



A useful synthetic equivalent of an acetone enolate

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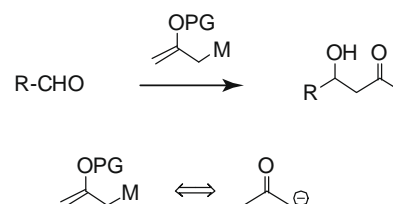
ABSTRACT

2-Methoxymethoxy-3-chloropropene derived organometallics act as synthetic equivalents of an acetone enolate. Indium-promoted reaction of this reagent with aldehydes affords aldol adducts in moderate to excellent yields. When the reaction was performed with zinc, aldol products were isolated in protected form as the corresponding MOM-enol ethers.

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The aldol reaction is an important tool for carbon–carbon bond formation in synthetic organic chemistry. This reaction allows for high levels of chemo-, regio-, diastereo- and enantioselectivity in the coupling of structurally complex reaction partners.¹ Ironically, the use of small, structurally simple proenolates can cause problems. Thus, acetone enolate is very difficult to be preformed, due to its high basicity and reactivity; therefore, aldol reactions of acetone are almost always performed under thermodynamic conditions. In most cases, the products of aldol condensation, that is, enones, are obtained, although a few examples are known where aldol adducts were isolated.² Under conventional experimental conditions, reactions with aromatic or conjugated aldehydes always produce Claisen–Schmidt-type products.³ A major breakthrough was the introduction of organocatalysis, which enabled the enantioselective aldol additions of acetone (and the related proenolates) to both aliphatic and aromatic aldehydes.⁴ Recently, aldolase antibodies have been shown to efficiently catalyze aldol additions of acetone.⁵ However, mechanistically different complementary methods for effecting this transformation are still required.⁶ It would also be desirable to obtain the aldol adduct in either free or latent (protected) form, by slight modification of the reaction conditions.

With this in mind we considered the allylation of aldehydes as an alternative approach for effecting the aldol reaction of acetone (Scheme 1). Indium- or zinc-mediated allylation of carbonyl groups



Scheme 1. Allylmetal as a synthetic equivalent of the acetone enolate.

is a well-known reaction, and the use of oxygenated allyl fragments is not without precedent.^{7,8} However, the oxygen-containing substituents have always been bound to the terminal positions of the allylic fragment.⁹ The use of 2-oxy-substituted allylmetallics, which would give rise to aldol-type products, has been far less investigated, maybe due to the anticipation of elimination of the oxy-substituent at the β -position with respect to the metal. To the best of our knowledge, only two such reactions have been reported: the first is the reaction of an 2-acetoxy-3-chloropropene-derived organostannane with aldehydes, which produces a mixture of the expected aldol and the corresponding enol acetate.¹⁰ The second example involves the reaction of a methoxy-substituted allylindium reagent with aldehydes, a procedure which was used as a synthetic equivalent of the Knoevenagel condensation.¹¹ We set out to explore the possibility of using 2-methoxymethoxy-3-chloropropene-derived organometallics as acetone enolate synthons. Interestingly, the parent compound has already been used as an electrophilic synthetic equivalent of acetone,

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Table 1
Indium-mediated reactions of 2-methoxymethoxy-3-chloropropene with aromatic aldehydes

Entry	Aldehyde	Product	Yield (%)
1			70
2			66
3			93
4			69
5			73
6			99
7			97

which effects acetylation of both carbon- and heteroatom-centered anionic species.¹²

Our first experiment comprised indium-mediated reaction of 2-methoxymethoxy-3-chloropropene with benzaldehyde, under Barbier conditions.¹³ Pleasingly, the aldol product was obtained in a good yield (Table 1, entry 1). It is of note that the product was obtained as the free aldol: this indicates that the deprotection step is assisted by the newly formed hydroxy group, as the organometallic reagent is not hydrolyzed under the reaction conditions. Other aromatic aldehydes behaved similarly, providing the expected products in good to excellent yields. In the case of thiophenecarbaldehyde, or furfural, simple filtration of the crude product through a short pad of silica afforded analytically pure products in essentially quantitative yields.

