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Intermolecular Radical Addition to Ketoacids Enabled by Boron Activation

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Supporting Information

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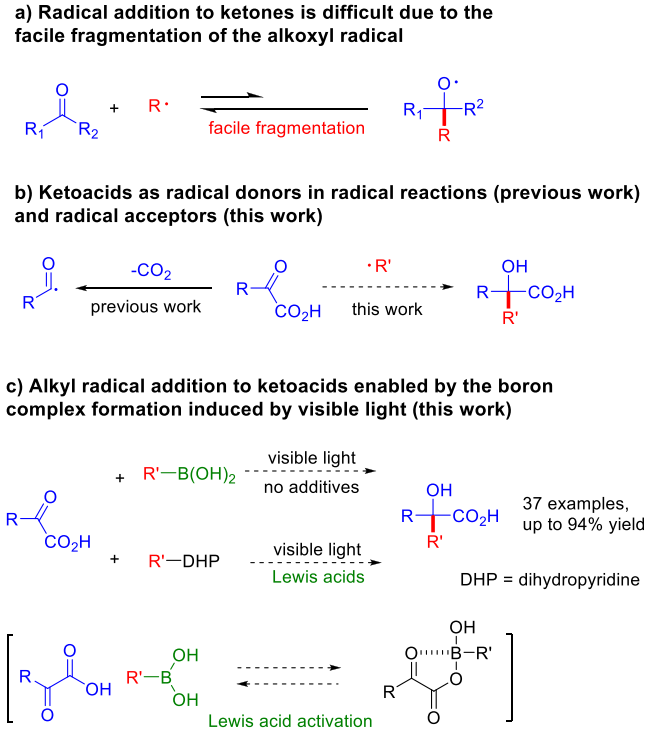
ABSTRACT: The intermolecular radical addition to the carbonyl group is difficult due to the facile fragmentation of the resulting alkoxyl radical. To date, the intermolecular radical addition to ketones, a valuable approach to construct quaternary carbon centers, remains a formidable synthetic challenge. Here, we report the first visible-light-induced intermolecular alkyl boronic acid addition to α-ketoacids enabled by the Lewis acid activation. The *in situ* boron complex formation is confirmed by various spectroscopic measurements and mechanistic probing experiments, which facilitates various alkyl boronic acid addition to the carbonyl group and prevents the cleavage of the newly formed C−C bond. Diversely substituted lactates can be synthesized from readily available alkyl boronic acids and ketoacids at room temperature merely under visible light irradiation, without any additional reagent. This boron activation approach can be extended to alkyl dihydropyridines as radical precursors with external boron reagents for primary, secondary, and tertiary alkyl radical additions. The pharmaceutically useful anticholinergic precursors are easily scaled up in multigrams under metal-free conditions in flow reactors.

The carbonyl group is a readily available building block for the synthesis of substituted alcohols.[1] While the nucleophilic addition to the carbonyl group is favorable and widely studied, the radical addition to the carbonyl group is difficult, as the resulting alkoxyl radical undergoes β-fragmentation readily to reverse the reaction, especially for the radical addition to ketones (Scheme 1a).[2] To date, the intermolecular radical addition to ketones,[3,4] which is valuable to construct quaternary carbon centers,[5] remains a formidable synthetic challenge. Lactates are important biological metabolites, which are precursors of poly-α-hydroxy acids for targeted drug delivery,[6] and include many prescription drugs such as anticholinergic Oxybutynin and Glycopyrrolate (see Scheme 3b for structures).[7] The α-ketoacid is a readily available synthetic building block to prepare lactates by nucleophilic additions with alkyllithiums or Grignard reagents.[8] However, these reactions are susceptible to air and moisture, and the strong nucleophilicity of these reagents unavoidably result in undesirable side reactions.[9] To this end, the new synthetic approaches to lactates, especially from different mechanistic manifolds, are in high demand.

