



## An expedient preparation of amine-free lithium enolates using immobilized amide reagents

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### ABSTRACT

Amine-free lithium enolates can be prepared by a simple procedure using polymer-immobilized lithium amides derived from known, easily accessible immobilized secondary amines, or from a new bidentate amine [lithium diisopropylamide (LDA) or lithium cyclohexylisopropylamide (LICA) analogues]. The procedure involves physical separation of the polymeric amine reagent and the enolate formed by simple washing with solvents. The amine-free enolates were identified by their characteristic NMR signals in THF solution. The enolates (and an azaenolate) obtained were used in selected reactions with electrophiles (PhCHO, MeCHO, PhCH = CHCOCN, BnBr) giving improved results. The higher reactivity of the lithium enolates toward 'difficult electrophiles' is demonstrated by quantitative levels of deuterium incorporation on D<sub>2</sub>O quenching, where the standard LDA-based method, that is, in the presence of amine gives a ca. 50% yield. Recycling of used polymers via the 'filtration procedure' is also easier and uncomplicated by possible side reactions with electrophiles and their possible effects on the polymeric reagents.

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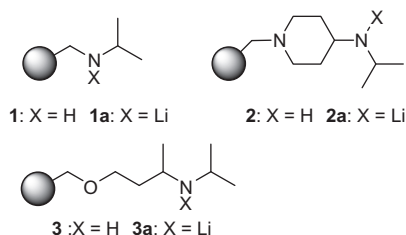
Lithium enolates of ketones, esters, and other carbonyl compounds are seemingly simple and widely used nucleophilic reactants in organic synthesis.<sup>1,2</sup> Lithiated carbonyl compounds are most conveniently prepared by deprotonation with lithium amide bases (LDA, LiHDMS, LICA, LiTMP, etc.).<sup>3</sup> The complex aggregation of enolates with amine by-products,<sup>4–7</sup> excess lithium amides used,<sup>8,9</sup> and donor solvents, as well the associated equilibria<sup>10</sup> are not appreciated widely by organic chemists. In synthetic practice the complexation and aggregation of these reagents with secondary amine by-products formed from the lithium amides used is usually not considered, although it carries important consequences.<sup>5,11–13</sup> It has been shown that the amines present in the reaction mixtures bind with metal enolates and influence the reactivity and selectivity of their reactions.<sup>4</sup> Most notable is the hindered alkylation<sup>14</sup> and deuteration<sup>4</sup> of enolates prepared using, for example, LDA, which may be rationalized by *internal proton return*.<sup>15</sup> In order to improve the alkylation yield and deuterium incorporation, special protocols were devised.<sup>5,14,16</sup> Amine-free enolates can be prepared by a few procedures and are used for structural and physicochemical studies.<sup>17</sup> Amine-free enolates result from reactions of isolated silyl enol ethers with methylolithium<sup>18</sup> or *t*-BuOLi.<sup>19,20</sup> Some ester enolates prepared with LDA in hexane solutions precipitate and can be isolated and crystallized as amine-free solids.<sup>21</sup> Volatile amines, such as DIPA formed from LDA, present in the enolate–amine mixture, can be removed by evaporation under vacuum.<sup>22</sup> There is however,

no simple preparative, one-step procedure for making solutions of lithiated amine-free ketones, esters, or like C–H acids susceptible to nucleophilic additions of alkylolithiums. All the current methods require manipulations of sensitive enolates (evaporation, crystallization, filtration, etc.) and/or additional synthetic steps (preparation of silyl ether derivatives).

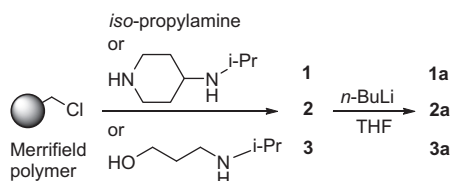
During our studies on deprotonations of covalently-immobilized ketones (mostly nortropinone derivatives)<sup>23–25</sup> with chiral lithium amides, we observed that the complexation of the lithium amides with ketones (or chiral amine by-products with ketone enolates), which is believed to be involved in the enantioselective differentiation,<sup>13</sup> is weak enough to allow for washing of the chiral reagents from the polymeric support.<sup>25</sup> This prompted us to see if a reversed situation, that is, immobilized lithium amide and dissolved ketone, could be used for the preparation of amine-free enolates. Utilization of this simple notion has not been reported, to the best of our knowledge. Immobilized lithium amide reagents, both chiral<sup>26–28</sup> and achiral,<sup>29</sup> have been used in reactions of ketone enolates including aldol reactions,<sup>26,27</sup> silylations,<sup>28</sup> and other reactions.<sup>27,30</sup> However, in all the reported procedures the reactions with electrophiles were effected in the presence of polymeric amines, and washing of the polymeric carrier was performed after completion of the reaction and quenching. This is likely based on the assumption of strong binding (aggregation) of the resulting enolates with secondary amines, and/or the necessary presence of the amine in the reaction with the electrophile. Herein, we report that amine-free enolates can be separated from polymers and can be used advantageously in synthetic reactions.

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**Figure 1.** Immobilized amines and the corresponding lithium amides tested in this study.



