MPB, *m*-methyoxybenzyl; MXM, *m*-xylylmethyl; NAP, 2-naphthyl-methyl; NMO, *N*-methylmorpholine *N*-oxide; PBB, *p*-bromobenzyl; PCB, *p*-chlorobenzyl; PDPM, *p*-phenyl diphenylmethanol; PMB, *p*-methoxybenzyl; PMBOM, *p*-(methoxybenzyloxy)methyl; PNB, *p*-nitrobenzyl; PBD, *s*-butyldimethylsilyl; TBDSS, *t*-butyldimethylsilyl; TBDSS, *t*-butyldimethylsilyl; TBDSOTf, *t*-butyldimethylsilyl iodide; Tr, trityl (triphenylmethyl); Ts, *p*-tolylsulfonyl. \* Corresponding author. Tel.: +1 732-594-3589; fax: +1 732 594 1499; e-mail: weissman@merck.com

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# 1. Introduction

The *O*-dealkylation of ethers, or ether cleavage, remains an integral functional group transformation, primarily as a deprotection step to unmask a hydroxyl group. The utility of this reaction extends to both academic and commercial pursuits including natural product, pharmaceutical and fine chemical syntheses.

This topic has most recently been reviewed in 1983 by Bhatt and Kulkarni<sup>1</sup> and in 1996 by Ranu and Bhar.<sup>2</sup> The former review attempted to cover all reagents of synthetic value through 1981 while the latter focused primarily on developments since the prior review. A review in 1997 by Guibé<sup>3</sup> on allylic protecting groups included a subsection on removal of this specific group. This review will cover the recent developments in the field from 1995 through the end of 2004, focusing on those reagents that are of practical, synthetic value and display some level of generality. Subject overlap with the prior reviews was kept to a minimum. The ethers covered are those in which the oxygen-bearing carbon atom being removed is only attached to other carbon or hydrogen atoms. Thus, such species as acetals, ketals, silvl ethers and tetrahydropyranyl ethers are excluded, as are methods that further functionalize the deprotected alcohols (acylation, silvlation, oxidation for example). The extent to which these excluded groups are affected (or not) by the reagents cited in the review, will be mentioned. In addition, in a few cases, we have included well-known reagents that have been utilized in large-scale syntheses. For the more practical methodologies, examples where the reagent was subsequently used in the synthesis of complex molecules has been included periodically. Whenever applicable, the reagent selectivity relative to other types of hydroxyl protecting groups will be highlighted, as this remains a key factor in the choice of reagent, especially in polyfunctional molecules. The review has been organized by functional group then by reagent type. The groups are: (1) aryl and alkyl ethers (including propargylic), (2) allyl ethers (including isoprenyl), (3) benzylic ethers (including trityl), and (4) cyclic ethers. In some Figures, an arrow has been placed to denote the dealkylation site, indicative of regio- or chemo-selectivity.

# 2. Deprotection of aryl and alkyl ethers

# 2.1. Methyl/ethyl ethers

**2.1.1. Lewis acids.** A Pfizer group<sup>4</sup> demonstrated the utility of BCl<sub>3</sub> as a dealkylating reagent can be greatly enhanced by the addition of tetrabutylammonium iodide. The reactions are run with 2.5 equiv of each reagent in DCM. This reagent combination displays enhanced reactivity over BBr<sub>3</sub> as shown in the bis demethylation of 3,5-dimethoxy-fluorobenzene (1) (Scheme 1). Methyl and ethyl aryl ethers are readily cleaved, but an isopropyl group is not.



Scheme 1.

The removal of a benzyl group was achieved in the presence of a methyl ether; also, an electron-withdrawing group (CN) can influence the removal of a *meta*-positioned methyl ether over an *ortho*-positioned methyl ether (Fig. 1). The reaction does not proceed in the absence of the iodide. The yields generally ranged from 70 to 98%. This methodology was recently employed in the synthesis of *rac*-Juglomycin  $A^5$ and some selective glucocorticoid receptor antagonists.<sup>6</sup>



Figure 1.

A unique intramolecular attack of a divalent sulphur atom was demonstrated to be the source of a selective *O*-demethylation of enterobactin analogue **2** in the presence of BBr<sub>3</sub> (Scheme 2).<sup>7</sup> The mechanism was proposed to proceed via a simultaneous attack of the S atom on the



#### Scheme 2.

oxygen bearing methyl group and the Br atom upon the sulphur bearing methyl group. The former having been activated by the boron halide creating an oxonium intermediate species.

An interesting series of selective *O*-demethylations was observed with tetrakis(2-hydroxyphenyl)ethene derivatives.<sup>8</sup> Reacting **3** with BBr<sub>3</sub> (1 equiv) gave the doubly deprotected (*Z*)-isomer (Scheme 3). In contrast, reaction with TMSI (1 equiv) gave the singly deprotected species in 50% yield. Higher yields could be attained by careful monitoring of the reaction with additional reagent.



#### Scheme 3.

Finn<sup>9</sup> has established an order of reactivity for the deprotection of aryloxy ethers with BBr<sub>3</sub> such that benzyl, propargyl and methyl ethers can be sequentially removed (Fig. 2). Allyl ethers undergo Claisen rearrangements under the reaction conditions (DCM, -20 °C to rt).



Figure 2.

The novel use of BeCl<sub>2</sub> for the demethylation of a series of aryl methyl ethers derived from benzophenones, xanthones, anthraquinones and substituted arenes (**4–6**) has been demonstrated in high yields using 3 equiv of reagent.<sup>10</sup> The reactions proceed to completion within 8 h in refluxing toluene. In the case of carbonyl-containing aryl methyl ethers in which the ether resides in the *ortho* position, the enhanced selectivity and reaction rate is attributed to coordination of the reagent to the carbonyl (Fig. 3).

The need for a scaleable process to dealkylate a nitrocatechol methyl ether led Learmonth<sup>11</sup> to re-investigate the



#### Figure 3.

aluminum chloride/pyridine combination (1:3 molar ratio) in environmentally-benign solvents. While typically performed in refluxing methylene chloride, this particular reaction gave better results in ethyl acetate (99% yield; 1.5 h-reflux) to provide drug candidate **7**, a selective inhibitor of catechol *O*-methyl transferase. Complex mixtures were obtained with typical demethylating reagents including BBr<sub>3</sub>, thiophenolate anion and pyridinium hydrochloride. Other demethylation examples with similar compounds (e.g., **8**) were reported in 70–96% yield (Fig. 4).





The synthesis of a series of 3,5,7-trihydroxy-6-methoxy flavones was predicated on the selective dealkylation of differentially protected intermediates.<sup>12</sup> The reaction of fully protected acetophenone **9** with AlCl<sub>3</sub> selectively removed only the isopropyl group in quantitative yield, whereas AlBr<sub>3</sub> showed less selectivity and removed the 6-methoxy in addition to the isopropyl. Selectivity for the 6-methoxy group was achieved using the combination of AlBr<sub>3</sub>/NaI in 94% yield. The selective removal of the isopropyl group in **10** was facilitated by converting the 3-position into a tosyloxy functionality in 90% yield (Fig. 5).



Figure 5.



#### Figure 6.

An improvement to the existing SiCl<sub>4</sub>/NaI methodology was reported from this laboratory by the addition of catalytic boron trifluoride.<sup>13</sup> While initially developed for the difficult double debenzylation of dihydrobenzoxathiin derivative **11** (81% yield) (Fig. 6) under investigation as a selective estrogen receptor modulator, the protocol was expanded to a variety of *O*-dealkylations. These included the removal of allyl and methyl groups from the corresponding aryl ethers (**12**) in MeCN at 70 °C (Fig. 7). Enhanced reaction rates were observed for all the examples with the catalyst present. Yields ranged from 82 to 98%.



#### Figure 7.

Removal of the novel *t*-amyl (TAM) group from alkyl ethers with *t*-butyldimethylsilyl triflate (TBDSOTf) has been described.<sup>14</sup> When 20 mol% of the reagent is used in dichloromethane, the corresponding alcohol is obtained in good to excellent yield (Scheme 4) but when 2,6-lutidine is employed with stoichiometric TBDSOTf, the corresponding silyl ether is obtained. Methyl and allylic ethers are immune to this reagent system. Trimethylsilyl triflate also effects the transformation to the alcohol.

$$C_{16}H_{34}O-TAM \xrightarrow{10\% \text{ mol TBDSOTf}} C_{16}H_{34}OH$$
  
rt/24 h

#### Scheme 4.

# Zinc bromide (3-5 equiv) in methylene chloride cleaves the t-butyl group from aliphatic, phenyl and benzyl ethers in yields from 78 to 82% (Scheme 5).<sup>15</sup>



#### Scheme 5.

A mixture of NiCl<sub>2</sub> (1 equiv) and zinc powder (3 equiv) in refluxing p-xylene was shown to O-dealkylate (Me, Et, *i*-Pr) anisole derivatives that are o-substituted with a nitrogen-



#### Scheme 6.

containing functionality which serves to chelate the metal and facilitate ether cleavage.<sup>16</sup> The reaction fails in the absence of such a nitrogen atom. Lengthy reaction times (3 days) are required for complete conversion (Scheme 6).

In 2003, the utility of ionic liquids (IL) was extended to include the ability to cleave alkyl ethers. Pioneering work by Driver and Johnson<sup>17</sup> showed that 3-methylimidazolium bromohydrogenate (HmimBr–HBr) could cleave anisole in modest yields at rt (62-65%)(Fig. 8).



#### Figure 8.

The scope of this methodology was expanded by Kemperman and co-workers<sup>18</sup> who investigated the ability of chloroaluminate ionic liquids, namely [TMAH][Al<sub>2</sub>Cl<sub>7</sub>] to cleave aryl methyl, allyl and benzyl ethers at 40 °C in >97% yield (Scheme 7).



#### Scheme 7.

They also studied the comparative dealkylative abilities of three chloroaluminate ionic liquids (TMAH, BMIM, EMIM) in the selective demethylation of 4,5-dimethoxy-indanone **13** (Fig. 9). All three showed improved reaction rates and selectivity to remove the 4-methyl group as compared to AlCl<sub>3</sub> (96%—24 h vs 70%—42 h). The TMAH IL was the preferred reagent as it is less costly to prepare (one step).





The enhanced rate is explained by the presence of a high concentration of chloride ions that accelerates the rate determining step, namely the attack on the methyl C atom.

Another IL system, 1-*n*-butyl-3-imidazolium tetrafluoroborate [Bmim][BF<sub>4</sub>] in combination with 1 equiv aq HBr, cleaved aryl methyl and aryl benzyl ethers, such as **14**, at 115 °C in excellent yields (85–95%) (Fig. 10).<sup>19</sup> The IL presence allows fewer HBr equivalents to be used than usual. PTSA can also be used as the proton source. The yields in the absence of the IL were significantly lower even at extended age periods. These IL systems are touted as conforming to the principles of green chemistry due to their recyclability, low cost, and safety profile.