Scheme 1. Alkyl Radical Addition to Ketoacids Enabled by Lewis Acid Activation



Ketoacids currently undergo decarboxylative acyl radical formations in radical reactions, and their engagement as the radical acceptors remains unknown (Scheme 1b).[10] Organoborons are environmentally friendly and readily available, and are stable synthetic building blocks with Lewis acidity.[11] In this communication, we report the first alkyl boronic acids radical addition to ketoacids with the Lewis acid activation from organoborons, which can be extended to alkyl dihydropyridine radical addition to ketoacids in the presence of external boron reagents (Scheme 1c).

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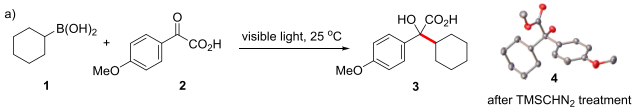
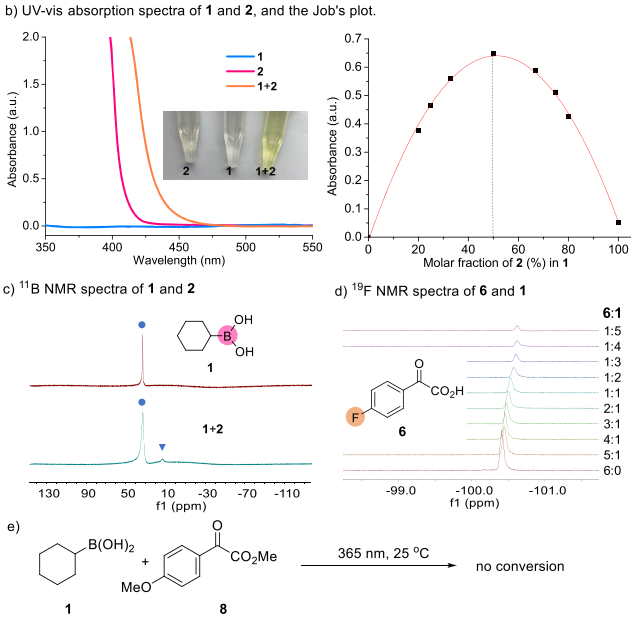
Our initial discovery arose from the serendipitous observation when cyclohexyl boronic acid **1** and *p*-methoxyphenyl ketoacid **2** were mixed. While the individual solutions of **1** and **2** in dichloromethane were colorless, a yellow color appeared simultaneously upon mixing (Scheme 2b). When the dichloromethane solution containing **1** and **2** was irradiated, the α-hydroxy acid **3** was obtained in 76% yield under the blue LED irradiation without any additional reagent (entry 1 of Scheme 2a). The use of a 23 W household fluorescence lamp gave a slightly increased 84% yield of **3** (entry 2). When using light irradiation with the band-pass at 475 nm, in which neither **1** nor **2** absorbs (Scheme 2b), a 64% yield of **3** was obtained (entry 3). The alkyl trifluoroborates **5** in aqueous conditions gave an optimal 95% yield of α-hydroxy acid **3**,[12] which gave lactate **4** after $TMSCHN_2$ treatment in 80% isolated yield (entry 4).[13] The reaction in the darkness gave **3** in only 21% yield (entry 5; see detailed optimization in Table S1).

Scheme 2. Visible-Light-Induced Reaction between Alkyl Boronic Acids and Ketoacids, and the Spectrometry Studies for the Boron Complex Formation



entry[a]	conditions	Conv.[b]	Yield of **3**[b]
1	4 W blue LED	87%	76%
2	23 W white CFL	>95%	84%
3	band-pass 475 nm	75%	64%
4	entry 2, RBF_3K **5** instead of **1**	>95%	95(80)%[c]
5	entry 2, no light	22%	21%



[a]Reaction conditions: **1** (0.30 mmol, 3.0 equiv) and **2** (0.10 mmol, 1.0 equiv) in 2.0 mL of CH_2Cl_2 with light irradiation at room temperature for 5 h, unless otherwise noted. [b]Conversions of ketoacid **2** and yields of α-hydroxy acid **3** were determined by ^1H NMR analysis. [c]The alkyl trifluoroborates **5** were used in 1:1 CH_2Cl_2/H_2O. Isolated yields of lactate **4** after esterification with trimethylsilyldiazomethane ($TMSCHN_2$) were in parentheses.

