

# Lithium Perchlorate<sup>1</sup>



[7791-03-9]  $\text{ClLiO}_4$  (MW 106.39)  
 InChI = 1/ClHO4.Li/c2-1(3,4)5;/h(H,2,3,4,5);/q;+1/p-1/fClO4.  
 Li/q-1;m  
 InChIKey = MHC FAGZ WMAW TNR-QJPVJGQWCT

(mild Lewis acid<sup>1</sup> for cycloaddition reactions,<sup>2</sup> conjugate additions,<sup>3</sup> ring opening of epoxides,<sup>4</sup> and ring expansion of cyclopropanes<sup>5</sup>)

**Physical Data:** mp 236 °C; bp 430 °C (dec);  $d$  2.428 g cm<sup>-3</sup>.  
**Solubility:** 60 g/100 mL H<sub>2</sub>O (25 °C); 150 g/100 mL H<sub>2</sub>O (89 °C); 152 g/100 mL EtOH (25 °C); 137 g/100 mL acetone (25 °C); 182 g/100 mL MeOH (25 °C); 114 g/100 mL ether.

**Form Supplied in:** white solid; widely available in anhydrous form or as the trihydrate; it is usually used in solution in ether or MeOH.

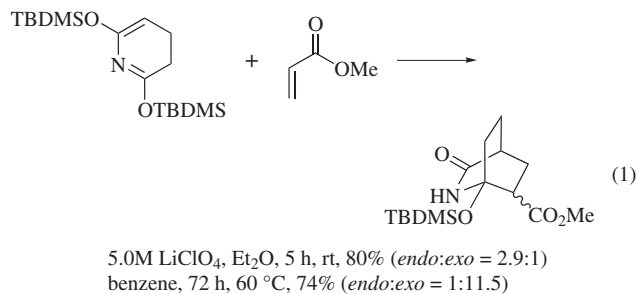
**Purification:** anhydrous lithium perchlorate is prepared by heating the commercially available anhydrous material or its trihydrate at 160 °C for 48 h under high vacuum (P<sub>2</sub>O<sub>5</sub> trap).

**Handling, Storage, and Precautions:** the anhydrous material should be used as prepared for best results. The decomposition of lithium perchlorate starts at about 400 °C and becomes rapid at 430 °C, yielding lithium chloride and oxygen. Perchlorates are potentially explosive and should be handled with caution.

## Original Commentary

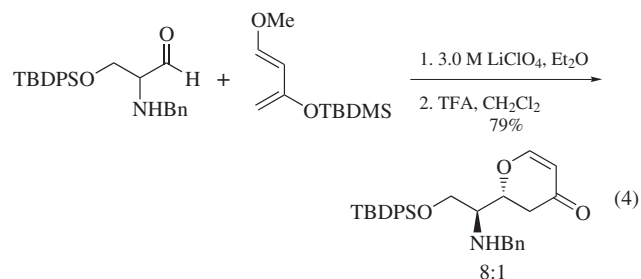
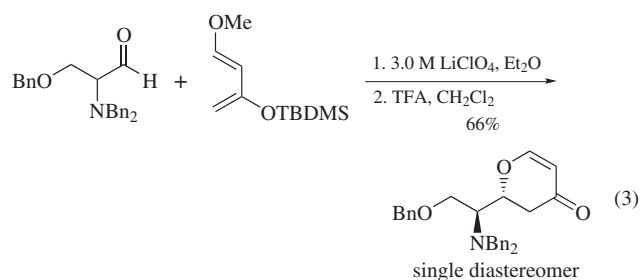
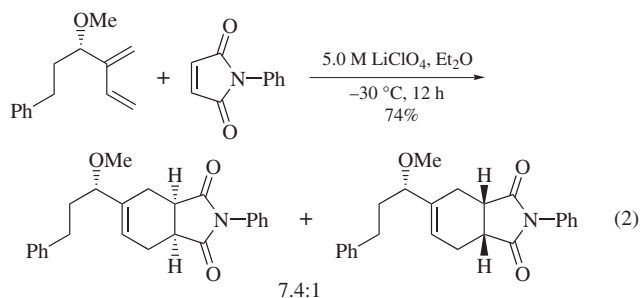
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**Lewis Acid Catalyst for Cycloaddition Reactions and Carbonyl Addition Reactions.** This reagent, usually prepared as a 5.0 M solution in diethyl ether, produces a dramatic rate acceleration of Diels–Alder reactions (eq 1). Evidence shows that this rate acceleration, which was initially thought to be a result of high internal solvent pressure, is due to the Lewis acid character of the lithium ion.<sup>6</sup>



