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Highly Chemoselective Reduction of Carbonyl Groups in the Presence of Aldehydes

Gulluzar Bastug, Steve Dierick, Frédéric Lebreux, and István E. Markó*

Université Catholique de Louvain, Laboratory of Organic and Medicinal Chemistry, Bâtiment Lavoisier, Place Louis Pasteur 1 bte L4.01.02., B-1348 Louvain-la-Neuve, Belgium

istvan.marko@uclouvain.be

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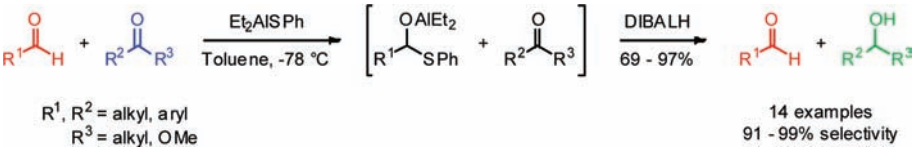
ABSTRACT



The exquisite ability of diethylaluminum benzenethiolate to efficiently discriminate between aldehydes and other carbonyl functions enables the chemoselective *in situ* reduction of ketones and methyl esters in the presence of aldehydes. This potent strategy avoids the usual drawbacks of traditional protecting group methodologies and could be extended to various other transformations.

Functional Group Interconversions (FGIs) form a central theme in organic chemistry.[1] Among them, modifying the oxidation state of carbonyl groups is of crucial importance.[1,2] The chemoselective reduction of aldehydes in the presence of less reactive carbonyl functions can be easily achieved using specially designed reagents.[3] However, the opposite transformation, i.e. the reduction of a carbonyl group, such as a ketone or an ester, in the presence of an aldehyde remains elusive.

Although specific protecting groups for aldehydes have been introduced,[4] several drawbacks still persist. In particular, their use in polyfunctional molecules is sometimes difficult and unselective. Moreover, this protecting group methodology requires a three-step process: protection, reaction, and deprotection. Accordingly, it is hardly surprising that modern synthetic endeavors, aimed at efficiency and convergency, will try to avoid such practice by attempting to minimize the number of steps, decreasing the amount of byproduct and saving time.[5]

A more elegant strategy can solve most of these shortcomings. Indeed, the aldehyde can be reversibly transformed *in situ* in an unreactive derivative, leaving other untouched carbonyl groups to react. This principle has been successfully applied by Reetz and Yamamoto for the chemoselective alkylation of ketones in the presence of aldehydes.[6] In his pioneering work, Luche used lanthanoids for the hemiacetalization of aldehydes, enabling the selective reduction of ketones.[7] Unfortunately, this aqueous system displays moderate selectivities and is limited to aliphatic substrates. In a one-pot procedure, Paradisi preferentially converted aldehydes into imines before reducing ketones with an alumino-hydride reagent, eventually releasing the unreacted aldehydes.[8] However, the intermediate imine is too reactive to extend this methodology to other transformations.

As part of an ongoing research program, aimed at the efficient assembly of α-methylene-γ-butyrolactones, we have recently reported a novel tandem Claisen−ene rearrangement (Scheme 1).[9] In the course of this process,

(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New-York, 1995.

(2) (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996. (b) Hudlický, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH: Weinheim, 2007.

(3) Burke, S. D.; Danheiser, R. L. *Handbook of Reagents for Organic Synthesis. Oxidizing and Reducing Agents*; Wiley: Chichester, 1999.

(4) (a) Kocieński, P. J. *Protecting Groups*, 3th ed.; Thieme: Stuttgart, 2004. (b) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: Hoboken, NJ, 2007.

(5) (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784. (b) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010. (d) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193.

(6) (a) Reetz, M. T.; Wenderoth, B.; Peter, R. *J. Chem. Soc., Chem. Commun.* **1983**, 406. (b) Maruoka, K.; Araki, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, 3101.

(7) (a) Gemal, A. L.; Luche, J.-L. *J. Org. Chem.* **1979**, *44*, 4187. (b) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

(8) Paradisi, M. P.; Zecchini, G. P.; Ortar, G. *Tetrahedron Lett.* **1980**, *21*, 5085.

(9) Leclercq, C.; Markó, I. E. *Tetrahedron Lett.* **2005**, *46*, 7229.

