Radical Reactions Initiated by Dimethylzinc
Ken-ichi Yamada, Yasutomo Yamamoto and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University,
Received July 8, 2004

Abstract: Alkyl radicals were efficiently generated from ethers and alkanes via hydrogen abstraction by the action of dimethylzinc–air to undergo addition to imines. This methodology realized the introduction of oxygenated C1–C3 units to imines. Further studies revealed an interesting chemoselectivity: ether radicals generated by dimethylzinc favor the addition to imines whereas triethylborane facilitates the addition of ether radicals to aldehydes. Besides, dimethylzinc was found to promote some unusual reactions such as the reaction of THF at the β-position with aldehydes and three-component coupling reaction of arylamine and two THF molecules.

1. Introduction

The history of radical chemistry goes back to 1900 when Gomberg reported the formation and reactions of the triphenylmethyl radical. The beginning of organic synthesis with radicals was 1937 when Hey and Waters assigned some known reactions to radical mechanisms. The same year, Kharasch recognized the anti-Markovnikov addition of hydrogen bromide to alkenes as a radical chain reaction. Radical chemistry showed its quality in organic synthesis when Barton developed useful functional group transformations via a radical process. Moreover, after the brilliant application of radical cyclization reactions to natural product synthesis by Stork and Curran, radicals have received wide recognition as a powerful synthetic tool.

Among radical species, ether radicals, as which α-alkoxyalkyl radicals are sometimes referred to, are characterized by the stability and the nucleophilicity, both of which originate from the electron-donating alkoxy substituent. Synthetic utility of ether radicals thus lies in their equivalence to α-alkoxy carbanion. A recent remarkable application is the G ring formation of cigatoxin by Hirama. An ether radical, generated from monothio acetal 1, underwent intramolecular addition to the alkenoate moiety to give the cigatoxin G ring of 2 (Scheme 1).

Scheme 1. The G ring formation in the total synthesis of cigatoxin

Other addition reactions of ether radicals to electron-deficient C=C multiple bonds were also reported. However, addition of ether radicals to C=O or C=N double bonds was scarcely studied until quite recently, though the resulting structural motifs, hydroxy- or aminoalkylated ethers, are often found in biologically active compounds, such as antibiotic (+)-tetronomycin (3) and (+)-furanomycin (4) and antineoplastic (+)-solamin (5) (Figure 1). In this account, we describe our recent results on the reactions of ether radicals mediated by organozinc and borane reagents.

2. The Beginning of Our Radical Chemistry

An encounter with unexpected reactions must be one of the most exciting and delightful events for researchers in chemistry. We were very lucky to find accidentally a new radical reaction. In 2000, we reported a catalytic asymmetric addition of diethylzinc to imines using a copper-chiral amidophosphane complex in the course of our study on development of asymmetric reactions. The addition of diethylzinc to a variety of N-sulfonylimines was catalyzed by a complex of copper(II) triflate and chiral amidophosphane 6 to give the corresponding sulfonamide with up to 94% ee in high yield (Scheme 2).

Scheme 2. The catalytic asymmetric addition of diethylzinc to N-sulfonylimines
We were then trying to apply other organozinc reagents to this reaction. Although we have already succeeded in addition of dimethyl- and diisopropylzinc to imines, at that time the reaction of N-tosyl benzaldehyde imine 7a with dimethylzinc failed to proceed even in refluxing toluene and gave back the starting imine. After several attempts, we were pleased to find by TLC monitoring that a clean reaction proceeded in THF with imine 7a and dimethylzinc giving only one product. However, to our surprise, the product was not the methyl-adduct but 8a, the adduct of solvent THF at the 2-position in nearly quantitative yield. The addition was found to occur in the absence of the copper-ligand complex.

Thus, dimethylzinc (a 1.0 M solution in hexane, 3.0 mL) was added at room temperature to a THF (22 mL, 0.27 mol) solution of imine 7a (1.0 mmol) in a 100 mL round-bottom flask equipped with a rubber balloon filled with argon. The mixture was stirred at the same temperature for 4 h to give 8a as a 3:2 mixture of the diastereomers in 94% yield (Scheme 3).