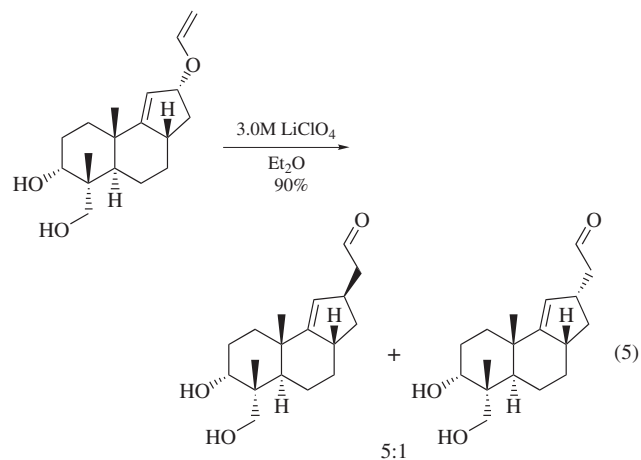
Under these conditions, reasonable levels of diastereoselectivity have been observed in the reaction between a chiral diene and *N*-Phenylmaleimide (eq 2).<sup>7</sup> An interesting protecting group dependence of diastereoselectivities has also been observed in the hetero-Diels–Alder reaction of *N*-protected  $\alpha$ -amino aldehydes

with 1-methoxy-3-*t*-butyldimethylsilyloxybutadiene to produce dihydropyrones (eqs 3 and 4).<sup>8</sup>

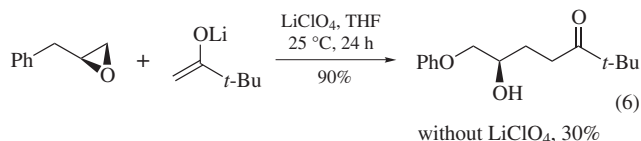


*O*-Silylated ketene acetals undergo 1,4-conjugate addition to hindered  $\alpha,\beta$ -unsaturated carbonyl systems<sup>3</sup> and quinones<sup>9</sup> in the presence of LiClO<sub>4</sub>.

**[1,3]-Sigmatropic Rearrangements.** In contrast to the [3,3]-sigmatropic rearrangement observed under thermal conditions, allyl vinyl ethers undergo [1,3]-sigmatropic rearrangements at rt when submitted to 1.5–3.0 M LiClO<sub>4</sub> in Et<sub>2</sub>O (eq 5).<sup>10</sup>



**Epoxide Opening.**  $\text{LiClO}_4$  is an efficient promoter for the regioselective nucleophilic opening of oxiranes with amines,<sup>11</sup> cyanide,<sup>12</sup> azide,<sup>13</sup> thiols,<sup>14</sup> halides,<sup>15</sup> and lithium acetylides.<sup>16</sup> The regioselective opening of oxiranes with lithium enolates derived from ketones has also been observed in the presence of  $\text{LiClO}_4$  (eq 6).<sup>17</sup>



