Exploration of Dimethylzinc-Mediated Radical Reactions

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ABSTRACT: In this account, our studies on radical reactions that are promoted by dimethylzinc and air are described. Advantages of this reagent and differences from conventional radical initiators, such as triethylborane, are discussed.

Keywords: radical reaction, dimethylzinc, C(sp³)–H bond functionalization, C–C bond formation, Umpolung

Introduction

It has been long time since the word "radical" changed its meaning in chemistry. In the beginning, a substituent that was unchanged during reactions was referred to as a "radical". Thus, a "methyl radical" was used in almost the same meaning as a "methyl group". In 1900, Gomberg showed for the first time the existence of a molecular entity having an unpaired electron,[1] which was then called "free radical", meaning a "radical" not bound to a molecule. Nowadays, the use of just "radical" to mean what was once called "free radical" is recommended in the chemical community.[2] Although the utility of radical species in organic synthesis is unquestionable, and developments in modern organic synthesis owe much to the field of radical chemistry,[3] it did not draw much attention of synthetic chemists for the first 60 years from its discovery. As found in the recollections by Ingold and Chatgilialoglu, "so far as the vast majority of chemists were concerned, radicals were overly reactive species of no practical value or interest since all radical-mediated reactions were presumed to give gunk and tars,"[4] and "most chemists have avoided radical reactions as messy, unpredictable, unpromising, and essentially mysterious."[5] Synthetic application of radical chemistry was pioneered in 1960 by Barton, who developed useful functional group transformations via a radical process.[6] The mid-1980s marked the start of regular reports on radical chemistry-based synthetic methods when Curran[7] and Stork[8] reported brilliant natural product syntheses, showing the power of radical cyclization reactions as a synthetic tool.[9] This may partly owe to the availability of radical kinetic data starting from the 1980s[10] and a useful radical mediator, tributyltin hydride.[11]

In radical chain reactions, a mediator, such as tributyltin hydride, plays an important role. When radical species A• undergoes addition to B=C bond, radical A–B–C• is produced (eq 1). The keys to successfully obtain A–B–C–H are (1) fast hydrogenation of A–B–C• to prevent undesired reactions, such as polymerization via the further addition to another molecule of B=C (eq 2), and (2) efficient regeneration of A• to propagate the chain reaction. Unless the reaction of A–B–C• with A–H (eq 3) is sufficiently fast to give A–B–C•H and A•, an appropriate mediator M–H is required to hydrogenate A–B–C• (eq 4). The resulting M• could be regenerated by the reaction with A–X (eq 5). The mediator and reaction conditions should be chosen carefully to avoid undesired reactions, such as A• + M–H and M• + B=C.
The choice of initiator is also important because it determines the conditions required for the initiation. For radical chain reactions, stoichiometric initiators, such as azo compounds,\textsuperscript{12} distannanes,\textsuperscript{13,14} and peroxides,\textsuperscript{12} are often used with heat or irradiation. The use of trialkylboranes, mainly triethylborane, with air as a radical initiator allows us to perform radical reactions even at –78 °C.\textsuperscript{15} Stoichiometric metal salts were also used to generate radical species from closed shell organic compounds by a single electron transfer process. Low-valent metal species, such as samarium(II) and titanium(III), generate ketyl radicals from carbonyl compounds.\textsuperscript{9a,16,17} Oxidants, such as manganese(III) and cerium(IV), are used to form electrophilic radicals from electron-rich olefins and enolates.\textsuperscript{9b,18} In short, the appropriate radical initiator and mediator depend on the reaction conditions and substrates utilized. Therefore, their development has greatly contributed to advancements in radical chemistry.\textsuperscript{13} We accidentally found that dimethylzinc acts as both an initiator and a mediator.

Discovery of a radical reaction with dimethylzinc–air

Due to the chemical and medicinal importance of optically active amines,\textsuperscript{19,20} we have been engaged in developing methodologies for asymmetric synthesis of chiral amines.\textsuperscript{21,22,23,24,25,26,27} During the course of the study, we examined an addition reaction of dimethylzinc to N-tosyl (Ts) imine 1a in tetrahydrofuran (THF), and encountered an addition reaction of the solvent THF3 to the imine to give THF adduct 3a, instead of the expected methyl adduct 2a (Scheme 1).\textsuperscript{28} The reaction failed to proceed in the absence of either dimethylzinc or air. Accordingly, radical species were expected to be involved in the reaction. A plausible mechanism is shown in Scheme 2. The chain reaction is initiated by the reaction of dimethylzinc and air to form methyl and methoxy radicals, which abstract a hydrogen atom at the α-position of THF. The resulting THF-2-y1 radical undergoes addition to the C=O bond of 1a to give aminyl radical 4a. The subsequent homolytic substitution (S\textsubscript{i2}2 reaction) at dimethylzinc produces methyl radical, which starts another chain of the reactions, and zinc amide 5a, which gives 3a after aqueous work-up. The following features of this reaction immediately attracted us: (1) A non-acidic C(sp\textsuperscript{3})–H bond, the α-C–H bond of THF, is functionalized in high efficiency under mild conditions, (2) Latent polarity of THF is reversed, that is, Umpolung of α-

\[
\begin{align*}
A^+ + B = \text{C} & \rightarrow A-B-C^- \quad (1) \\
A-B-C^- + B = \text{C} & \rightarrow A-B-C-B^- \rightarrow \text{polymerization} \quad (2) \\
A-B-C^- + A^+ & \rightarrow A-B-C-H + A^- \quad (3) \\
A-B-C^- + M^+ & \rightarrow A-B-C-H + M^- \quad (4) \\
M^+ + A^- & \rightarrow A^+ + M^- \quad (5)
\end{align*}
\]