**Scheme 1.** Preparation of polymer-supported secondary amine precursors of polymeric lithium amides.

**Table 1**  
Loading and yield of the prepared supported amines

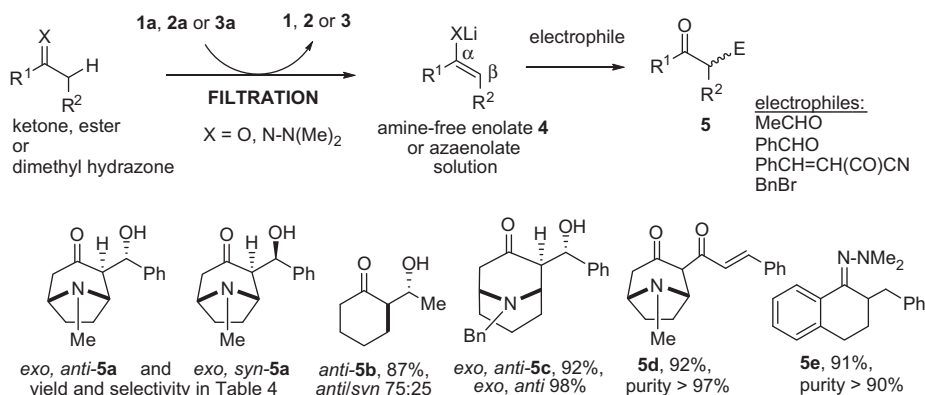
Amine	Loading <sup>a</sup> (mmol/g)	Theoretical loading (mmol/g)	Yield of amination <sup>a</sup> (%)
<b>1</b>	1.61 <sup>b</sup>	1.64 <sup>b</sup>	98
<b>2</b>	1.44 <sup>b</sup>	1.44 <sup>b</sup>	100
<b>3</b>	0.850 <sup>c</sup>	1.08 <sup>c</sup>	79

<sup>a</sup> Based on gravimetric analysis of the amount of HCl released or bound by the gel (mass of Et<sub>3</sub>N·HCl).

<sup>b</sup> Prepared from high-loading Merrifield polymer (Fluka, 1.70 mmol/g).

<sup>c</sup> Prepared from standard-loading Merrifield polymer (Novabiochem 1.20 mmol/g).

To test the hypothesis, four ketones ( $\alpha$ -tetralone, tropinone, cyclohexanone, and *N*-benzylnorgranatanone) were selected and used as probes. Possible enolate washing from three polymer-supported amide reagents (**1a**, **2a**, **3a**, Fig. 1) was best assessed using the most suitable ketone for gravimetric analysis,  $\alpha$ -tetralone. The Li amides derived from amines **1–3** represented immobilized LDA and lithium cyclohexylisopropylamide (LICA). The additional nitrogen atom in **2** was expected to stabilize the amide owing to its bidentate nature and chelation of lithium,<sup>13</sup> making the reagent robust and easier to prepare and to work with.



**Scheme 2.** Selected reactions of amine-free lithium enolates and azaenolates.

**Table 2**  
Efficiency of ketone enolate syntheses (Scheme 2)

Lithium amide	Ketone	Conversion of ketone into lithium enolate in filtered solution	Washed lithium enolate from polymer (%)	Ketone extracted from polymer after quenching (%)
<b>1a</b>	$\alpha$ -Tetralone	$\geq 96$	80	20
<b>2a</b>	$\alpha$ -Tetralone	$\geq 98$	74	25
<b>3a</b>	$\alpha$ -Tetralone	$\geq 95$	46	55
<b>2a</b>	Tropinone	$\geq 98$	70	20 <sup>a</sup>
<b>2a</b>	<i>N</i> -Benzylnorgranatanone	$\geq 98$	$\geq 98$	nd
<b>2a</b>	Cyclohexanone	$\geq 98$	74	10 <sup>a</sup>

<sup>a</sup> The low overall recovery results from loss of more volatile ketones during evaporation of solvents.

The polymer-supported secondary amine precursors of the amides were prepared from Merrifield gel by standard methods (Scheme 1, Table 1).

After a typical reaction of the polymeric lithium amide and the test ketone in THF, the liquid phase was separated from the polymer and the polymer washed with a small portion of solvent (Scheme 2).<sup>31</sup> Direct NMR analysis (via the No-D NMR technique)<sup>32</sup> of the THF solutions showed high conversions into enolates (Table 2) as judged from the integration of characteristic enolate and ketone signals. For comparison the enolates were prepared using the literature method, that is, repetitive vacuum evaporations of mixtures resulting from reaction of LDA and the ketones.<sup>22</sup> The mass of the ketones formed from the enolates and recovered from the polymer also indicated high, although not quantitative, enolate extraction (Table 2). The estimated yield of enolate extraction in the case of volatile ketones such as tropinone or cyclohexanone was lower due to their volatility; this could also be inferred from the yields of the products in the subsequent reactions of the enolates with electrophiles (e.g., the aldols, Scheme 2).

From these data in Table 2, it is clear that the simple amide **1a** and the bidentate (LICA analogue **2a**) outperform the spacer-modified analogue of LDA **3a**. The much lower recovery (extraction) of enolates from **3a** is most likely a result of higher affinity of lithium to oxygen. Binding of lithium to the tertiary nitrogen atom, although weaker than to oxygen, could also be responsible for slightly diminished enolate recovery from **2a** compared to simple amide **1a**.

Characteristic NMR data of representative enolates (including one ester) obtained directly from the THF solutions washed off the polymer **2**, are shown in Table 3.

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