Angewandte
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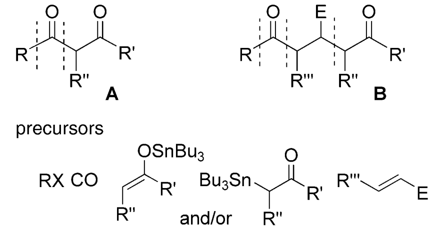
Synthesis of Diketones

Cascade Carbonylation Methods Leading to β-Diketones and β-Functionalized δ-Diketones**

Katsukiyo Miura, Mami Tojino, Naoki Fujisawa, Akira Hosomi, and Ilhyong Ryu**

The development of efficient synthetic strategies for the one-pot generation of multiple bonds is highly desirable. In this regard, radical strategies continue to attract much attention because of their considerable potential in this area.[1,2] Most viable cascade processes are, however, intramolecular sequences rather than the inherently more general intermolecular reactions. Herein we report a novel efficient intermolecular cascade sequence based on tin enolate mediated radical carbonylations,[3,4] in which three or four carbon-containing compounds are coupled to afford β-diketones **A** or β-functionalized δ-diketones **B**, respectively (Scheme 1).



Scheme 1. Precursors for the synthesis of β-diketones and β-functionalized δ-diketones.

The three-component radical coupling reaction was affected by combining octyl iodide (**1a**), carbon monoxide, and a tin enolate to give the anticipated β-diketone **4a** in 64% yield after isolation by flash chromatography on silica gel. The reaction with aromatic iodide **1e** also worked well and gave **4b** (Scheme 2). These results clearly demonstrated that tin enolates act as potentially useful acceptors of acyl radicals.

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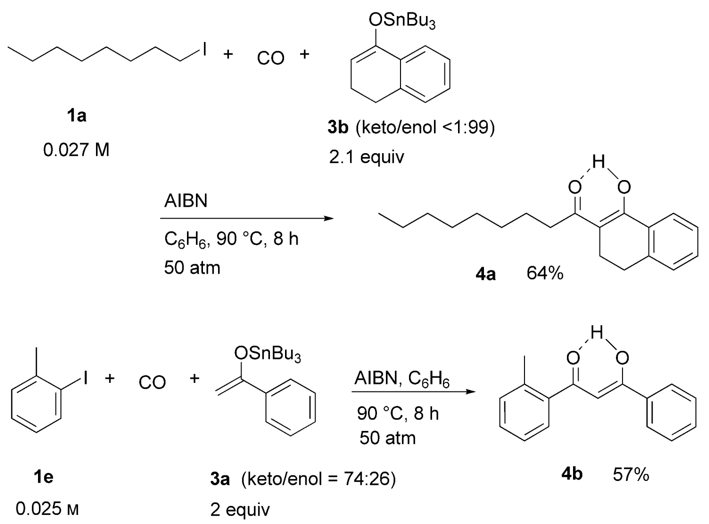
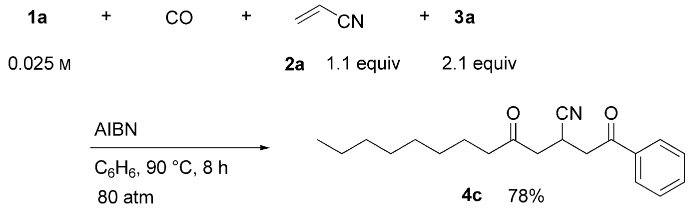


Scheme 2. Tin enolate mediated carbonylative three-component coupling reactions.

Next, we examined a mixed alkene system, comprised of tin enolates and electron-deficient alkenes,[5] in which we expected that nucleophilic acyl radicals would prefer electron-deficient alkenes rather than electron-rich tin enolates, providing a useful method for the synthesis of β-functionalized δ-diketones.

We were pleased to observe that the envisaged four-component coupling reaction occurred as expected. When a solution of 1-iodooctane (**1a**; 0.6 mmol, 0.025 M) in benzene, acrylonitrile (**2a**; 0.7 mmol), 1-phenyl-1-(tributylstannyloxy)-ethene (**3a**; 1.3 mmol; 74:26 keto/enol isomers), and AIBN (0.2 mmol) were heated at 90 °C for 8 h under CO (80 atm), the reaction proceeded cleanly to give the envisaged β-cyano-substituted δ-diketone **4c** in 78 % yield after isolation by flash chromatography on silica gel (Scheme 3). The formation of β-diketone was not detected in the crude reaction mixture.

