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Tandem radical addition–aldol condensations: evidence for the formation of zinc enolates in diethylzinc mediated radical additions to *N*-enoyloxazolidinones

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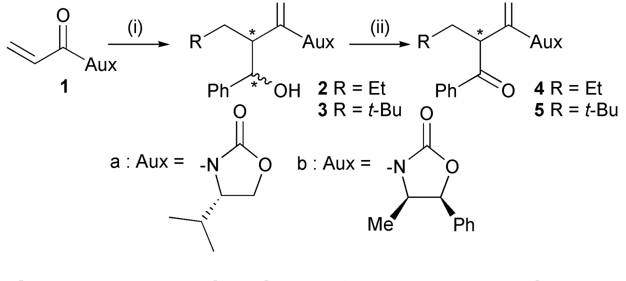
Diethylzinc mediated addition of alkyl radicals to chiral *N*-enoyloxazolidinones is immediately followed by homolytic substitution at zinc leading to a zinc enolate; the trapping of the latter in a subsequent aldol condensation serves as a useful mechanistic probe; overall this reaction sequence constitutes a novel example of a one pot, three-component, radical-polar crossover reaction.

The striking similarity between the reactivities of diethylzinc and triethylborane with regard to their ability to mediate radical additions to imines and enones has been demonstrated in our recent work.[1,2] When Et_2Zn was allowed to react with cyclohexenone in the presence of air and an alkyl iodide, a conjugate addition of the corresponding alkyl radical resulted.[2] Under inert atmosphere, Et_2Zn is reputed not to react with enones in the absence of any additive.[3] The proposed mechanism[2] implies a radical addition which finally leads to a zinc enolate through homolytic substitution at zinc by an intermediate enoxyl radical.

Following on from this work, we have shown that these reactions could be extended to acrylimides bearing an Evans-type oxazolidinone auxiliary.

These substrates were used to demonstrate the involvement of zinc enolates *via* the trapping of the latter with benzaldehyde. Similar experiments have already been reported for the trapping of boron enolates in the reaction of triethylborane with enones.[4] In this article, we describe the first example of a one-pot, diethyl zinc-mediated reaction between an alkyl iodide, an *N*-enoyloxazolidinone, and benzaldehyde. The results are given in Scheme 1 and in Table 1.

Enantioselective radical conjugate additions have been elegantly performed using a Lewis acid to control the transfer of chirality.[5] In all likelihood, according to Scheme 2, diethylzinc acts as a chelating agent. The addition of the alkyl radical is immediately followed by the formation of a covalent zinc–oxygen bond through an S_H2 reaction, which leads to a zinc enolate.



Scheme 1 *Reagents and conditions*: (i) $ZnEt_2$ (2 equiv.), PhCHO (1.1 equiv.), *t*-BuI (none or 10 equiv.), CH_2Cl_2, air (20 ml), −10 °C; (ii) PCC, CH_2Cl_2, room temp., quantitative.

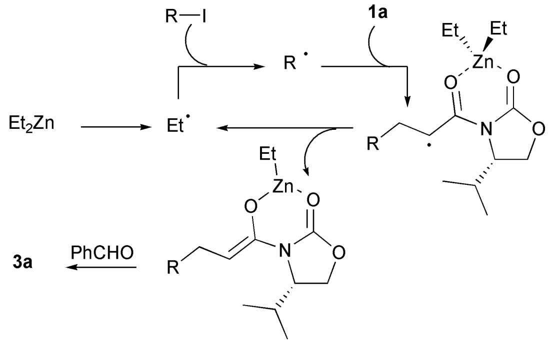
Copper(II)-catalysed enantioselective additions of diethylzinc to cyclohexenone followed either by aldol condensation,[6] or by the trapping of the enolate with an acetal[7] have recently been reported. In our model systems, the trapping of zinc enolates with benzaldehyde led to the corresponding aldols as mixtures of all four possible diastereomers which could not be separated. In order to simplify the analysis, the isolated mixture was immediately oxidised, which gave a mixture of two diastereomers in a ratio varying from 60:40 to 88:12.[8,9] In order to exclude the possibility that the measured diastereomeric ratio could have been affected by some epimerisation occurring during the oxidation step, both isomers of **5a** were reacted again separately with PCC in dichloromethane. No epimerisation was detected with either diastereomer.[10]

The addition of Et_2Zn to **1b**, when performed at −60 °C, resulted, after oxidation, in a lower overall isolated yield of **5b** (37%). No improvement in the diastereoselectivity was observed. The addition of *t*-butyl radical to both substrates provided strong evidence that a radical mechanism was indeed operating. However, in the case where diethylzinc was used alone, the contribution of a pure organometallic pathway to the formation of **4** could not be conclusively ruled out. When substrate **1b** was allowed to react with Et_2Zn alone and benzaldehyde, after repeated freeze–thaw pump cycles, 90% of

Table 1

Entry	Substrate	*t*-BuI	Product (yield %)	Oxidation product	D.r.[a]
a	**1a**	None	**2a** (84), m.i	**4a**	88:12
b	**1a**	10 equiv.	**3a** (71), m.i	**5a**	60:40
c	**1b**	None	**2b** (82), m.i	**4b**	88:12
d	**1b**	10 equiv.	**3b** (60), m.i	**5b**	77:23

[a] Diastereomeric ratio determined by NMR.