3. Radical Addition of Ethers to Imines

The addition of ether solvents was quite general (Table 1). Cyclic 5-membered 1,3-dioxolane and 6-membered tetrahydropyran and 1,4-dioxane were applicable (entries 1–3). Linear ethers, diethyl ether and dimethoxymethane also underwent addition to imine (entries 4 and 5). The reaction proceeded whether imine had an electron-withdrawing or -donating group on phenyl groups (entries 6–9). The N-tosyl group of imines was not essential for the reaction and N-methoxycarbonylimine 7f and N-(4-methoxyphenyl) imines 7g and 7h were also good reaction partners (entries 10–12). In general, the addition was not very stereoselective to give the products as a mixture of diastereomers with a ratio of 11:9 to 9:2 depending on the substrates.

When the reaction was conducted in degassed THF taking care to avoid air invasion, THF–adduct 8a was produced in only 4% yield even after prolonged 48 h, and most of the starting imine 7a was recovered. To the contrary, the reaction was dramatically accelerated with continuous air bubbling into the reaction mixture, giving the adduct 8a in 95% yield after 1 h. These results imply that the initiation step of this addition reaction would be the generation of a methyl radical by SH2 (Substitution Homolytic Bimolecular) reaction of dimethylzinc and air oxygen (Figure 2). The generated methyl radical abstracts an α-hydrogen atom from THF to form radical 9, which undergoes addition to an imine. The resulting aminyl radical 10 reacts with dimethylzinc to give zinc amide 11, which is converted into the adduct 8a after aqueous work-up, and a methyl radical, which propagates a chain reaction. Because more than a stoichiometric amount of dimethylzinc is needed for the total conversion of the starting imines, the abstraction of an α-hydrogen atom of THF by the aminyl radical 10 should be negligible.

### Table 1. Addition of ethers to imines initiated by dimethylzinc

<table>
<thead>
<tr>
<th>entry</th>
<th>7</th>
<th>R'</th>
<th>ether</th>
<th>t (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>Ph</td>
<td>Ts</td>
<td>1,3-dioxolane</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>7a</td>
<td>Ph</td>
<td>Ts</td>
<td>tetrahydropyran</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>7a</td>
<td>Ph</td>
<td>Ts</td>
<td>1,4-dioxane</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>7a</td>
<td>Ph</td>
<td>Ts</td>
<td>Et2O</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>7a</td>
<td>Ph</td>
<td>Ts</td>
<td>(MeO)2CH2</td>
<td>144</td>
</tr>
<tr>
<td>6</td>
<td>7b</td>
<td>Ph</td>
<td>Ts</td>
<td>THF</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>7c</td>
<td>Ph</td>
<td>Ts</td>
<td>THF</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>7d</td>
<td>Ph</td>
<td>Ts</td>
<td>THF</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>7e</td>
<td>Ph</td>
<td>Ts</td>
<td>THF</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>7f</td>
<td>Ph</td>
<td>Ts</td>
<td>THF</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>7g</td>
<td>Ph</td>
<td>Ts</td>
<td>THF</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
<td>7h</td>
<td>Ph</td>
<td>Ts</td>
<td>THF</td>
<td>42</td>
</tr>
</tbody>
</table>

*a Conducted at 0 °C.

![Figure 2. Plausible mechanism of the dimethylzinc–mediated radical addition of THF to imine.](image)

4. Ether Radicals Generated by Other Initiators

We tested the efficiency of benzyloxide (BPO) and triethylborane–air radical initiators that were reported to generate a radical from THF, in the addition to imine (Table 2). Imine 7a was almost quantitatively recovered after treatment with benzyloxide in refluxing THF for 24 h (entry 1). This result suggests that the addition of THF radical to imine should be reversible and a fast trap of the resulting aminyl radical is a crucial step. The reaction of imine 7a in THF with triethylborane–air provided the ethyl–adduct 12b in 29% yield after 48 h without production of THF–adduct 8a (entry 2).

The efficacy of three other organozinc reagents than dimethylzinc in this reaction was also evaluated. Using diethylzinc or diisopropylzinc, the addition of ethyl or iso-
propyl, and the reduction of the imine took place rather than the addition of THF (entries 3 and 4). When diphenylzinc was used as an initiator, phenyl-adduct 12d was obtained in 7% yield and most of the starting imine was recovered (entry 5). These results indicate that the instability of the methyl radical is advantageous for the efficient generation of THF radical.

