## Me<sub>2</sub>Zn as a radical source in Reformatsky-type reactions

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Experimental evidence for the generation of radicals by  $Me_2Zn$  used in Reformatsky reactions was unequivocally established with a radical trap.

A renewed interest in the classical Reformatsky reaction, from the point of view of stereoselectivity, has emerged in recent literature.<sup>1</sup> We,<sup>2</sup> and Feringa et al.,<sup>3</sup> have recently described catalytic enantioselective Reformatsky reactions of Me<sub>2</sub>Zn and iodoacetate, with ketones, aldehydes and imines, in the presence of catalytic amounts of ClMn(salen) (20 mol%), N-methylephedrine (20-30 mol%) and 3,3'-trimethylsilylBINOL (20 mol%) derivatives as the chiral catalysts. In all these protocols, Me<sub>2</sub>Zn was used as a transmetallating reagent with iodoacetate. Although it was reported that the transmetallation between R<sub>2</sub>Zn and iodoacetate was feasible, discordant results were also obtained.<sup>4</sup> In these cases the most reactive Et<sub>2</sub>Zn was used. Me<sub>2</sub>Zn was by itself not able to transmetallate with ethyl iodoacetate, even if it was used in large excess. We have used air and other oxidants to promote the Reformatsky reaction, in order to favour the transmetallation.<sup>2d,5</sup> During these preliminary studies, both Feringa et al. and ourselves have suggested that a radical cycle (Fig. 1), established by the admission of air, or by other oxidants, was responsible for the effective generation of the Reformatsky reagent, by formation of methyl radical.<sup>2,3</sup>

In recent years there has been an increased interest in various radical additions initiated by the  $R_2Zn-O_2$  system, especially regarding organic substrates which contain donor sites capable of forming the Lewis acid/base adducts with  $R_2Zn$  that are actually involved in the reaction with  $O_2$ .<sup>6</sup> Lewiński and co-workers have shed light on the reaction between Me<sub>2</sub>Zn and air, showing that the formation of unstable peroxo species is favoured.<sup>7</sup> In this communication, we present spectroscopic evidence for the presence of radical intermediates in our and Feringa *et al.*'s Reformatsky reactions<sup>2,3</sup> by trapping the ethoxycarbonylmethyl radical (1) with phenyl *tert*-butyl nitrone (PBN), (Scheme 1).

When  $CH_2Cl_2$  solutions of ethyl iodoacetate (0.08 M) and PBN in the presence of  $Zn_2Me$  (0.08M) were analyzed by EPR spectroscopy, a doublet of triplets was observed (Fig. 2a).

The spectrum was attributed to spin adduct **2**, resulting from addition of radical **1** to PBN (Scheme 1), as suggested by the value of the spectroscopic parameters ( $a_N = 14.94$  G,  $a_H = 4.63$  G, g = 2.0058) which are very close to those previously reported for the same radical adduct in benzene.<sup>8</sup>



Fig. 1 Proposed catalytic cycle for the oxidatively promoted Reformatsky reactions.



**Fig. 2** EPR spectra of spin adducts **2** (*a*) and **3** (*b*) generated from reaction of Me<sub>2</sub>Zn and air in the presence (*a*) and in the absence (*b*) of ethyl iodoacetate in CH<sub>2</sub>Cl<sub>2</sub> and PBN as the spin trap at room temperature (microwave power, 5 mW; modulation frequency, 100 kHz; modulation amplitude, 0.4 G). (*c*) EPR spectrum of CH<sub>2</sub>Cl<sub>2</sub> solution containing ethyl iodoacetate and PBN.

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Of particular relevance is the relatively high value of the  $\alpha$ hydrogen coupling in the spin adduct (4.63 G) which has been attributed to an increase in the spin density on nitrogen, as a consequence of the stable pentacyclic conformation that can be adopted by the radical, in which the  $\alpha$ -hydrogen is accommodated in a pseudoaxial position.<sup>8</sup>

When the same experiment is repeated in the absence of ethyl iodoacetate the spectrum due to spin adduct **3**, resulting from addition of methyl radical to PBN, was instead observed (see Fig. 2b). Again, the EPR signal was assigned to the methyl adduct on the basis of the spectroscopic parameters ( $a_N = 15.13$  G,  $a_H = 3.38$  G, g = 2.0059) which are very close to those previously reported for the same radical adduct in benzene.<sup>9</sup> This was the only radical species detected by EPR, indicating that oxygenated radical species are not significantly formed under this condition. Blank experiments performed in the absence of Me<sub>2</sub>Zn gave no EPR signals (see Fig. 2c).

The above results clearly suggest dimethylzinc and oxygen can initiate the reaction by releasing a methyl radical that, in the absence of ethyl iodoacetate and in the presence of PBN, is preferentially captured by the spin trap. In the presence of the halogenated compound, the rate of the halogen abstraction by the methyl radical is so fast<sup>10</sup> that the intermediate radical **1** is instead captured by the spin trap.

Recently Lewiński *et al.* pointed out as a basic assumption that in  $Me_2Zn$  radical mediated reactions, alkyl radicals R (generated through the oxygenation reaction) act as the chain carriers. The most effective initiation system involves  $Me_2Zn$ ,<sup>11</sup> which, according to recent findings,<sup>7</sup> can be selectively transformed into MeZnOMe by 1,4-diazabutadiene derivatives without the generation of free methyl radicals. The transformation of MeZnOOMe induced by the presence of ligands can be an alternative way to provide radical species in radical organic reactions promoted by the  $R_2Zn-O_2$  system. The present results, however, show that the presence of ligands is not required to efficiently produce alkyl radicals in  $Me_2Zn$ radical mediated reactions.

To summarize, we report the spin trapping by a nitrone of alkyl radicals generated from Me<sub>2</sub>Zn and promoted by air. Dimethylzinc and oxygen would initiate the reaction by releasing a methyl radical, which then abstracts an iodine atom from ethyl iodoacetate to generate radical **1**. Although radical generation with diethylzinc involving halogen abstraction has already been reported in the literature,<sup>12</sup> spectroscopic evidence for the generation of radical by Me<sub>2</sub>Zn in the presence of air<sup>13</sup> was unequivocally established in Reformatsky reactions by spectroscopic methodology.

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