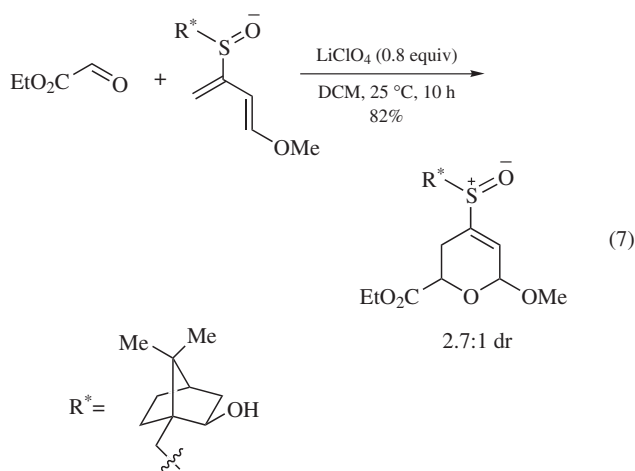
**Ring Expansion.** The condensation of aldehydes and ketones with diphenylsulfonium cyclopropylide produces oxaspiropentanes which undergo ring expansion to produce cyclobutanones upon treatment with lithium perchlorate.<sup>18</sup>

## First Update

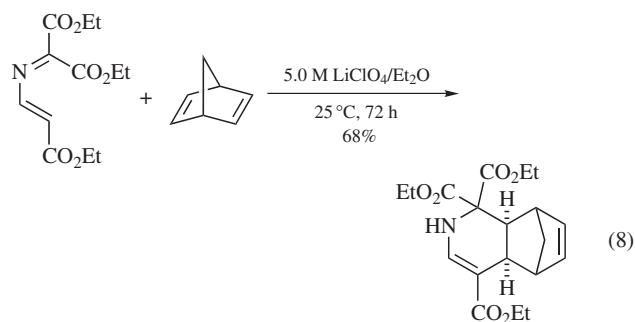
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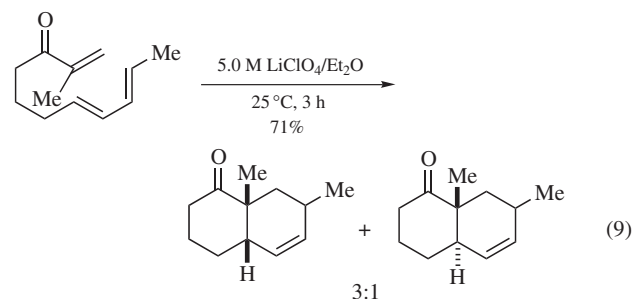
**Diels–Alder.** Lithium perchlorate accelerates various Diels–Alder reactions. In the first report of a hetero-Diels–Alder reaction of an enantiopure 2-sulfinylbuta-1,3-diene, it was found that addition of lithium perchlorate led to a significant decrease in reaction time and also a moderate increase in diastereoselectivity (eq 7).<sup>19</sup>



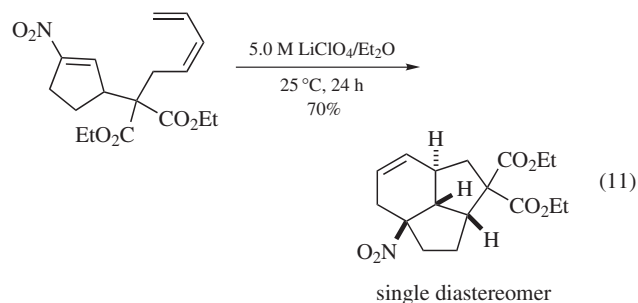
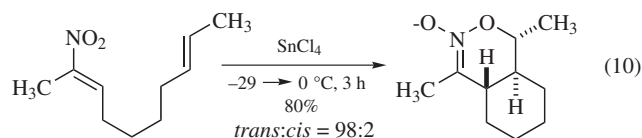
A 5.0 M solution of lithium perchlorate in diethyl ether (LPDE) was also found to catalyze an inverse electron demand [4+2] cycloaddition between electron deficient aza-dienes and norbornadiene (eq 8). The reaction does not occur in refluxing toluene in the absence of the salt.<sup>20</sup>