The pyridine–hydrochloride system for the *O*-demethylation reaction has been modified by applying microwave irradiation under solvent free conditions.<sup>20</sup> The reactions of variously substituted anisoles (**15**) are complete within 16 minutes and provide the corresponding phenols in good to excellent yields (65–95%) (Fig. 11).





The conventional pyridine–hydrochloride system was demonstrated by Schmid<sup>21</sup> on a pilot-plant scale (190 L glassware) on methoxyphenylbutyric acid (16). The reaction was run at 200 °C and was complete after 2 h to give des-methyl product in 96% yield (Scheme 8). The authors cite the undesirable features of the standard selections of methods available for their choice of this approach.



# Scheme 8.

**2.1.2. Hydrides.** A selective *O*-demethylation of **17** was observed in the presence of an aryl methyl ether utilizing LAH (6 equiv) in refluxing toluene (Scheme 9).<sup>22</sup> Thus a series of ring-constrained analogues of buprenorphine were *O*-demethylated in the 6-position via assistance by the neighboring oxygen atom that presumably forms an



Scheme 9.

aluminum hydride species that attacks the lithium-activated methyl ether moiety.

**2.1.3.** Oxidative. The mild deprotection of oligosaccharide propargylic ethers **18**, via isomerization to the allenyl ether, followed by treatment with 5 mol%  $OsO_4$  with NMO in aq acetone at rt has been described by Mereyala (Fig. 12).<sup>23</sup> High yields (88–97%) of the corresponding alcohol were obtained (10–18 h). Acid-sensitive groups such as isopropylidene and cyclic ketals were unreactive under these conditions. Other ethers deprotected similarly are allenyl, allyl and enol ethers (i.e., compound **19**) (Fig. 12). In the latter two cases, both aliphatic and aromatic examples were given.



Figure 12.

A new protocol for the deprotection of aryl propargylic ethers using 4 mol% (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> with triethylamine (8 equiv) in aq DMF at 80 °C has been described (Scheme 10).<sup>24</sup> Adjacent methyl aryl ethers are unaffected under the reaction conditions. Isolated yields generally range from 55 to 75%. Compatibility with several aryl substituents such as aldehydes, ketones, and halides was demonstrated.



# Scheme 10.

Sulphur transfer agent, tetrathiomolybdate  $((BnNEt_3)_2-MoS_4)$  has been shown to deprotect propargyl ethers of aliphatic alcohols (**20**) and phenols (**21**) in MeCN at 28 °C (Fig. 13).<sup>25</sup> This system is selective for the propargyl ether



#### Figure 13.

in the presence of reducible functionalities, such as  $NO_2$  and Ac, as well as methyl and allyl aryl ethers. Yields range from 75 to 95% with 1.0 equiv of the reagent. The reagent is readily prepared from ammonium molybdate, hydrogen sulfide and tetrabutylammonium chloride.

The selective *O*-demethylation of an ether adjacent to a hydroxyl group in carbohydrate substrates (i.e., **22**) was accomplished with (diacetoxyiodo)benzene (DIB) and I<sub>2</sub> under irradiative conditions (tungsten lamp) (Scheme 11).<sup>26</sup> In this tandem radical hydrogen abstraction–oxidation approach the abstraction from the methyl group yields a C-radical that is stabilized by the nearby (2.3–2.8 Å) oxygen atom. Oxidation of the C-radical provides an oxycarbenium ion that is trapped by acetate from the reagent to form a mixture of acetals (*O*-acetoxymethyl and methylenedioxy) that upon basic hydrolysis provides the diol in 77% overall yield in one-pot.



#### Scheme 11.

**2.1.4. Base.** The previous report of nucleophilic attack of iodide on the methyl group of *o*-anisic acid as a dealkylation method, led Nishioka to study other nucleophiles, namely amines, for this dealkylation.<sup>27</sup> A study of various solvent and amine combinations led to the optimized system in which substituted derivatives of *o*-anisic acid were reacted with 3 equiv of piperidine in DMAC (Scheme 12). This approach is *o*-selective (relative to the benzoic acid moiety) as *m*- and *p*-methoxy substituents were unaffected.



The hindered bases NaHMDS and LDA (1.5 equiv) were both shown to dealkylate aryl and heteroaryl methyl ethers in 81–94% yield in THF/DMEU at 185 °C in a sealed tube.<sup>28</sup> The selective mono *O*-demethylation of *o*-dimethoxybenzenes (e.g., **23**) can be achieved with the former base (Scheme 13) while selective *O*-debenzylation of benzyloxy anisoles (e.g., **24**) can be attained with the latter (2.5 equiv) (Scheme 14).



Scheme 13.





Another well-studied class of basic reagents are the sodium thiolates. An AstraZeneca group showed the improved selectivity for the demethylation of a differentially protected substrate en route to the synthesis of key chiral intermediate **25** (Scheme 15).<sup>29</sup> Initially, BBr<sub>3</sub> was used but showed selectivity for removing the ethyl group, not the desired methyl group. Aq HI was only partially selective for the methyl group but satisfactory results were obtained with sodium ethanethiolate in DMF (>20 h).



#### Scheme 15.

While sodium ethanethiolate is an often-used methodology for the demethylation of aryl ethers, little was known about its regioselectivity. A systematic study of this reagent in DMF was undertaken and revealed notable trends.<sup>30</sup> For benzophenone derivatives (e.g., 26), the methyl ether para to the ketone is selectively removed in the presence of other methyl ethers even when they are situated on another aromatic ring (Scheme 16). Even a modest degree of chemoselectivity (2:1) was observed in the presence of a para benzyl ether. The role of electronic factors was studied with a series of simple anisole derivatives. A clear pattern emerged whereby EWG in the para (CN, NO<sub>2</sub>, Ac) gave improved results (77-89% yield) in comparison to electron neutral and EDG (H, halides, alkyl, alkoxy) that gave poor results (5–10% yield). The position of the EWG also had an effect as the *m*-acetyl example gave a reduced yield (18% vs 77%) compared to the para case. para-Substituted halides (Br, Cl) gave anomalous results (27-47% yield) perhaps due to thiol formation.



Х	R	R'	yield
$CH_2CH_2$	OMe	Н	87%
$CH_2CH_2$	Н	OMe	83%
$CH_2CH_2$	OMe	OMe	77%
0	OMe	OMe	75%
NEt	OMe	OMe	54%

#### Scheme 16.

The catalytic use of in situ generated phenylthiolate anion in NMP for the rapid (<30 min) removal of methyl and benzyl group from aryl ethers (Scheme 17) was reported.<sup>31</sup> Potassium carbonate (2–5 mol%) was combined with thiophenol to prepare the reagent that shows the usual favorable reactivity towards aromatic ethers containing EWG.



#### Scheme 17.

A systematic study of the dealkylating capabilities of in situ formed phenylthiolate anion was investigated by Chakraborti.<sup>32</sup> NMP was the solvent of choice based on their standard reaction of the dealkylation of 2-methoxynaphthalene, while DMEU and DPMU also gave high yields albeit in vacuo (146 and 106 °C, respectively). Several bases in NMP (5 mol%) gave >90% yield for the standard reaction including potassium carbonate, sodium bicarbonate, sodium hydroxide and lithium amide. Aside from demethylation, this reagent also removed propargyl, allyl, and benzyl groups from their respective 2-naphthyl ethers (**27**) (Scheme 18). A similar electronic effect was observed (vida supra).



The odor associated with the use of sodium ethanethiolate and its reaction by-product, ethyl methyl sulfide, led Frey to employ longer chain thiols to avoid this environmental issue.<sup>33</sup> The combination of dodecanethiol and sodium methoxide (1.7 equiv each) in DMF gave a 99% yield of phenol **28** (Scheme 19). This protocol was extended to other anisole derivatives in excellent yield. Modest regioselectivity for the mono-demethylation of the *meta* position of 3,4-dimethoxybenzonitrile (5:1) was reported.



Scheme 19.

The use of metal thiolates continues to attract attention as a viable method to dealkylate aromatic ethers. The first example of *tris O*-demethylation with this protocol was described by Tanaka and co-workers<sup>34</sup> en route to the total synthesis of (-)-Macrocarpal C, a biologically active compound. For the last step, 10 equiv of lithium *p*-thiocresolate in HMPA-toluene under refluxing conditions gave **29** in 58% yield (Fig. 14).



Figure 14. Structure of (-)-Macrocarpal C.

**2.1.5. Acid.** The key step in the synthesis of marine natural product isoaaptamine (**30**) was a selective *O*-demethylation using 48% HBr.<sup>35</sup> This served to remove the methyl group from the C-9 position in 81% yield (Scheme 20). Increasing the reaction temperature to 145 °C led to removal of both methyl groups. This compound is under investigation for broad-spectrum antimicrobial activity.



Scheme 20.

**2.1.6. Other.** The scope of the deprotection of aryl methyl ethers under Birch conditions (Li metal–ethylenediamine (EDA)) was studied by Sugai.<sup>36</sup> The formation of the overreduced species was suppressed by using an optimized amount of reagent. Demethylation of **31** with Li (5 equiv) and EDA (7 equiv) in THF at -10 °C/3 h gave an 81% yield of the phenol with only 6% of the over-reduced cyclohexene. In dimethyl ether **32**, selective monodemethylation could be achieved in 90% when the reaction was run at -10 °C and the second could be removed in 57% overall yield if run at 0–22 °C. Sterically hindered anisole derivatives, such as **33** could be demethylated in 82–83% yield (Fig. 15). Silyl ethers and esters do not survive these strongly basic conditions.



Figure 15.

The total synthesis of (-)-cylindrocyclophane A by Hoye included the novel perdemethylation of tetra-*O*-methyl ether **34** with MeMgI under solvent-free conditions at 160 °C (1 h/60% yield) (Fig. 16).<sup>37</sup> The AlBr<sub>3</sub>/EtSH reagent system that was successful for Evans' vancomycin synthesis did not work.



**Figure 16.** Structure of (–)-Cylindrocyclophane A.

# 2.2. Branched alkyl ethers

The utility of aluminum chloride as an ether cleaving



reagent was extended by Banwell who demonstrated that it could selectively cleave isopropyl aryl ethers in the presence of methyl aryl ethers under mild conditions.<sup>38</sup> The methodology was initially applied to the synthesis of complex marine natural product **35** (Scheme 21) but works equally well for simpler, differentially-protected arenes. Aluminum chloride showed superior selectivity in comparison to boron trichloride. While functional groups such as halides, aldehdyes and acetates were well tolerated, the presence of alkynes led to complex mixtures. The concurrent removal of a TIPS group was also observed in one example.

