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Direct Trapping of Sterically Encumbered Aluminum Enolates

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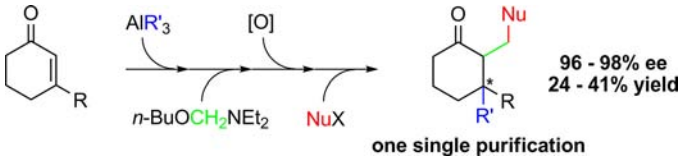
ABSTRACT



The formation of chiral and sterically congested cyclohexanone derivatives has been achieved through a multistep sequence with one single purification step. (*n*-Butoxymethyl)-diethylamine was identified as a highly efficient reagent for the direct trapping of aluminum enolates. The Lewis acidic character of aluminum suffices to activate the α-aminoether to form *in situ* an electrophilic iminium species. In return the aluminum enolate is rendered more nucleophilic by coordination of the butoxy group and formation of an aluminate.

One of the most powerful and versatile reactions for the creation of stereogenic centers in an enantioselective fashion is the asymmetric conjugate addition (ACA).[1] The use of a copper catalyst together with a chiral ligand allows the selective addition of several organometallic nucleophiles namely zinc, aluminum, or Grignard reagents.[2] The beauty of the reaction lies, besides high enantioselectivities, in the regioselective formation of a reactive enolate that can be used for further transformations.[3] This domino reaction has been extensively used to build up multiply substituted carbocycles with contiguous stereogenic centers.[3,4] Several different types of electrophiles such as aldehydes, acetals, and alkyl halides have been utilized.[4−6] However in many cases additives are necessary. Lewis acids for example activate acetals to facilitate the trapping reaction.[5] HMPA on the other hand can be used to complex the cation to render the enolate more nucleophilic.[6] In recent years several new methods appeared that allow the formation of enantiopure quaternary stereogenic centers by ACA.[1f] This makes the methodology even more valuable most notably for its application in natural product synthesis. In contrast, subsequent trapping reactions next to these quaternary all-carbon centers have been scarcely described.[4] Mostly for steric reasons the reactivity of the corresponding enolates is strongly diminished when the adjacent substituents are bigger than two methyl groups. The method of choice is in many cases a preceding trapping as a silyl enol ether or *O*-acylation of the enolate.[7] These intermediates can be used to reform the enolate in a separate step under different reaction conditions

(1) For reviews on asymmetric conjugate additions, see: (a) Krause, N. *Angew. Chem., Int. Ed.* **1998**, *110*, 295. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (e) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (f) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295.

(2) (a) For reviews on copper catalyzed ACA, see: Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (b) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039.

(3) For reviews on domino processes, see: (a) Tietze, L. *Chem. Rev.* **1996**, *96*, 115. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1.

(4) For reviews on tandem transformations triggered by ACA, see: (a) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 366. (b) Galeštoková, Z.; Šebesta, R. *Eur. J. Org. Chem.* **2012**, *34*, 6688.

(5) (a) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358. (b) Welker, M.; Woodward, S. *Tetrahedron* **2010**, *66*, 9954.

(6) (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755. (b) Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A. *Chem.—Eur. J.* **2010**, *16*, 9890. (c) Ngoc, D. T.; Albicker, M.; Schneider, L.; Cramer, N. *Org. Biomol. Chem.* **2010**, *8*, 1781. (d) Tissot, M.; Poggiali, D.; Hénon, H.; Müller, D.; Guénée, L.; Mauduit, M.; Alexakis, A. *Chem.—Eur. J.* **2012**, *18*, 8731.

(7) (a) Smith, A. B., III; Nolen, E. G., Jr.; Shirai, R.; Blase, F. R.; Ohta, M.; Chida, N.; Hartz, R. A.; Fitch, D. M.; Clark, W. M.; Sprengeler, P. A. *J. Org. Chem.* **1995**, *60*, 7837. (b) Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835. (c) Alexakis, A.; March, S. *J. Org. Chem.* **2002**, *67*, 8753. (d) Vuagnoux-d'Augustin, M.; Alexakis, A. *Tetrahedron Lett.* **2007**, *48*, 7408. (e) Welker, M.; Woodward, S. *Tetrahedron* **2010**, *66*, 9954. (f) Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 21.