5. Differentiation of Imine and Aldehyde with Use of Dimethylzinc and Triethylborane

Since imines were good acceptors for dimethylzinc-air-initiated radical addition of ethers, we then examined the addition to aldehydes in order to establish the generality. Contrary to our expectation, the reaction of benzaldehyde 13 with THF radical was sluggish under dimethylzinc-air conditions, producing THF adduct 14 in less than 8% yield even after 5 days (Table 3, entry 3). In comparison with the addition to imine 7g (entry 1), this result showed that dimethylzinc-air-initiated radical addition of ethers was highly imine-selective. To the best of our knowledge, it was the first example for differentiation of C=O and C=N double bonds as radical acceptors. Furthermore, using triethylborane instead of dimethylzinc, the addition of THF radical proceeded smoothly both to C=N and C=O double bonds (entries 2 and 4). These results showed that a radical initiator could control the chemoselectivity.

Table 3. Radical addition of THF to benzaldehyde 13 and imine 7g with Me₂Zn and Et₃B

<table>
<thead>
<tr>
<th>entry</th>
<th>initiator</th>
<th>temp</th>
<th>time (h)</th>
<th>product, yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BPO</td>
<td>reflux</td>
<td>24</td>
<td>8a, trace</td>
</tr>
<tr>
<td>2</td>
<td>Et₃B-air</td>
<td>rt</td>
<td>48</td>
<td>12b, 29%</td>
</tr>
<tr>
<td>3</td>
<td>Et₃Zn-air</td>
<td>rt</td>
<td>4</td>
<td>8a, 48%; 12a, 2%; 12b, 33%</td>
</tr>
<tr>
<td>4</td>
<td>iPr₂Zn-air</td>
<td>rt</td>
<td>8a, 6%; 12a, 27%; 12c, 34%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ph₂Zn-air</td>
<td>rt</td>
<td>4</td>
<td>12d, 7%</td>
</tr>
</tbody>
</table>

6. Addition of THF Radical to Aldehydes Initiated by Triethylborane

In general, addition of alkyl radicals to carbonyl groups is difficult because of reversibility, which reflects the instability of an alkoxyl radical and a strong C=O π bond. However, triethylborane can trap the alkoxyl radical intermediate arising from the addition of an alkyl radical to aldehyde. In 1999, Nagaoka and Yoshimitsu reported the triethylborane-air initiated radical addition of THF to aldehyde 16 with good diastereomer ratio. Remarkable improvement in yield and reaction time was achieved with large excess of THF and triethylborane, and using tert-butyl hydroperoxide (TBHP) instead of air (Scheme 5).

Scheme 5. Addition of THF to aldehyde 16 with triethylborane

In this reaction, an ethyl radical generated from triethylborane achieved C-H cleavage and functionalization at the α-position of THF. This method was applied to the synthesis of biologically active acetogenin polyketides, which possess α-substituted (tetrahydrofuran-2-yl)methanol as common structural motifs. For instance, they accomplished synthesis of (+)-muricatacin (22) starting from α-hydroxalkylation of THF with triethylborane-TBHP-initiated radical reaction. After acetylation, the desired diastereomer 20 was obtained in 55% yield. Enzymatic resolution of acetate 20 with porcine liver esterase (PLE) afforded enantiomerically enriched acetate (+)-20 with 79% ee in 49% yield. Subse-
quent α'-C–H oxidation, deacetylation and recrystallization gave optically pure (-)-muricatacin (22).

**Scheme 6.** Yoshimitsu and Nagaoka’s synthesis of (-)-muricatacin (22)

\[
\begin{align*}
\text{C}_{12}H_{25}O + \text{Et}_2B & \xrightarrow{\text{TBHP}} \text{C}_{12}H_{25}O + \text{Et}_2B \\
& \xrightarrow{\text{Me}_2Zn, \text{EtOH, rt}} \text{C}_{12}H_{25}O + \text{Et}_2B \\
& \xrightarrow{\text{K}_2\text{CO}_3, \text{EtOH, rt}} \text{C}_{12}H_{25}O + \text{Et}_2B \\
& \xrightarrow{\text{PPTS, benzene reflux}} 94%
\end{align*}
\]

**Scheme 7.** Unexpected reaction of Me2Zn-generated THF radical with aldehyde 12

\[
\begin{align*}
\text{O} & \xrightarrow{\text{Me}_2\text{Zn (portionalwise air)}} \text{O} \\
& \xrightarrow{\text{C}_2\text{H}_2\text{SO}_4, \text{acetone}} \text{O} \\
& \xrightarrow{\text{0 °C, 15 min}} \text{O}
\end{align*}
\]

A plausible mechanism is shown in Scheme 8. The addition of THF α-radical 9 to aldehyde 12 generates unstable alkoxyl radical 27, and the reverse reaction is much faster than the reaction of alkoxyl radical 27 with dimethylzinc to afford 28 and a methyl radical. The reaction of THF α-radical 9 with oxygen produces peroxy radical 29, which can abstract hydrogen at the β-position of THF. Further reaction of α-peroxoygenated THF β-radical 30 with aldehyde 12 produces alkoxyl radical 31, which is converted to relatively stable peroxy radical 32 via intramolecular hydrogen abstraction.