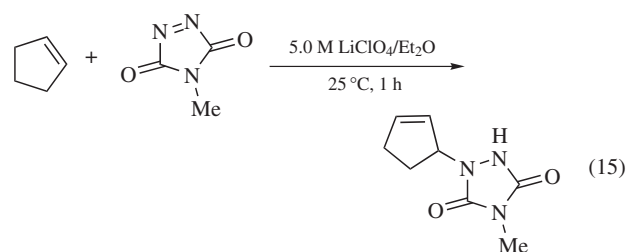
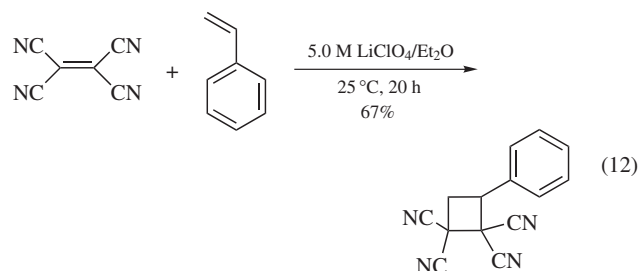
Lithium perchlorate effectively accelerates various intramolecular Diels–Alder (IMDA) reactions (eq 9). For example, thermal cycloaddition to the decalone ring system occurred in 20 h at 120 °C (*cis:trans* = 1.2:1), whereas the use of a 5.0 M solution of lithium perchlorate in diethyl ether afforded a 77% yield of the product in 3 h (*cis:trans* = 3.0:1). The addition of 10 mol % camphorsulfonic acid in the presence of LPDE not only accelerates the reaction but also enhances the diastereoselectivity.<sup>21</sup>



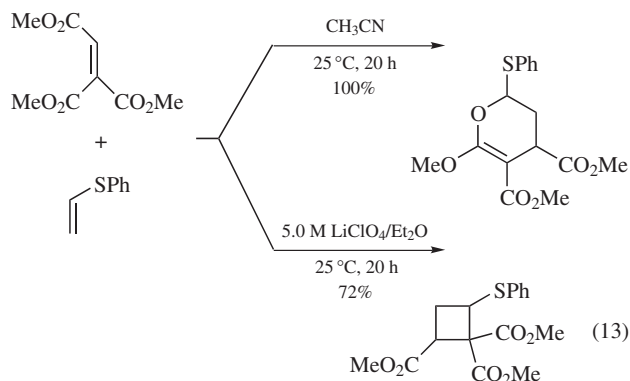
LPDE causes a remarkable change in the reactivity of nitroalkenes in IMDA reactions. In the presence of most Lewis acids, conjugated nitroalkenes behave as heterodienes giving rise to cyclic nitronates (eq 10).<sup>22</sup> However, the use of LPDE as the reaction medium leads to the formation of carbocycles. (eq 11)<sup>23</sup>



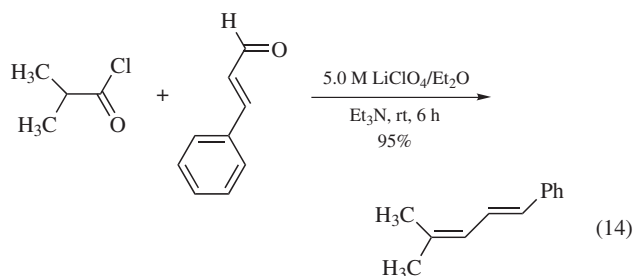
**[2+2] Cycloadditions.** LPDE has also found use in promoting [2+2] cycloadditions which are not feasible otherwise. The reaction of tetracyanoethylene (TCNE) with styrene does not occur under ambient conditions. At high pressure, an unstable 1:1 [4+2] cycloaddition product is formed. The use of 5.0 M LPDE as the reaction medium led to the formation of the [2+2] adduct (eq 12).



