

# INCREASING PRACTICABILITY OF AIR-SENSITIVE SYNTHETIC REACTIONS

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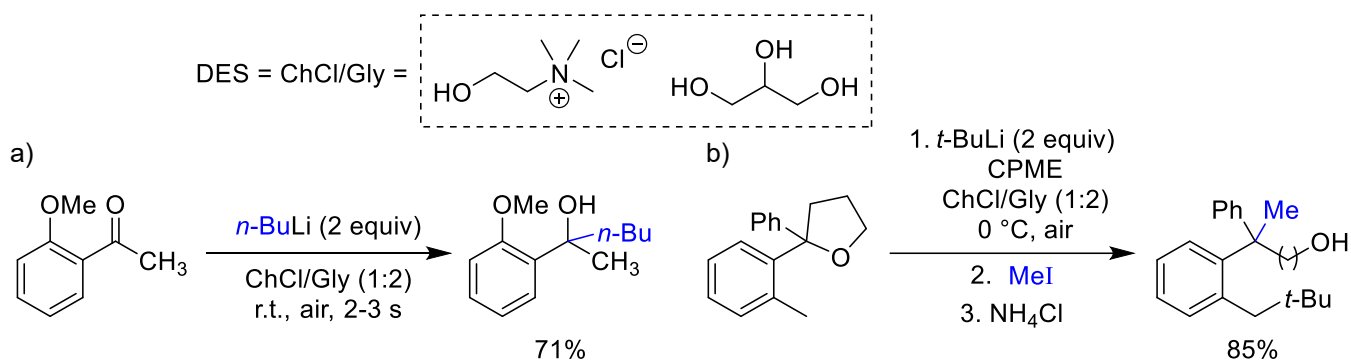
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## INTRODUCTION

In synthetic organic chemistry, some important reagents and reactions require specialized handling under inert conditions owing to their air and/or moisture sensitivities. Nevertheless, these reactions are widely employed in the pharmaceutical and polymer industries to make a variety of important products.<sup>1</sup> For example, organolithium reagents are used to form new carbon-carbon bonds,<sup>2</sup> but are pyrophoric and must be protected from air and water.<sup>3,4</sup> Transition-metal-catalyzed reactions, including many named coupling reactions, also often require air- and moisture-sensitive conditions to avoid catalyst degradation and consequent decrease of catalytic activity.<sup>5</sup> Several strategies are being explored to improve the ease of use of these air-sensitive reagents, which will be discussed in this short review.

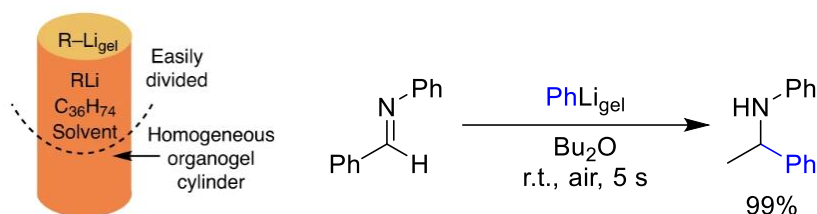
## INCREASING THE EASE OF MANAGEMENT IN ORGANOLITHIUM CHEMISTRY

Between 2014 and 2016, the Hevia and Capriati groups reported the use of deep eutectic solvents (DES) to carry out reactions with organolithium reagents under aerobic conditions (Figure 1).<sup>6-9</sup> The DES typically consists of choline chloride (a quaternary ammonium salt) in a polyol such as glycerol. Hydrogen bonding between the halide ion of the quat salt and the polyol is thought to be responsible for retarding hydrolysis of the organolithium reagent so that the latter reacts instead with the desired substrate.



**Figure 1. Example of reactions developed by a) the Hevia group and b) the Capriati group.<sup>6,9</sup>**

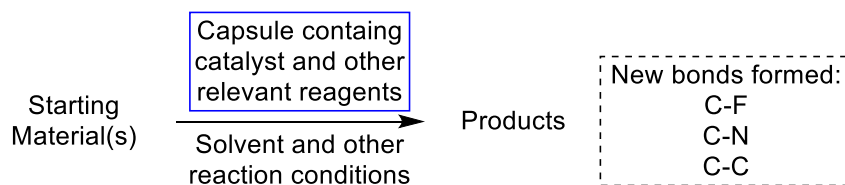
In 2023, the Smith group made organolithium reagents (*n*-BuLi, PhLi) more convenient to handle by incorporating them into organogels prepared from hexatriacontane (C<sub>36</sub>H<sub>74</sub>, m.p. 74-76 °C) (Scheme 1).<sup>10</sup> The organolithium organogels, which can be prepared in less than 10 minutes, can be stored for many hours under aerobic conditions. In subsequent organic reactions, the products are obtained in moderate to high yields without the need for exclusion of air and moisture.



**Scheme 1. General characteristics of organolithium organogels made by the Smith group and a sample reaction.**<sup>10</sup>

## INCREASING THE EASE OF MANAGEMENT OF METAL-CATALYZED REACTIONS

In 2015, the Buchwald group showed that transition-metal-catalyzed reactions could be carried out in air if the catalysts, ligands, and bases were first encapsulated in paraffin capsules.<sup>11</sup> These capsules, which are stable enough to be stored in air, can be used for carbon-fluorine, carbon-nitrogen, and carbon-carbon couplings (Scheme 2). In 2021, AbbVie scientists developed a similar method using hydroxypropyl methylcellulose (HPMC) to encapsulate air-sensitive reagents.<sup>12</sup> These HPMC capsules come in different sizes and have long shelf lives of 2 years at 25 °C and 65% humidity. The encapsulated reagents can be used in reaction screening and in the synthesis of small libraries prepared by Suzuki-Miyaura couplings, Buchwald-Hartwig couplings, and metallophotoredox aryl aminations (Scheme 2).



**Scheme 2. General description encapsulation methods developed by the Buchwald group and AbbVie.**<sup>11,12</sup>

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