



# Decarbonylative radical conjugate addition of aliphatic aldehydes for alkylation of electron-deficient alkenes

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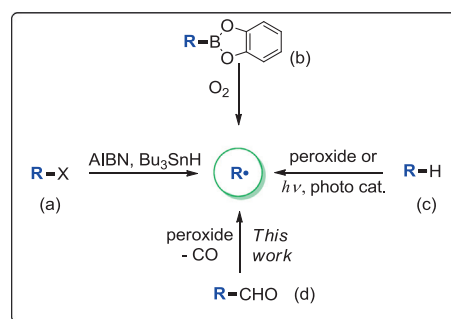
## ABSTRACT

A convenient metal-free decarbonylative radical conjugate addition of aliphatic aldehydes to electron-deficient alkenes is developed. With DTBP as an oxidant and radical-initiator, this reaction smoothly converts  $\alpha$ -unsubstituted,  $\alpha$ -mono-substituted and  $\alpha$ -di-substituted aliphatic aldehydes into the corresponding primary, secondary and tertiary alkyl radicals, and subsequently allows for the cascade construction of C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bond via radical conjugate addition.

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## Introduction

Radical conjugate additions (RCAs) represent a powerful strategy to build up molecular complexity benefiting from the readily availability of alkene feedstock [1]. RCAs frequently proceed under pH-neutral conditions, show a greater functional group tolerance than ionic counterparts and display exceptional chemoselectivity for 1,4- over 1,2-addition, to make them finding widespread applications in natural products synthesis [2]. However, for the alkylation of electron-deficient alkenes, these utilities have been hampered by limited precursors and laborious procedures for the generation of alkyl radicals. For example, alkyl halides were the most prevalent alkyl radical precursors, but often accompanied by the use of AIBN as radical initiator and toxic tributyltin hydride as halide acceptor (Scheme 1a) [3]; while xanthates [4], B-alkylcatecholboranes [5] and other C–X bonds [1] were also reported as alkyl radical precursors, but the pre-functionalization was necessary (Scheme 1b). Theoretically speaking, alkanes should be the ideal alkyl radical precursors via the direct homolytic abstraction of hydrogen, however, this pathway was limited to symmetric structures existing only one type of sp<sup>3</sup> C–H bond [6a–e] to reduce the possible regioisomers (Scheme 1c), or sp<sup>3</sup> C–H bond adjacent to N/O atoms [6f,g] and other functional groups [6h]. Thus, more convenient methods to provide alkyl radicals with varied structures from readily available sources would be highly desirable.



Scheme 1. Various alkyl radical precursors for RCAs.

Aliphatic aldehyde would be such a type of ideal radical precursor for RCAs according to our recent studies on oxidative decarbonylative reactions. With peroxides as radical initiator and oxidant, the decarbonylative couplings of aldehydes with arenes [7a], heteroarenes [7b], styrene derivatives [7c,e], and the alkylation-cyclization cascade reaction of acrylamides [7f] were successively developed in our group. These decarbonylative reactions were further updated by other groups, with dioxygen as the radical initiator and oxidant. [8] Similarly, the radical type decarbonylative alkylations of aldehydes with C=C and C≡C were developed by Z.-P. Li [9a] and J.-H. Li [9b] respectively. Further, A RCA of aliphatic aldehydes to diaryl alkynoate was reported by Pan *et al.* to provide the alkylation/arylation product after

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decarbonylation and decarboxylation cascade [9c]. For the mechanism of these radical type decarbonylative reactions, it's widely accepted that an aliphatic aldehyde was successively transformed into an acyl radical, to provide the corresponding alkyl radical after spontaneous decarbonylation [7–9]. Thus, we postulated that the combination of radical type decarbonylation of aliphatic aldehydes and subsequent conjugate addition to electron-deficient olefins should provide a feasible method for the alkylation of these alkenes.

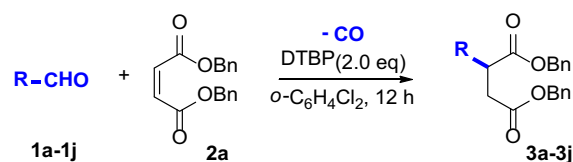
## Results and discussion

Based on our recent studies [7e] and the above mechanistic analysis, we first chose pivaldehyde (**1a**) as the potential radical precursor, and methyl acrylate as the RCA acceptor in the presence of peroxides; which did produce trace amount of RCA product but the polymerization of methyl acrylate was too serious to improve it. So we switched to choose the more electron deficient and structurally symmetric maleate as the RCA acceptor to accelerate the intermolecular radical type nucleophilic addition and suppress the self-polymerization. With dibenzyl maleate (**2a**) used as the RCA acceptor in the presence of TBHP, the decarbonylative RCA of pivaldehyde (**1a**) successfully afforded the desired radical addition product **3a** in 65% yield (Table 1, entry 1). The subsequent optimization revealed that the yields were critically affected by the oxidant used, and the yield raised to 71% with di-*tert*-butyl peroxide (DTBP) added as the oxidant (entry 2); while other peroxides such as dicumyl peroxide (DCP), aqueous hydroperoxide and benzoyl peroxide (BPO) resulted in much lower yields (entries 3–5). Dioxxygen was also effective, albeit with only 38% yield. Since the decarbonylation of acyl radical to generate the corresponding alkyl radical requires relatively high temperature, the reaction temperature had an obvious influence on this decarbonylative RCA (entries 7 and 8), and reacting at 130 °C provided the best outcome. Next, the effect of solvent on this