**Scheme 8.** Plausible mechanism for the generation of α-oxygenated THF β-adducts

Although the addition of THF to an aldehyde with dimethylzine–air gave THF α-adduct in quite low yield, the starting aldehyde was completely consumed and many products were generated. We determined some of their structures after oxidation, and to our great surprise, THF α-adducts 24, 25 and 26 were obtained in 10%, 8% and 17% yields, respectively, as well as α-adduct 23 in 10% yield (Scheme 7). Regioselectivity was improved by heating a reaction mixture at 50 °C with portionwise addition of dimethylzinc, giving only THF β-adduct 24 in 54% yield.

**Scheme 9.** The preparation of alcohol 34 via dimethylzine-mediated radical addition of tert-butyl methyl ether to imine 7a

A plausible mechanism is shown in Scheme 8. The addition of THF α-radical 9 to aldehyde 12 generates unstable alkoxyl radical 27, and the reverse reaction is much faster than the reaction of alkoxyl radical 27 with dimethylzinc to afford 28 and a methyl radical. The reaction of THF α-radical 9 with oxygen produces peroxy radical 29, which can abstract hydrogen at the β-position of THF. Further reaction of α-peroxoygenated THF β-radical 30 with aldehyde 12 produces alkoxyl radical 31, which is converted to relatively stable peroxy radical 32 via intramolecular hydrogen abstraction.

**8. Ether Radicals as Oxygenated C1–C3 Units**

Having developed a mild and efficient method for the radical addition of ethers to imines, we expected the utility of ether radicals as oxygen-functionalized carbon units. tert-Butyl methyl ether and 2,2-dimethyl-1,3-dioxolane (35) were found to be good oxygenated one- and two-carbon units, respectively. The addition of tert-butyl methyl ether to 7a was mediated by dimethylzinc–air to give adduct 33 in 59% yield (Scheme 9). Adducts 36 were obtained in good yields by the reaction of imines 7 and ether 35 (Table 4). Diastereoselectivity in the reaction of aromatic imines 7a–e, 7i, and 7j (7:3–9:1, entries 1–7) was better than that of aliphatic ones 7k and 7i (1:1 and 3:2, entries 8 and 9). The tert-butyl group and the isopropylidene group were easily cleaved by standard deprotection protocol, giving amino alcohol 34 and amino diols 37 in almost quantitative yield, respectively. Although the direct introduction of a three-carbon unit to imine 7a using 2,2-dimethyl-1,3-dioxane was not so satisfactory (33% yield), the one-carbon elongation of amino diol 37a was an adequate alternative to give 4-aminobutenoate 39 in 86% yield over two steps (Scheme 10). One-carbon unit introduction was achieved also by the conversion of diol 37a to alcohol 34 in 91% overall yield from 7a. Scheme 11 shows the characteristic chemoselectivity of this reaction. The ether radical underwent addition predominantly to the C=N double bond of 7m to give aldehyde 36j in 80% yield.

Our attempts for the diastereoselective addition of ethers 40 having chiral centers are shown in Scheme 12. The addition of dioxolane 40a at the 5-position took place only on the opposite side to the adjacent methyl group, giving 41a in 20% yield as a 4:1 mixture of the diastereomers arising from the stereochemistry at the benzylic carbon. The major product of this reaction was 42, the adduct at the 4-position of the ether, indicating the ability of quaternary carbon formation by this radical addition reaction. The stereochemistry in the addition of dioxolane 40b was also controlled by the adjacent methyl group to give cis-methyl product 41b in 29% yield.