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Initiation step

Radical initiation by triethylborane

Triethylborane\(^{15}\) and diethylzinc\(^{30}\) were frequently used as radical initiators in organic synthesis, although dimethylzinc was an uncommon initiator. The utility of organoboron as radical initiators was first reported in olefin polymerization in 1957.\(^ {31}\) Nowadays, autoxidation of organoborons, especially triethylborane, is a widely utilized method to initiate radical reactions.\(^ {15}\) Much effort has been made to clarify the mechanism of the autoxidation.\(^ {32,33}\) Although it has not been fully understood, the plausible mechanism at present is as follows: Alkylperoxyborane is initially produced presumably via simultaneous or stepwise alkyl migration of oxygen-coordinated boron (eq 6), although an alternative caged S:\(2\)-recombination mechanism (eq 7) is not completely excluded.\(^ {34}\) Homolytic cleavage of the O\(-\)O bond then occurs to give O-centered radicals (eq 8). Interestingly, this step does not proceed without trialkylborane.\(^ {33b,34}\) These O-centered radicals further react with trialkylborane to generate alkyl radicals (eqs 9 and 10).

The generation of alkyl and alkoxy radicals were both confirmed by spin-trapping with ESR\(^ {35}\) and MS.\(^ {36}\) It is noteworthy that more alkoxy and less alkyl radicals were observed as the concentration of trialkylborane was lowered.\(^ {35}\) This observation strongly supports the above mechanism; it is the reaction of the O-centered radicals and trialkylborane that generates alkyl radicals (eqs 9 and 10). Therefore, the autoxidation is likely not as simple as the direct generation of alkyl radicals by the S:\(2\) reaction of trialkylborane and triplet oxygen (eq 11).\(^ {15,32b}\)

\[
\begin{align*}
R_B + O_2 & \rightarrow R_B^\cdot \text{O}_2
\end{align*}
\]

Radical initiation by dialkylzinc

Initiation of a radical reaction by dialkylzinc was also found in olefin polymerization in 1959.\(^ {37}\) In contrast to trialkylborane, not so many reports were available about the autoxidation of dialkylzinc.\(^ {33c,34,38}\) As with trialkylborane, the initial product of the autoxidation was identified as alkylperoxyzinc species (eq 12).\(^ {39}\) Recently, the formation of both alkyl and alkoxy radicals in the autoxidation of dialkylzinc was confirmed by spin-trapping with ESR.\(^ {40}\)

\[
\begin{align*}
R_B + O_2 & \rightarrow R_B^\cdot \text{O}_2
\end{align*}
\]

Therefore, it would be reasonable to assume that the mechanism is as shown in eqs 13–15, although it is unclear whether or not it requires dialkylzinc for the second step to proceed as in the case of trialkylborane.\(^ {33b,330}\)

\[
\begin{align*}
R_Zn + O_2 & \rightarrow RZnOOR \\
RZnOOR & \rightarrow RZn\cdot + RO\cdot \\
RZn\cdot + R\cdot & \rightarrow RZn\cdot OR + R\cdot \\
RO\cdot + R_Zn & \rightarrow RZnOR + R\cdot
\end{align*}
\]

Later, we found that the radical reaction was initiated with dimethylzinc and tert-butyl hydroperoxide in the absence of air.\(^ {41,42}\) This also supports the above mechanism. Probably, an alkylperoxyzinc species is formed with the evolution of methane (eq 16) and the subsequent homolysis (eq 13) takes place.

\[
\begin{align*}
Me_2Zn + t-BuOOH & \rightarrow MeZnOO\cdot Bu + CH_4
\end{align*}
\]

Both trialkylborane and dialkylzinc species are pyrophoric and ignite on contact with air, so that they are used for a rocket igniter. It should be noted that the neat compounds must be handled with special care. However, dimethylzinc and some other species (Me\(_2\)Zn, Et\(_2\)Zn, i-Pr\(_2\)Zn, Bu\(_2\)Zn, Et\(_2\)B, and Bu\(_2\)B) are commercially available as a hydrocarbon solution, which has much less reactivity towards air. This allows us to use these reagents with usual care that is taken in the use of common organometallic solutions, such as normal butyllithium, and makes these reagents suitable for organic synthesis.

The influence of the radical initiator

We first examined the reaction of 1a and THF using other radical initiators (Table 1). Other dialkylzinc reagents such as diethyl, disopropyl, and diphenylzinc were less efficient, producing significant amounts of alkyl adducts 2b–d as well as the reduced product 2e.

Table 1. Effect of the radical initiator on the addition of THF to 1a.

<table>
<thead>
<tr>
<th>Initiator</th>
<th>equiv</th>
<th>time (h)</th>
<th>yield of 2</th>
<th>yield of 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me(_2)Zn</td>
<td>3</td>
<td>4</td>
<td>not detected</td>
<td>94%</td>
</tr>
<tr>
<td>Et(_2)Zn</td>
<td>3</td>
<td>4</td>
<td>2b 33%, 2e 2%</td>
<td>48%</td>
</tr>
<tr>
<td>i-Pr(_2)Zn</td>
<td>3</td>
<td>4</td>
<td>2c 34%, 2e 27%</td>
<td>6%</td>
</tr>
<tr>
<td>Ph(_2)Zn</td>
<td>3</td>
<td>4</td>
<td>2d 7%</td>
<td>not detected</td>
</tr>
<tr>
<td>Et(_2)B</td>
<td>3</td>
<td>48</td>
<td>2b 29%</td>
<td>not detected</td>
</tr>
<tr>
<td>Bz(_2)O(_2)</td>
<td>0.1</td>
<td>24</td>
<td>not detected</td>
<td>trace</td>
</tr>
</tbody>
</table>