We next measured the UV−vis absorption spectra of alkyl boronic acid **1** and ketoacid **2**, with which the Job's plot revealed the 1:1 ratio of the boron complex formation (Scheme 2b).[14] We also measured the ^{11}B NMR spectrum of **1** and found an upfield new peak appearing at 13.5 ppm when mixing with **2**, indicating the changed boron chemical environment (Scheme 2c). From the titration experiments via ^{19}F NMR spectrometry, the ^{19}F NMR signal of fluorinated ketoacid **6** shifted upfield with the addition of boronic acid **1** (Scheme 2d). A set of control spectrometry measurements were next performed with cyclohexyl boronic ester **7**, *p*-methoxyphenyl ketoester **8**, or *o*-nitrobenzoic acid **9**, and the spectrometry characterization indicated no boron complex formation (see Figures S3−S4).[15] In addition, the control reaction under 365 nm UV light irradiation gave no conversion between *p*-methoxyphenyl ketoester **8** and boronic acid **1** (Scheme 2e). Taken together, the carboxylic acid, boronic acid, and the carbonyl group are all essential for the boron complex formation and the visible-light-induced reactions.

We next investigated if this boron complex formation and subsequent radical addition to ketoacids are general to other alkyl boronic acids (Scheme 3a). While there were reports on the transition-metal-catalyzed aryl or allyl boronic acid additions to the carbonyl group, the alkyl boronic acids were not viable substrates due to the facile β-elimination.[16] The secondary cyclopentyl, cyclohexyl, cycloheptyl, and indanyl trifluoroborate **5**, **10**−**12** all reacted smoothly with ketoacid **2** under visible light irradiation to give isolated 67−80% yields of lactates **4**, **10a**−**12a** after $TMSCHN_2$ treatment. The noncyclic secondary boronic acids **13** and **14** were compatible to give lactates **13a** and **14a** in 71% and 75% yields, respectively. The heterocyclic *N*-tosylpiperidinyl boronic acids **15** afforded lactates **15a** in 79% yields. The primary phenethyl, benzyl, and ethyl boronic acids **16**−**18** gave 52−65% yields of lactates **16a**−**18a** in the mixed solvents with 5% hexafluoroisopropyl alcohol (HFIP).[17] The tertiary boronic acids were unreactive in the reaction, possibly due to the difficult boron complex formation from the steric hindrance.

The ketoacid scope was also investigated. The electron-neutral or electron-deficient substituted ketoacids **19**−**24** reacted with boronic acid **1** or trifluoroborate **5** to give 45−66% yields of lactates **19a**−**24a** after $TMSCHN_2$ treatment (Scheme 3a). The *ortho*, *para*, and *meta* aryl substitutions did not affect the reaction to give lactates **25a**−**28a** in 60−70% yields. The electron-donating alkoxyl and *N*-*tert*-Boc aryl substituents gave 83−85% yields of **29a**−**31a**. The heterocyclic thiophene ketoacid gave **32a** in decreased 33% yield, and the bicyclic naphthalene-derived ketoacids **33**−**34** reacted smoothly to give lactates **33a**−**34a** in 51−73% yields. Various pharmaceutically relevant and chemical biologically useful functional groups such as trifluoromethoxy and terminal alkynes were tolerated to give **35a**−**36a** in 78−82% yields. Significantly, the homoserine-derived ketoacid **37** gave the corresponding lactate **37a** in 90% yield. Such mild reaction conditions indicated future bioconjugation potentials.[18]

Next, practical aspects of the reaction were evaluated with a photochemical flow reactor. This approach has historically afforded chemists greater control, selectivity, and scalability than batch reactions.[19] We injected the alkyl boronic acid **1** and ketoacid **2** to the flow reactor under household 23 W CFL lamp irradiation (Scheme 3b, Figures S18−S19). After 10 h of reaction in 210 mL of the reaction mixture, the quaternary α-hydroxy acid **3** could be prepared in 1.69 g in 75% isolated yield. The synthetic analogues of **3** were practically one esterification step away from the racemic forms of anticholinergic drugs Oxybutynin/Glycopyrrolate. With its mild, metal-free, and