A dramatic change is observed in the reactivity of electrophilic alkenes with phenyl vinyl sulfide. When the reaction is performed in acetonitrile, the formation of [4+2] cycloadducts is observed and no cyclobutane is detected. However, in 5.0 M LPDE, efficient [2+2] cycloaddition takes place and no [4+2] adducts are formed (eq 13).<sup>24</sup>

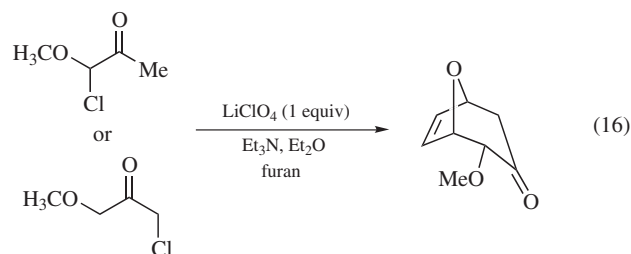


The ability of LPDE to effect [2+2] cycloadditions was utilized to synthesize alkenes using a tandem cycloaddition–cycloreversion reaction. The reaction shown in eq 14 proceeds through the formation of a ketene which reacts with the aldehyde to give the [2+2] adduct, which upon cycloreversion affords the alkene.<sup>25</sup>

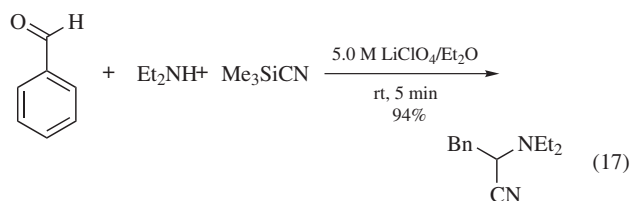


**Ene Reactions.** The ene reaction has also been shown to be susceptible to rate acceleration by LPDE. The reaction between cyclopentene and *N*-methyltriazolinedione was accelerated by a factor of 240 (eq 15). LPDE was also observed to promote metallo-ene reactions wherein the ene used was allyltrityl tin.<sup>26,27</sup>

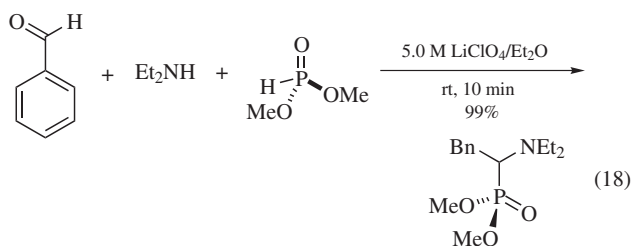
**[4+3] Cycloaddition.** It has been shown that oxyallyl synthons can be generated in situ and trapped with furan in a [4+3] cycloaddition reaction. This one-pot sequence can be used to synthesize bicyclo[3.2.1] ring systems (eq 16).<sup>28</sup>



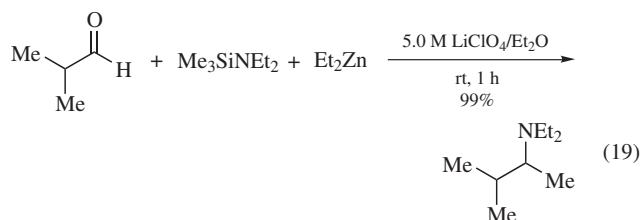
**Three Component Condensations Involving Aldehydes.** Many Mannich-type reactions of aldehydes are facilitated by LPDE. The advantage of using LPDE is that the reactions can be performed under significantly milder conditions and in a shorter time. It has been found that aminocyanation of aldehydes can be achieved in about 5 min and in excellent yields (eq 17).<sup>29</sup>



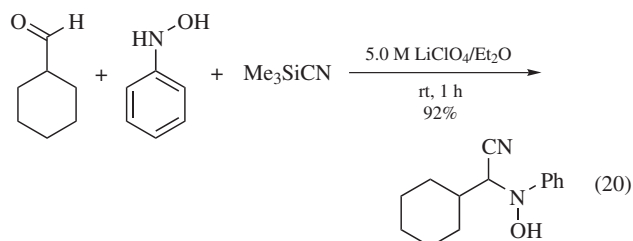
In a similar fashion, rapid amino phosphonation of aldehydes has also been achieved.<sup>30</sup> Optically active  $\alpha$ -aminophosphonates were also synthesized using this method (eq 18).