Bartoli extended the utility of cerium chloride/NaI to include the dealkylation of alkyl (1° and 2°) and aromatic *t*-butyl ethers. High yields of the alcohols were obtained (>93%) in MeCN using 1 equiv of reagent (Scheme 22).<sup>39</sup>

RO-tBu 
$$\xrightarrow{\text{CeCl}_3/\text{Nal}}_{\text{MeCN}}$$
 ROH  

$$\begin{array}{c} \text{R= octyl (94\%)} \\ \text{R = Ph (93\%)} \\ \text{R = (R)-menthyl (>98\%)} \end{array}$$

Scheme 22.

# 3. Allyl and related ethers

The protection of alcohols with allyl and related (prenyl, methyallyl, cinnamyl, homoallyl) groups is predominantly confined to carbohydrate synthesis due to their stability under the conditions required for glycoside formation. These groups are moderately stable to acids and bases, and offer the potential for selective dealkylation of differentially protected sites. Initially, the deprotection schemes involved a metal- or base-induced (potassium *tert*-butoxide in DMSO) isomerization to the 1-propenyl analog then hydrogenolysis or oxidative cleavage. More recently though, direct methods have been added to the arsenal of deprotection methodologies.

# 3.1. Allyl ethers

**3.1.1. Bases.** Bailey has described the *O*-deallylation of primary, secondary and tertiary allyl ethers with pyrophoric *t*-butyllithium (1 equiv/-78 °C) in pentane (Scheme 23).<sup>40</sup> The corresponding alcohols were obtained in >89% yield after warming to rt (1 h). Selectivity for the allyl group in the presence of benzyl, acetonide and TBDS protecting groups was demonstrated. The reaction works less well in EE and THF, the result of poorer aggregation in these solvents. The authors propose an  $S_N2'$  mechanism for the reaction.

RO-Allyl	t-BuLi pentane -78 °C to rt	ROH	
		R = <u>n</u> -hexyl (92%) R = 2-heptyl (97%) R = 1-adamantyl (9	4%)

Scheme 23.

**3.1.2. Sodium borohydride.** The combination of sodium borohydride and Lewis acids provides the basis for a series of new deallylation methodologies. This combination generally produces diborane in situ. Use of zirconium (IV) chloride (1 equiv) with NaBH<sub>4</sub> in THF was shown to deprotect a series of *O*-allyl aromatic (i.e., **36**) and aliphatic ethers in 80–95% yield at rt (Scheme 24).<sup>41</sup> Selectivity in the presence of an aromatic methyl and benzyl ether was shown.





The NaBH<sub>4</sub>/BF<sub>3</sub> system deallylated both aliphatic and aryl ethers in yields ranging from 75 to 95% at rt (Scheme 25).<sup>42</sup>

RO-Allyl 
$$\xrightarrow{\text{NaBH}_4/\text{BF}_3}$$
 ROH  
THF/rt/1 h  
R = Bn (95%)  
R = *n*-pentyl (75%)  
R = Ph (93%)

#### Scheme 25.

The iodine–borohydride combination also is an efficient deallylation system for both aliphatic and aromatic ethers (Scheme 26) and was unreactive towards neighboring methyl and benzyl ethers, as well as a THP group.<sup>43</sup> Similar results were observed with borane–dimethyl sulfide solution.

RO-Allyl 
$$\xrightarrow{\text{NaBH}_4/\text{I}_2}$$
 ROH  
THF/0 °C  
R = Benzyl (95%)  
R =  $p$ -NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> (93%)  
R =  $p$ -BnOC<sub>6</sub>H<sub>4</sub> (89%)

#### Scheme 26.

Sodium cyanoborohydride (1 equiv) with TMS-Cl (1 equiv) in MeCN (15 min) is another reagent combination that converts allyl ethers to the alcohol in yields up to 98% (Scheme 27).<sup>44</sup> Similar chemoselectivity was observed (vida supra).



**3.1.3. Electrochemical reduction.** The reductive deprotection of allyl ethers via electrochemically generated nickel has been reported by Duñach. The reaction employs 10 mol% Ni(II) complexes, typically with 2,2'-bipyridyl ligands, in DMF at rt (Scheme 28).<sup>45</sup> Aryl, aliphatic and benzylic allyl ethers can be cleaved with this method while demonstrating selectivity in the presence of enol and homoallyl ethers. Some reducible groups (esters, nitriles) were unaffected by the reaction conditions but an *o*-bromo group was removed.



#### Scheme 28.

The two electron reduction of the starting complex to Ni(0)is followed by oxidative insertion to the C-O bond to provide a Ni(II)  $\pi$ -allyl complex, a subsequent 1e<sup>-</sup> reduction forms a Ni(I)  $\pi$ -allyl intermediate.<sup>46</sup> The addition of  $Mg^{2+}$  ions to facilitates the reaction by undergoing a metal exchange reaction to form a magnesium phenate that is hydrolyzed to the phenol, thus enhancing the catalytic cycle. A similar result was obtained by replacing the Ni with 10 mol% PdCl<sub>2</sub>, again in DMF at rt.<sup>47</sup> The reduction of both allyl and cinnamyl groups in the presence of reducible groups were achieved. Hudlicky<sup>48</sup> selectively removed a cinnamyl group in the presence of an allyl group in a series of conduritol substrates while retaining the stereochemical integrity of the alcohol (Scheme 29). These results are not achievable with conventional reagents according to the authors. In another case, a benzyl group was left intact under the same conditions.49



<u>R</u>	yield
4-CO <sub>2</sub> Me	94
4-CHO	91
4-Br	72
4-OMe	76
4-OBn	73

Scheme 30.

Electrochemically generated nickel ('EgNi'; 4 equiv) from a nickel anode in DMF deallylates aryl ethers in the presence of sodium acetate and Et<sub>4</sub>NBF<sub>4</sub>.<sup>50</sup> Again, neighboring ester or nitrile groups were unaffected, as were neighboring methyl or benzyl groups (Scheme 30).

**3.1.4. Other reductions.** A chemical electron-transfer approach for this transformation was described by Hilmersson utilizing  $SmI_2$  (5 equiv) in aq THF in the presence of an amine (Scheme 31).<sup>51</sup> Aryl, primary and anomeric ethers are rapidly cleaved with this reagent in high yields while methyl, thioethyl and benzylic ethers are unaffected.

Scheme 31.

A more practical deallylation procedure by Ogasawara<sup>52</sup> used DIBAL (1.5 equiv) with 1 mol% [NiCl<sub>2</sub>(dppp)] in ethereal solvents at rt (Scheme 32). Selectivity towards an allyl ether in the presence of a methyl ether was shown for the aryl allyl ether substrates (82–90% yield) while aliphatic allyl ethers with benzyl, prenyl, or THP protected ethers present were selectively removed (80–95%). When ester groups were present, the replacement of DIBAL with 3–4 equiv sodium borohydride gave the alcohols in 73–85% yield. The reduction is thought to proceed via the known hydroalumination–elimination pathway. This methodology was applied to the total/formal synthesis of khafrefungin (87% yield; Fig. 17),<sup>53</sup> *rac*-guanacastepene (71% yield),<sup>54</sup> and desmethoxymitomycin A (Et<sub>3</sub>Al used in place of DIBAL; 86%).<sup>55</sup>



Scheme 32.



Figure 17. Structure of khafrefungin.

While the electron-transfer induced demethylation of aryl ethers using low valent titanium was described in 1991, its application towards allyl ethers was only recently reported by Banerji.<sup>56</sup> The reagent, generated by the Rieke method (TiCl<sub>3</sub>–Li–THF) can be activated by the addition of 1 equiv



#### Scheme 33.

iodine to allow the deprotection of a phenol (Scheme 33) and cholesterol (6 h/rt) in 83 and 79% yield, respectively. Higher temperatures, longer reaction times and lower yields were observed in the absence of iodine.

3.1.5. Palladium-based reagents. The palladium-based reagents continue to attract attention based on their catalytic nature and ability to operate under mild conditions, although mostly in acidic media (allyl scavenger) or in the presence of a reducing agent. Thayumanavan<sup>57</sup> developed an elegant methodology using merely 1 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in MeOH at rt with potassium carbonate (3 equiv). This system was highly effective for aryl allyl ethers with either EWG or EDG present (82-96%). Compatibility with reducible functional groups (CN, NO<sub>2</sub>, CHO) was observed, as was high chemoselectivity for removal of an aryl allyl ether in the presence of an alkyl allyl ether. The latter can be deprotected at higher temperatures. The author applied this methodology to the synthesis of dendrons and others to the synthesis of 7,7'-disubstituted binols (90% yield),<sup>58</sup> and chiral 1,4-butanediols (89% yield),59 both of which involved a double deprotection (Fig. 18).



Figure 18. Conditions: 1-5 mole%  $Pd(PPh_3)_4$ , 6 equiv  $K_2CO_3$ , EtOH (6-16 h).

Nagakura<sup>60</sup> reported a single example whereby sodium toluenesulfinate performed better than other standard acidic allyl scavengers in the deprotection of a glucofuranose derivative with 7 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> (25 min/99% yield) (Scheme 34).





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Deprotection of allyl ethers employing 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in conjunction with solid-supported barbituric acid (**37**) in THF at 90 °C/24 h gives the product alcohols in 80–100% yield for a series of aryl and carbohydrate (*sec*-alcohol) systems (Scheme 35).<sup>61</sup> Similar chemoselectivity and functional group compatibility was described (vida supra).



Scheme 35.

Another selective, yet mild set of deallylation conditions with  $Pd(PPh_3)_4$  was presented by Chandrasekhar.<sup>62</sup> In concert with polymethylhydrosiloxane (PMHS; 2 equiv) and zinc (II) chloride (18 mol%), this system is able to deprotect a variety of allyl ethers including aryl, benzylic, acyclic secondary, aliphatic and carbohydrate substrates at rt in yields from 85 to 94% (Scheme 36). Chemoselectivity was demonstrated in the aliphatic series as prenyl, Bn, THP, MOM and TBS protecting groups were not removed from doubly-protected 1,5-pentanediol (85–92%).



#### Scheme 36.

Hara<sup>63</sup> reported the deprotection of *O*-allylphenols with catalytic 10% Pd/C in 10% KOH in MeOH. The reaction time was highly dependant on the aryl ring substituents; electron donating substituents required longer periods (24–96 h) while electron withdrawing groups proceeded faster (9 h). Related protecting groups (methallyl, isoprenyl and 1,1-diemthyl-2-propenyl) were also cleaved in the *p*-nitrophenyl ether series in >95% yield (Scheme 37). Chemoselectivity for the allyl group in the presence of benzyl, methyl and alkyl THP ethers was seen. Compelling evidence that the reaction proceeds via the SET mechanism was presented.