\(^{33}\) Conducted in refluxing THF.
The formation of alkyl adducts 2b–d could be understood in terms of the nucleophilicity of the alkyl radicals generated from the dialkylzinc reagents, except for diphenylzinc. The nucleophilicity (i-Pr' > Et' > Me') is in inverse proportion to the yield of 3a. The more nucleophilic the alkyl radical is, the more the addition of the alkyl radical should compete. In addition, diisopropylzinc acted as a hydride donor to give 2e. The bond dissociation energy (BDE) of the R–H bond would also be important. The BDE (Me–H, 439; Et–H, 421; i-Pr–H, 411 kJ/mol) is proportional to the yield of 3a. As the BDE decreases, the hydrogen abstracting ability of the corresponding alkyl radical presumably reduces, and therefore, less THF–2yl radicals should form in the reaction. The advantage of dimethylzinc, therefore, would be the formation of the least nucleophilic and most unstable alkyl radical, methyl radical, as well as the absence of a β-hydride. Moreover, the concentration of O-centered radical species is higher in the reaction mixture of dimethylzinc–air than that in the case of diethylzinc–air. This is probably because the reaction of O-centered radicals and dimethylzinc (eqs 14 and 15) is unfavorable compared to triethylborane and other dialkylzincs due to instability of the forming methyl radical. The high concentration of O-centered radicals could also increase the rate of the hydrogen abstraction, because hydrogen abstraction by alkoxyl radicals is much faster than that by alkyl radicals. Phenyl radicals might be too unstable to form effectively from diphenylzinc.

Conventional radical initiators such as triethylborane and dibenzyol peroxide were totally inefficient. When triethylborane was used, ethyl adduct 2b was produced with no detectable amount of 3a in the crude product. The difference from the reaction using diethylzinc is interesting yet not fully understood. Possibly, the concentration of ethoxyl radicals is higher in the reaction mixture with diethylzinc than with triethylborane, which might quench ethoxyl radicals more quickly (eq 10). In the reaction using dibenzyol peroxide, 1a was almost quantitatively recovered after 24 h. This result clearly indicates that the direct abstraction of a hydrogen atom from THF by aminyl radical 4a should be a minor pathway and dialkylzinc or triethylborane, which traps the aminyl radical intermediates, is required for the addition reactions to proceed smoothly. This also explains the requirement of an excess amount of dimethylzinc for complete conversion of 1a.

### Hydrogen abstraction step: generation of other carbon-centered radicals

#### Alkoxalkyl radicals from ethers

As shown in Scheme 3, cyclic ethers were generally good nucleophiles to give aminobenzylated ethers in good yields. The hydrogen atoms at the α-position of the ethers were preferentially replaced by an aminobenzyl group. Although the ethers were usually used as a solvent in the reactions (125–270 equiv), the amount was reducible with iron salt as an additive.

When there are more than two non-equivalent hydrogen atoms next to the oxygen functionality, regioselectivity was usually not sufficient; the reaction of 1,3-dioxolane quantitatively produced a 7:2 regioisomeric mixture of 6a and 6b. This regioselectivity is in good agreement with the reported relative rate of hydrogen abstraction at the 2- and 4-positions by tert-butoxy radical (3:1 at 60 °C). This indicates that O-centered radical species rather than methyl radical should mainly abstract the hydrogen atom.

![Scheme 3. Addition of ether to 1a.](image)

THF and 1,3-dioxolane gave products 3a and 6a,b in better yields (94–99%) than their 6-membered analogues, tetrahydropryan (THP) and 1,4-dioxane (9a,b and 10, 83–84%). This is probably due to faster hydrogen abstraction from 5-membered cyclic ethers because of the back-hyperconjugation and release of the ring strain in the formed radical. Probably, the back-hyperconjugation also contributes to increasing the nucleophilicity of the radicals. Interestingly, regioisomer 9b was obtained in the reaction of THP. This also likely reflects the decreased radical stabilizing ability of the oxygen atom in the 6-membered ring.

Acyclic ethers, such as diethyl ether, dimethoxymethane, and tert-butyl methyl ether, gave products 11–13 in good but lower yields (59–77%) than cyclic ethers (81–99%).
Better results were obtained when larger excess amounts (270–500 equiv) of acyclic ethers were utilized. Dimethoxymethane gave a 4:3 mixture of regioisomers 12a,b. In general, the diastereoselectivity was fair (11.9–4:1).

t-Butyl ether 13, the product of the reaction with tert-butyldimethyl ether, was converted into amino alcohol 14 in high yield (Scheme 4). Thus, tert-butyldimethyl ether is a hydroxymethyl anion equivalent. 4,4,5,5-Tetramethyl- and 2,2-dimethylhexa-1,6-dioxolanes were also utilized as oxygenated C1 and C2 units; adducts 7 and 8 were converted into amino alcohols 14 and 15 in good yields. Lewis acid lowered the energy level of the LUMO of 1a by complexation and increased the rate of the radical addition step. Although the yield was low and regioselectivity was uncontrolled, an acyclic alkane, hexane, also produced adducts 17a,b. The adduct of 1-hexyl was not detected in this reaction, probably due to the following reasons: (1) abstraction of the terminal methyl hydrogen of hexane is most unfavorable, and (2) a primary alkyl radical, 1-hexyl, is less nucleophilic than the secondary alkyl radical species.