**9. Reaction with Amines**

We encountered another unexpected reaction during the study on the three-component reaction of benzaldehyde, p-anisidine, and THF (Scheme 4). Aminoalcohol 43a

**Scheme 9.** The preparation of alcohol 34 via dimethylzine-mediated radical addition of tert-butyl methyl ether to imine 7a

\[
\begin{align*}
7a + \text{Me}_2\text{Zn} & \xrightarrow{\text{rt, 49 h}} \text{7a} \\
& \xrightarrow{\text{O–TBu, TFA, 0 °C, 1 h}} \text{33} \\
& \xrightarrow{\text{NH–T} \beta} \text{34} \\
& \xrightarrow{\text{59%}} \text{34} \\
& \xrightarrow{\text{94%}} \text{34}
\end{align*}
\]
Table 4. The dimethylzinc-mediated radical addition of dioxolane 35 to imines 7 and hydrolysis of acetonides 36 giving diols 37

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>36a</th>
<th>Y (%)</th>
<th>37a or 37b Y (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>36a</td>
<td>91%</td>
<td>(RS,RS)-37a quant</td>
</tr>
<tr>
<td>2</td>
<td>4-ClC₂H₅</td>
<td>36b</td>
<td>91%</td>
<td>37b 93%</td>
</tr>
<tr>
<td>3</td>
<td>4-MeOC₂H₅</td>
<td>36c</td>
<td>91%</td>
<td>37c 93%</td>
</tr>
<tr>
<td>4</td>
<td>4-MeC₂H₅</td>
<td>36d</td>
<td>91%</td>
<td>37d 95%</td>
</tr>
<tr>
<td>5</td>
<td>2-MeC₂H₅</td>
<td>36e</td>
<td>91%</td>
<td>37e 94%</td>
</tr>
<tr>
<td>6</td>
<td>3-pyridyl</td>
<td>36f</td>
<td>91%</td>
<td>37f 98%</td>
</tr>
<tr>
<td>7</td>
<td>2-furyl</td>
<td>36g</td>
<td>91%</td>
<td>37g 96%</td>
</tr>
<tr>
<td>8</td>
<td>Ph(CH₃)₂</td>
<td>36h</td>
<td>91%</td>
<td>37h 90%</td>
</tr>
<tr>
<td>9</td>
<td>c-C₅H₁₁</td>
<td>36i</td>
<td>91%</td>
<td>37i 90%</td>
</tr>
</tbody>
</table>

a Determined by ¹H NMR of the crude products. b The dr of 37 was the same as that of the starting 36 (entries 2–7).

Scheme 10. Conversion of 37a to one- and three-carbon introduction products 34 and 39

Scheme 11. Chemoselective addition of ether 35 to imino-aldehyde 7m

Scheme 12. Attempted diastereoselective reactions with imine 7a and ethers 40

(Scheme 13) was isolated in 9% yield along with THF-imine adduct 8n in 74% yield. In the absence of aldehyde 12, 43 was obtained in good yield (R = OMe, 73%; R = H, 90%). A plausible mechanism is shown in Scheme 13. At first, oxidation of an α-alkoxyalkyl radical generates an oxonium ion 44, and subsequent nucleophilic addition of an amine to 44 gave aminal intermediate 45, which was in equilibrium with imine 46. Then nucleophilic addition of THF radical 9 to imine 46 proceeded to give aminoalcohol 43. The corresponding aminal intermediate X was obtained in the reaction of THF, which supported the above scenario.

Scheme 13. Reaction of amines 14 with dimethylzinc–generated THF radical 9

10. Radicals from Alkanes

For lack of the radical stabilizing effect by an α-alkoxy group, C–H bonds of plane alkanes are stronger than the α-C–H bonds of the corresponding ethers; for example, the bond dissociation energy (BDE) of tetrahydrofuran-2-yl-H is 92 kcal/mol and that of cyclopentyl-H is 94.5 kcal/mol. Nevertheless, the instability of the methyl radical (BDE 105 kcal/mol for Me–H) suggests the possibility of the direct generation of alkyl radicals from plane alkanes. In fact, 5- to 8-membered cycloalkyl radicals were generated from the corresponding cycloalkanes by dimethylzinc–air to undergo addition to N-tosylimine 7a giving 47 in fair to good yield (Scheme 14). In the absence of boron trifluoride, the yields of 47 were lowered to 35–68%. It was our honor that Scheme 14 appeared on the cover of Tetrahedron Letters.

Scheme 14. Generation of cycloalkyl radicals and its addition to 7a mediated by dimethylzinc–air

11. Other Radical Reactions with Organozine Reagents

Several examples of the use of diethylzinc–air as a radical initiator were reported by other groups. Diethylzinc–air could
initiate tinhydride-mediated radical reactions. The intramolecular radical cyclization of aryl iodide 48 was initiated by diethylzinc–air at 20 °C to give dihydrobenzofuran 49 in 82% yield (Scheme 15).