Aliphatic and aryl ethers are readily cleaved in air with novel ( $\pi$ -allyl) palladium complex **38** in aniline.<sup>64</sup> The aryl





#### Scheme 38.

ethers required only 0.1 mol% catalyst and reactions were complete, generally, in less than an hour at 30 °C (Scheme 38) whereas the aliphatic systems needed 2 mol% and 2–8 h for complete reaction at 50 °C. The reagent is compatible with aryl functionalities like CN, CHO, ester, ketone and Br. Hydroxyl protecting groups such as Ac, MOM, acetonide, THP and TBDMS were unreactive towards these conditions. Enhanced selectivity for this complex vs Pd(PPh<sub>3</sub>)<sub>4</sub> was recorded for allyl allyloxybenzoates, whereby the former reagent shows little affinity for the ester and the latter deallylates both sites. Ozawa proposed a mechanism whereby the typical oxidative addition to the C–O bond is not involved.

**3.1.6. Oxidative.** Stoichiometric DDQ (1.2 equiv) removes allyl groups from primary alcohols under mild conditions in DCM in 85–92% yield but is unreactive towards anomeric and secondary alcohols (Scheme 39).<sup>65</sup> Selectivity for the allyl groups of a primary alcohol in presence of a benzyl group was observed but reverse selectivity was seen for a benzyl group in the presence of an anomeric allylic ether. Removal of the hydroquinone by-product can often hinder product isolation with this reagent though.



Scheme 39.

Scheme 40.



The oxidative deprotection of allyl ethers utilizing tetrabutylammonium peroxydisulfate, readily prepared from tetrabutylammonium hydrogensulfate and potassium peroxydisulfate, was reported by Kim.<sup>66</sup> The one-pot procedure with 1 equiv iodine served to hydrolyze the proposed vinyl hemiacetal intermediate to the product alcohol (Scheme 40). Removal of the allyl group from 1°, 2° and 3° ethers was achieved, as was the typical compatibility with other hydroxyl protecting groups. Another report used sodium methoxide instead of I<sub>2</sub> to hydrolyze the reaction intermediates.<sup>67</sup>

**3.1.7. Lewis acids.** Two groups have reported on the application of cerium (III) chloride heptahydrate/sodium iodide to the deprotection of allyl ethers. In one instance the use of refluxing MeCN was advocated (69–98% yield) for a series of aryl and aliphatic systems (Scheme 41).<sup>68</sup>



#### Scheme 41.

In the other report,<sup>69</sup> MeCN gave marginal results but success was achieved in nitromethane, but only for primary and secondary aliphatic moieties (Scheme 42). Use of 1,3-propanethiol as an allyl iodide scavenger improved the reaction efficiency. In both cases, selectivity in the presence of Bn and THP protecting groups was observed.

RO 
$$\frac{\text{CeCl}_3-\text{Nal}}{\text{MeNO}_2 \text{ reflux}}$$
 ROH  
 $R = c-C_6H_{11} (83\%)$   
 $R = n-C_8H_{17} (84\%)$   
 $R = Ph (30\%)$ 

Scheme 42.

**3.1.8. Metal-catalyzed isomerization.** The deallylation of glycosides via isomerization with  $10 \text{ mol}\% [Ph_3P]_3RuCl_2$  in refluxing toluene (4 h) with DIEA, followed by hydrolysis of the enol ether with HgCl\_2–HgO was reported by Roy (Scheme 43).<sup>70</sup> The advantage over other metals is the



availability, lower cost, and better selectivity. Unaffected protecting groups include *O*-isopropylidine, Ac, and Bn. The reaction can be run in one-pot and gave the products in excellent yield (84-96%). The authors note the first generation Grubb's catalyst (**39**) also is effective in this regard, albeit in lower yields.

Meanwhile,  $Cossy^{71}$  found that the second generation Grubbs' catalyst (**40**; 3–8 mol%) is an effective catalyst for this purpose. In a limited number of examples, deprotection of allyl ethers derived from secondary and tertiary alcohols was effected in refluxing DCM (12 h), followed by acidification (75–95% yield) (Scheme 44). A methallyl example also worked whereas an isoprenyl group was unaffected.



#### Scheme 44.

Kitamura<sup>72</sup> screened a variety of ligands in combination with  $[(CpRu(II)(MeCN)_3]PF_6$  at 30 °C in trying to develop an efficient deprotection protocol for allyl ethers. The optimized conditions used quinaldic acid (**41**) (1:1 mole ratio with catalyst) to cleave allyl ethers with turnover numbers (TON) of up to 1000 (0.5–3 h) (Scheme 45). Compatible solvents include MeOH and mixed systems (1:1) with water, MeCN, DMF and THF. The scope of substrates included the allyl ethers of primary, secondary and tertiary alcohols, as well as phenols. Compatibility with neighboring alkenes and alkynes in the aliphatic series was also reported, without signs of isomerization. The allyl group of a multi-functional dipeptide was chemoselectively removed in >99% yield. An improved synthesis of this catalyst was recently reported.<sup>73</sup>



Scheme 45.

**3.1.9. Miscellaneous.** The advent of fluorous chemistry has led to the development of an *O*-allyl removal process whereby initial reaction of the sugar substrates with  $I(CF_2)_6X$  (X=Cl, F) gives the perfluoroalkylated species which is removed with Zn powder in refluxing EtOH to





provide the alcohol in 72–93% yield for the two-step procedure (Scheme 46).<sup>74</sup>

The in situ generation of trimethylsilyl iodide (from TMS-Cl and Nal), a well-known reagent for the demethylation of ethers, has been applied to deallylation as well.<sup>75</sup> Phenolic benzylic and aliphatic ethers were rapidly deprotected using 1.5 equiv of reagent (>90% yields) (Scheme 47). The selective deprotection of an allyl ether in the presence of an aliphatic methyl ether in a sugar substrate was reported.



#### Scheme 47.

A new protecting group for phenols, cyclohex-2-en-1-yl ether, has been described by Depreux.<sup>76</sup> Ether formation is achieved by reacting 3-bromocyclohexene with the phenol and potassium carbonate in acetone at rt/24 h. The deprotection of a collection of protected phenols was accomplished with anhydrous HCl in ether at rt in yields mostly > 85% (Scheme 48). Aryl substituents such as nitro, methyl ester, bromide and acetate were not affected. The selective deprotection in the presence of methyl or allyl ethers was most notable (Scheme 49).



Scheme 48.





# 3.2. Branched allyl ethers (prenyl ethers and others)

The selective cleavage of a prenyl ether in the presence of an allyl or crotyl ethers was performed by Oshima using TiCl<sub>4</sub>/*n*-Bu<sub>4</sub>NI (1.1 and 1.0 equiv, respectively).<sup>77</sup> Aryl prenyl ethers with a directing group in the *o*-position were easily cleaved at -78 °C over 10–60 min (Scheme 50). In the absence of such a neighboring group, no reaction was



#### Scheme 50.

observed; such that an *o*-prenyl ether can be removed in the presence of a *p*-prenyl ether for the related benzaldehyde derivative. Aliphatic  $(1^{\circ} \text{ and } 2^{\circ})$  prenyl ethers are also reactive with this reagent at 0 °C. The author supposes the neighboring atom coordinates the iodo-titanium ate species, thus activating the iodide toward nucleophilic attack of the oxygen-bearing carbon atom of the ether.

Another Lewis acid based system, catalytic zirconium (IV) chloride/sodium iodide, deprenylates both aryl and aliphatic ethers in refluxing MeCN over 1-2 h (Scheme 51).<sup>78</sup> The product alcohols were obtained in 78–92% yield with selectivity demonstrated in the presence of allyl or crotyl ethers in a differentially protected aliphatic diol.

$$\begin{array}{c} \text{RCH}_2\text{CH}_2\text{O} & \overbrace{\text{MeCN reflux}\\ 1-2 \text{ h}} \\ \text{RCH}_2\text{CH}_2\text{OH} \\ \hline \\ \text{R} = \text{BnO (91\%)} \\ \text{R} = \text{Allyl-O(CH}_2)_4 (86\%) \\ \text{R} = \text{Crotyl-O(CH}_2)_4 (79\%) \end{array}$$

# Scheme 51.

The zirconium (IV) chloride/sodium borohydride combination (1, 4 equiv, respectively) also cleaves prenyl ethers at rt (Scheme 52).<sup>79</sup> Yields in the range of 70–96% were obtained selectively for aryl prenyl ethers in the presence of OBn, OMe and prenyl esters.



Scheme 52.

Ytterbium triflate (5 mol%) is another reagent that selectively catalyzes the removal of a prenyl group in the presence of allyl or crotyl ethers under mild conditions (Scheme 53).<sup>80</sup> Yields of 74–90% were observed for aryl ethers with various electronic substituents and one example



Scheme 53.

with a differentially-protected furanose (OBn, OMe) that was selectively deprotected in 80% yield.

*p*-Toluenesulfonic acid (PTSA) efficiently removes prenyl aryl ethers selectively under mild conditions in DCM over 1-4 h (70–98% yield) (Scheme 54).<sup>81</sup> Other hydroxyl protecting groups not affected by these conditions include methyl, benzyl and allyl ethers.



#### Scheme 54.

DDQ (1.2 equiv) can also deprotect prenyl ethers of  $1^{\circ}$ ,  $2^{\circ}$  and  $3^{\circ}$  aliphatic ethers in aq DCM at rt, even selectively in the presence of an allyl protected alcohol (86% yield), as in the case of differentially-protected 1,5-pentane-diol (Scheme 55).<sup>82</sup> Mn(OAc)<sub>3</sub> can be used as a re-oxidant allowing the DDQ equiv to be reduced to 0.1 but leads to prolonged reaction time (18 h vs 90 min). The reaction is thought to proceed via DDQ hydride abstraction from the activated methylene carbon followed by quenching of the resulting carbocation with water and subsequent decomposition of the hemiacetal.



#### Scheme 55.

Similar reactivity was described using iodine (1.5 equiv) in DCM under mild conditions (Scheme 56).<sup>83</sup> Addition of molecular sieves is critical to the success of the reaction in order to trap the HI formed in the reaction to prevent reaction with acid-labile groups, such as isopropylidene. Substoichiometric amounts of iodine (0.4 equiv) can be used but requires a longer reaction period (4.5 h vs 15 min with 1.5 equiv for the menthol example). A side-by-side comparison of these two reagents, as well as mechanistic



insight into the iodine system is provided in a full paper by Vatèle.<sup>84</sup>

Remarkable selectivity in the order methylprenyl>prenyl>methallyl≫ allyl was observed by Vogel using 10 mol% diphenyldisulfone ((PhSO<sub>2</sub>)<sub>2</sub>) in a sealed tube at 80 °C (61–93% yield) (Scheme 57).<sup>85</sup> Such that tripledifferentially protected glucofuranoside **42** can be deprotected step wise in the order given above leaving an allyl protected site unaffected. The authors explain this reactivity order by noting the energy barrier of a direct hydrogen abstraction mechanism, depends on the ionization energy of the alkene. The more highly substituted alkenes have lower energy barriers as it can better stabilize charge-transfer configurations of the transition states.