Dimethylzinc showed higher performance than diethylzinc and triethylborane in this reaction as well (Scheme 6). With diethylzinc or triethylborane, less cyclohexyl adduct 16b and more ethyl adduct 2b were produced. This is also explainable by the lower nucleophilicity of methyl radical than that of ethyl radical, as well as higher concentration of methoxyl radical than that of ethoxy radical as previously discussed.

**Scheme 4.** Conversion of ether-adducts into amino alcohols.

**Generation of alkyl radicals from alkanes**

Thanks to low nucleophilicity and stability of methyl radicals, the dimethylzinc–air condition was also suitable for direct generation of alkyl radicals from alkanes. The reaction gave better results with large excess amounts (500 equiv) of cycloalkanes, and adducts 16a–d were produced from 5- to 8-membered cycloalkanes in good yields (Scheme 5).

**Scheme 5.** Addition of alkane to 1a.

In this reaction, the addition of trifluoroborate diethyl etherate improved the yield of the products. Probably, the

**Scheme 6.** Higher performance of dimethylzinc in the reaction of 1a and cyclohexane compared to diethylzinc and triethylborane.

**Generation of primary alkyl radicals from 1-iodoalkanes**

Because of the lower stability of a primary alkyl radical than secondary and tertiary alkyl radicals, its generation by halogen abstraction usually requires stoichiometric tin compounds and haloalkanes. Even though dimethylzinc–air generates methyl radicals, which are less stable than primary alkyl radicals, the direct generation of a primary alkyl radical from alkane was unsuccessful due to predominant hydrogen abstraction from methylene groups as mentioned above. However, dimethylzinc–air enables the generation of primary alkyl radicals from 1-iodoalkanes via iodine abstraction without the use of tin compounds (Scheme 7).

**Scheme 7.** Addition of alkyl iodide to 1a.
The reaction likely involves the addition of a primary alkyl radical rather than alkylzinc species because (1) only a trace amount of the product was obtained in the absence of air, (2) the production of the methyl adduct 2a was only negligible either in the presence or absence of air, and (3) the formation of alkylzinc species from alkyl iodides and dimethylzinc is unlikely because the process would involve the formation of the less stable methyl radical from a more stable primary or secondary alkyl radical via S_n2 process.\(^{[59]}\) Labile functionalities under anionic conditions, such as the chlorine atom of 2g and the ester group of 2h, were tolerated. While the addition of primary alkyl radicals required 5 equiv of the corresponding iodide (2f–h), 1.5 equiv was sufficient for the addition of the secondary alkyl radical (2e). This is probably due to the lower stability and nucleophilicity of the primary alkyl radicals than the secondary alkyl radical.

In this reaction, the yields of the products were significantly decreased in the absence of either copper triflate or trifluoroborate diethyl etherate. The copper salt may function as a Lewis acid and/or facilitate the generation of methyl radical.\(^{[59]}\) In this reaction, activation of the C=N bond by Lewis acids was required probably because of the low nucleophilicity of primary alkyl radical species. Indeed, the addition of a more nucleophilic radical, acyloxymethyl radical, which has an oxygen functionality at the α-position, proceeded smoothly in the absence of Lewis acids (Scheme 8).\(^{[60]}\) The product 18a was easily hydrolyzed to give amino alcohol 14. In this reaction, the use of triethylborane in place of dimethylzinc was beneficial to give the product more cleanly in higher yield, albeit longer reaction time was required.

![Scheme 8](image)

Scheme 8. Addition of iodomethyl ester to 1a.

In these reactions, it is probably methyl radical that abstracts iodine from iodoalkanes because iodine abstraction by O-centered radical species is quite unlikely on the basis of the BDE of O–I and Me–I bonds (213 and 239 kJ/mol, respectively).\(^{[15]}\) Therefore, not only methoxyl radical but also methyl radical should exist at effective concentration in the reactions of dimethylzinc–air. Although C-centered radicals should form at higher concentration with diethylzinc and triethylborane, the use of these radical initiators in this reaction resulted in the production of a significant amount of ethyl adduct 2b (Scheme 9).

![Scheme 9](image)

Scheme 9. Higher performance of dimethylzinc in the reaction of 1a and 1-iodohexane compared to diethylzinc and triethylborane.

This result is noteworthy because the iodine exchange between primary alkyl radical species is a fast reaction,\(^{[61]}\) and an excess amount of 1-iodohexane was utilized in the reaction. Therefore, the formation of 2b as a major product suggests that the addition of ethyl radical to 1a might be fast enough to compete with the iodine abstraction. The low nucleophilicity and stability of methyl radical is advantageous in this reaction to allow exothermic iodine abstraction to generate primary alkyl radical before the addition of methyl radical takes place.

**Addition step: other radical acceptors**

**Electronic influence of C-substituents of the imine**

Imines bearing other C-substituents, such as a substituted phenyl group (α- and p-tol, p-anisyl, p-chlorophenyl, and 1- and 2-naphthyl), a heteroaromatic ring (2- and 3-pyridyl, and 2-furyl), and an alkyl group (2-phenylethyl and cyclohexyl), were applicable to the addition reactions.\(^{[28,53,54,55,56,60]}\) The reaction efficiency was affected by the electronic character of the imine. The reactions of the electron-deficient p-chlorobenzaldimine generally proceeded smoothly, while those of the electron rich p-anisaldimine were retarded and required more reagents and/or longer reaction time for completion (Scheme 10). Particularly, the addition of trifluoroborate diethyl etherate as a Lewis acid was required for the reaction of p-anisaldimine 1e with iodomethyl pivalate to complete. These results clearly indicate that these radical additions are governed by the interaction between the SOMO of the nucleophilic radicals and the LUMO of the imines.