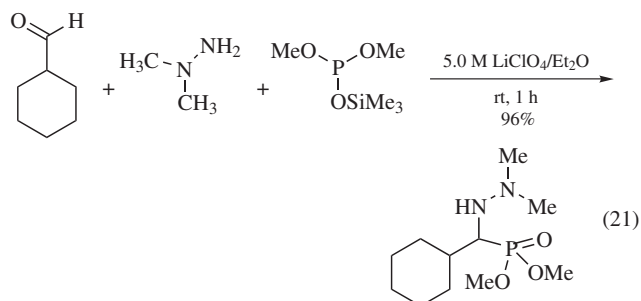
Reductive aminoalkylations of aldehydes proceed well with a variety of nucleophiles (eq 19).<sup>31</sup>



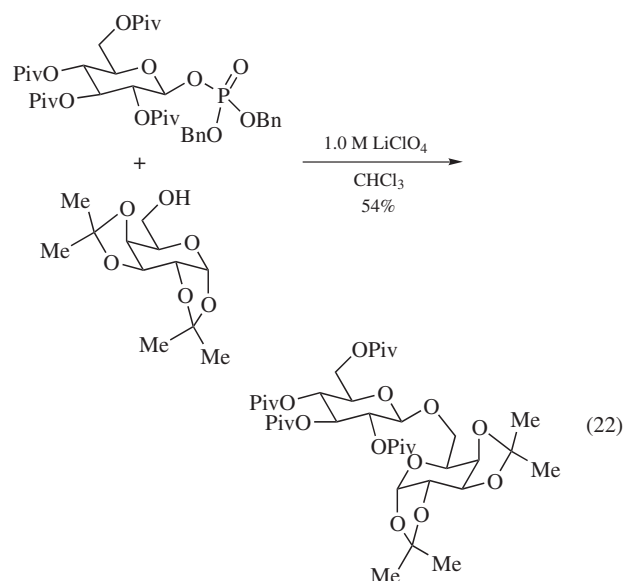
LPDE also promotes the rapid formation of  $\alpha$ -cyanohydroxylamines (eq 20). This reaction works well even for alkyl and heterocyclic aldehydes in addition to aromatic aldehydes.<sup>32</sup>



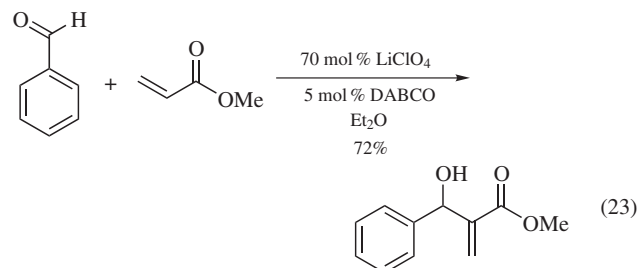
Relatively obscure functionalities like  $\alpha$ -hydrazinophosphonates can also be assembled using LPDE (eq 21).<sup>33</sup>



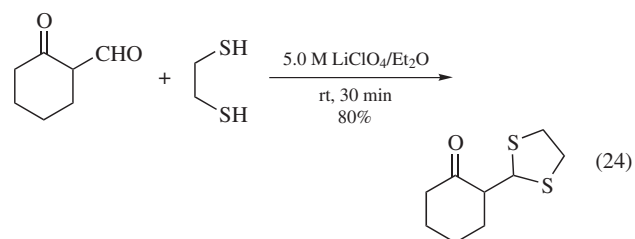
**Glycosidation.** Stereoselective glycosidation is an important reaction and LPDE has made possible the activation of glycosyl donors without the assistance of strong Lewis acids (eq 22).<sup>34</sup>



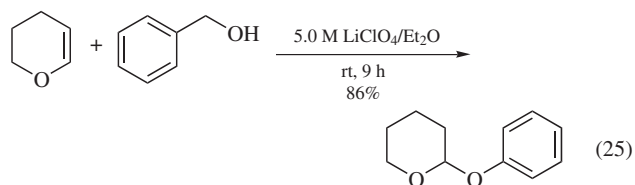
**Morita–Baylis–Hillman Reaction.** The Morita–Baylis–Hillman reaction is often limited by long reaction times even when a strong base such as DABCO is used. Kobayashi has reported the acceleration of this reaction by lithium perchlorate. It was found that a combination of 5 mol % DABCO and 70 mol % of LiClO<sub>4</sub> accelerated the reaction by 800 times, furnishing a variety of methyl acrylate adducts in good yield (eq 23).<sup>35</sup>