Similar reactivity has been observed using catalytic amounts of the polysulfone derived from methylidene–cyclopentane and sulphur dioxide.<sup>86</sup>

Hara<sup>63</sup> reported on the deprotection of branched *O*-allylphenols with catalytic 10% Pd/C in 10% KOH in MeOH. Methallyl, isoprenyl and 1,1-dimethyl-2-propenyl groups were cleaved in the *p*-nitrophenyl ether series in >95% yield (Fig. 19).



Figure 19. Conditions: 10% Pd/C, 10% KOH-MeOH, rt 24-30 h.

Bartoli's cerium(III) chloride heptahydrate/sodium iodide reagent more easily removes the branched allyl protecting groups than the parent allyl group itself.<sup>68</sup> Crotyl, cinnamyl and  $\beta$ -methallyl octyl ethers were deprotected in 2–10 h versus 30 h for the allyl octyl ether. The prenyl example





gave a low yield though. A differentially protected monosaccaride was triply de-cinnamylated in the presence of Aloc (Scheme 58), and TBDPS groups in 52–88% yield.

# 4. Benzylic and related ethers

# 4.1. Benzylic ethers

**4.1.1. Lewis acids.** Yamamoto<sup>87</sup> reported a novel debenzylation of aryl ethers such as **43** using catalytic amounts (1-3 mol%) of rare earth metals including scandium(III) triflyl methide Sc(CTf<sub>3</sub>)<sub>3</sub> (Fig. 20). Reactions are run in anisole over 0.5–2.5 h at 100 °C and the product obtained in 87–97% yield. Cleavage of secondary benzyl ethers resulted in poor yields due to competitive dehydroxylation and/or debenzyloxylation, however activated benzyl ether **44** gave a near quantitative yield of the corresponding *sec*-alcohol with several reagents including free triflimide.





Falck et al.<sup>88</sup> devised a novel approach to the selective cleavage of benzyl ethers using a combination of  $CrCl_2$  (3 equiv) and LiI (4 equiv) in wet ethyl acetate at 75 °C.  $CrCl_2$  or LiI alone resulted in little or no cleavage, however a combination of  $CrCl_2/LiBr$  or  $CrCl_2/n$ -Bu<sub>4</sub>NI was quite effective. Functional groups like esters, THP and silyl groups are tolerated. Selective cleavage of a secondary benzyl ether in a glycerol derivative depicted excellent selectivity. An allylic benzyl ether, which was resistant to standard dealkylating conditions, was deprotected in high yield with this method (Fig. 21).



Debenzylation of D-glucuronolactone derivative **45** was accomplished without compromising the anomeric center, acetonide, or lactone functional groups. In a subsequent study, the group expanded the scope of this technology for the regioselective deprotection of polybenzylated carbohydrates.<sup>89</sup> Yields ranged from 79 to 95%. Inositol derivative **46** was selectively cleaved at the C<sub>2</sub> position resulting in 81% yield of the parent alcohol. Three-point coordination between Cr and the carbohydrate is critical for optimal regioselectivity (Fig. 22).



#### Figure 22.

When preparing isoxazole containing natural products, Piancatelli<sup>90</sup> used CrCl<sub>2</sub>/LiI for the selective cleavage of a secondary benzyl ether in the presence of a primary benzyl ether and a free hydroxyl group albeit in lower yield (23%) (Scheme 59).





Benzyl ethers *ortho* to a carbonyl group were selectively deprotected with MgBr<sub>2</sub> in ether–benzene solution.<sup>91</sup> De-*O*-benzylation of various benzene and naphthalene aldehyde derivatives gave yields ranging from 63 to 95% (Scheme 60). A six-membered chelation ring generated via coordination of the carbonyl and the *ortho* ether groups is believed to facilitate the bromide anion mediated debenzylation. The role of Et<sub>2</sub>O as a coordinating solvent is also considered critical. Generally, high yields were reported for benzylic derivatives while moderate yields were obtained for naphthalene derivatives.



#### Scheme 60.

Iodotrimethylsilane (TMSI) mediated bis-debenzylation of **47** provided a selective estrogen receptor modulator (SERM) candidate in our laboratory (Fig. 23).<sup>92</sup> The combination of thiourea and *N*-methylimidazole was effectively used to scavenge the benzyl iodide by-product,



**Figure 23.** Conditions: TMSI (6.9 eq), thiourea (2.5 eq), *N*-methylimidazole (1.3 eq),  $CH_3CN$ , -10 °C to rt, 82%.

which would otherwise result in significant amounts of ring and *N*-benzylated impurities. The reaction ran at -10 °C to rt over 12 h, and the scavengers were completely removed during an aqueous work up. Catalytic hydrogenolysis was not effective due to the presence of sulphur in the benzoxathiin ring, which resulted in catalyst poisoning.

Rajakumar and Murali emphasized the need for dioxane as the solvent in the deprotection of phenolic ethers using  $TiCl_4$ .<sup>93</sup> A nucleophilic cleavage of an intermediate *O*-TiCl\_3 complex by solvent molecules is believed to facilitate the deprotection. Tetrahydrofuran was not feasible as it was cleaved by  $TiCl_4$  resulting in the formation of *p*-chlorobutanol. Use of catalytic TiCl<sub>4</sub> was not effective. The deprotection of a series of benzyl and allyl ethers was described (yields: 78–90%). The synthesis of cresol (**48**) is typical. (Scheme 61).



#### Scheme 61.

**4.1.2. Reductive cleavage.** Clerodane diterpenoids are potential medicinal and insecticidal agents. In the course of preparing an advanced intermediate **49** for the synthesis of clerodanes, a mild and efficient reductive cleavage of benzyl ethers was developed by Liu using lithium naphthalenide (LN) (Fig. 24).<sup>94,95</sup> Hydrogenolysis was incompatible with the disubstituted double bond, while acidic reagents such as ferric chloride gave exclusively cyclic products. Alcohols, C=C bonds, and protecting groups including THP, silyl, and methoxy methyl ethers are compatible with the reaction conditions. For ketone substrates like **50**, prior enolization with LDA was advised before deprotection.



LN (6 eq),THF, LDA (1.5 eq), LN (8 eq) -25 °C, 80 min,94 % 1 h, 82 % An excellent application of this methodology was reported by Xu and co-workers<sup>96</sup> during the total synthesis of a novel tetraterpenoid, methyl isosartortuoate. Near quantitative cleavage of benzyl ether **51** in the presence of a TBS and isopropylidene acetal groups was observed at 0 °C (Scheme 62).



#### Scheme 62.

Early biological studies charge Brefeldin A (BFA) with antifungal, antitumor, antiviral and nematocidal activities. In the total synthesis of BFA and 7-*epi*-BFA, respectively, bis debenzylations of intermediates **52** and **53** were successfully achieved with LN (Fig. 25).<sup>97</sup> Reductive cleavage of **52** using sodium in liquid ammonia was not selective.





The reductive cleavage technique was modified by Yus and co-workers<sup>98</sup> who used catalytic naphthalene (8 mol%) with excess lithium for the cleavage of benzyl ethers, such as **54**, **55** and expanded its use for the cleavage of allyl ethers (Fig. 26). Substrates were added to the reagent at temperatures ranging from -78 °C to rt. In general, benzyl ethers gave better yields. The same protocol was used for the deprotection of *N*-substituted tosylamides, carboxamides and *N*,*N*-disubstituted amides.



Figure 26. Conditions: Li (excess),  $C_{10}H_8$  (8 mol%), THF, -78 to  $-10\ ^\circ\text{C}.$ 

Sinaÿ used triisobutylaluminium (TIBAL) for a regioselective de-*O*-benzylation of monosaccharidic benzylated phenylsulfonylethylidene (PSE) acetals (Fig. 27).<sup>99</sup> The reaction was run at 50 °C in toluene. The presence of two



TIBAL (6 eq) Toluene, 50 °C 2h, 97 %

# Figure 27.

contiguous *cis*-oriented alkoxy groups appears to be crucial for selective mono de-*O*-benzylation. While such substrates give quantitative yield of a mono debenzylated product, substrates with no *cis*-oriented alkoxy groups have resulted in decomposition. In a case where the substituents at positions 1–3 are all *cis* oriented, a mixture of products was obtained, including a ring opening product that resulted from reduction at the anomeric center ( $C_1$ –O bond cleavage).

A mild and novel potassium-induced electron transfer process resulted in selective cleavage of benzyl ethers.<sup>100</sup> The reaction proceeded at rt in 92–99% yield using K–*t*-BuNH<sub>2</sub>/*t*-BuOH/18-crown-6 (Fig. 28). The method is compatible with TBDMS, THP, epoxy ethers and conjugated C=C bonds. The compatibility of TBDMS and THP groups under basic medium makes this method particularly advantageous. The same protocol was used for cleavage of benzylidene acetals giving the corresponding diols in 73–94% yield. The linking of K<sup>+</sup> with 18-crown-6 is believed to promote the electron transfer from K to the substrate, facilitating formation of an alkoxide anion. Proton transfer from *t*-BuOH or *t*-BuNH<sub>2</sub> to the alkoxide is the final step in the proposed mechanism.



Figure 28. Conditions: K (10 eq), t-BuNH<sub>2</sub> (2 eq) t-BuOH (2 eq), 18-crown-6 (0.1 eq).

Pan et al.<sup>101</sup> used the same method for an efficient final step quadruple debenzylation in the total synthesis of a possible cytotoxic and hepatoprotective agent. The final product  $(\pm)$ , maackin (**56**), was obtained in 72% yield (Scheme 63).





 $R = MeOC_{6}H_{4}, 81 \%$   $R = 3-OHC-C_{6}H_{4}, 61\%$ R = CbzNHCHMeCO, 96%

# Scheme 64.

Indium-mediated reductive cleavage of *p*-nitrobenzyl (PNB) ethers was accomplished in aqueous ammonium chloride (Scheme 64).<sup>102</sup> On treatment with indium metal the nitro group was reduced and the ether bond cleaved, liberating the free alcohol along with a *p*-toluidine by-product that was removed during aqueous workup. Other groups like methoxy, Ac, aldehyde, and Cbz groups were unaffected. The same reagent can also be used for deprotection of *p*-nitrobenzyl esters.

A Japanese group<sup>103</sup> demonstrated this indium-based methodology in the total synthesis of anti-inflammatory flavonoids. Selective removal of the PNB ether of a polyprotected intermediate **57** gave a 73% yield of the corresponding alcohol (Fig. 29).



Figure 29. Conditions: ln/NH<sub>4</sub>Cl (aq), MeOH/i-PrOH 85 °C, 73%.