**Scheme 15.** Initiation of tin-mediated radical cyclization of 48 by diethylzinc–air

![Scheme 15](image)

Diethylzinc–air mediated the diastereoselective addition of alkyl radicals to glyoxylate imines having a chiral auxiliary. Addition of a tert-butyl radical to glyoxylate imine 50 gave adduct 52 with diastereomer ratio of 93:7 in 69% yield using diethylzinc–air (Scheme 16). Chelate complex 51 may be involved because the diastereoselectivity of the addition was decreased to 35:65 using triethylborane, which is unable to form a bidentate complex, instead of diethylzinc.

**Scheme 16.** Diethylzinc-mediated radical addition to chiral glyoxylate imine 50

![Scheme 16](image)

Conjugate addition of alkyl radicals to alkenones was also mediated by diethylzinc–air. The reaction of cyclohexenone (53) and diethylzinc with or without alkyl iodides gave adduct 54 in good yields (Scheme 17).

**Scheme 17.** Conjugate addition of alkyl radicals to enone 53 using diethylzinc–air

![Scheme 17](image)

12. **Other Reactions with Triethylborane**

Compared with diorganozincs, triethylborane is a quite popular radical initiator. In 1970, Brown revealed that conjugate addition of trialkylborane is a radical reaction from the fact that galvinoxyl inhibited the reaction. Afterward, a number of studies developed the radical chemistry of organoboranes, especially of triethylborane. Compared with typical radical initiators such as azobisisobutyronitrile (AIBN) and benzoyl peroxide, triethylborane initiates radical reaction even at -78 °C and is useful in stereoselective reactions. For example, Sibi reported highly enantioselective conjugate addition of an alkyl radical to 55 in the presence of chiral oxazolidinone cinnaamate 56 and Lewis acid, giving adduct 57 with 97% ee in 91% yield (Scheme 18).

In addition, triethylborane can avoid the use of tin reagents. Naito reported the addition of an alkyl radical to glyoxylate oxime ether 58 with triethylborane and alkyl iodide (Scheme 19). On the other hand, the addition of isopropyl iodide with AIBN and tributyltin hydride in refluxing toluene gave adduct 59 in 39% yield, and with V-70 and tributyltin hydride at room temperature did not afford any addition product. Based on these results, it was suggested that triethylborane also acts as a Lewis acid as well as an initiator.

**Scheme 19.** Addition to glyoxylate oxime ether 58 with triethylborane

![Scheme 19](image)

Moreover, triethylborane is stable in alcohol and water, and thus it is possible to perform radical reactions in aqueous media. Oshima demonstrated the utility of water in the atom transfer radical cyclization of 60. Interestingly, the desired product was not obtained at all in hexane or benzene although the reaction proceeded smoothly in water (Scheme 20). *Ab initio* calculation suggested that water lowers the barrier to rotation and promotes the formation of a less stable E-rotamer from which cyclized product 61 was generated.

**Scheme 20.** Et3B–induced atom transfer radical cyclization in water

![Scheme 20](image)

13. **Summary**

We have developed methodology to generate ether radicals through α-hydrogen abstraction from ethers by the action of dimethylzinc–air. The good hydrogen abstraction ability of the methyl radical and the initiation at room temperature are the advantages of the use of dimethylzinc in radical reactions.

**References**

4. (a) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M.

Vol.62 No.11 2004


Ken-ichi Yamada is an assistant professor of Kyoto University. He received his Ph.D. from the University of Tokyo in 2001 under the supervision of Professor M. Shibasaki. In 2002, he received the Toray Award in Synthetic Organic Chemistry, Japan. His research interests are in synthetic organic chemistry, asymmetric synthesis, and organometallic chemistry.

Yasutomo Yamamoto is a teaching assistant for the 21st Century COE (Center of excellence) Program “Knowledge Information Infrastructure for Genome Science”. He received his M.S. degree (2004) from Kyoto University. His research interests are in synthetic organic chemistry, asymmetric synthesis, and organometallic chemistry.

Kiyoshi Tomioka is a Professor of the Graduate School of Pharmaceutical Sciences, Kyoto University. He received his Ph.D. from the University of Tokyo in 1976 under the direction of Prof. S. Yamada. He worked as a postdoctoral fellow with Prof. A. I. Meyers at Colorado State University in 1976-1978. He joined the University of Tokyo as a Research Associate in 1978 and was promoted to Associate Professor in 1983. He moved to Osaka University as a Professor in 1992. He has been Professor at Kyoto University since 1996. He received The Pharmaceutical Society of Japan Award in 2003. His research interests are in synthetic organic chemistry, asymmetric synthesis, organometallic chemistry, and molecular architecture.