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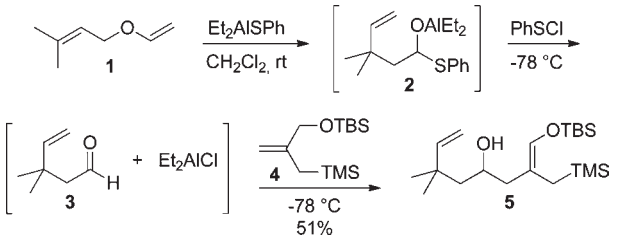
diethylaluminum benzenethiolate (Et_2AlSPh),[10] which was used as a mild Lewis acid to catalyze the initial Claisen rearrangement, added to the *in situ* generated aldehyde as soon as it was formed. The resulting *O*,*S*-aluminum acetal **2** proved to be surprisingly robust, and the aldehyde **3**, needed for the subsequent ene reaction, had to be unmasked by the addition of phenylsulfenyl chloride.[11]

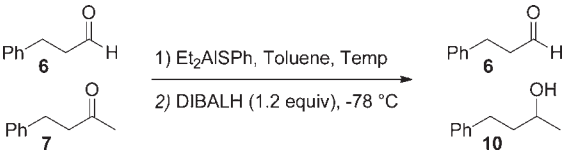
Scheme 1. Tandem Claisen–Ene Rearrangement



Attracted by this unexpected reactivity, we investigated the behavior of this particular Lewis acid toward various aldehydes and ketones. In the event, hydrocinnamaldehyde (**6**) and benzylacetone (**7**) were reacted individually, at −78 °C, with diethylaluminum benzenethiolate in hexane giving the corresponding *O*,*S*-aluminum acetals **8** and **9**, respectively (Figure 1). According to the ^{13}C NMR analyses of the crude reaction mixtures measured at 25 °C, we were pleased to notice that (i) aldehyde **6** was completely transformed into the acetal **8** and did not undergo a Tishchenko reaction (spectrum A)[12,13] and (ii) ketone **7** reacted partially to give ketal **9** (spectrum B). In a competitive experiment, hydrocinnamaldehyde (**6**) and benzylacetone (**7**) were treated with 1 equiv of Et_2AlSPh. Gratifyingly, aldehyde **6** was smoothly converted into the acetal **8** while the ketone **7** remained unaltered (spectrum C).

Encouraged by these preliminary observations, we designed a protocol for the selective reduction of benzylacetone (**7**) in the presence of an equimolar amount of hydrocinnamaldehyde (**6**). Some relevant results are presented in Table 1. It transpires, from this optimization study, that the temperature for the formation of the acetal is, as expected, crucial; the lower the temperature, the better the selectivity and the higher the yield (entries 2–5). Another important parameter to control proved to be the quantity of diethylaluminum benzenethiolate. Indeed, if a near-stoichiometric quantity of this reagent is employed, the selectivity drops to 78% (entry 6). On the other hand, the use of 1.4 equiv of this Lewis acid provides the highest levels of chemoselectivity albeit at the expense of the conversion (entry 7).[14] The best compromise between high selectivity and good yield involves the use 1.1 equiv of Et_2AlSPh. Furthermore, the temperature of reduction also has some influence on the selectivity and should be at −78 °C or below. Finally, replacing toluene with dichloromethane or tetrahydrofuran does not improve the yield but decreases the selectivity (entries 8, 9).

Table 1. Optimization of the Chemoselective Reduction of Hydrocinnamaldehyde (**6**) in the Presence of Benzylacetone (**7**)



entry	temp	Et_2AlSPh	selectivity[a]	yield[b]
1[c]	–	0 equiv	0%	50%
2	rt	1.1 equiv	42%	65%
3[d]	−15 °C	1.1 equiv	48%	68%
4	−15 °C	1.1 equiv	66%	77%
5	**−78 °C**	**1.1 equiv**	**98%**	**89%**
6	−78 °C	1.02 equiv	78%	81%
7	−78 °C	1.4 equiv	99%	72%
8[e]	−78 °C	1.1 equiv	88%	86%
9[f]	−78 °C	1.1 equiv	85%	89%

[a] Selectivity is defined as (secondary alcohol − primary alcohol)/(secondary alcohol + primary alcohol) and determined by GC. [b] GC yields measured with dodecane (1 equiv) as an internal standard. [c] 1.0 equiv of DIBALH was used. [d] Reduction was performed at −15 °C. [e] Toluene was replaced by CH_2Cl_2. [f] Toluene was replaced by THF.

