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Unexpected reaction of a dimethylzinc-generated THF radical with aldehydes

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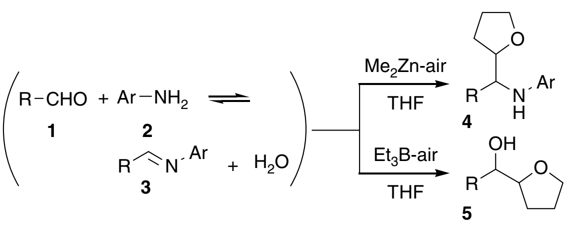
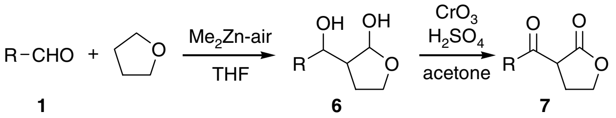
Abstract—A dimethylzinc–air-generated THF radical reacted with aldehydes at the β-position of an α-oxygenated THF.

We have recently reported that ether radicals, generated directly from ethers by the α-hydrogen abstraction with dimethylzinc–air, reacted with imines to give the corresponding ether addition products in high yields.[1] Continuing studies revealed that the dimethylzinc-generated THF α-radical underwent the initiator dependent chemoselective addition reaction with an equilibrium mixture of an aldehyde **1** and an arylamine **2**, giving the imine **3**-selective addition products **4** without production of aldehyde adducts **5**, whereas a triethylborane-initiated THF α-radical gave THF α-radical adducts **5** (Scheme 1).[2]

The reaction of a dimethylzinc-initiated THF α-radical with aldehydes **1** did not give expected THF α-radical adducts **5**, recovering aldehydes **1** in such a reaction time required for completion of an imine reaction. It was contrasted to the triethylborane-generated THF α-radical, developed by Yoshimitsu and Nagaoka, that reacts with aldehydes **1**, giving the corresponding THF α-radical adducts **5** in reasonably high yields.[3] Further studies toward understanding this initiator dependent chemoselectivity led us to the unexpected reaction of a THF radical with aldehydes **1**, giving the corresponding β-radical adducts **6** of an α-oxygenated THF (Scheme 2).[4]



Scheme 1. Initiator dependent chemoselective addition of THF radical.



Scheme 2. Reaction of a dimethylzinc-initiated THF radical with aldehydes **1**.

A solution of benzaldehyde **1a** (R = Ph) in THF was treated with 12 equiv of 1.0 M hexane solution of dimethylzinc under continuous oxygen gas bubbling at room temperature for 7 days. Since the products involved an inseparable mixture of **6**, the crude mixture was further treated with Jones reagent in acetone at 0 °C for 15 min to give a mixture of chromatographically separable at least four ketone products, **8** (10%), **7a** (10%), **9** (8%), and **10** (17%) (Fig. 1).[5,6] The ketone **8** was derived from a direct addition product **5** (R = Ph) of a THF α-radical to **1a**, whereas **7a**, **9**, and **10** were produced through **6** and its derivatives by the addition of a radical at the β-position of α-oxygenated THF.[7]

Improvement in the production of **7a** was carried out by the portionwise addition of a solution of dimethylzinc into a solution of **1a** in THF based on the consideration that the formation of **9** and **10** might be reduced under the conditions of low concentration of a methyl radical

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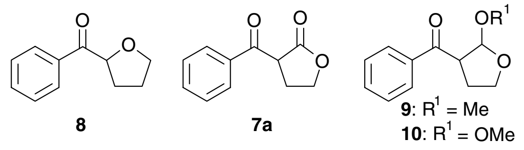
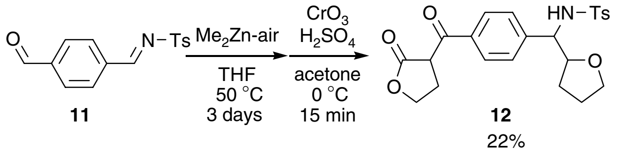


Figure 1. Oxidation products **7a**, **8**–**10** of radical adducts.

that is generated from dimethylzinc. Upon a repeated addition of 3 equiv of dimethylzinc solution by the 12 h interval into a THF solution of **1a**, nearly complete consumption of **1a** was observed after 4 days reaction to give an increased yield of **7a** (34%) and decreased yields of **8** (4%) and **9** (4%) without production of a detectable amount of **10**.