**Imines having other N-substituents**

Imines bearing other types of N-substituents were also applicable, and the best choice of the substituent likely depends on the reaction conditions. In the reaction of THF with dimethylzinc–air, N-p-methoxyphenyl (PMP) imine 1d gave the product 3d more slowly and required twice the amount of dimethylzinc than N-Ts imine 1a (Scheme 11).\(^{[62]}\) In contrast, 1d reacted more rapidly to give 18d than
1a to give 18a in the reaction of iodomethyl pivalate with triethylborane–air.

\[
\begin{array}{c}
\text{Ar} \quad \text{Ts} + \text{O} & \xrightarrow{\text{MeZn 3 equiv}} & \text{Ar} \quad \text{Ts} \\
1a: \text{Ar} = \text{Ph} & \quad & 1f: \text{Ar} = \text{Ts} \\
1b: \text{Ar} = 4-\text{ClC}_{6}\text{H}_{4} & \quad & 1a: \text{Ar} = 4-\text{MeOOC}_{6}\text{H}_{4} \\
1c: \text{Ar} = 4-\text{MeOOC}_{6}\text{H}_{4} & \quad & 1d: \text{R} = \text{Ts} \\
1e: \text{Ar} = 4-\text{MeOOC}_{6}\text{H}_{4} & \quad & 1e: \text{Ar} = 4-\text{MeOOC}_{6}\text{H}_{4} \\
1f: \text{Ar} = 4-\text{MeOOC}_{6}\text{H}_{4} & \quad & 1f: \text{Ar} = 4-\text{MeOOC}_{6}\text{H}_{4} \\
\end{array}
\]

Scheme 10. Electronic effect on the radical addition to imine.

These results suggest that the rate-determining step of the reaction with dimethylzinc would be the addition step (Scheme 2), whilst the rate-determining step with triethylborane is the trap of the aminyl radical. Accordingly, the reaction of 1a, having a LUMO of lower energy level, should be faster than dimethylzinc, is used, and on the contrary, the reaction of 1d, which produces a more Lewis base aminyl radical, should be faster with triethylborane.

Alternatively, there is a possibility that activation of the imines by triethylborane as a Lewis acid is operative in the radical addition reactions.\(^{(63,64,65)}\) Triethylborane can only make a complex with the more Lewis basic imine, 1d, which then undergo the addition reaction more smoothly than non-activated 1a.

Recently, we found that N-alkoxy carbonyl imines are highly superior acceptors in triethylborane-mediated radical addition reactions.\(^{(66)}\) The reaction of N-tert-butoxycarbonyl (Boc) imine 1f with iodomethyl pivalate at –20 °C was even faster than that of N-PMP imine 1d at room temperature (Scheme 11). Comparing the reactions of electron-rich p-ansaldimines 1c and 1g highlights the high performance of N-alkoxy carbonyl imines. Without trifluoroborate diethyl etherate, the reaction of N-Ts imine 1c did not reach to completion even after 60 h at room temperature using excess amount of triethylborane. In contrast, the reaction of N-Boc imine 1g completed after 10 h at 0 °C to give product 18g in high yield.

The high performance of the N-Boc imines is also explainable in terms of the LUMO energy level of the imines and the Lewis basicity of the resulting aminyl radicals. Because the pK\(_a\) value of a carbamate (EtO\(_2\)C\(\text{NH}_2\), 24.2)\(^{(67)}\) is between those of a sulfonamide (PhSO\(_2\text{NH}_2\), 16.1)\(^{(68)}\) and an aniline (PhNH\(_2\), 30.6)\(^{(69)}\), the electron-withdrawing character of a Boc group should lie between a Ts and a PMP group. Therefore, N-Boc imines should have LUMOs with lower energy level and be more reactive toward nucleophilic radicals than N-PMP imines. At the same time, the resulting N-Boc aminyl radicals should have higher Lewis basicity and react more rapidly with triethylborane to propagate the chain reactions than N-Ts aminyl radicals. The superiority of an N-alkoxy carbonyl imine over an N-Ts imine was not observed in the reaction with dimethylzinc; the reaction of N-methoxy carbonyl imine 1e was slightly slower than that of 1a. This is consistent with the above-mentioned assumption that the addition step should be the rate-determining step in the reaction with dimethylzinc.

The results with p-ansaldimines 1c and 1g, however, cannot be fully explained by the above-mentioned two factors. As described above (Scheme 10), trifluoroborate diethyl etherate accelerates the reaction of 1e. This indicates that not the aminyl radical trap but the addition step should become rate-determining when an electron-rich imine is utilized as a radical acceptor, even in the reaction using triethylborane. Therefore, the reaction in Scheme 11 indicates that N-Boc imine 1g is more reactive toward pivaloyloxymethyl radical than N-Ts imine 1c; the order of the reactivity is contradictory to the aforementioned
electron-withdrawing power of the substituents. It is a plausible explanation that triethylborane activates N-alkoxy-carbonyl imines bearing an electron-donating aromatic ring by complexation, but does not activate N-Ts imines. However, we have not yet succeeded in observing a sign of the complexation either in $^1$H, $^13$C, or $^{11}$B NMR of the mixture of 1f and triethylborane.$^{[70,71,72]}

N-Alkoxycarbonyl imine showed its quality as a good radical acceptor also in the addition reaction of imidomethyl radical.$^{[73]}

The imidomethyl radical, which was generated from N-iodomethylsuccinimide using triethylborane, reacted with N-Boc imine 1f to give 1,2-diamine 19f. In contrast, N-Ts imine 1a mainly gave ethyl adduct 2b, and the imidomethylated product 19a was marginally produced.