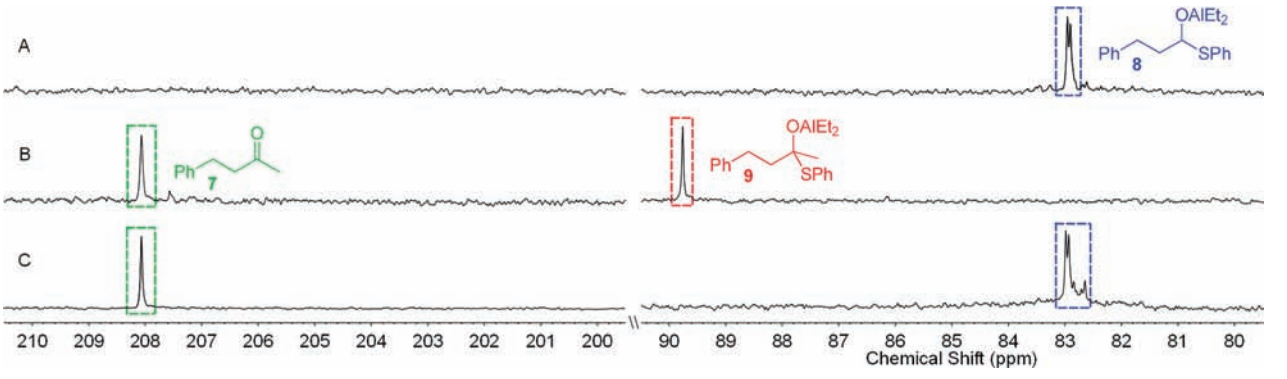
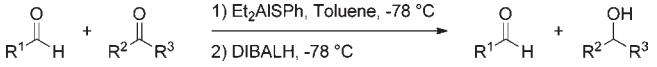
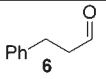
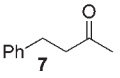
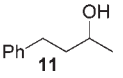
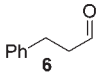
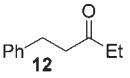
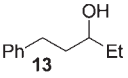
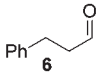
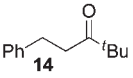
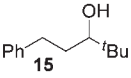
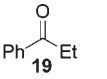
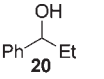
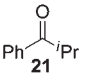
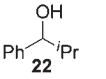
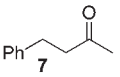
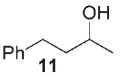
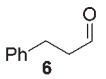
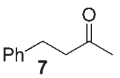
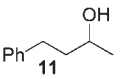
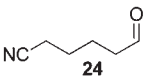
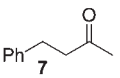
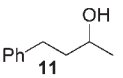
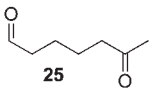
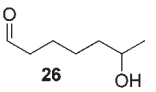
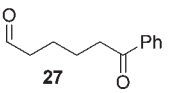
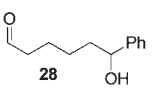


Figure 1. Partial ^{13}C NMR spectra of the aluminum adducts.

Table 2. Chemoselective Reduction of Ketones



entry	aldehyde	ketone	product	selectivity[a]	yield[b]
1	 **6**	 **7**	 **11**	98%	89%
2	 **6**	 **12**	 **13**	97%	85%
3	 **6**	 **14**	 **15**	99%	84%
4	 **16**	 **17**	 **18**	91%	85%
5	 **16**	 **19**	 **20**	91%	82%
6	 **16**	 **21**	 **22**	97%	82%
7	 **23**	 **7**	 **11**	> 99%[c]	91%[d]
8[e]	 **6**	 **7**	 **11**	97%	89%
9	 **24**	 **7**	 **11**	97%	86%
10	 **25**		 **26**	92%	69%[d],[f]
11	 **27**		 **28**	98%	79%[d],[f]

[a] Selectivity is defined as (secondary alcohol − primary alcohol)/(secondary alcohol + primary alcohol) and determined by GC for intermolecular reaction and by ^{1}H NMR for intramolecular reaction. [b] GC yields measured with dodecane (1 equiv) as an internal standard. [c] No trace of neopentylalcohol was detected in the crude mixture by GC. [d] Isolated yields after column chromatography on silica gel. [e] Performed in the presence of 1-octyne (1 equiv). [f] Isolated as the acetate derivative.[15]