Cleavage of *p*-cyanobenzyl ethers (OBnCN) was observed using triethylgermyl sodium (Et<sub>3</sub>GeNa) in dioxane (Fig. 30).<sup>104</sup> The reagent, prepared from Et<sub>6</sub>Ge and Na in HMPA, was also effective for the cleavage of amines and thiols. An electron-transfer mechanism was proposed. Thus, reduction of *p*-cyanobenzyl ether by Et<sub>3</sub>GeNa generates a radical anion that is cleaved to form an alkoxyl anion, which is then protonated by water to give the desired alcohol.



Figure 30. Conditions: Et<sub>3</sub>GeNa (2.4 eq)/1,4-dioxane/HMPA/50 °C.

A combination of excess lithium and ethylenediamine in oxygen-free THF was effective in deprotecting benzyl and aryl methyl ethers (Fig. 31).<sup>105</sup> Formation of a radical anion via coordination of Li with substrate, diamine and THF is considered crucial for the demethylation reaction. When



# Figure 31.

both *ortho* positions are occupied by an alkyl group, accelerated rates and high yields were recorded. *para*-Allyl and *ortho* halogen groups displayed a retarding effect. Demethylation of aryl ethers with *para* electron-with-drawing substituents resulted in decomposition.

Application of this methodology to geranyl benzyl ether (**58a**) gave geraniol in 92% yield (Fig. 32). Allylic and propargylic ethers are not compatible as the former is isomerized and the later is reduced. The group also developed *m*-xylylmethyl (MXM) as an alternative alcohol protecting group that is cleaved faster under reductive conditions but is immune to hydrogenation conditions using Pd/C at atmospheric pressure.



# Figure 32.

Cossy et al.<sup>106</sup> disclosed the use of Weinreb amides as latent carbonyl protecting groups for a combined nucleophilic addition/Birch reduction process to generate  $\omega$ -hydroxy ketones. Once a stable tetrahedral intermediate was generated by the addition of an organometallic reagent to the Weinreb amide, Birch reduction led to rapid cleavage of Bn, PMB and Tr protecting groups. Generally yields of the hydroxy ketone ranged from 58 to 92%. The transformation of **59** to **60**, is typical (Scheme 65). Alkynes are not reduced at lower temperatures, however, if the reduction step is carried out at higher temperatures for extended period of time, partial and over-reduction of ketones was observed.





Scheme 66.

The group relied on the same technology<sup>107</sup> for the final step in the total synthesis of (+)-(2'S,3'R)-zoapatanol **61**. A 60% yield was reported for the three steps namely: Weinreb amide formation, prenyl group installation and bisdebenzylation (Scheme 66).

**4.1.3.** Acidic reagents. During the synthesis of an azafagomine derivative with glycosidase inhibitory activities, Bols and co-workers<sup>108</sup> selectively debenzylated a primary benzyl ether. The desired transformation was accomplished in neat acetyl bromide. Subsequent *O*-deacylation gave the target precursor **62** in 73% overall yield (Scheme 67).



#### Scheme 67.

Benzyl ethers were cleaved with in situ generated HBr, prepared from a reaction between acetyl bromide and an alcoholic solvent.<sup>109</sup> *Tris*-debenzylation of **63** gave ester **64**, in 80% yield (Scheme 68). Deprotection of *N*-*t*-Boc, *N*-Cbz and *N*-Ac groups was also effective under these conditions.





Sterically hindered benzyl ethers that resisted hydrogenolysis with a variety of catalysts including Pd/C and Pd(OH)<sub>2</sub>, were readily removed by reaction with *N*-bromosuccinimide and light in the presence of aqueous



Figure 33. Conditions: NBS (2.5 eq),  $CaCO_3$  (4 eq) white light (375 W),  $CCl_4:H_2O$  (2:1).

calcium carbonate (Fig. 33).<sup>110</sup> This mild in situ HBr generating tactic was used for the debenzylation of several galactopyranoside derivatives in 72–95% yield. The reaction conditions are compatible with the presence of glycosyl, thiophenyl, phthalimide, fluoride, and ester groups.

Aqueous HBr in the presence of tetrabutylammonium bromide cleaves benzyl ethers<sup>111</sup> in 53–87% yield. The highest yield was reported for deprotection of 4-benzyloxy-3,5-dimethylbenzoic acid (**65**) (Fig. 34), however 4-benzyloxybenzoate subjected to the same reaction conditions resulted in no debenzylation.



#### Figure 34.

Cleavage of diphenylmethyl ethers was accomplished in refluxing benzene in the presence of excess benzoic acid and catalytic amounts of TsOH, the intermediate ester was then hydrolyzed to the alcohol (Scheme 69). The process was carried out with removal of water via a Dean–Stark trap.<sup>112</sup>

Ph<sub>2</sub>CH-OR 
$$\xrightarrow{\text{cat. TsOH}}$$
 PhCO<sub>2</sub>R + H<sub>2</sub>O  
aq base ROH R = (CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>  
89%

#### Scheme 69.

**4.1.4. Hydrogenolysis.** Titanium loaded hexagonal mesporous silica (Ti-HMS) accelerates the deprotection of benzyl ethers in the presence of acid sensitive functional groups



(Fig. 35).<sup>113</sup> The reaction was run in the presence of 10 mol% of Ti-HMS using 5% Pd/C at 1 atm of H<sub>2</sub>. TBDMS, THP and acetal groups are tolerated. Among other strongly acidic cation-exchange resins screened Amberlite IR-120B demonstrated a similar selectivity for benzyl ether **66**.

Raney-Ni demonstrated improved catalytic activity in a multiphase system (aqueous KOH–isocotane-Aliquat<sup>®</sup> 336) (Fig. 36).<sup>114</sup> The modifier, Aliquat<sup>®</sup> 336, is believed to promote catalytic activity and chemoselectivity by coating the catalyst particles. This process does not discriminate aldehydes and carbon–carbon double bonds. A chemoselective debenzylation of Boc-*O*-benzylserine (**67**) resulted in the recovery of quantitative amount of Boc-serine.



Figure 36. Conditions: Aliquat 336 (0.35 equiv), Raney Ni (5%) isooctane, KOH (2%aq.), H<sub>2</sub>, 50 °C.

A one-pot deprotection of benzyl and PMB ethers with excess chlorosulfonyl isocyanate (CSI)/Na<sub>2</sub>CO<sub>3</sub> followed by treatment with NaOH/MeOH was reported (Fig. 37).<sup>115</sup> In the case of PMB ethers, reaction with CSI was done at -78 °C in DCM while Bn ethers required refluxing conditions. CSI is believed to activate the ether bond via formation of the corresponding *N*-chlorosulfonyl-*N*-benzyl-carbamoyl derivative, which is easily hydrolyzed at rt using NaOH. Generally good yields were obtained, however lower yields were indicated for benzophenone and benzonaphthol, 33 and 16%, respectively. Selective deprotection of Bn ethers was achieved in the presence of allylic groups, an unprotected alcohol, cyclic/TBDPS ethers, and esters.

OBn



CSI (reflux), NaOH (rt) 84%

CSI (-78 °C), NaOH (rt) 86%

Figure 37.



Scheme 70.

# 4.2. PMB ethers

**4.2.1. Lewis acids.** Falck et al.<sup>116</sup> employed the  $CrCl_2/LiI$  methodology to PMB ethers as seen in the final step in the asymmetric synthesis of a marine eicosanoid, constanolactone **68** (Scheme 70).

Sharma<sup>117</sup> has recently reported a fast and mild process for the cleavage of PMB ethers using catalytic amount of ZrCl<sub>4</sub> in MeCN (Scheme 71) in 72–92% yield within 30–90 min. PMB ethers were cleaved in the presence of acid sensitive Boc, isopropylidene, glycosidic groups THP/MEM ethers, and base sensitive Ac, Bz groups. Substrates with *O*-allyl and *O*-prenyl ethers were cleaved efficiently. Trityl ethers are not immune to this reagent, as a substrate with both trityl and PMB ethers underwent double deprotection resulting in 76% yield of a diol. In a comparative study, the group demonstrated that ZrCl<sub>4</sub> was superior to other Lewis acids like AlCl<sub>3</sub>, BiCl<sub>3</sub>, TiCl<sub>4</sub> and FeCl<sub>3</sub>.



# Scheme 71.

A combination of  $CeCl_3 \cdot 7H_2O$  and NaI in refluxing acetonitrile selectively cleaves PMB ethers to the corresponding alcohols (Fig. 38).<sup>118</sup> Solvents known to strongly coordinate with cerium, including DMF and ethyl acetate, were avoided. PMB ethers are cleaved in the presence of esters and protecting groups like THP, Ac, benzyl and methoxy groups, however the method is not selective towards TBDMS ethers. Lower chemical yields were reported when using catalytic amounts of reagent. An additional electron donating group on the ring accelerates the rate of cleavage as seen in the deprotection of 2,4dimethoxybenzyl ether **69**. A reverse effect was observed with electron withdrawing substituents.



#### Figure 38.

Complexation of a strong Lewis acid,  $SnCl_4$ , with polyhydroxylated carbohydrates resulted in unusual regioselectivity and partial deprotection of PMB ethers. (Fig. 39).<sup>119</sup> Preferential mono or bis cleavage of PMB ethers was achieved with careful control of reaction conditions (amount of  $SnCl_4$  and temperature). The formation of a tri-oxo tin complex involving the 6-O-PMB



#### Figure 39.

is proposed to account for the mono-selectivity. The reaction conditions are compatible with benzyl, TMS, and methoxy protecting groups, also, a substrate bearing an extremely acid sensitive isopropylidene acetal gave a high yield (90%) of the corresponding alcohol.

Bouzide et al.<sup>120</sup> described the combination of catalytic AlCl<sub>3</sub> or SnCl<sub>2</sub>·2H<sub>2</sub>O with EtSH as an efficient and selective deprotecting agent for PMB ethers (Fig. 40). The mild reaction conditions tolerate functional groups like methoxy, TBDPS, benzyl, acetyl and *p*-nitrobenzoyl esters. Deprotection of PMB protected *p*-cresol, using AlCl<sub>3</sub> resulted in a mixture of *p*-cresol (32%) and *o*-alkylated by-product (62%), however *o*-alkylation was significantly reduced (12%) when using SnCl<sub>2</sub>·2H<sub>2</sub>O. *o*-Substituted aryl PMB ethers, and those with electron withdrawing groups generally afford high yield of the corresponding alcohols. In a subsequent report, the group has expanded the application of this protocol to the regioselective cleavage of PMB ethers of furanose derivatives.<sup>121</sup>







Mannitol derivatives are known to have HIV protease inhibitory activities. A Pharmacor group<sup>122</sup> recently utilized a similar tactic in the preparation of one of these derivatives (**70**) in 85% yield (Scheme 72).

