

## Benzyl radical addition reaction through the homolytic cleavage of a benzylic C–H bond†‡

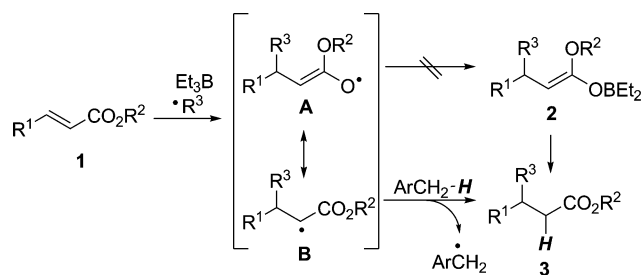
Masafumi Ueda, Eiko Kondoh, Yuta Ito, Hiroko Shono, Maiko Kakiuchi, Yuki Ichii, Takahiro Kimura, Tetsuya Miyoshi, Takeaki Naito and Okiko Miyata\*

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Direct generation of a benzyl radical by C–H bond activation of toluenes and the addition reaction of the resulting radical to an electron deficient olefin were developed. The reaction of dimethyl fumarate with toluene in the presence of Et<sub>3</sub>B as a radical initiator at reflux afforded 2-benzylsuccinic acid dimethyl ester in good yield.

Free radical reactions represent one of the most straightforward tools for carbon–carbon bond formation in organic synthesis.<sup>1,2</sup> Consequently, extensive studies have been demonstrated for obtaining novel radical reactions. Among them, the radical reaction mediated by triethylborane, which is recognized as an excellent radical initiator, mediator and terminator, has recently led to many novel and useful synthetic applications.<sup>3</sup> However, Et<sub>3</sub>B-mediated radical addition to  $\alpha,\beta$ -unsaturated ester **1** generally does not give the corresponding adduct **3** in the absence of a hydrogen donor such as tributyltin hydride (Scheme 1).<sup>3a,4</sup>



**Scheme 1** Triethylborane-mediated radical addition to an  $\alpha,\beta$ -unsaturated ester.

This drawback is attributed to the observation that the intermediate enoxy radical **A** generated by the 1,4-radical addition cannot be trapped by Et<sub>3</sub>B. Therefore, Et<sub>3</sub>B does not function as a radical terminator. We postulated that the enoxy radical **A** and the  $\alpha$ -carbonyl radical **B** have the ability to extract a benzylic hydrogen

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe, 658-8558, Japan. E-mail: miyata@kobepharmaceutical-u.ac.jp; Fax: +81-78-441-7556

† This work is dedicated to the memory of Athel Beckwith, a teacher and scientist from whom we learned how to study chemistry by example. His pioneering advances in radical chemistry laid the foundation for much of the current radical clock methodology.

‡ Electronic supplementary information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/c0ob01148g

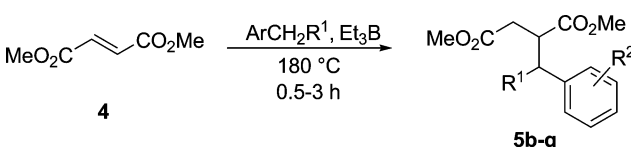
atom to generate stable benzyl radical derivatives, which can be used for the addition reaction. Although various strategies have been developed for the generation of a carbon radical center, C–H bond activation is a particularly promising and economically attractive method for the direct generation of a carbon radical.<sup>5–9</sup> Albini and co-workers have reported the generation of a benzyl radical from toluene by photosensitization; however, the addition reaction afforded a mixture of many products.<sup>10</sup> Herein, we report a novel approach for the generation of a benzyl radical and the addition reaction to an electron deficient olefin in connection with our recent efforts in radical chemistry.<sup>11</sup>

For our initial optimization studies, dimethyl fumarate **4** as a radical acceptor and toluene as benzyl radical source and solvent were selected (Table 1). When the radical reaction was carried out with 2 equiv. of Et<sub>3</sub>B in toluene (concentration 0.05 M) at room temperature, the dimethyl fumarate **4** was rapidly consumed but no isolable products were afforded, probably due to the slow hydrogen abstraction which led to the polymerization of an intermediate radical (entry 1). The reaction was run at reflux to improve the efficiency of hydrogen abstraction from toluene by an  $\alpha$ -carbonyl radical. The desired benzyl adduct **5a** was obtained as expected, albeit in 41% yield (entry 2). Upon decreasing the concentration to 0.025 M and the amount of Et<sub>3</sub>B to 1 equiv., the yield increased to 53% (entry 4). The reaction in the absence of Et<sub>3</sub>B proceeded very slowly to give **5a** in low yield (entry 6). This result indicates that Et<sub>3</sub>B plays an important role at the radical initiation step. The