An asymmetric reaction was realized using enantioenriched N-sulfanyl imines (Scheme 12).$^{[74]}

Tetramethyldioxolane underwent addition to 1b with 9:1 diastereoselectivity, and gave 7a with 80% ee after oxidation by m-chloroperbenzoic acid (m-CPBA). Because of the lower electron-withdrawing power of the sulfanyl group than that of a Ts group, the addition of trifluoroborane diethyl etherate was necessary for the reaction to proceed smoothly. To the best of our knowledge, this is the first example of a radical addition reaction to N-sulfanyl imines.$^{[75]}

The diastereoselectivity was enhanced when 1l, bearing a more bulky sulfanyl group, was employed.$^{[76]}$

Both adducts were converted into optically active amino alcohol (–)-14.

![Scheme 12. Asymmetric radical addition to N-sulfanyl imines.](image)

α,β-Unsaturated imines

Although the reaction of naphthalimidine 1j and THF gave product 3j as a major product, a significant amount of the conjugate addition product 20 was also obtained (Scheme 13).$^{[76]}$

This result indicates that conjugate addition should occur when α,β-unsaturated imines are employed. Indeed, the reaction of cinnamaldehyde 1k with THF preferentially provided the conjugate addition product 21 after reduction of the imine moiety.$^{[76]}$

Dropwise addition of 1k over 6 h was important to obtain 21 in good yield (vide infra).

![Scheme 13. Conjugate addition of THF to α,β-unsaturated imines.](image)

α,β-Unsaturated carbonyl compounds

Encouraged by the above results, the reactions of cinnamaldehyde (22a), methyl cinnamate (22b), and chalcone (22c) with THF were attempted (Scheme 14).$^{[77]}

Although the reaction of 22c produced the desired adduct 24c in 16% yield along with 24% of an α-hydroxylated adduct 24e, only a complex mixture and a small amount of the hydroxylated adduct 24b resulted from the reactions of 22a and 22b, respectively. These results clearly show that the enoxyl radicals resulting from the addition of THF-2-yl radical should have inferior stability and reactivity toward dimethylzinc to those of the N-Ts enamidyl radicals resulting from 1k.

![Scheme 14. Attempted addition of THF to α,β-un saturated carbonyl compounds.](image)

Further investigation led us to find alkylidenemalonate 25 as a good radical Michael acceptor of a synthetic equivalent of cinnamate. Conjugate addition of ethers to 25 proceeded using dimethylzinc and was facilitated in the presence of trifluoroborane diethyl etherate (Scheme 15).$^{[78]}

The reaction likely proceeds via intermediate radical 26, which is stabilized by the two electron-withdrawing groups. Dimethylzinc then traps 26 and regenerates methyl radical to form zinc enolate 27, which is converted into products 28–31 after hydrolysis.$^{[79]}$
The competitive reaction using 32 revealed that the C=O bond of alkylidenemalonate is a superior radical acceptor to the C=N bond of pivaloyloxy methyl imine, producing aldehyde 28f rather than amine 31 as a major product after hydrolysis (Scheme 16).

Scheme 16. Competitive reaction between alkylidenemalonate and N-Ts imine moieties.

Alkylidenemalonate 25 was also applicable to conjugate addition of acyloxymethyl (Scheme 17). Notably, phenethylidenemalonate, prone to olefin migration, was applicable, and 33l was obtained in good yield. This malonate 25i, however, was incompatible with the Lewis acid, and this resulted in the requirement of longer reaction time and more dimethylzinc. It was important to conduct this reaction under argon atmosphere to prevent autooxidation of pivaloyloxymethyl radical (vide infra). The reaction was probably initiated by zinc tert-butyl peroxide formed in situ (eqs 16 and 13).

Scheme 17. Conjugate addition of pivaloyloxymethyl to alkylidenemalonates.

To realize an asymmetric variant of this reaction, an 8-phenylmenthyl group (δMen) was an appropriate chiral auxiliary. The conjugate addition of teteramethyldioxolane to 25j provided 31l with 93:7 facial selectivity (Scheme 18). The dioxolane is a hydroxymethyl anion equivalent; 31j was converted into chiral lactone 35 without any loss of stereoisomeric purity via mono methyl ester 34, with quantitative recovery of the chiral auxiliary.

Scheme 18. Diastereoselective conjugate addition to bis-8-phenylmenthyl alkylidenemalonate.

Aldehyde

In contrast to the reaction of triethylborane, addition of THF to benzaldehyde proceeds only negligibly when dimethylzinc is used (Scheme 19). This is probably due to inadequate reactivity of dimethylzinc toward alkoxyl radicals, which form by the addition of THF-2-yl radical to the C=O bond of the aldehyde. Intramolecular radical addition to an aldehyde is as fast as that to an alkene, although reverse reactions are much faster. Therefore, it is reasonable to assume that the addition of THF-2-yl should occur both in the reactions with dimethylzinc and triethylborane. The reverse reaction gives back the aldehyde and THF-2-yl radical when dimethylzinc is used, whereas triethylborane could trap the oxyl radical.
intermediate to give 36 after hydrolysis. The slow trapping of the intermediate by dimethylzinc could be attributable to the instability of methyl radical, which is released in the S_{n}2 process as discussed above. Indeed, the reaction using diethylzinc (6 equiv), in which the trapping should be more exothermic due to the stability of ethyl radical, produced a small but notable amount of 36 (18%) after 144 h. \[^{21}\] As previously proposed, the rapid trapping by triethylborane might be due to the precoordination of the aldehyde to the boron atom when the addition occurs. \[^{142c}\]

![Scheme 19](image)

**Scheme 19.** Marked difference between dialkylzinc and Et, B in the reaction of THF and benzaldehyde.

Taking advantage of this property, chemoselective reactions of C=N and C=C bonds in the presence of a C=O bond were realized (Scheme 20). \[^{13,62,78}\] Importantly, C=C bond formation selectively occurred without any protection of the aldehyde moieties of 1m and 25f to directly give aldehydes 3m and 28f.