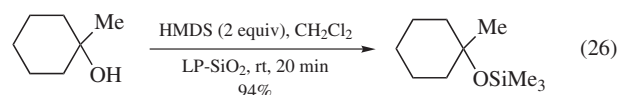
**Protecting Group Synthesis.** There are many methods available to protect aldehydes and ketones as dithioacetals but it is difficult to obtain selectivity if there is a ketone and an aldehyde moiety in the same molecule. LPDE can thioacetalize aldehydes much faster than ketones, providing the opportunity for chemoselective protection (eq 24).<sup>36</sup>



LPDE can be used as an effective solvent for the protection of a variety of alcohols (primary, secondary, tertiary, allylic) as the corresponding THP-ethers (eq 25).<sup>37</sup>

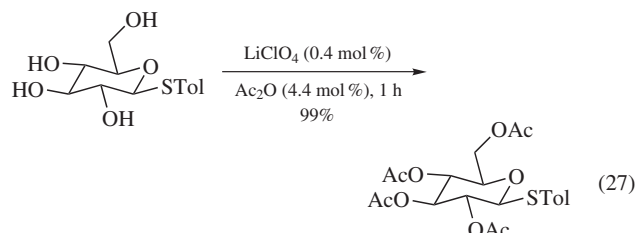


Protection of alcohol functional groups by silylation is routinely necessary in organic synthesis, and hence mild protocols to effect such transformations are always desirable. It has been found that lithium perchlorate dispersed on silicagel promotes the silylation of a wide variety of alcohols (primary, secondary, tertiary, allylic) using HMDS (eq 26). Even in the presence of amines, the hydroxyl functionality is selectively silylated. Another advantage of this protocol is that the LP-SiO<sub>2</sub> can be reused several times.<sup>38</sup>

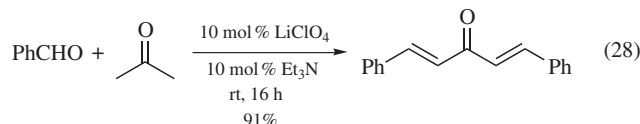


Fully acylated monosaccharides are widely used starting materials for the synthesis of oligosaccharides and glycoconjugates.

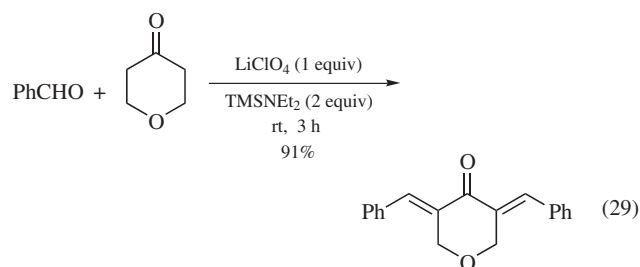
Although a variety of methods exist for the acetylation of carbohydrates, many of them are not compatible with certain functional groups and they require an excess of acetic anhydride which impedes their scale-up (eq 27). Also, the easy isomerization from pyranose to furanose form requires that the reagents/catalysts be mild enough. Lithium perchlorate was found to be an efficient catalyst for this transformation giving products in very high yields using a minimal excess of acetic anhydride.<sup>39</sup>