**Table 1** Benzyl radical addition to dimethyl fumarate **4**

Entry	Concentration (M)	Et <sub>3</sub> B (equiv.)	Temp.	Yield (%) <sup>a</sup>
1	0.05	2	rt	—
2	0.05	2	reflux	41
3	0.025	2	reflux	48
4	0.025	1	reflux	53
5	0.025	0.5	reflux	48
6	0.025	none	reflux	8 (83) <sup>b</sup>
7	0.01	1	reflux	74

<sup>a</sup> Isolated yield. <sup>b</sup> Yield in parentheses is for the recovered starting material **4**.

**Table 2** Radical addition to dimethyl fumarate with various toluene derivatives

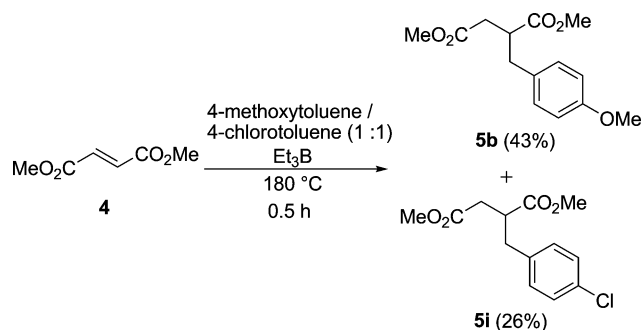
Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%) <sup>a</sup>
1 <sup>b</sup>	H	4-OMe	<b>5b</b>	88
2 <sup>c</sup>	H	3-OMe	<b>5c</b>	77
3 <sup>c</sup>	H	2-OMe	<b>5d</b>	77
4 <sup>c</sup>	H	3,4-di-OMe	<b>5e</b>	39
5 <sup>b</sup>	H	4-Me	<b>5f</b>	68
6 <sup>b</sup>	H	3-Me	<b>5g</b>	52
7 <sup>c</sup>	H	2-Me	<b>5h</b>	19
8 <sup>d</sup>	H	4-Cl	<b>5i</b>	63
9 <sup>d</sup>	H	4-Br	<b>5j</b>	66
10 <sup>d</sup>	H	4-F	<b>5k</b>	36
11 <sup>d</sup>	H	4-I	<b>5l</b>	30
12 <sup>d</sup>	H	3-Cl	<b>5m</b>	57
13 <sup>c</sup>	H	2-Cl	<b>5n</b>	43
14 <sup>d</sup>	H	4-CO <sub>2</sub> Me	<b>5o</b>	64
15 <sup>b</sup>	Bn	H	<b>5p</b>	65 (6 : 1) <sup>d</sup>
16 <sup>c</sup>	Me	H	<b>5q</b>	28 (1 : 1) <sup>d</sup>

<sup>a</sup> Isolated yield. <sup>b</sup> Reactions carried out with 0.3 equiv. of Et<sub>3</sub>B. <sup>c</sup> Reactions carried out with 0.9 equiv. of Et<sub>3</sub>B. <sup>d</sup> Ratio was determined by <sup>1</sup>H NMR. The relative stereoconfiguration was not determined. <sup>e</sup> Reactions carried out with 0.6 equiv. of Et<sub>3</sub>B.

best result was obtained when the concentration was 0.01 M with 1 equiv. of Et<sub>3</sub>B (entry 7). The product, 2-benzylsuccinate, represents an important compound because of its utility as an intermediate in the synthesis of biologically active compounds and functional materials.<sup>12</sup> Although several synthetic methods including multi-step processes have been reported,<sup>13</sup> the direct introduction of the benzyl group to fumarate has been less frequently reported.<sup>14</sup> Thus, our direct benzylation reaction is characterized as atom economical, straightforward and a valuable reaction.