(8) (a) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem.—Eur. J.* **2007**, *13*, 9647. (b) Palais, L.; Alexakis, A. *Chem.—Eur. J.* **2009**, *15*, 10473.

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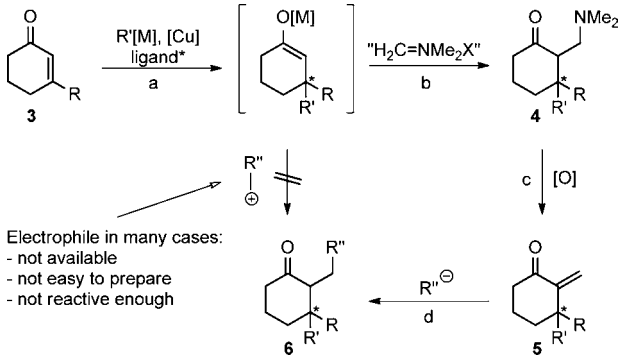
and above all with a countercation of choice such as lithium which ensures high nucleophilicity.[8,9] Nevertheless this step requires additional synthetic effort and these intermediates are often unstable and very difficult to purify.[7f]

In the course of our research toward natural product synthesis we desired to build up highly substituted cyclohexanone derivatives (**6**) with a variety of substituents in the α-position (Scheme 1). Yet, many of the corresponding electrophiles were not available or not reactive enough to be introduced as such in a trapping reaction next to a quaternary all-carbon center. To circumvent this problem we moved to a different strategy which implied the installation of an exocyclic methylene group by the trapping of a small C1-electrophile (Scheme 1, b–c). This reactive Michael acceptor should then allow the nucleophilic introduction of a variety of substituents in the α-position that are otherwise not accessible (Scheme 1, d).

Scheme 1. Conception of the Multistep Sequence

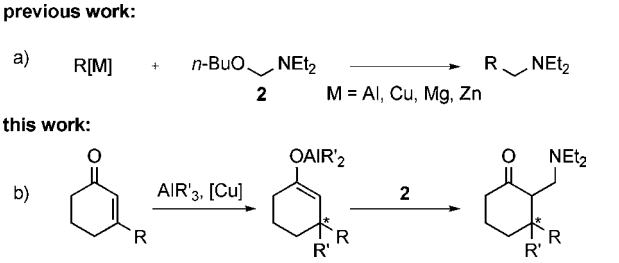


The reagent of choice to install a methylene group next to a carbonyl group is normally the Eschenmoser salt (Scheme 1, b).[10] Trapping of an enolate gives an aminomethyl substituent which can be readily eliminated to furnish the exocyclic double bond (Scheme 1, c). Nevertheless initial experiments to trap encumbered enolates after a preceeding ACA remained unsuccessful, and we assumed that maybe the low solubility of the Eschenmoser salt was partially responsible for the low reactivity.

Our search for alternatives led us to an old class of compounds, α-aminoethers. These reagents were used for the aminomethylation of Grignards reagents,[11] organo zinc[12] and organo copper compounds[13] decades ago (Scheme 2, a). In 1980 we used α-aminoethers in combination with organocopper and for the first time with organoaluminum compounds in our own laboratory.[14] α-Aminoethers such as **2** can be activated by Lewis acids and form *in situ* an iminium salt similar to the Eschenmoser reagent. These reagents are liquid, stable, and readily available. Regardless of these interesting properties α-aminoethers have never been used for the reaction with enolates. However Šebesta and co-workers reported recently the direct trapping of magnesium enolates with α-amidoethers.[15] Yet, stoichiometric amounts of $TiCl_4$ as an external Lewis acid had to be added and only trapping next to tertiary centers was described.

In recent years several methods for the metal catalyzed ACA of trialkyl aluminum reagents were developed in our laboratory.[8,16] The distinct Lewis acidic character of these reagents is crucial for the activation of the carbonyl group and allows the formation of quaternary all-carbon stereogenic centers. We recognized that these reagents should also be capable of activating an α-aminoether to release a highly electrophilic iminium ion which can react with the metal enolate (Scheme 1, b).