oxidative RCA was investigated, and running the reaction in dichlorobenzene (*o*-C<sub>6</sub>H<sub>4</sub>Cl<sub>2</sub>) provided the highest yield. The reaction can also be conducted in low polarity solvents such as chlorobenzene and toluene, and more polar solvents such as acetonitrile, DMSO, DMF and NMP (*N*-methyl pyrrolidone), while the low polarity solvents generally provided better yields than the more polar ones (entries 9–15). The usage of 2.0 eq of DTBP was required to realize the full conversion of RCA acceptor (**2a**), reducing the dosage of DTBP to 1.5 and 1.0 eq resulted in lower yields of 64% and 51%, respectively (entries 16 and 17).

We next tested the generality of this decarbonylative RCA with different aliphatic aldehydes (**1b–1j**) under the optimized conditions (Table 2). While the  $\alpha$ -di-substituted pivaldehyde (**1a**) provided tertiary carbon radical after decarbonylation, the  $\alpha$ -mono-substituted aliphatic aldehydes including 2-methylpropanal (**1b**), 2-methylbutanal (**1c**), 2-methylpentanal (**1d**), 2-ethylbutanal (**1e**), 2-ethylpentanal (**1f**), cyclohexanecarbaldehyde (**1g**) and cyclopentanecarbaldehyde (**1h**) would provide secondary carbon radicals, which all took part in this decarbonylative RCA to provide the corresponding alkylation product successfully. What's more, the linear ( $\alpha$ -unsubstituted) aliphatic

**Table 2**  
The scope of the aliphatic aldehydes on this decarbonylative RCA.<sup>a</sup>



<b>1a</b>	pivaldehyde	<b>1b</b>	2-methylpropanal
<b>1c</b>	2-methylbutanal	<b>1d</b>	2-methylpentanal
<b>1e</b>	2-ethylbutanal	<b>1f</b>	2-ethylhexanal
<b>1g</b>	cyclohexanecarbaldehyde	<b>1h</b>	cyclopentanecarbaldehyde
<b>1i</b>	3-methylbutanal	<b>1j</b>	butanal

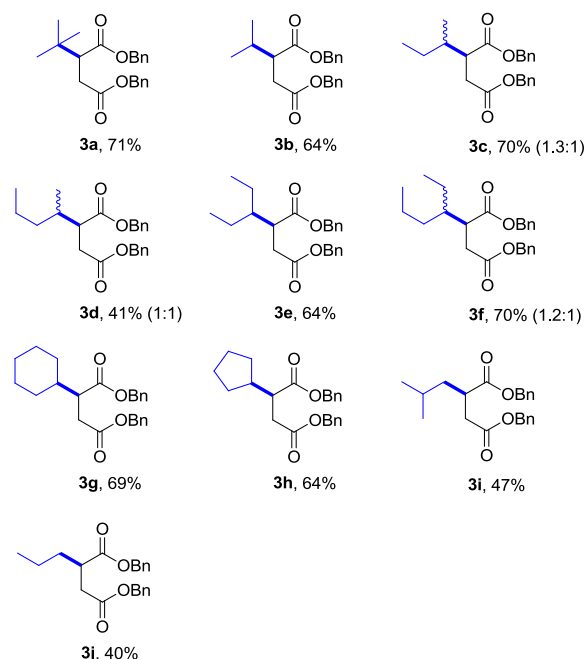
**Table 1**  
Optimization of the oxidative RCA.<sup>a</sup>

Entry	[O]	Solvent	Temp. (°C)	Yield [%]
1	TBHP	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	130	65
2	DTBP	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	130	71
3	DCP	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	130	50
4	H <sub>2</sub> O <sub>2</sub>	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	130	49
5	BPO	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	130	48
6	O <sub>2</sub>	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	130	38
7	DTBP	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	110	51
8	DTBP	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	150	57
9	DTBP	PhCl	130	67
10	DTBP	Toluene	130	51
11	DTBP	CH <sub>3</sub> CN	130	48
12	DTBP	DMSO	130	45
13	DTBP	DMF	130	9
14	DTBP	NMP	130	11
15	DTBP	dioxane	130	12
16 <sup>b</sup>	DTBP	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	130	64
17 <sup>c</sup>	DTBP	<i>o</i> -C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	130	51

<sup>a</sup> Conditions: **2a** (0.2 mmol), **1a** (0.6 mmol, 3.0 equiv), oxidant (0.4 mmol, 2.0 equiv), solvent (1.0 mL), reacted for 12 h under air unless otherwise noted. Isolated yields.

<sup>b</sup> 1.5 eq of DTBP was added.

<sup>c</sup> 1.0 eq of DTBP was added.



<sup>a</sup> Conditions: **2a** (0.2 mmol), **1** (0.6 mmol, 3.0 equiv), DTBP (0.4 mmol, 2.0 equiv), *o*-C<sub>6</sub>H<sub>4</sub>Cl<sub>2</sub> (1.0 mL), reacted at 130 °C for 12 h under air unless otherwise noted. Isolated yields with the ratio of diastereomers shown in parenthesis.

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