**4.2.2. Oxidative cleavage.** The use of stoichiometric DDQ for the oxidative cleavage of PMB and related ethers remains a popular protocol.<sup>123</sup> However, two distinct drawbacks remain: its cost and the difficulty of removing the HDDQ by-product. Chandrasekhar and Yadav devised a novel DDQ regeneration technique via oxidative recycling using excess ferric chloride (Fig. 41).<sup>124</sup> The reaction is run in aq DCM using 10 mol% DDQ and 3 equiv FeCl<sub>3</sub>.



Figure 41. Conditions: DDQ (10 mol%), FeCl<sub>3</sub> (3 eq), CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O (10:1).

The same strategy was later employed by the group for the cleavage of a PMB ether in the asymmetric synthesis of an anti-convulsive drug, (S)-vigabatrin (Scheme 73).<sup>125</sup>



#### Scheme 73.

Researchers from the same laboratory have also reported using  $Mn(OAc)_3$  for the recycling of DDQ.<sup>126</sup> Presumably, the quinone is regenerated by an electron-transfer mechanism which results in a simultaneous reduction of Mn(III) to Mn(II). Acid sensitive groups like TBS and THP are tolerated; base sensitive benzoyl groups are also compatible with this reagent system. A homoallylic PMB ether and a PMB sugar ether gave good yields, while a propargylic ether gave moderate yield (61%) (Fig. 42). The reaction was run (10–24 h) in DCM using 10 mol% of DDQ and 3 equiv  $Mn(OAc)_3$ .





**4.2.3. Reductive cleavage.** During the synthesis of *O*-vinyl ether phospholipid plasmalogen, Bittman et al.<sup>127</sup> were unable to use DDQ and CAN as the oxidative removal of PMB resulted in destruction of the core structure. However, a Birch reduction was successfully applied and the final product **71** isolated in 95% yield (Scheme 74). Interestingly, the use of Li was not suitable as it isomerized the double bond.



#### Scheme 74.

In the asymmetric synthesis of Curacin A, a novel antimitotic agent, Onoda et al.<sup>128</sup> encountered product decomposition during oxidative cleavage with DDQ to remove a PMB group from advanced intermediate **72**. Alternatively, the combination of MgBr<sub>2</sub>·OEt<sub>2</sub> and Me<sub>2</sub>S was effective, however five repeated reactions were required to isolate 76% of **73** (Scheme 75). Deprotection of aliphatic PMB ethers, proceeded in modest to good yields (35–90%) and PMB ethers were selectively cleaved in the presence of benzyl, TBDMS ethers, and acetonides. Cleavage of MOM and BOM ethers was not successful.



Scheme 75.

Unexpected PMB ether cleavage during a glycosylation lead Hinklin and co-workers to discover the use of primary and secondary sulfonamides with catalytic amounts of TfOH or silver triflate as effective deprotecting agents for PMB ethers (Fig. 43).<sup>129</sup> The group has further developed the use of sulfonamide-functionalized resins (safety-catch resin) for solid phase organic synthesis, using dioxane as a solvent. Competitive sulfonimine formation which results in lower yields for some substrates was avoided by using secondary sulfonamides.



Figure 43. Conditions: 0.55 eq TsNH<sub>2</sub>, 0.1 eq TfOH, Et<sub>2</sub>O.

A mixture of sodium cyanoborohydride and boron trifluoride etherate in refluxing THF cleaved PMB ethers.<sup>130</sup> The reaction is rather efficient and clean with aliphatic PMB ethers. *p*-Nitrophenol was deprotected with only  $BF_3 \cdot OEt_2$ , as competing reduction of the nitro group results in the presence of NaCNBH<sub>3</sub>. Deprotection of cinnamate **74**, gave the corresponding phenol in 77% yield without affecting the cinnamate moiety (Scheme 76). While a carbonyl group is deoxygenated with this procedure, double bonds and ester groups are tolerated. Amine and amide functional groups





have an inhibitory effect due to possible complex formation with  $\mathrm{BF}_3$ .

# 4.3. Removal of new protecting groups

Sharma and Rakesh<sup>131</sup> developed the *p*-phenyl benzyl (PPB) group as a new protecting group for alcohols. Protection is done under acidic conditions by reacting the parent alcohol with *p*-phenylbenzyl trichloroacetamidate in the presence of TfOH or under basic conditions by reacting the alcohol with PPBBr in the presence of NaH. Unlike the PMB group, the PPB group is compatible under acidic conditions, and its deprotection accomplished under known oxidative cleavage techniques (DDQ/Mn(OAc)<sub>3</sub>). Selective cleavage was obtained in the presence of benzyl and diphenylmethyl groups (Fig. 44).



Figure 44. Conditions: DDQ (10 mol%), Mn(OAc)<sub>3</sub> (3 eq).

Continuing to develop new masking/unmasking techniques for alcohols, Sharma<sup>132</sup> recently reported two acid-tolerant protecting groups; namely *p*-phenyldiphenyl methanol (PDPM) and *p*-phenylphenyl diphenylmethanol (PPDPM). The alcohols were protected by reacting the substrates with PPDM-OH and PPDPM-OH in the presence of catalytic amount of Yb(OTf)<sub>3</sub> in DCM at rt. The *p*-phenyl group facilitated the cleavage under oxidative conditions and enhanced the rate of acid catalyzed hydrolysis. Eight examples were given for installation and removal of these protecting groups along with *p*-methoxydiphenyl methanol (MDPM). Generally MDPM and PDPM groups were cleaved with DDQ and PPDPM ethers were cleaved with catalytic TFA (10 mol%) (Fig. 45).



Figure 45.

*p*-Halobenzyl ethers (PBB = *p*-bromobenzyl; PCB = *p*-chlorobenzyl) were successfully used as protecting groups by Buchwald.<sup>133</sup> These ethers are then converted to labile arylamines via Pd-catalyzed amination. Rapid deprotection of the amine benzyl ethers was observed with Lewis acids (TiCl<sub>4</sub>, SnCl<sub>4</sub>). Alternatively, dichloroacetic acid (DCA), cerium (IV) ammonium nitrate and ZnCl<sub>2</sub> can be used. Selective cleavage was achieved in the presence of silyl ethers (TIPS), PMB groups and glycal double bonds (Fig. 46).



#### Figure 46.

The PMB-like protecting group *p*-(methoxybenzyloxy)methyl (PMBOM), devised by Trost et al.<sup>134</sup> was critical in the total synthesis of Corianin, a possible therapeutic agent for schizophrenia. The best diastereoselecivity was obtained using this protecting group during the addition of lithiated acetonitrile in the preparation of an early intermediate, presumably due to the ability of Li to coordinate with the  $\pi$ -cloud of the aromatic ring. The PMBOM group is installed in almost quantitative yield by reacting the alcohol with PMBOM-Cl in the presence of DIEA at rt. Selective cleavage of this protecting group was accomplished at the latter stage of the synthesis using DDQ (Scheme 77).





Burke and co-workers<sup>135</sup> chose the PMB (*p*-methoxybenzyl) and *m*-methoxybenzyl (MMB) groups to protect two –OH groups during the synthesis of (+)-breynolide (Fig. 47),



Figure 47. Conditions: DDQ, DCM:H<sub>2</sub>O (10:1), rt.

a compound that displayed oral hypocholesterolemic activity in rats. While PMB was oxidatively removed at an intermediate stage using DDQ at rt with in 20 min, MMB survived acidic conditions that were required for the spiroketalization step that was used to set the correct stereochemical configuration of the final product. The MMB ether was cleaved using DDQ over 48 h, before the TBDPS ether and two acetate moieties were hydrolyzed.

Spencer and co-workers<sup>136</sup> developed 2-naphthylmethyl (NAP) as a protecting group for alcohols. NAP is more labile to catalytic hydrogenolysis than the benzyl group and selective removal could be achieved in the presence of Bn, free hydroxyl, ketone and MeO groups, giving 86–96% yields (Fig. 48).



Figure 48. Conditions: H<sub>2</sub>, Pd/C, EtOH, rt.

In a subsequent study,<sup>137</sup> the group explored the sequential removal of PMB and NAP protecting groups by oxidative cleavage. Their study showed CAN was superior to DDQ in the selective removal of PMB, and DDQ is more efficient for the cleavage of NAP in the presence of benzyl protecting groups. The first total synthesis of GlyCAM-1 oligosaccharide structures by Matta et al.<sup>55b</sup> was credited to the stability of NAP under acidic as well as basic conditions.

Ciguatoxin CTX3C (**75**) is one of the principal agents for seafood poisoning, and its total synthesis depended on liberating three hydroxyl group in the final step. Reductive cleavage of the Bn ethers was complicated due to the allylic ether in ring A, and use of DDQ resulted in decomposition. Hirama and his co-workers<sup>138</sup> were able to improve the total synthesis using a more acid-stable NAP protecting group, which survived acidic reaction conditions. DDQ assisted *tris*-deprotection of NAP at the final stage resulted in a 63% yield of **75** (Scheme 78).



#### Scheme 78.

#### 4.4. Trityl ethers

**4.4.1. Lewis acids.** Sabitha et al.<sup>139</sup> demonstrated that bismuth chloride is an efficient catalyst for the rapid cleavage of trityl ethers. The detritylation proceeded within minutes in the presence of a variety of acid and base sensitive functional groups as well as carbohydrates, terpenes and amino acids (Fig. 49).



Figure 49. Conditions: BiCl<sub>3</sub>, (5 mol%), MeCN, rt, 10 min.

The novel catalytic detritylation with ceric triflate Ce(OTf)<sub>4</sub> (Fig. 50) at rt was reported.<sup>140</sup> The reaction, run in wet acetonitrile under mild conditions, cleaved Tr and DMT protecting groups in 82–95% yield. Generally, the rate of cleavage was faster for DMT groups as cleavage of DMT-protected anisyl alcohol was instantaneous giving the parent alcohol in 95% yield. Primary and secondary aliphatic, benzylic, trityl and DMT ethers were easily converted to their corresponding alcohols. An effective detritylation of nucleosides was demonstrated in the transformation of **76** to the parent alcohol.



#### Figure 50.

Another group<sup>141</sup> used BCl<sub>3</sub> in DCM at -30 °C for the selective removal of primary and secondary trityl ethers in the presence of TBDMS, TBDPS, TES, Bn, PMB, and Pv groups. Removal of trityl-protected 5-hydroxypentanal resulted in an in situ cyclization, giving a lactol. Cleavage was complete within 15 min resulting in 80–99% yield of the corresponding alcohols (Fig. 51). Commercially



Figure 51. Conditions: 1. BCl<sub>3</sub> (0.6 eq), CH<sub>2</sub>Cl<sub>2</sub>, 30 min. 2. MeOH.

available solutions of  $BCl_3$  in DCM, hexanes, heptanes and xylenes were equally effective.  $BF_3 \cdot OEt_2$  was less effective, and  $BBr_3$  resulted in rapid deprotection and loss of selectivity.