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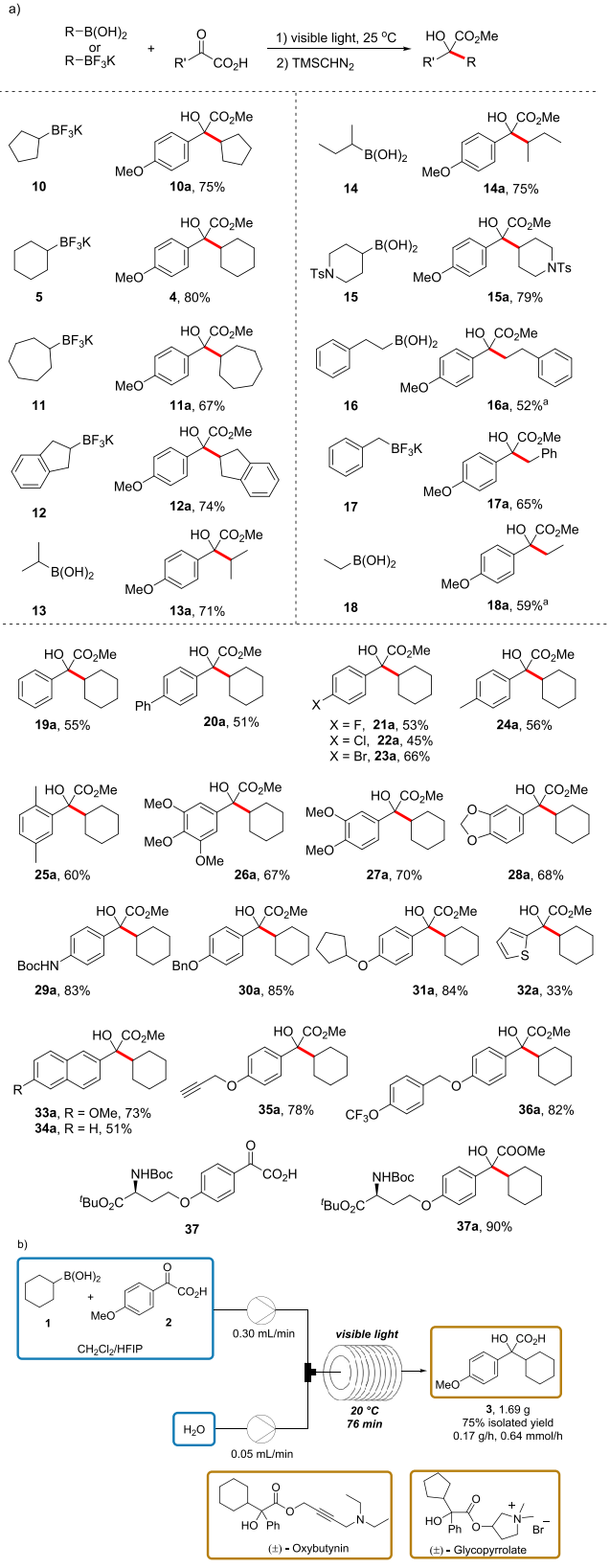
Scheme 3. Substrate Scope of the Alkyl Boronic Acid Addition to Ketoacids

