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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_2O 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 regents.

Lithium enolates of ketones, esters, and other carbonyl compounds are seemingly simple and widely used nucleophilic reactants in organic synthesis.[1,2] Lithiated carbonyl compounds are most conveniently prepared by deprotonation with lithium amide bases (LDA, LiHDMS, LICA, LiTMP, etc.).[3] The complex aggregation of enolates with amine by-products,[4–7] excess lithium amides used,[8,9] and donor solvents, as well the associated equilibria[10] 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.[5,11–13] 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.[4] Most notable is the hindered alkylation[14] and deuteration[4] of enolates prepared using, for example, LDA, which may be rationalized by *internal proton return*.[15] In order to improve the alkylation yield and deuterium incorporation, special protocols were devised.[5,14,16] Amine-free enolates can be prepared by a few procedures and are used for structural and physicochemical studies.[17] Amine-free enolates result from reactions of isolated silyl enol ethers with methyllithium[18] or *t*-BuOLi.[19,20] Some ester enolates prepared with LDA in hexane solutions precipitate and can be isolated and crystallized as amine-free solids.[21] Volatile amines, such as DIPA formed from LDA, present in the enolate–amine mixture, can be removed by evaporation under vacuum.[22] 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 alkyllithiums. 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)[23–25] 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,[13] is weak enough to allow for washing of the chiral reagents from the polymeric support.[25] 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[26–28] and achiral,[29] have been used in reactions of ketone enolates including aldol reactions,[26,27] silylations,[28] and other reactions.[27,30] 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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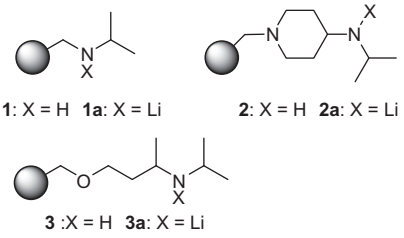
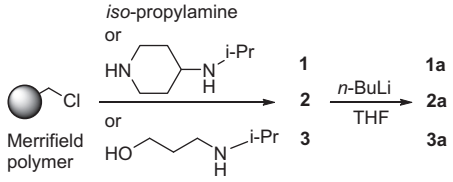


Figure 1. Immobilized amines and the corresponding lithium amides tested in this study.



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[a] (mmol/g)	Theoretical loading (mmol/g)	Yield of amination[a] (%)
1	1.61[b]	1.64[b]	98
2	1.44[b]	1.44[b]	100
3	0.850[c]	1.08[c]	79

[a] Based on gravimetric analysis of the amount of HCl released or bound by the gel (mass of $Et_3N{\cdot}HCl$).
[b] Prepared from high-loading Merrifield polymer (Fluka, 1.70 mmol/g).
[c] Prepared from standard-loading Merrifield polymer (Novabiochem 1.20 mmol/g).

To test the hypothesis, four ketones (α-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, α-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,[13] making the reagent robust and easier to prepare and to work with.

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 (%)
1a	α-Tetralone	⩾96	80	20
2a	α-Tetralone	⩾98	74	25
3a	α-Tetralone	⩾95	46	55
2a	Tropinone	⩾98	70	20[a]
2a	*N*-Benzylnor-granatanone	⩾98	⩾98	nd
2a	Cyclohexanone	⩾98	74	10[a]