Scheme 2. Conception of the New Trapping Reaction

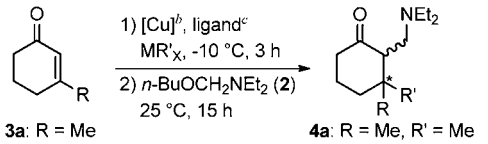


To investigate the above-mentioned concept methylcyclohexenone **3a** was reacted with trimethylaluminum in different solvents followed by quenching with the α-aminoether **2** (Table 1, entries 1–4). We were pleased to observe full conversion and perfect selectivity for the transformation of the aluminum enolate to the desired product **4a** in diethyl ether (entry 4). Also in all other tested solvents the aluminum species present in the mixture were able to activate the α-aminoether and the trapped product **4a** was obtained in selectivities higher than 63%.

Next, the amount of trimethylaluminum and α-aminoether **2** could be decreased to 1.2 and 1.5 equiv respectively (entries 5–6). This is remarkable because aluminum and also zinc enolates are able to transfer the remaining alkyl substituents on the metal in significant amounts.[17] The fact that no large excess of the electrophile is needed displays

(9) Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904.
(10) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed.* **1971**, *10*, 330.
(11) (a) Robinson, G. M.; Robinson, R. *J. Chem. Soc., Trans.* **1923**, *123*, 532. (b) Theodore Stewart, A., Jr.; Charles, R. *J. Am. Chem. Soc.* **1955**, *77*, 1098. (c) Yankep, E.; Charles, G. *Tetrahedron Lett.* **1987**, *28*, 427. (d) Yankep, E.; Kapnang, H. *Tetrahedron Lett.* **1989**, *30*, 7383.
(12) Miginiac, L.; Mauze, B. *Bull. Soc. Chim. Fr.* **1968**, *6*, 2544.
(13) (a) Germon, C.; Alexakis, A.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1984**, *9–10*, 377. (b) Epsztein, R.; Le Goff, N. *Tetrahedron Lett.* **1985**, *26*, 3203.
(14) Germon, C.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1980**, *21*, 3763.
(15) Bilčík, F.; Drusan, M.; Marák, J.; Šebesta, R. *J. Org. Chem.* **2012**, *77*, 760.
(16) (a) Alexakis, A.; Albrow, V.; Biswas, K.; d'Augustin, M.; Prieto, O.; Woodward, S. *Chem. Commun.* **2005**, 2843. (b) Hawner, C.; Müller, D.; Gremaud, L.; Felouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769. (c) Müller, D.; Tissot, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 3040.
(17) Rathgeb, X.; March, S.; Alexakis, A. *J. Org. Chem.* **2006**, *71*, 5737.

Table 1. Initial Trapping Test Reactions with the Aminoether **2**[a]



3a: R = Me
3b: R = *i*-Bu

4a: R = Me, R' = Me
4b: R = Me, R' = Et
4c: R = *i*-Bu, R' = Me

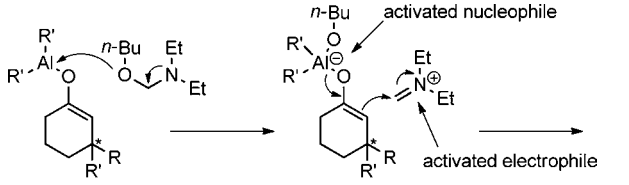
entry	R	MR'_X	solv.	**2** (equiv)	GC yield (%)[d]
1	Me	$AlMe_3$	THF	3	87
2	Me	$AlMe_3$	Tol	3	67
3	Me	$AlMe_3$	DCM	3	63
4	**Me**	**$AlMe_3$**	**Et_2O**	**3**	**>95**
5[e]	Me	$AlMe_3$	Et_2O	3	>95
6[e]	Me	$AlMe_3$	Et_2O	1.5	>95
7[e,f]	**Me**	**$AlMe_3$**	**Et_2O**	**1.5**	**>95**
8[e,f]	***i*-Bu**	**$AlMe_3$**	**Et_2O**	**1.5**	**93**
9	Me	MeMgBr	Et_2O	3	0
10	Me	$ZnEt_2$	Et_2O	3	54
11[g]	Me	MeMgBr	Et_2O	3	0
12[g]	Me	$ZnEt_2$	Et_2O	3	47