![Scheme 20](image)

**Scheme 20.** Chemoselective reactions in the presence of aldehyde.

The three-component reaction of THF, aldehyde, and amine was also realized. Amine 3d was produced in the reaction of benzaldehyde and \( p \)-anisidine in THF with dimethylzinc, probably through the addition of THF-2-y1 radical to \( N \)-PMP imine 1d that is formed \textit{in situ} (Scheme 21). \[^{82}\] Interestingly, when triethylborane was used in place of dimethylzinc, amine 3d was a minor product, and alcohol 36 was mainly produced. The high ability of aldehyde as a radical acceptor in the presence of triethylborane was also reported in the literatures. \[^{82}\]

![Scheme 21](image)

**Scheme 21.** Reactions of THF with a mixture of benzaldehyde and \( p \)-anisidine.

The inertness of the aldehyde functionality enabled a radical addition–aldol-type cyclization cascade (Scheme 22). The dimethylzinc-mediated addition of dioxolane to alkyldienemalonate 25k gave enolate intermediate 37, which then underwent an aldol-type cyclization to give 38. \[^{83}\] The reduction with triethylsilane in TFA provided tricyclic lactone 39.

![Scheme 22](image)

**Scheme 22.** Radical addition–aldol-type cyclization cascade.

**Reactions caused by oxygenated byproducts**

The autoxidation of ethers is a well-recognized hazard in laboratories. The reaction of C-centered radical with triplet oxygen is diffusion-controlled, \[^{18}\] giving peroxyl radical (eq 17), which then results in peroxy and hydroperoxide (eqs 18 and 19). However, we usually observed only a tiny amount of peroxy or hydroperoxide after the reactions with dimethylzinc and air. This is probably because dimethylzinc reduces peroxyl radical and hydroperoxide via zinc peroxy (eqs 20 and 21) to finally give zinc alkoxide (eqs 13–15). This is an important feature of the reactions with dimethylzinc and air from a safety point of view.

\[
\begin{align*}
R^+ + O_2 & \rightarrow ROO^+ \quad (17) \\
ROO^+ + R^+ & \rightarrow ROOR \quad (18) \\
ROO^+ + RH & \rightarrow ROOH + R^+ \quad (19)
\end{align*}
\]
In the aforementioned radical reactions, a part of the generated C-centered radicals is oxidized by molecular oxygen without undergoing the addition reactions. During the investigation, we observed some products attributable to reactions of these oxygenated byproducts. The first example is amino alcohol 40, found as a byproduct in the three-component reaction (Scheme 21). This product was obtained in good yield when the reaction was conducted in the absence of an aldehyde (Scheme 23).\[^{85}\] Probably, oxygenated THF 41, which is generated via the above-mentioned process, is responsible for the formation of 40. The ring opening of 41 gives aldehyde 42, which forms imine 43 with the aniline. The addition of THF-2-yl radical to 43 would provide 40.

The second example is lactol 44, an addition product of α-oxygenated THF to aldehyde at the β-position (Scheme 24).\[^{86}\] When a mixture of aldehyde and dimethylzinc in THF was heated at 50 °C for 2 days, 44 was produced and isolated as β-keto lactone 45 after oxidation.

The formation of this product is also explainable as a reaction of 41. Enolate 46 would be generated from aldehyde 42,\[^{87}\] an open-ring form of 41, and undergo an aldol reaction with the aldehyde to give 44 after hydrolysis. Our previous proposal, including intramolecular 1,4-hydrogen abstraction of THF-2-ylperoxyl radical (eq 22), was revealed to have too high activation energy based on DFT calculations.\[^{88}\]

![Image of Scheme 23 and Scheme 24]

When the conjugate addition of pivaloyloxymethyl radical to alkylidenemalonates (Scheme 17) was conducted in the presence of air, α-hydroxymethylated adduct 46 was obtained (Scheme 25).\[^{41}\] Formaldehyde was likely formed by oxygenation of pivaloyloxymethyl radical and reacted with the zinc enolate intermediate. In marked contrast to the zinc enolate of fumarate,\[^{89}\] that of malonate did not undergo α-alkylation either with π-allyl palladium, iodomethane, benzaldehyde, or acrylate.\[^{77}\] This reaction is the only intermolecular reaction of malonate-derived zinc enolate we have ever observed.

![Image of Scheme 25]

Chain transfer step: reactions of radical intermediates

An addition reaction of the N-Ts enaminy1 intermediate

In the reaction of N-Ts cinnamaldimine 1k and THF, it was important to add 1k slowly into the reaction mixture to obtain adduct 48 in good yield after hydrolysis and reduction (Scheme 26). When it was added in one portion, the reaction of THF with two molecules of 1k took place, and 49 was mainly produced.

