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Carbon-Carbon Bond Formation Catalyzed by Lithium Perchlorate in Dichloromethane

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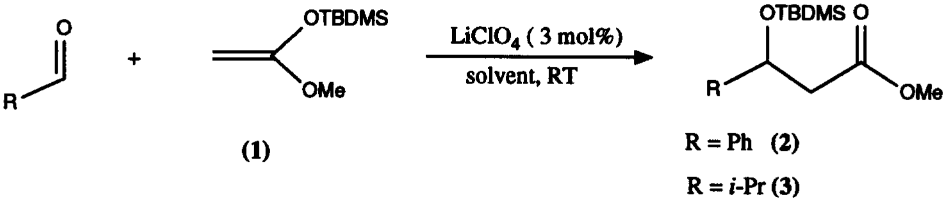
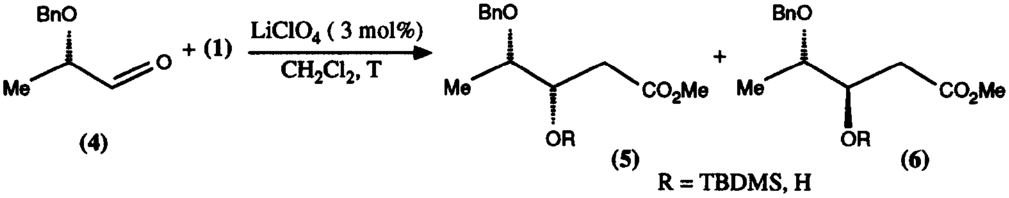
Summary: *A catalytic amount of lithium perchlorate suspended in dichloromethane provides a mild and effective medium for Mukaiyama aldol reactions of aldehydes with silyl ketene acetal* (**1**). *2-Cyclohexenone undergoes clean 1,4-addition under similar conditions. Catalyst activity is much higher in dichloromethane than in diethyl ether.*

Concentrated homogeneous solutions of lithium perchlorate ($LiClO_4$) in diethyl ether (1-5 M) induce a variety of synthetically interesting transformations.[1] An inherent disadvantage of such a reaction medium is the environmental implication associated with disposal of the excess perchlorate. Recently, we reported on the use of both excess and catalytic (3 mol%) $LiClO_4$ as a Lewis acid in diethyl ether for mediating Mukaiyama aldol reactions.[2] A high degree of diastereoselectivity was observed with a chiral α-benzyloxyaldehyde as substrate and this was attributed to a chelation control mechanism.[3] The catalytic transformations in diethyl ether are rather sluggish, however, in the case of simple aldehydes. For example, the reaction of benzaldehyde with the silyl ketene acetal (**1**) (TBDMS = *t*-butyldimethylsilyl) requires 5 days at room temperature to reach 86% conversion.[4]



It was of interest, therefore, to find conditions that accelerate such catalytic transformations. We now report on the use of catalytic amounts of $LiClO_4$ suspended in dichloromethane as a mild and efficient means for effecting C-C bond formation. Addition of 3 mol% $LiClO_4$ to a solution of benzaldehyde and (**1**) in dichloromethane led to complete conversion to the *O*-silylated product (**2**) within 15 min. This was isolated in quantitative yield following silica gel chromatography.[5] Aliphatic aldehydes were found to react less rapidly under similar conditions. Nevertheless, a reaction time of 18 h at room temperature sufficed for complete conversion of *iso*-butyraldehyde to the desired product (**3**), isolated in 87% yield. In these reactions the $LiClO_4$ does not dissolve, which suggests that heterogeneous catalysis may be involved. Furthermore, the catalyst is recyclable. Thus, following completion of the Mukaiyama addition the reaction mixture could be decanted from the lithium salt which was then used in a further reaction. This led to equally effective catalysis both in terms of reaction time and yield.