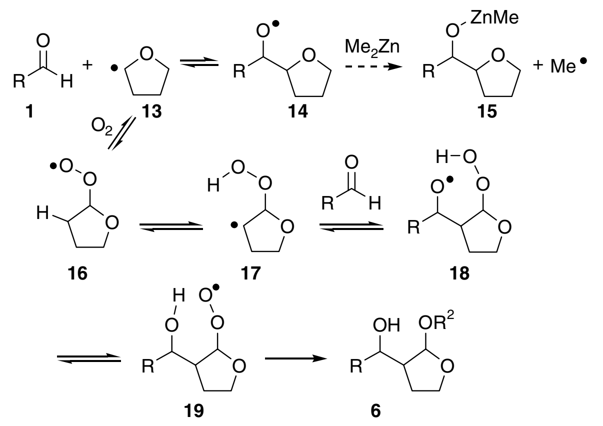
The reaction efficiency was much more improved by heating a reaction mixture at 50 °C with 12 h interval portionwise addition of 3 equiv of a hexane solution of dimethylzinc to **1a** in THF under a stream of air for 2 days, giving after oxidation keto-lactone **7a** in 54% isolated yield (Table 1, entry 1). It was striking to note that a THF α-adduct **8** and β-adducts **9** and **10** were not produced in detectable amounts under such conditions. 4-Methoxy- and 4-chloro-benzaldehydes **1b**,**c** with electron-donating and -withdrawing substituents, 2-methylbenzaldehyde **1d**, and 1-naphthaldehyde **1e** were converted to the keto-lactones **7b**–**e** in 31–43% yields (entries 2–5). 2-Furaldehyde **1f** and cyclohexanecarboxaldehyde **1g** were also applicable to the reaction, giving β-adducts **6f** and **7g** in 34% and 24% yields, respectively (entries 6 and 7). Thus the β-radical addition of α-oxygenated THF to aldehydes **1** was shown to be general.

It is interesting to show the species and chemoselective reaction in that the compound **11** bearing both an aldehyde and an imine groups in a molecule reacted with a THF radical in the selective way to afford the adduct **12** in 22% yield. A THF α-radical and an oxygenated THF β-radical chemo- and species-selectively attacked imine and aldehyde functionalities, respectively (Scheme 3).



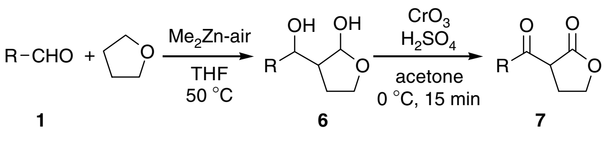
Scheme 3. Species- and chemoselective reaction of dimethylzinc-generated THF radicals with imino-aldehyde **11**.

It has been known that radical additions to carbonyl functionalities are generally disfavored because of their reversibility, which reflects instability of an oxygen-centered radical and a strong $C{=}O$ π bond.[8–12] The encountered formation of a β-radical adduct **6** is probably attributable to the instability of an alkoxy radical **14**, generated by direct addition of a THF α-radical **13** to a carbonyl group of **1** (Scheme 4). The reverse reaction is faster than the reaction with dimethylzinc to give rise to a zinc alkoxide **15** through formation of a methyl radical.[13] Rather than the formation of **14**, a THF α-radical **13** undergoes the reaction with oxygen to produce a peroxy radical **16** that in turn abstracts a hydrogen atom at the β-position of **16** to result in the formation of an α-peroxygenated THF β-radical **17**.



Scheme 4. Plausible mechanism for the generation of an α-oxygenated THF β-radical **17** and formation of **6**.

Table 1. Reaction of an α-oxygenated THF β-radical with aldehydes **1**



Entry	**1**	R	Me_2Zn (equiv)	Time (days)	Yield (%)
1	**1a**	Ph	12	2	54
2	**1b**	$4-MeOC_6H_4$	24	5.5	35
3	**1c**	$4-ClC_6H_4$	9	3	31
4	**1d**	$2-MeC_6H_4$	18	4	43
5	**1e**	1-Naph	18	3	36
6	**1f**	2-Furyl	12	2	34[a]
7	**1g**	$c-C_6H_{11}$	9	1	24

[a] Combined yield of a diastereomeric mixture of diols **6**.

Further reaction of **17** with a carbonyl group of **1** generates an alkoxy radical **18**, which is then converted to a relatively stable peroxy radical **19** through intramolecular hydrogen atom abstraction and end up with **6** ($R^2 = H$, OZnMe, etc.).[14] An excess of methyl radical allows to couple with a peroxy radical **19** to result in the actual formation of an alcohol precursor of **10**, of which detection supported above scenario.

In conclusion, we have encountered an unexpected generation of an α-peroxygenated THF β-radical from THF α-radical in the reaction of aldehydes with dimethylzinc–air-initiated THF radical, which constitutes one of the critical factors governing initiator dependent imine/aldehyde chemoselectivity. Furthermore, the present behavior of THF radicals suggests alternative strategy for the radical addition to carbonyl derivatives. Although a chemical yield is far from practical level, the new findings described herein become the basis of new radical chemistry.

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