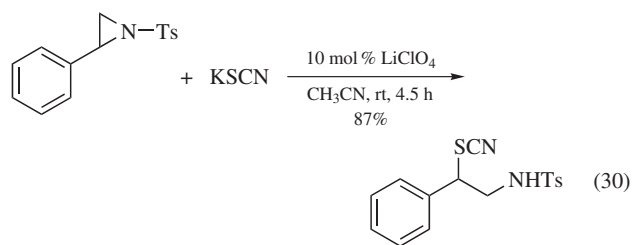
**Amine-catalyzed Aldol Condensation.** Lithium perchlorate has been shown to promote aldol condensation reactions. This methodology is particularly useful when a cross aldol condensation is desired since self-condensation is minimized. The alkylidene ketone products have wide application in palladium catalysis and this method is an inexpensive and convenient alternative for their synthesis (eq 28). The use of a stoichiometric amount of LiClO<sub>4</sub> completes the reaction in 2 min.<sup>40</sup>



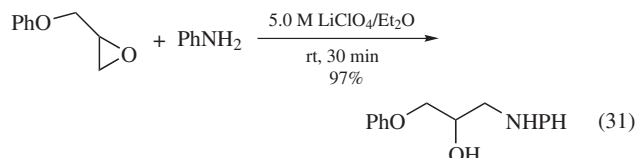
Bis(arylmethylidene)pyranones were also synthesized by aldol condensation using lithium perchlorate (eq 29).<sup>41</sup>



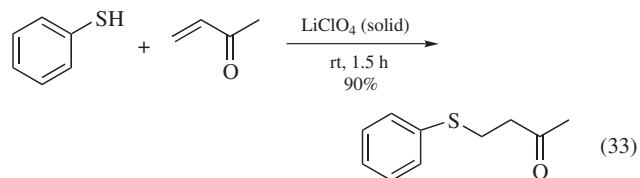
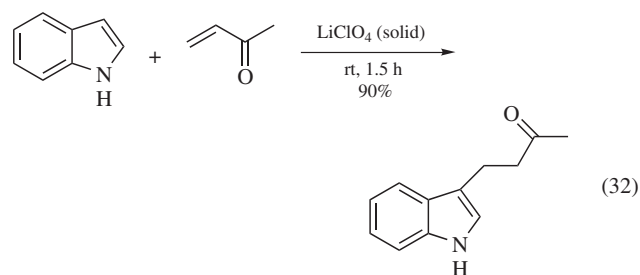
**Regioselective Ring Opening of Aziridines with Thiocyanate.** Lithium perchlorate in acetonitrile was found to affect a regioselective ring opening of aziridines leading to  $\beta$ -aminothiocyanates (eq 30).<sup>42</sup>



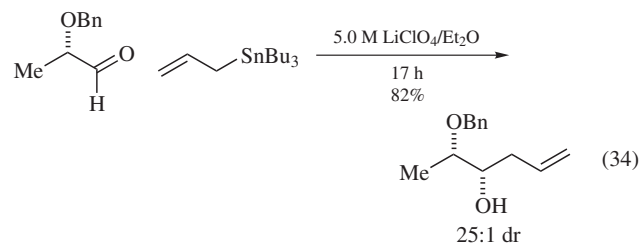
**Epoxide Ring Opening by Poor Nucleophiles.** The opening of epoxides by nucleophiles is a strategic transformation for the production of vicinal functionality (eq 31). However, these reactions often require elevated temperatures and a large excess of the nucleophile, and are very difficult to perform in an efficient manner with weak nucleophiles. The use of LPDE circumvents many of these problems. Weak nucleophiles like *O*-trimethylsilylhydroxylamine and indole also undergo this reaction in the presence of LPDE.<sup>43</sup>



**Conjugate Addition of Thiols and Indoles to  $\alpha,\beta$ -Unsaturated Carbonyl Compounds.** Lithium perchlorate is a clean and efficient catalyst for the addition of thiols and indoles into  $\alpha,\beta$ -unsaturated carbonyl compounds. The reactions are done without solvent and the yields are high with no observed polymerization (eqs 32 and 33).<sup>44</sup>



**Addition of Allyltin to Aldehydes.** Allylation of aldehydes is an important and frequently utilized carbon-carbon bond forming process which can be catalyzed by LPDE. The chelation controlled addition of tributylallyltin to  $\alpha$ -alkoxy aldehydes yields products with high diastereoselectivity (eq 34).<sup>45</sup>



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