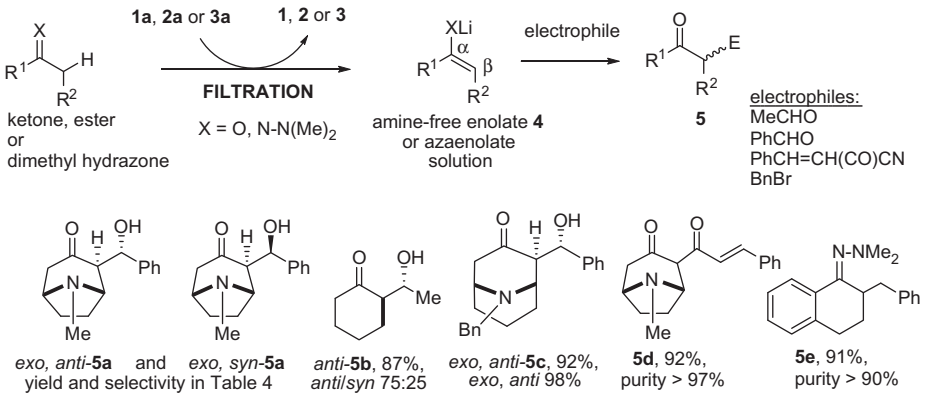
[a] The low overall recovery results from loss of more volatile ketones during evaporation of solvents.

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).[31] Direct NMR analysis (via the No-D NMR technique)[32] 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.[22] 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.



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

Table 3
Characteristic ^{1}H NMR and ^{13}C NMR data of selected lithium enolates **4** obtained via the method shown in Scheme 2

Carbonyl compound	^{1}H NMR (400 MHz) spectra recorded in THF using the No-D method		^{13}C NMR (100 MHz) spectra recorded in THF using the No-D method		
	^{1}H β	Others	^{13}C α	^{13}C β	Others
Cyclohexanone	4.11 (br s, 1H)	1.98–1.95 (m, 2H), 1.90–1.87 (m, 2H), 1.62–1.58 (m, 2H), 1.48–1.44 (m, 2H)	159.6	89.6	33.9, 25.8, 25.2, 24.7
Cyclopentanone	3.82 (d, *J* = 1.5 Hz, 1H)	1.20–1.16 (m, 2H), 2.02–1.98 (m, 2H)[a]	166.9	88.1	33.5, 29.8, 23.0
3-Pentanone (*E* and *Z*)	3.95–3.85 (m, 1H)	2.05–1.95 (m, 2H), 1.52–1.42 (m, 3H), 1.05–0.95 (m, 3H)	163.9 163.6	85.6 84.3	27.4, 13.3, 12.9 33.3, 12.8, 11.3
N-Methyl-4-piperidone	4.04 (br s, 1H)	2.82–2.18 (m, 2H), 2.40 (t, *J* = 5.8 Hz, 2H), 2.19 (s, 3H), 2.00–1.97 (m, 2H)	157.9	88.4	56.4, 54.8, 46.4, 34.6
α-Tetralone	4.96 (t, *J* = 4.6 Hz, 1H)	7.87 (d, *J* = 7.6 Hz, 1H), 7.07–6.96 (m, 3H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.35–2.29 (m, 2H)	157.9	94.5	139.4, 138.5, 126.4, 126.1, 125.7, 123.2, 30.8, 24.1
Acetophenone	4.33 (s, 1H), 4.08 (s, 1H)	7.80 (d, *J* = 7.3 Hz, 2H), 7.21–7.17 (m, 2H), 7.13–7.09 (m, 1H)	166.4	80.3	144.7, 127.8, 126.6, 126.3
Tropinone	4.17 (d, *J* = 4.9 Hz, 1H)	3.02 (d, *J* = 4.7 Hz, 2H), 2.41–2.36 (m, 1H), 2.24 (s, 3H), 1.92–1.88 (m, 1H), 1.62–1.58 (m, 2H), 1.43–1.35 (m, 2H)	156.9	94.2	60.2, 59.2, 40.2, 36.7, 36.4, 30.5
t-Butyl acetate	4.51 (br s, 2H)	1.10 (s, 9H)	165.8	87.1	35.5, 28.9

[a] Some enolate signals were masked by solvent signals (THF).