Chelation control could be realised in the reaction of **(1)** with the chiral aldehyde **(4)** (Bn = benzyl). Clean conversion was achieved within 20 minutes at room temperature (Scheme) and the addition products **(5)** and **(6)** were obtained as a mixture of predominantly silylated and desilylated (5-12%) aldols in an overall ratio of 86:14 **(5)**:**(6)**.[6] Once again, the preferential formation of the *syn*-product **(5)** is explained in terms of a chelated intermediate.[2]



(4) **(5)** **(6)**

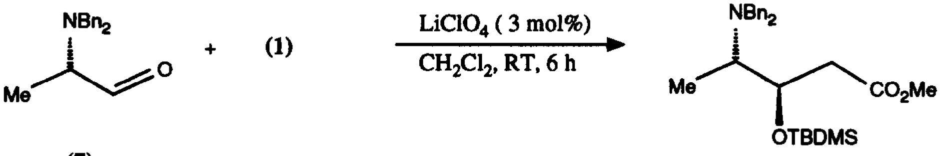
R = TBDMS, H

Temperature (T/ °C)	**Reaction time**	**(5):(6)**
22	20 min	86:14
-15	3 h	90:10
-30	4 h	92: 8

The diastereoselectivity of the process increased somewhat with decreasing temperature and at -30°C the *syn*:*anti* ratio was determined to be 92:8, conversion being complete after 6 h. Treatment of the combined reaction mixture with 40% aqueous HF in acetonitrile effected desilylation and the free aldol was isolated in 84% overall yield.

As before, the $LiClO_4$ remained undissolved during the course of the reactions. In an ether medium, $LiClO_4$ is able to form soluble etherates and it is conceivable that this factor is directly responsible for the difference between the two solvent systems. $LiClO_4$ acts as a Lewis acid in these reactions by coordinating with the carbonyl function, leading to activation.[7] In ether, the substrate is in competition with the solvent for coordination to the lithium cation whereas in dichloromethane, no such competition exists, and enhanced reactivity is observed inspite of poor (or no) solubility.

Another example of the use of $LiClO_4$/dichloromethane pertains to the reaction of the *N,N*-dibenzyl-protected amino aldehyde (7) derived from L-alanine. Smooth aldol reaction with (1) in the presence of catalytic quantities of $LiClO_4$ was observed at room temperature. The transformation, when attempted in diethyl ether, is successful only when an excess of the lithium salt (5 M) is used. The product (8) is obtained as a single diastereoisomer, corresponding to non-chelation control (93% conversion, 58% isolated yield).

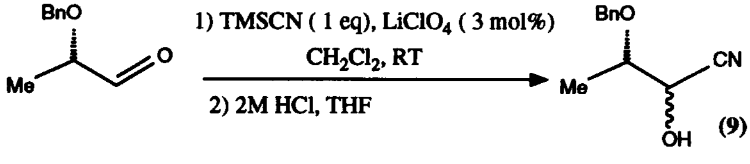


(7) (8)

diastereoselectivity > 98%

N,N-Dibenzylamino aldehydes show a high propensity for non-chelation control in a variety of nucleophilic addition reactions.[8] Thus, the magnesium chloride-mediated aldol addition of enolsilanes occurs with non-chelation control, but the resultant aldols undergo rearrangement under the reaction conditions.[9] This is not observed in the present system.

$LiClO_4$ also proved to be a catalyst for the addition of trimethylsilyl cyanide (TMSCN) to the aldehyde **(4)** in dichloromethane. The reaction proceeds within 16 h at room temperature with 3 mol% catalyst and subsequent acidic work-up (2M HCl/THF) led to isolation of the corresponding cyanohydrin **(9)** in 87% yield. In contrast to the Mukaiyama reaction, however, the diastereoselectivity of the TMSCN addition was poor (57:43, *syn*:*anti*) which may be attributed to reversibility of the reaction.[10]

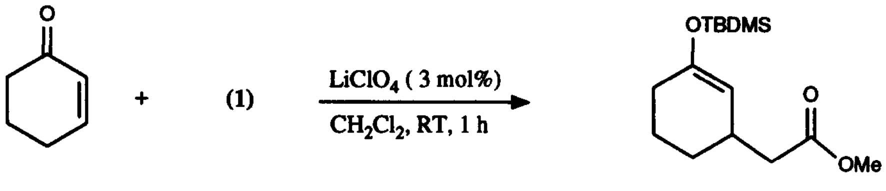


(9)