With the optimization study completed, the scope and limitations of this novel, chemoselective reduction methodology were investigated next (Table 2). In the aliphatic series, increasing the steric hindrance around the ketone function has little effect on the selectivity and yield. Both remain excellent (entries 1−3). The aromatic substrates give slightly lower yields and selectivities (entries 4−6). It is worth noting that, in these cases, an important influence of steric hindrance is operating, with the isopropyl group significantly raising the selectivity. An impressive result arises from the reduction of benzylacetone in the presence of pivalaldehyde. In this case, no trace of neopentyl alcohol could be detected (entry 7). Thus, a quaternary center α to the aldehyde group does not prevent the formation of the corresponding *O*,*S*-acetal. Moreover, functionalities sensitive to diisobutylaluminum hydride, such as alkynes and nitriles, are well tolerated under these conditions (entries 8, 9). Finally, the synthetically useful intramolecular version of our protocol proceeds smoothly to give outstanding selectivities and good yields (entries 10, 11).[15]

(10) (a) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 446. (b) Mori, I.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron* **1984**, *40*, 4013. (c) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 3985.

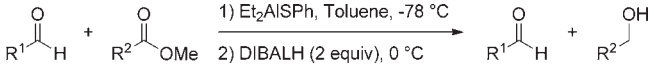
(11) The addition of PhSCl to the *O*,*S*-aluminum acetal **2** afforded not only inert $(PhS)_2$ but also Et_2AlCl, the Lewis acid required for the ene reaction, thereby increasing further the efficiency of the overall process.

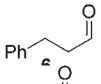
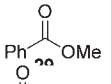
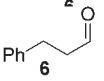
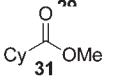
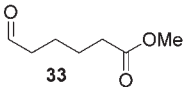
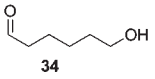
(12) The presence of several signals around 83 ppm in the ^{13}C NMR spectrum of **8** suggests that this species might exist in a dimeric form or even as an oligomeric assembly. Studies are currently underway to establish the aggregation state of **8** in solution.

(13) Cronin, L.; Manoni, F.; O' Connor, C. J.; Connon, S. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3045.

(14) Using a large excess of diethylaluminum benzenethiolate leads to the partial ketalization of the ketone which could not be reduced further.

Table 3. Chemoselective Reduction of Methyl Esters



entry	aldehyde	ester	product	selectivity[a]	yield[b]
1				> 99%[c]	97%
2				> 99%[c]	93%
3				98%	71%[d]

[a] Selectivity is defined as (alcohol from ester − alcohol from aldehyde)/(alcohol from ester + alcohol from aldehyde) and determined by GC for intermolecular reaction and by ^{1}H NMR for intramolecular reaction. [b] Isolated yields after column chromatography on silica gel. [c] No trace of hydrocinnamic alcohol was detected in the crude mixture by GC. [d] Isolated as the acetate derivative.[15]

Having successfully demonstrated the synthetic potential of our methodology, we turned our attention to the more challenging reduction of methyl esters in the presence of aldehydes. Some of our results are collected in Table 3. In these cases, 2 equiv of diisobutylaluminum hydride have been used in the reduction step which was performed at 0 °C. Pleasantly, the reduction of both aromatic and aliphatic methyl esters could be accomplished in good yields and with excellent levels of chemoselectivity in the presence of an aliphatic aldehyde (entries 1, 2). An intramolecular version of this process gave remarkable selectivity, though the yield was slightly lower (entry 3).[15]

In summary, the reduction of ketones and methyl esters in the presence of aldehydes was achieved with high yields and excellent chemoselectivity. The method is efficient for both aliphatic and aromatic substrates and tolerates increasing steric hindrance around both carbonyl groups. Moreover, all the reagents employed in this reaction are commercially available and cheap.[16] Further studies on extending this methodology to various nucleophilic additions on differentially activated carbonyl functions are actively being pursued in our laboratory. The results of our progress will be reported in due course.

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Supporting Information Available. Full experimental and characterization details for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Since the resulting hydroxy aldehydes were in equilibrium with their hemiacetal forms, they were acetylated in order to obtain unambiguous characterization data.

(16) Diethylaluminum benzenethiolate is easily prepared *in situ* from triethylaluminum and thiophenol.

The authors declare no competing financial interest.