Aliphatic aldehydes behaved similarly, although the reactions were slower and the yields were somewhat lower (Table 2). With both aromatic and aliphatic aldehydes, the reaction was sometimes preceded by quite a long induction period (from several hours to even a day); activation of indium, by the addition of a catalytic amount of 1,2-dibromoethane, resolved this problem and the reactions started without a delay. The reaction works best with primary aldehydes, while with secondary aldehydes the conversions were slower and incomplete (e.g., entries 4 and 6). The reactions with aldehydes containing stereogenic centers were not stereoselective, as the products were obtained as equimolar mixtures of diastereoisomers (entries 6 and 8). A highly enolizable β -ketoester behaved as a nucleophile: apparently, an InCl_3 -catalyzed reaction

Table 2
Indium-promoted reactions with aliphatic aldehydes

Entry	Carbonyl compound	Product	Yield ^a (%)
1			50 (60)
2			59
3			85
4			40
5			57
6			35 ^b (45)
7			96
8			37 ^b (59)
9			87

^a Yield of isolated, pure compounds; yields in parentheses are calculated on the basis of recovered starting compounds.

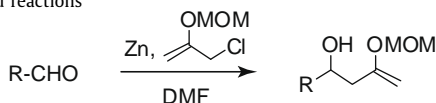
^b Obtained as an equimolar mixture of diastereoisomers. DMS = dimethylsilyl; Ms = mesyl.

with the formaldehyde synthon (MOM-ether) is much faster than the allylation (entry 9).

An attractive and synthetically useful variant of the reaction would be the preparation of the aldol adducts in protected form. When the reaction of 2-MOMO-allyl chloride with aldehydes was performed with zinc, under anhydrous conditions, the corresponding enol ethers were obtained (Table 3). The reaction works with both aromatic and aliphatic aldehydes, although the yields are somewhat lower, compared to the indium-promoted reactions. In order to suppress the relatively long induction periods, the zinc should be activated in situ by addition of a small amount of HgCl_2 and iodine to the reaction mixture.¹⁴ In the case of crotonaldehyde, pinacol coupling was a serious problem which reduced the yield (entry 5); cinnamaldehyde also furnished the corresponding pinacol as the dominant product, indicating that conjugated aldehydes, which are capable of strong stabilization of the radical anion generated by a single electron reduction, are not suitable substrates for this type of transformation.

In conclusion, we believe that the chemistry described offers a potentially useful complement to the existing methods of aldolization with acetone. Research directed towards the introduction of

Table 3
Zinc-promoted reactions



Entry	Aldehyde	Product	Yield ^a (%)
1			72
2			67
3			40
4	$n\text{-C}_{11}\text{H}_{23}\text{-CHO}$		49 (63)
5			35
6			54

^a Yield of isolated, pure compounds; yield in parentheses is calculated on the basis of recovered starting compound.

other protecting groups, as well as the application of this method to different enolate synthons is underway.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2009.09.113.

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- Typical experimental procedure*: A mixture of aldehyde (0.11 mmol), 2-methoxymethoxy-3-chloropropene (0.33 mmol), In powder (0.33 mmol), THF (0.3 mL), H₂O (0.9 mL) and one drop of 1,2-dibromoethane was stirred at rt, while the progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with H₂O, extracted with CH₂Cl₂, dried over anhyd MgSO₄ and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography on SiO₂ afforded the analytically pure product. Complete characterization data for all products can be found in the Supplementary data.
- Typical experimental procedure*: To a mixture of aldehyde (0.33 mmol), 2-methoxymethoxy-3-chloropropene (1 mmol) and Zn powder (1 mmol) in DMF (1 mL) were added catalytic amounts of HgCl₂ and I₂, and the reaction mixture was stirred at rt, while the progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was partitioned between Et₂O and NaHCO₃, the organic extract was washed with H₂O, dried over anhyd MgSO₄, concentrated under reduced pressure and purified by dry-flash chromatography on SiO₂, to afford the analytically pure product. Complete characterization data for all products can be found in the Supplementary data.