Table 4
Selectivity in the aldol reaction of tropinone lithium enolate depending on the presence of an amine and the conditions used

Entry	Reaction of the ketone with the lithium amide		Reaction of the enolate with PhCHO		Yield (%)	Selectivity (*exo*, *anti* to *exo*, *syn*)
	Time	Temperature (°C)	Time	Temperature (°C)		
Enolate generated with LDA—reaction in the presence of amine (DIPA)						
1	30 min	−78	10 min	−78	95	98:2
2	30 min	0	10 min	0	58 (12% of by-products) [a]	25:75
*Enolate generated with immobilized lithium amide **2a**—reaction without separation of the enolate from the polymeric amine*						
3	4 h	−78	2 h	−78	84 (33% of by-products) [a]	54:46
4	2 h	0	10 min	0	60 (20% of by-products) [a]	17:83
*Enolate generated with immobilized lithium amide **2a**—amine-free reaction with separated polymeric amine*						
5	4 h	−78	10 min	−78	69	99:1
6	30 min	−78	10 min	−78	71	98:2
7	2 h	0	10 min	−78	61	97:3
8	30 min	0	10 min	0	56	15:85
9	4 h[a]	−78	10 min	−78	60	93:7

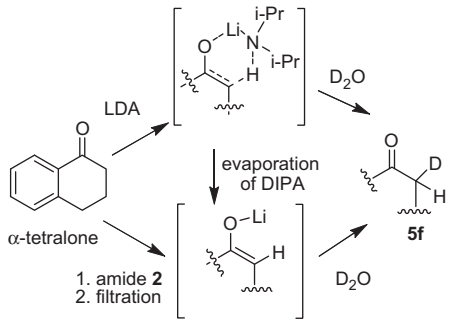
[a] Formation of bisaldol and other unidentified products was evident from NMR analysis of the reaction mixture.

The THF solutions of enolates, filtered from the polymeric carrier were used directly in reactions with electrophiles. The procedure provided the simplest way for performing amine-free enolate reactions. Comparison of the results of the aldol reaction of tropinone with benzaldehyde under amine-free conditions, that is, an enolate solution filtered from the polymeric reagent, with the standard method, that is, the reaction in the presence of polymeric amine, showed better control over side reactions giving less bis-aldol and other unidentified by-products (Table 4). The diastereoselectivity found was the same as with LDA in solution. Interestingly, changing to amine-free conditions was helpful for a higher reaction temperature with benzaldehyde (Table 4, 0 °C). At higher temperatures (generally >−18 °C), the reaction in the presence of amines, regardless of polymeric or DIPA, was severely complicated by by-products. Moreover, the filtered enolates reacted with other electrophiles (Scheme 2) giving better results.[33] The yields and crude product purities (typically >95% by NMR) compared favorably with those results under regular conditions (ca. 75% yield after purification).[34,35] Attempted direct alkylation of α-tetralone enolate was however plagued by polyalkylation. This could be circumvented by the use of azaenolate (a dimethylhydrazone derivative)[36] and a suitable carbonyl regenerating method.[37,38] In light of the known lithiation of polymer-immobilized hydrazones,[39–41] it was not surprising that the reversed case of polymeric amide reaction followed by filtration and benzylation (BnBr) was also effective (91%, Scheme 2).

Recycling of polymers **1** and **2** after repetitive use with various ketones was tested for up to five cycles with no detectable detrimental effect on the activity, loading, or purity of the prepared products, contrary to the procedure without enolate separation. Physical separation of the lithiation step from the electrophilic reaction prevents any problems including the known alkylation of lithium amide precursors (secondary amines).[4]

The new method was found to be valuable for the generation of enolates for selective deuteration. Deuteration of, LDA or other lithium amide generated, enolates is known to be hindered[4] by the *internal proton return* phenomenon.[15] Several methods for improving the scarce deuterium incorporation after quenching enolates with heavy water have been proposed including addition of an extra equivalent of *n*-BuLi after deprotonation,[4] removal of the amine, or the use of silyl enol ethers.[16] Use of the polymeric lithium amide reagent combined with its separation before quenching the enolate with D_2O offers a simple (as exemplified by α-tetralone reactions in Scheme 3)[42] and highly effective means of selective α-deuteration of carbonyl compounds.[43] The monodeuteration of the amine-free enolate prepared both by tedious repetitive evaporation of DIPA, or by polymeric amide/filtration achieves a quantitative level, as detected by NMR analysis (Table 5). Quenching the enolate-amine aggregate[5] with D_2O gave, in our hands at best, ca. 50% deuterium incorporation.