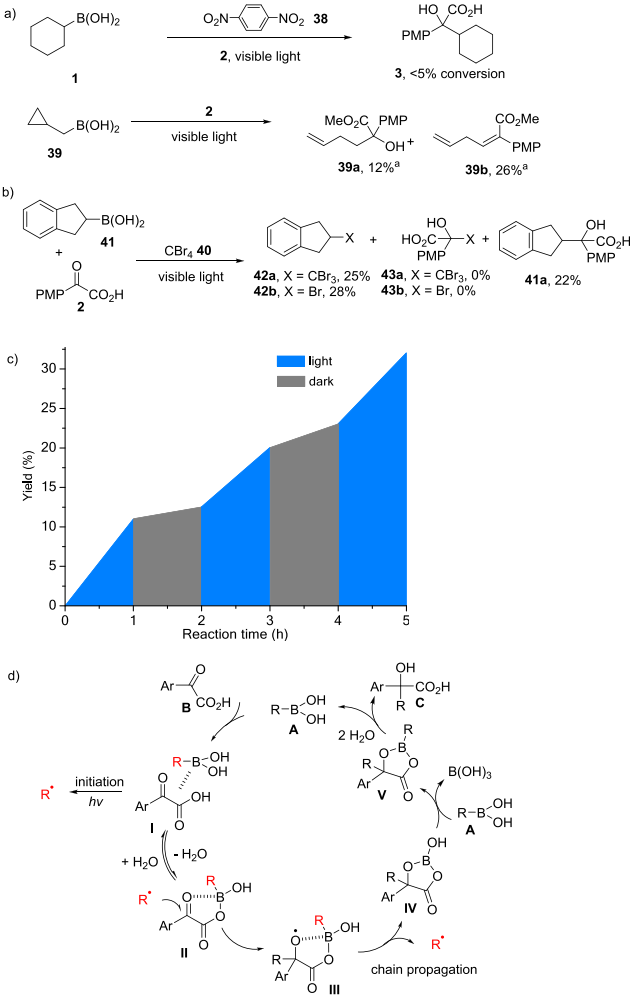


[a]The reaction time was 48 h, and 5% HFIP was added as cosolvent.

additional-reagent-free character, we expect this visible-light-induced alkyl boronic acid addition method will be an attractive approach to prepare lactates in the pharmaceutical industry.

We further investigated the reaction mechanisms. When the radical scavenger 1,4-dinitrobenzene **38** was incubated with boronic acid **1** and ketoacid **2**, the formation of α-hydroxy acid **3** was completely inhibited (Scheme 4a, Figure S9). The radical

Scheme 4. Mechanistic Investigations



[a]The combined yields after $TMSCHN_2$ treatment were reported.

clock cyclopropylmethyl boronic acid **39** resulted in the cyclopropyl ring-opening adduct **39a** and subsequent dehydration adduct **39b** in 12% and 26% yields, respectively. Tetrabromomethane **40** was next added to the reaction conditions of **41** and **2** to trap the potential radical intermediates (Scheme 4b, Figure S11).[20] Other than lactate **41a** formation in 22% yield, the tribromomethyl-**42a** and bromo-**42b** were observed in 25% and 28% yields, respectively, deriving from alkyl boronic acid **41**. In contrast, neither the tribromomethyl-**43a** nor bromo-**43b** adduct from ketoacid **2** was observed, which suggested no ketyl radical was formed from ketoacids during the reaction.[21] We further performed the on−off-light experiment between boronic acid **1** and ketoacid **2** and observed the occurrence of the dark reaction (Scheme 4c, Figure S13). These results suggested the alkyl radical intermediate and the radical chain reaction mechanism.[22]

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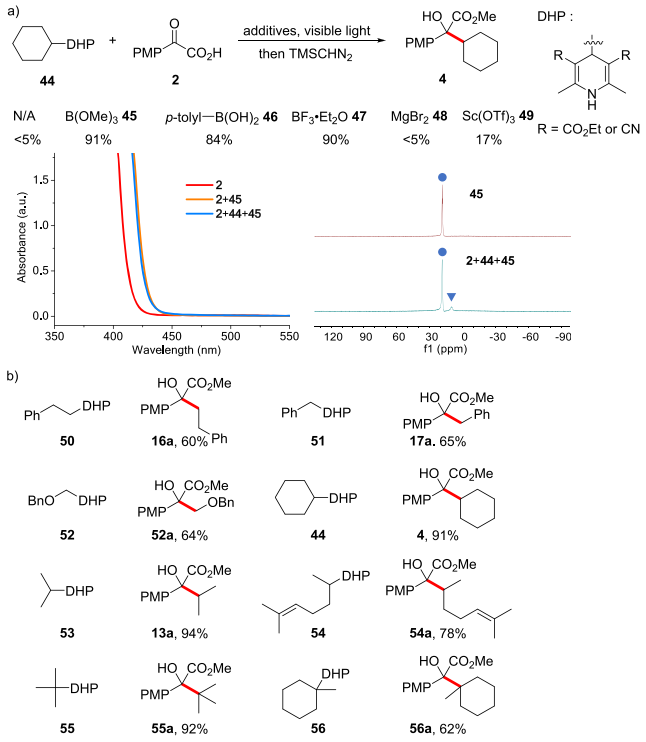
With the detailed mechanistic investigation, we propose the reaction is initiated by the boron complex formation between alkyl boronic acid **A** and ketoacid **B**, which is represented either as the Lewis acid−base pair **I** or as the boron anhydride **II** (Scheme 4d).[23] This boron complex can be photoexcited to generate the alkyl radical R· for radical initiation, which then yields the cyclic boron radical intermediate **III**. The delocalized radical intermediate **III** is stabilized by the boron complex to prevent the C−C bond cleavage reaction and undergoes the C-B bond cleavage reaction to eliminate the alkyl radical R· for chain propagation.[24] The intermediate **IV** then undergoes an ester exchange reaction with alkyl boronic acid **A** to yield the resulting cyclic boron complex **V**, which was suggested by the NMR spectrometry (Figures S7−S8).[25] The intermediate **V** then undergoes hydration to yield the quaternary α-hydroxy acid product **C** and releases the alkyl boronic acid **A** for the next boron complex formation.[26]