[a] Reactions performed on a 0.3 mmol scale, under a N_2 atmosphere with 2 equiv of the organometallic reagent. [b] In the case of zinc or Grignard reagents 5 mol % copper(II) triflate were used. In the case of aluminum reagents a solution of copper(II) naphthenate in pentane was used (5 mol %). [c] In the case of zinc or Grignard reagents 6 mol % of an *N*-heterocyclic carbene were used (see Supporting Information). In the case of aluminum reagents 6 mol % of SimplePhos ligand **7** were used (see Table 2). [d] Yield after the second reaction step, determined by GC-MS (see Supporting Information). [e] 1.2 equiv of the aluminum reagent was used. [f] Trapping reaction: 3 h instead of 15 h. [g] 1.0 equiv of trimethylaluminum was added after addition of the aminoether **2**.

the clear preference of aluminum to transfer the enolate and not the methyl groups to the iminium electrophile. In the following the reaction time could be decreased to 3 h without any loss in conversion or selectivity (entry 7). The optimized reaction conditions were then used with a new substrate **3b** that possesses a bulky isobutyl substituent in the β-position. To our delight even the corresponding sterically encumbered aluminum enolate reacted cleanly to afford the desired product **4c**. Full conversion and still a high selectivity of 93% was observed after a short reaction time of 3 h which underlines again the high efficiency of this transformation (entry 8).

During our optimization the decrease of trimethylaluminum to 1.2 equiv drew our attention because there was not more than 0.2 equiv of free trimethylaluminum left to activate the α-aminoether **2**. This means that the aluminum enolate itself is able to activate the α-aminoether, since full conversion to the trapped product is observed. To gain deeper insight into the reaction mechanism the trapping reaction was repeated with zinc and magnesium enolates which were created under similar reactions conditions.[18] In the case of the magnesium enolate no trapping product could be detected whereas the zinc enolate gave the desired product with a selectivity of 54% (entries 9–10). Knowing that the Lewis acidity of these reagents is much lower compared to aluminum, 1.0 equiv of trimethylaluminum was added after the addition of the α-aminoether. The examples before have shown that this reagent can activate the α-aminoether and furnish the desired product. Nevertheless still no product was obtained from the magnesium enolate, and also in the case of zinc no improvement of the result could be achieved (entries 11–12). These surprising results lead us to the assumption that not only the presence of aluminum species but also especially the presence of an aluminum enolate is detrimental to a highly selective reaction. It is known that the reaction of a trialkyl aluminum compound with a Lewis base forms a so-called aluminate where the nucleophilicity of the substituents on the aluminum is strongly enhanced. Cramer and co-workers have already shown that this works also with aluminum enolates which can be activated by stoichiometric amounts of methyllithium.[6c] Therefore we think that our aluminum enolate plays a double role in the reaction (Scheme 3). The coordination of the α-aminoether **2** to an aluminum enolate and the subsequent transfer of the *n*-butoxy group to the aluminum could not only form the desired electrophile but also activate the enolate in the same step. The formation of a good electrophile and a good nucleophile at the same time in close proximity could explain the high efficiency of the transformation.

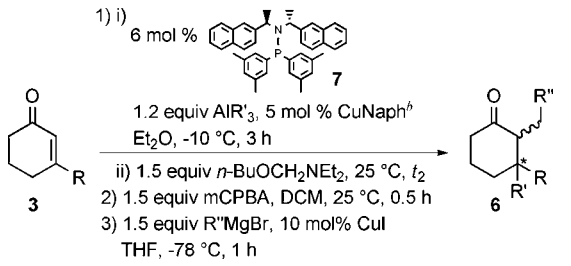
Scheme 3. Proposed Reaction Mechanism

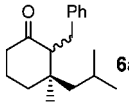
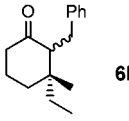
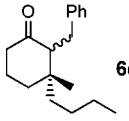
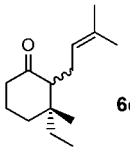
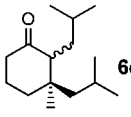
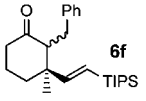
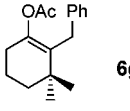