In conclusion, we have shown that contrary to current common practice, lithium enolates can be separated from the



Scheme 3. Deuteration of α-tetralone enolate via an amine-aggregate and via an amine-free enolate.

Table 5
Efficiency of deuteration of the enolate via Scheme 3

Method of lithium enolate generation	Deuteration of ketone (% deuterium incorporation) by ^{1}H NMR
LDA	48–51
LDA, evaporation of DIPA	110–112[a]
Lithium amide **2a**, filtration	104–106[a]

[a] A level of deuteration exceeding 100% (by NMR) is the result of a small percentage of α,α-dideuterated ketone being present.

polymer-supported reagents used to generate them (lithium amides and amines), and used favorably for reactions with electrophiles. Filtration from the polymeric reagents is the simplest method, conceptually and technically, for making amine-free enolates for spectroscopic and physicochemical studies. The obtained lithiated derivatives react cleanly minimizing product purification. Recycling of the polymeric reagents used in this way is also unproblematic.

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3. *Abbreviations:* DIPA, diisopropylamine; LICA, lithium cyclohexylisopropylamide; LiHDMS, lithium hexamethyldisilazide; LiTMP, lithium 2,2,6,6-tetramethylpiperidide; LDA, lithium diisopropylamide.
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31. *General procedure for the preparation of the amine-free enolate solution of **4**:* The immobilized amine (**1**, 0.600 g, 1.61 mmol/g, 0.966 mmol, placed in a solid-phase synthesis vessel fitted with a sintered glass filter disc combined with a siphon tube and stopcock) was dried under vacuum in a desiccator for 24 h, flushed with argon for 10 min, washed with THF (3 × 5 mL), then suspended in THF (4 mL), and the suspension cooled to 0 °C. After 15 min, *n*-BuLi (2.5 M in hexanes, 1.2 mL, 3.0 mmol) was added. The suspension was intermittently agitated by a flow of argon (the polymer turned brown). After 1.5 h, the THF solution was separated by applying a positive pressure of argon and the gel washed with THF (4 × 5 mL)-the filtered solutions were discarded. The polymeric gel (lithium amide) was covered with THF (<1 mL) and the suspension was cooled to −78 °C. A solution of a ketone or other enolate precursor (0.80 mmol) in THF (2 mL) was added dropwise and the mixture agitated intermittently for 1.5 h. The enolate solution was siphoned from the polymer through a sintered glass filter, and collected in a flask. For the NMR analysis in THF, the solution was warmed to, rt and an aliquot transferred (ca. 1 mL, using a syringe) to a dry, Ar-filled and sealed with a septum NMR tube. The spectra in THF were recorded at once by the No-D NMR method.
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42. α-Tetralone was suitable for testing deuteration because of its low volatility and lack of a basic amine nitrogen, in contrast to the other ketones used in this study.
43. *Typical procedure for the amine-free enolate deuteration:* A solution of α-tetralone [3,4-dihydronaphthalen-1(2*H*)-one, 0.154 g, 0.672 mmol] in THF (3 mL) was added to a suspension of lithium amide **2a** (0.600 g, 1.44 mmol/g, 0.865 mmol) at −78 °C and the mixture was agitated intermittently by a flow of argon. After 1.5 h, the solution was siphoned from the polymer through a sintered glass filter and collected in a flask cooled to −78 °C. The polymer was washed with THF. D_2O (0.5 mL, 22.5 mmol) was added to the combined, cooled to −78 °C, filtrate and the resulting mixture was stirred for 2–5 min, then dried over anhydrous $CaSO_4$, filtered, and the drying agent washed (THF 2 × 5 mL). The combined organic solutions were concentrated under vacuum to give 2-deutero-3,4-dihydronaphthalen-1(2*H*)-one (**5f**).