(4)

syn:*anti* 57:43

Finally, we were interested to determine whether the enhanced activity of $LiClO_4$ in dichloromethane would enable conjugate additions of **(1)** to α,β-unsaturated ketones to be realised under catalytic conditions.[11] To this end, the addition of **(1)** to 2-cyclohexenone was attempted under the standard conditions.[12] Complete and regioselective conversion to the desired adduct **(10)** was in fact achieved within 1 h (> 97% isolated yield) in a group transfer type of process.[13]



(10)

In summary, we have discovered that a suspension of 3 mol% of $LiClO_4$ in dichloromethane provides a considerably more reactive medium than homogeneous solutions in diethyl ether for Mukaiyama aldol reactions and 1,4-additions to α,β-unsaturated ketones. Depending on the substrate, chelation- or non-chelation control additions to funtionalised aldehydes can be achieved catalytically and the catalyst may be recycled with no observable loss in efficacy. Thus, $LiClO_4$ in dichloromethane is a viable alternative to related catalytic systems.[4,12-14]

Further studies on the use of lithium salts as Lewis acid catalysts in selective C-C bond-forming processes are in progress in our laboratories.

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3 Subsequent GC analysis indicated slightly reduced stereoselectivity (up to 94:6) than that originally reported and between 5 and 15% desilylated product.

4 For previous examples of Lewis acid catalyst systems for Mukaiyama reactions see: (a) Sato, S.; Matsuda, I.; Izumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5517. (b) Reetz, M.T.; Vougioukas, A.E. *ibid.* **1987**, *28*, 793. (c) Mukaiyama, T.; Kobayashi, S.; Tamura, M.; Sagawa, Y. *Chem. Lett.* **1987**, 491. (d) Wada, M.; Takeichi, E.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 990. (e) Le Roux, C.; Maraval, M.; Borredon, M.E.; Gaspard-Iloughmane, H.; Dubac, J. *Tetrahedron Lett.* **1992**, *33*, 1053. (f) Odenkirk, W.; Whelan, J.; Bosnich, B. *ibid.* **1992**, *33*, 5729. (g) Terada, M.; Gu, J.H.; Deka, D.C.; Mikami, K.; Nakai, T. *Chem. Lett.* **1992**, 29. (h) Bach, T.; Fox, D.N.A.; Reetz, M.T. *J. Chem. Soc., Chem. Commun.* **1992**, 1634.

5 **Typical procedure for LiClO$_4$-mediated Mukaiyama reaction in dichloromethane:** To a solution of benzaldehyde (0.05 ml, 0.50 mmol) in dichloromethane (10 ml) was added the silyl ketene acetal **(1)** (110 mg, 0.55 mmol) followed by LiClO$_4$ (dried under vacuum, 150°C, 16 h) (1-2 mg, 3 mol%). The reaction was stirred at room temperature under argon for 15 min, then treated with saturated aqueous NaHCO$_3$, the organic layer was separated, dried (MgSO$_4$) and concentrated in vacuum. The residue was chromatographed on silical gel, eluting with hexane/ethyl acetate (10:1) to afford **(2)** as a colourless oil (172 mg, 100%).

6 Ratio determined by GC analysis.

7 See (a) Lefour, J.-M.; Loupy, A. *Tetrahedron* **1978**, *34*, 2597. (b) Loupy, A.; Meyer, G.; Tchoubar, B. *Tetrahedron* **1978**, *34*, 1333. (c) Murthy, A.S.N.; Bhardwaj, A.P. *J. Chem. Soc., Perkin Trans. 2* **1984**, 727.

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10 The use of stoichiometric quantities of Lewis acid (e.g. TiCl$_4$, MgBr$_2$, SnCl$_4$) at -78°C leads to diastereomeric ratios between 74 : 26 and 80 : 20; see: Reetz, M.T.; Kesseler, K.; Jung, A. *Angew. Chem.* **1985**, *97*, 989; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 989.

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12 For recent examples of related Lewis acid-mediated 1,4-additions see: Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *45*, 6815 and references therein.

13 (a) Reetz, M.T.; Heimbach, H.; Schwellnus, K. *Tetrahedron Lett.* **1984**, *25*, 511. (b) Heimbach, H. *Dissertation*, Universität Marburg, 1982. (c) Webster, O.W.; Hertler, W.R.; Sogah, D.Y.; Farnham, W.B.; RajanBabu, T.V. *J. Am. Chem. Soc.* **1983**, *105*, 5706.

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