For the formation of the desired double bond we chose a subsequent oxidation elimination sequence. First we tried a one-pot procedure, but the elimination step was quite sluggish and seemed to be hampered by the aluminum species or amines in the mixture. Even changing the diethyl ether to DCM, which is the standard solvent for this type of reaction, did not allow full conversion after several hours. Since the oxidation and elimination in a separate reaction needed only 30 min to reach full conversion, we decided that a workup after the trapping reaction was the most practical. The alternative methylation with MeI also gave inferior results for this elimination. In the following, products **5** turned out to be unstable toward dimerization and could not be purified or stored for a long time. Nevertheless products **5** were obtained with just minor impurities after the three reaction steps, which was confirmed by NMR and GC-MS analysis. Therefore it was possible to carry out the following conjugate addition to the exocyclic double bond again without prior purification. All products **6** were finally isolated by column chromatography after the last step which constitutes an altogether four-step process with one single purification.

(18) The generation of the enolates was tested to be complete and with a GC yield of 80–95%. For further information, see the Supporting Information.

Table 2. Initial Trapping Test Reactions with the Aminoether **2**[a]



entry	R'	product[c]	t_2 (h)	dr	yield (%)[d]	ee (%)[e]
1	Me	 **6a**	3	3:2	37 (78)	97
2	Et	 **6b**	3	3:2	41 (80)	98
3[f]	*n*-Bu	 **6c**	6	1:1	27 (72)	96
4	Et	 **6d**	3	2:1	35 (81)	98
5	Me	 **6e**	3	7:3	24 (70)	97
6	Me	 **6f**	6	2:1	30 (74)	96
7[g]	Me	 **6g**	3	-	35 (81)	-

[a] Reactions performed on a 1.0 mmol scale, under a N_2 atmosphere. [b] CuNaph = solution of copper(II) naphthenate in pentane. [c] Absolute configuration according to published results (see Supporting Information). [d] Isolated yield over four steps. Average yield per step in parentheses. [e] Determined from a small sample after the asymmetric conjugate addition by chiral GC. [f] Reaction time for the ACA was 6 h. [g] Ac_2O was added after the Grignard addition, 1 h at −78 °C.

After having established the reaction sequence we investigated different combinations of substrates, aluminum reagents, and nucleophiles (Table 2). First different trialkylaluminum sources were used. The trapping reaction worked equally well with larger alkyl groups although a slightly longer reaction time was needed. The products could be isolated in 27% to 41% yield, and the corresponding average yields per step lay between 72% and 80% (entries 1−3). Although the aluminum enolates play an important role, the trapping step was not hampered by the larger substituents such as *n*-butyl (entry 3). In the next step the Grignard reagent for the second conjugate addition was changed. Alkyl and alkenyl nucleophiles worked equally well as the phenyl Grignard before, and it was even possible to install two vicinal isobutyl substituents on the cyclohexanone **6e**. The sequence delivered the highly encumbered product in an acceptable overall yield of 24% or 70% per step respectively (entry 5). Another valuable compound is product **6f** which can be further functionalized on the protected double bond. In this case it was crucial for the first ACA step to use a large silyl group which can prevent the otherwise favored 1,6-addition. On the other hand the bulky substituent is unfavorable for the subsequent α-functionalization. Nevertheless trapping with the α-aminoether **2** worked smoothly, and the final product **6f** was isolated in 30% yield over the four steps (entry 6). Notably, high enantioselectivities between 96% and 98% ee were reached for all products due to the high efficiency of the SimplePhos ligand **7**. The diastereomeric ratios lay between 1:1 and 7:3 and increased with the increasing size of the substituents. Finally the intermediate magnesium enolate was reacted in a fifth step with acetic anhydride, and compound **6g** was obtained in a 35% yield or an 81% average yield respectively. This extension of the methodology shows already how to avoid the problem of diastereoselectivity.

In conclusion we developed a four-step sequence involving an unprecedented electrophilic trapping reaction with an α-aminoether. This one-pot functionalization of aluminum enolates works with just 1.5 equiv of the reagent, it does not need any additional Lewis acid, and it still works efficiently next to quaternary stereogenic centers. After the complete sequence highly functionalized cyclohexanone derivatives **6** were obtained in good overall yields.

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Supporting Information Available. Experimental procedures, NMR spectra, and chiral separations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.