Scheme 2

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the starting material was converted into the corresponding aldol.

According to these results, it appears that *N*-enoyloxazolidinones behave similarly to enones[2] and not like other carboxylic α,β-unsaturated derivatives such as esters, which were shown not to react with boranes[11] and diethylzinc.[2] The reactivities of these different substrates correlate with the electron spin densities found on the oxygen atom in the intermediate enoxyl radical (Table 2): the higher the ρ value (*i.e.*, the more the unpaired electron is delocalised on oxygen), the higher the reactivity of the radical with respect to the S_H2 reaction at zinc.

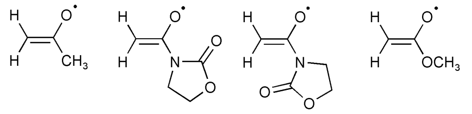
We have attempted to rationalise these results by performing *ab initio* DFT calculations at the UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31+G(d,p) level with the Gaussian 98 package.[12] We selected three simple radicals as models for the intermediates involved in the above mentioned reactions. The highest spin density was found for radical **a**, followed by radical **b**. Both radicals were shown to react with Et_2Zn *via* homolytic subtitution. Radical **c** possesses the lowest spin density on oxygen in the series, it does not react with diethylzinc. It is noteworthy that the spin density on the oxygen atom in **b** varies with the conformation around the C–N bond.

Surprisingly, these reactions did not work at all when triethylborane was used as the mediator. Only telomers were obtained. We have calculated the spin densities in the protonated radical **d** (Fig. 1) with a view to better account for the association of the second oxygen with diethylzinc. The calculated spin density on oxygen is dramatically increased. This might explain why diethylzinc is operative while triethylborane is not. However in the presence of Lewis acids such as BF_3 or $Yb(OTf)_3$ the reactions conducted with triethylborane did not give the desired aldols.

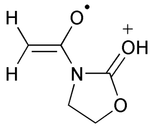
These reactions could be extended to the synthesis of γ-lactones according to Scheme 3. As an example, when treated with diethylzinc in the presence of *t*-BuI and benzaldehyde, the fumaric monoester **6** led to a completely regioselective reaction. Through a domino reaction ending with the lactonisation step, **7** was formed in high yield as a 87 : 13 mixture of diastereoisomers. The ratio was determined by NMR, from the dd signals of H_2 in both isomers at 5.03 and 4.76 ppm, respectively. The cleavage of the C–N bond with LiOOH[13] led to a unique isomer of acid **8** due to epimerisation.

In conclusion, the diethylzinc/O_2 mediated radical addition to *N*-enoyloxazolidinones, involves the formation of a zinc enolate. This allows the one-pot three component reaction of an alkyl iodide with an activated olefin, and benzaldehyde. This new protocol avoids the need to preform the enolate as required in standard procedures. Since an iodine atom transfer step to ethyl radical is involved in the reaction mechanism, the reaction is limited to the use of secondary or tertiary alkyl iodides. The scope of this reaction regarding the use of other types of alkyl radical precursors and its applications in other domino multicomponent processes is currently under investigation.

Table 2



	a	b *s-cis*	b *s-trans*	c
$\rho^{\alpha-\beta}$ (O)	0.3285	0.2807	0.2634	0.2179
$\rho^{\alpha-\beta}$ (CH_2)	0.8794	0.9204	0.9019	0.9460

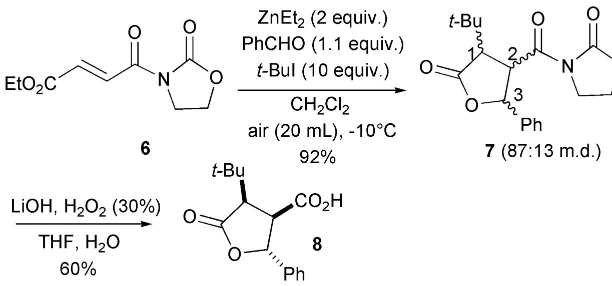


d

$\rho^{\alpha-\beta}$ (O) 0.3375

$\rho^{\alpha-\beta}$ (CH_2) 0.8405

Fig. 1



Scheme 3

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