Catalytic indium tribromide in aq MeCN was used for a chemoselective cleavage of trityl ethers by Yadav and coworkers.<sup>142</sup> Trityl ethers were deprotected in high yields (80–95%) (Fig. 52). The reaction can also be carried out in water at 60 °C in the presence of 5 mol% InCl<sub>3</sub> or InBr<sub>3</sub>. Olefins, esters, acetonides, acetates, benzoates, *t*-Boc, Cbz groups and Bn, Me, PMB and TBDPS ethers are not affected. The process is environmentally benign as the catalyst could be recovered during workup and recycled.



Figure 52. Conditions: lnBr<sub>3</sub> (5 mol%), heat, MeCN, 2-3 h.

Trityl protecting groups were selectively removed in the presence of TBDMS and TIPS, using MgBr<sub>2</sub> in refluxing benzene (Scheme 79).<sup>143</sup> Diminished activity of the reagent was observed in the presence of coordinating solvents like Et<sub>2</sub>O. The same conditions work for removal of isopropyl-idene protecting groups.



#### Scheme 79.

**4.4.2.** Acidic reagents. A facile cleavage of Tr and DMT ethers using catalytic  $CBr_4$  in refluxing MeOH gave 85–93% yields of products (Fig. 53).<sup>144</sup> The more acid sensitive DMT group is cleaved more rapidly and at lower temperatures than the Tr ether. Other protecting groups like Bn, Me, Ac, Ts, allyl, phenyl, propargyl, PMB and TBDPS are not cleaved. Acid sensitive protecting groups such as Boc and Cbz are also unaffected. The deprotection is attributed to an in situ generation of HBr from  $CBr_4$  and MeOH.



Figure 53. Conditions: CBr<sub>4</sub> (10 mol%), MeOH/reflux, 1.5-3.5 h.

Chen and co-workers<sup>145</sup> further improved this protocol whereby the in situ generation of HBr is achieved under mild conditions using photo-irradiation. They have provided several examples of the chemoselective deprotection of Tr-protected saccharides in high yield (86–95%).

The combination of  $I_2$  in alcoholic solvents was effectively used for deprotection of Tr and DMT ethers (Fig. 54).<sup>146</sup> Traces of in situ generated HI are believed to be the reactive species.



# Figure 54.

Keith<sup>147</sup> recently used the same tactic for selective *o*-cleavage of PMB and MOM ethers. Three examples of PMB ethers were cited in moderate yields (50-71%) (Fig. 55). Higher yields were obtained for cleavage of MOM ethers (36-99%).



#### Figure 55.

The deprotection of primary DMT ethers was accomplished using ultrasound in MeOH–CCl<sub>4</sub> (1:1) at ambient temperatures.<sup>148</sup> This technique was used for the cleavage of DMT ethers in the presence of C=C bonds, esters, TBDMS, and Ac, groups. Nine examples were provided with yields ranging from 69 to 100%. Dinucleotide **77** gave quantitative yield of alcohol **78** (Scheme 80).





 $Das^{149}$  developed economical, silica-supported sodium hydrogen sulfate (NaHSO<sub>4</sub>–SiO<sub>2</sub>) as a novel heterogeneous catalyst for deprotection of Tr ethers. Excellent yields (90– 100%) were obtained within 3 h (Fig. 56). Other protecting groups including Bn, MOM, MEM, Allyl, Ac, Bz and Ts were not removed. Tr-protected amines are cleaved. The reaction was run in DCM–MeOH (9:1) using a catalytic amount of reagent (exact amount not specified).



Figure 56. Conditions: NaHSO<sub>4</sub>-SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH (9:1), rt/2.5 h.

A low-valent titanium (LVT) reagent was developed as a single electron reductant for detritylation.<sup>150</sup> The reaction gave 15–92% yields of free alcohols. The rate of cleavage of protected phenols with LVT reagents is in the order *O*-allyl>*O*-trityl>*O*-benzyl. The technique is also applicable for the cleavage of *N*-trityl bond in trityl amines.

# 5. Cyclic ethers

The ring-opening reactions of cyclic ethers differs dramatically from the dealkylation of alkyl ethers. Whereas the former is mainly intended to further functionalize the substrate, the latter is primarily utilized to deprotect an alcohol. The emerging trend in cleavage of cyclic ethers is the asymmetric ring opening of epoxides. This topic has just recently been reviewed (>100 references).<sup>151</sup> Accordingly, only a few examples will be covered herein, representing the 'best in class' for a particular transformation.

#### 5.1. Acylative cleavage

Bromoacetyl bromide can readily cleave THF to give the dibromo ester in high yield (Scheme 81).<sup>152</sup>



#### Scheme 81.

Ionic liquids have been applied to the cleavage of cyclic ethers as well. The combination of 1-ethyl-3-methylimidazolium heptachlorodialuminate [emim] [Al<sub>2</sub>Cl<sub>7</sub>] with benzoyl chloride generates the iodobenzoate adducts in variable yields depending on the mole fraction of AlCl<sub>3</sub> used and the substrate (Scheme 82).<sup>153</sup>



R = OBn (91%)

R = Ph (91%)

The regioselective acylative cleavage of monosubstituted epoxides, most notably, with samarium iodide in the presence of acetyl chloride was described by Kim (Scheme 83).<sup>154</sup> The corresponding iodo-esters derived from attack of the iodide at the less substituted carbon atom of the ring were obtained in excellent yield under mild conditions.

The acylative cleavage of epoxides and THF with organomercury compounds (**79**, **80**) in the presence of aluminum and an acid chloride provides the corresponding chloroesters in good-excellent yields (Scheme 84).<sup>155</sup>



Scheme 84.

# 5.2. Synthesis of halohydrins

A recent development in the synthesis of chlorohydrins is the first use of an ionic liquid in this regard. A series of terminal and bicyclic epoxides were converted into the chlorohydrin with high stereo- and regioselectivity with catalytic amounts of  $\text{bmimPF}_6$  with TMS-Cl (Scheme 85).<sup>156</sup>



#### Scheme 85.

The chemoselectivity of triphenylphosphonium bromide over HBr for the ring opening of epoxides in the presence of acid-sensitive functionalities has been reported (Scheme



Scheme 86.

86).<sup>157</sup> The corresponding bromohydrins were synthesized in high yield in the presence of an ethylene ketal, benzyloxymethoxy ether and a trimethylsilyl ether functionality via competition experiments.

Denmark reported the first enantioselective ring opening of *meso* epoxides to prepare enantio-enriched chlorohydrins using SiCl<sub>4</sub> and catalytic HMPA. The reaction is promoted with catalytic phosphoramide **81** (Scheme 87). Selectivity was highly substrate dependent, as the acyclic substrates gave better results than the cyclic ones.



#### Scheme 87.

# 5.3. Synthesis of functionalized sec-alcohols

The discovery of catalysts for the asymmetric ring-opening of epoxides via hydrolytic kinetic resolution (HKR) is an emerging trend in the synthesis of the highly-valued enantiopure alcohols. Jacobsen's chiral salen Co(III) complexes are able to generate these products in high ee and yield via the HKR protocol. The reaction of phenols with mono-substituted epoxides provide the corresponding  $\alpha$ -aryloxy alcohol,<sup>158</sup> whereas with water as the nucleophile, chiral 1,2-diols are generated. Cyclic oligomeric analogues of the first-generation catalyst provide enhanced reactivity and stereoselectivity.<sup>159</sup> Some of the phenol– epoxide combinations that were unreactive towards the



monomeric catalyst gave impressive results with the oligomer.

The synthesis of  $\beta$ -amino alcohols by means of a vanadium (III)chloride-catalyzed epoxide ring opening, in the presence of an aromatic amine under mild conditions (Scheme 88).<sup>160</sup>

The epoxide ring opening catalyzed with 1 mol% copper(II) tetrafluoroborate with various alcohols gives the corresponding hydroxy ethers in excellent yield under mild conditions (Scheme 89).<sup>161</sup>



#### Scheme 89.

The reductive cleavage of benzannulated ethers with alkali metals, followed by treatment with electrophiles gave the unsymmetrical disubstituted biaryls or naphthalenes in moderate–high yield (Scheme 90).<sup>162</sup>



Scheme 90.

En route to *cis*-1,2-disubstituted cyclobutanes, Ghosh implemented a novel ring opening of ether **82** under Wolff–Kishner conditions (Scheme 91).<sup>163</sup>



#### Scheme 91.

The reaction of epoxy alcohol **83** with diethylaminosulfur trifluoride (DAST) gave exclusive formation of fluorinated vinyl ether **84** (Scheme 92).<sup>164</sup> This methodology was applied to the synthesis of fluorinated cyclic vinyl ethers via ring expansion of *syn* bicyclic epoxy alcohols (Scheme 93), the *anti* isomers led to mixtures of products.<sup>165</sup>



pentane, rt

88%

Scheme 93.

The inversion of configuration of sterically hindered epoxides has been accomplished by Prieto.<sup>166</sup> A two-step procedure via cleavage of the epoxide with cesium propionate followed by activation of the resulting regioisomeric hydroxy-esters as the mesylate and ring closure with potassium carbonate (Scheme 94).



Scheme 94.

A series of epoxides were cleaved with  $5 \mod 8 \operatorname{B}(C_6F_5)_3$  with propargyl and allyl alcohol to give the corresponding hydroxy ethers in yields from 78 to 95% yield (Scheme 95).<sup>167</sup> Neighboring silyl and benzyl ethers were unaffected.



#### Scheme 95.

Trimethyl aluminum catalyzes the addition of alkynyl lithium reagents to alkoxy-substituted epoxides to give the hydroxy alkynes. The catalyst efficiency was directly related to the proximity of the alkoxy group to the epoxide as evidenced by the regioselectivity observed in bis epoxide **85**. The reaction is proposed to proceed via a pentacoordinate organoaluminum complex (Scheme 96).<sup>168</sup>



A catalytic version of the titanium-mediated epoxide ring opening reaction was developed by Gansäuer using a stoichiometric reductant (manganese) to regenerate the catalyst in the presence of collidine.<sup>169</sup> The protocol can tolerate functionalities, such as chlorides, ketones and benzyl ethers that are usually reactive towards typical electron transfer reagents (Scheme 97).



Scheme 97.

By modifying the titanium catalyst with (-)-menthol (**86**), this same group applied this methodology to generate *sec*-alcohols from 80 to 91% ee (Scheme 98).<sup>170</sup>





An unprecedented nickel-catalyzed reductive coupling of alkynes with alkyl-substituted epoxides provides the corresponding enol ethers with high regioselectivity (>95:5) for both the epoxide and the alkyne (Scheme 99).<sup>171</sup> Notable is the unexpected *endo* epoxide-opening product.



Scheme 99.

Intramolecular examples are also described.

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# **Biographical sketch**



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