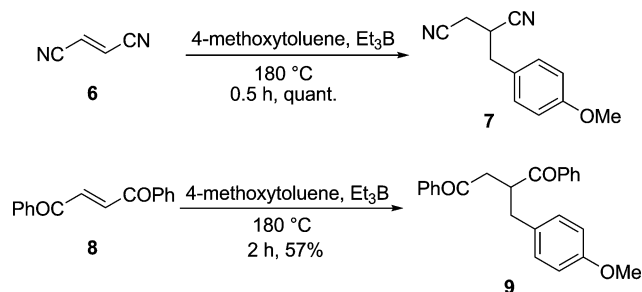
To examine the scope of this direct benzylation, various toluene derivatives were subjected to the radical reaction (Table 2). We were pleased to observe that electron rich or poor toluene derivatives were readily accommodated, producing the expected adducts **5b–o**. It should be noted that the reaction proceeded with even less than 1 equivalent of Et<sub>3</sub>B, owing to the higher reaction temperature employed. Reactions of 2-, 3- and 4-methoxytoluenes proceeded effectively with good yields (entries 1–3), while a lower yield was observed in the reaction with 3,4-dimethoxytoluene (entry 4). *p*- and *m*-Xylene were also suitable reagents to use; however, *o*-xylene gave a low yield of product **5h** because of its steric properties (entries 5–7). A halogen and an ester substituent showed tolerance towards this radical reaction (entries 8–14). Notably, the bromo and the iodo groups, which did not affect the course of the reaction, could serve as a handle for further transformations. Interestingly, the addition of dibenzyl produced the adduct **5p** in 68% yield with a 6 : 1 mixture of stereoisomers, although a reduced yield of **5q** and no stereoselectivity were observed with ethylbenzene (entries 15 and 16).

A competition experiment was conducted to study the influence of the electronic nature of the benzyl radical on reactivity towards the electron deficient olefin (Scheme 2). As a result of the

**Scheme 2** Competition experiment.

reaction with an equimolar mixture of 4-methoxytoluene and 4-chlorotoluene, the 4-methoxybenzyl radical exhibited higher reactivity in the formation of **5b**. This indicated that the methoxy group as an electron donating group increased the SOMO energy level of the nucleophilic benzyl radical; thus, interaction of the LUMO of the olefin with the SOMO of the benzyl radical would be enhanced.

We have also extended the acceptor tolerance to 1,2-dicyano- and 1,2-diketone olefins (Scheme 3). Fumaronitrile **6** showed excellent reactivity giving the desired product **7** in quantitative yield. 1,2-Diketone **8** was also found to react with 4-methoxytoluene to afford the adduct **9**, albeit in relatively lower yield due to the competition with the ethyl radical addition reaction.

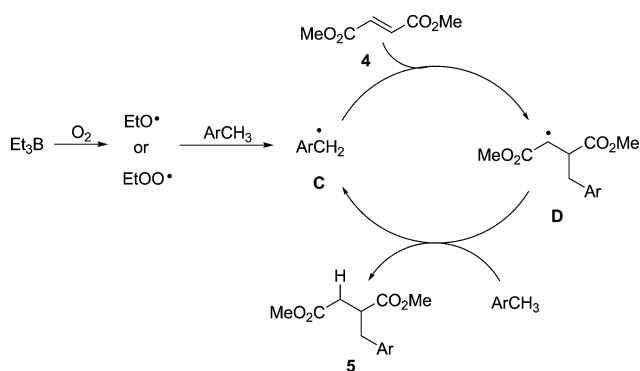
**Scheme 3** 4-Methoxybenzyl radical addition to the electron deficient olefins.

A possible reaction pathway is presented in Scheme 4. The first step involves the generation of an ethoxy radical and an ethylperoxy radical by the oxidative decomposition of Et<sub>3</sub>B with molecular oxygen. The radicals then abstract a hydrogen atom from the toluene derivatives to produce a benzyl radical **C**. The benzyl radical can add to fumarate to form the  $\alpha$ -carbonyl radical **D**. The trapping of the radical **D** by toluene derivatives gave product **5** and the regeneration of the benzyl radical which is used for the radical chain cycle.

In conclusion, we have demonstrated the direct generation of a benzyl radical by C–H bond activation of toluenes and the addition reaction of the resulting radical to an electron deficient olefin.

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**Scheme 4** Possible reaction pathway.

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