After the successful alkyl boronic acid addition to ketoacids with boron complex formation, we were curious if other alkyl radical precursors could engage in radical carbonyl additions with this approach. The alkyl-substituted dihydropyridines (DHPs) are readily available alkyl precursors and can be prepared from aldehydes in one step.[27] While visible light irradiation of cyclohexyl-DHP **44** ($E_{1/2}^{ox}$ = +0.65 V vs F_c^+/F_c in DMSO) and ketoacid **2** gave no conversion,[28] the addition of external boron reagents significantly affected the reaction outcomes (Scheme 5a). The trimethyl borate $B(OMe)_3$ **45**

Scheme 5. Radical Addition to Ketoacids by Alkyl-DHPs with External Boron Reagents



afforded the desired lactate **4** in 91% yield after $TMSCHN_2$ treatment, and aryl boronic acid **46** or trifluoroborane etherate $BF_3{\cdot}Et_2O$ **47** also gave lactate **4** in 84−90% yields. In contrast, the commonly used Lewis acid magnesium bromide $MgBr_2$ **48** or scandium triflate $Sc(OTf)_3$ **49** gave only <5% and 17% yields of **4** (see Figure S15 for the complete screen of additives). We next measured the UV−vis absorption spectrometry of ketoacid **2** with different boron reagents and found the bathochromic shift to be similar to that for the addition of alkyl boronic acids (Scheme 5a, Figure S5). The ^{11}B NMR spectrometry of $B(OMe)_3$ **45** and ketoacid **2** also showed a clear upfield shift at 10.2 ppm, indicating the new boron complex formation.

We then tested different alkyl-DHP derivatives under visible light irradiation and observed primary and secondary alkyl-DHPs **44**, **50**−**54** engaged in the ketoacid additions smoothly, in which 60−94% yields of lactates were obtained (Scheme 5b). Gratifyingly, the tertiary alkyl-DHPs **55** and **56** reacted well to give lactates **55a**−**56a** with two adjacent quaternary carbon centers in 62−92% yields, which were steric-crowded lactates and synthetically challenging. These results indicated that the boron complex formation with external boron reagents may overcome the steric hindrance limitation imposed by the use of tertiary alkyl boronic acids.[29]

In conclusion, we have reported the first visible-light-induced alkyl radical addition to ketoacids enabled by Lewis acid activation. The boron complex formation between boronic acids and ketoacids facilitates the alkyl radical addition to the carbonyl group and prevents the cleavage of the newly formed C−C bond. The dihydropyridines engage in radical additions to ketoacids with external boron reagents to enable the primary, secondary, and tertiary alkyl radical addition reactions. This reaction is readily performed in photochemical flow reactors to enable the multigram synthesis of pharmaceutically important lactates under metal-free conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b09099.

Complete mechanistic experiments, optimization tables, experimental methods, and additional experimental data (PDF)

NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(3) ΔE_{frag} is around 0.4 to −13.2 kcal/mol for tertiary alkoxyl radicals.

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