There are two possible pathways for the production of 49. The first possibility is a Mannich-type reaction of zinc enamide intermediate 5k and 1k, followed by elimination of tosylamide (Path A, Scheme 26). If Path A is operative, the rate-determining step of the reaction to give 4k should be the formation of THF-2-yl radical and not the addition step, because the slow addition of 1k efficiently suppressed the formation of 49. If the addition step is rate-determining,
the product ratio should be determined by the competition between THF-2-y1 radical and zinc enamide 5k to react with 1k. Therefore, the slow addition of 1k would reduce the rates of both reactions, and the ratio of 48 and 49 should be unchangeable. The second possibility is the addition of radical intermediate 4k to 1k (Path B). In Path B, the competition between dimethylzine and 1k to react with 4k determines the product ratio of 48 and 49. The slow addition kept 1k at low concentration and would increase the possibility for 4k to be trapped by dimethylzine rather than to further react with 1k. If the resulting 5k never undergoes the further reaction to give 49, 48 is produced after hydrolysis.

Radical coupling reactions of the intermediates

When the reaction of THF with alkylidenemalonate 25a (Scheme 15) was conducted using triethylborane in place of dimethylzine, significant amounts of α-ethylated products 51 and 52 were obtained (Scheme 27). In contrast, none of these byproducts were observed with diethylzine. The α-ethylation to give 51 or 52 is probably due to the radical coupling of 26' and ethyl radical. This indicates that the reaction of intermediate 26' with triethylborane to give boron enolate 27' (M = B) is so slow that the coupling reaction would compete. Accordingly, dialkylzine should be the radical mediator of choice for the addition reaction of alkylidenemalonate.

The hetero-coupling of radical intermediates was also observed in the reactions of N-Ts imine. When the reaction of 1a with iodomethyl pivalate was performed at -78 °C, N-alkylated product 53 was obtained as a byproduct (Scheme 28). The alkylation probably resulted from the coupling of aminyl radical 54a and pivaloyloxymethyl radical. The alternative possibility to give this product via nucleophilic substitution of the iodomethyl ester and 18a or 55a was excluded, because the alkylation did not occur at room temperature. Probably, the addition of pivaloxyloxymethyl radical to 1a and/or the reaction of 54a with triethylborane were so slow at -78 °C that the radicals accumulated in such concentration for the radical coupling to compete. Similar N-ethylations were also reported in the addition reactions of ethyl radical to C=N bonds of N-Ts imine and hydrazine using triethylborane.

Hydrogen transfer of the intermediates

The aminyl radical intermediate undergoes not only the radical coupling but also the intramolecular hydrogen abstraction. The reaction of iodomethyl pivalate and N-Ts α-toluididine 1n using triethylborane provided bis(pivaloxyloxymethylated product 56 as well as the expected adduct 18n (Scheme 29).

This product was probably produced via radical coupling between pivaloxyloxymethyl radical and 57, which resulted from intramolecular hydrogen abstraction of intermediate 54n.
Therefore, this reaction is a cascade of three reactions: the radical addition, the intramolecular hydrogen abstraction, and the radical coupling. Importantly, neither the N-alkylation (Scheme 28) nor the hydrogen abstraction (Scheme 29) took place with the corresponding N-Boc imines, showing that the reaction rates of the addition and the aminyl radical trap were both sufficiently fast.

![Scheme 29. Formation of 56 via intramolecular hydrogen abstraction of 54n.](image)

Another type of cascade reaction was observed in the reaction of N-Ts imine 1a and diethyl ether using dimethylzinc. Along with the major product 11, bisaminobenzylated product 58 was also obtained in 14% yield (Scheme 30). This product was probably produced via intramolecular hydrogen transfer of aminyl radical intermediate 59 to give 61, because intermolecular hydrogen abstraction of 11 or 60 by methyl or methoxyl radical is highly unlikely in the presence of excess amount of ether. Although the yields were quite low, these cascade reactions (Schemes 29 and 30) consist of two regioselective C–C bond forming reactions at remote positions.

![Scheme 30. Formation of 59 via intramolecular hydrogen abstraction of 60.](image)

Recently, we succeeded in realizing a cascade reaction of the aminyl radical as the main reaction. In the reaction of cyclohexanecarbaldimine 1o and iodomethyl pivalate using triethylborane, aminyl radical intermediate 54o underwent intramolecular hydrogen transfer to give 62, which abstracted iodine from iodomethyl pivalate to afford the iodinated adduct 18p (Scheme 31).

![Scheme 31. Addition–hydrogen-abstraction–iodination cascade in the reaction of 1o and iodomethyl pivalate with triethylborane.](image)

These cascade reactions indicate that the first radical addition occurs not to the acceptors that coordinate to the radical mediators but to those without such complexation. The resulting intermediates are then trapped with the mediators or undergo the subsequent reactions. These results, however, do not deny the possibility that more Lewis basic radical acceptors would precoordinate to diethylzinc and triethylborane before undergoing addition reactions.

**Summary and Outlook**

In this account, our studies on radical reactions using dimethylzinc were overviewed. The use of dimethylzinc–air with C=N and C=C bonds enabled the C–C bond forming reactions accompanied with the C–H bond activation of ethers and alkanes. The generation of primary alkyl radicals was also realized without using tin reagents. These successes relied on the following characters of dimethylzinc: (1) it generates methyl radical, the least nucleophilic and least stable alkyl radical, and O-centered radical species at higher concentration than other initiators such as diethylzinc and triethylborane, and (2) it is highly reactive towards the aminyl radical and α,α-bis(alkoxycarbonyl)alkyl radical intermediates. Compared to the time when we began this study, the C–H activation with radical methodology is now a surprisingly hot field of research. From the viewpoint of regioselectivity, however, the current technologies still have some limitations. The intramolecular hydrogen transfer process, discussed in the last section, would provide a powerful solution for this problem. Since our reports, dimethylzinc has become more and more popular as a radical initiator. We believe that the advantage of dimethylzinc is still to be explored.
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