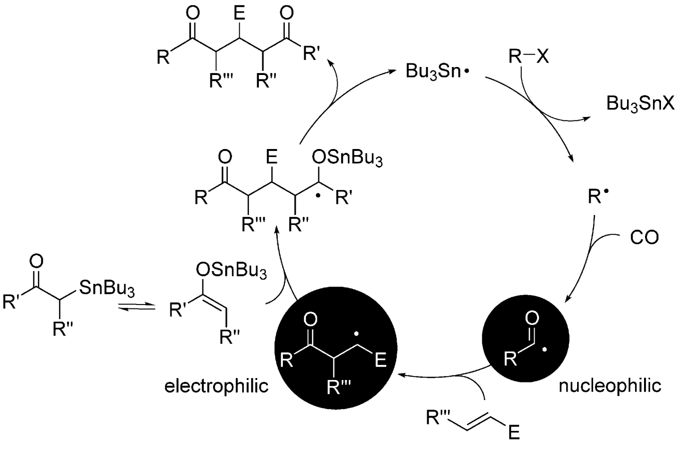


Scheme 3. Tin enolate mediated carbonylative four-component coupling reactions.

An expanded series of substrates **1** and alkenes **2** reveals several generalities of the present four-component coupling reaction (Table 1). Both methyl vinyl ketone (**2b**) and ethyl acrylate (**2c**) worked well to give the corresponding 3-acetyl-1,5-diketone **4d** and 3-ethoxycarbonyl-1,5-diketone **4e**, respectively (Table 1, entries 1 and 2). On the other hand, the use of acrolein was unsuccessful owing to its preferential aldol condensation with the tin enolate.[6] Vinyl sulfone **2d** gave the corresponding product **4f** in rather modest yield (Table 1, entry 3). In the reaction with *N*-crotonyloxazolidinone (**2e**), the corresponding four-component coupling product **4g** was obtained as a 1:1 mixture of diastereomers (Table 1, entry 4). In the case of **1f**, 5-*exo* radical cyclization preceded the intermolecular reaction to give **4o** (Table 1, entry 12).

Although tin enolates **3a** and **3b** derived from α-tetralone and acetophenone, respectively, exhibited excellent reactivity, the chain propagation ability of tin enolates **3c** and **3d** derived from cyclohexanone and pinacolone, respectively, appeared to be less efficient. However, the use of larger excesses of these enolates compensated for the modest reactivity (Table 1, entries 6 and 7).

The formation of 1,5-diketones **4** can be explained by the free-radical chain-propagation mechanism outlined in Scheme 4. Two key factors that made the present cascade reactions possible are as follows: 1) The key acyl radical, which is nucleophilic by nature, favors addition to electron-deficient alkenes rather than to electron-rich tin enolates, and the resulting alkyl radical is electrophilic enough to prefer electron-rich tin enolates. 2) S_H2'-type reaction of the resulting radical with tin *O*-enolates would be expected to shift the direction of the equilibrium with *C*-enolates.



Scheme 4. Radical chain mechanism for the four-component coupling reaction.

In summary, the use of the tin enolates as radical mediators for radical carbonylations led to the development of novel intermolecular cascade reactions, which combine three or four carbon-containing compounds in a single process. This procedure allows access to variously functionalized β- and δ-diketones from readily available starting materials.

Experimental Section

General procedure: Benzene (26 mL), **1a** (154 mg, 0.6 mmol), **2a** (41 mg, 0.7 mmol), **3a** (522 mg, 1.3 mmol), and AIBN (31 mg, 0.2 mmol), were placed in a 50-mL stainless-steel autoclave equipped with an inserted glass liner. The autoclave was closed and purged with carbon monoxide (3 × 10 atm). The autoclave was then charged with CO (80 atm) and heated, with stirring, at 90 °C for 8 h. After excess CO was discharged at room temperature, the solvent was evaporated, and the residue was purified by chromatography on silica gel (hexane, then hexane/Et_2O 7:3). The hexane eluant contained tributyltin iodide, and the hexane/Et_2O eluant contained pure **4c** (157 mg, 78%).

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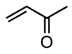
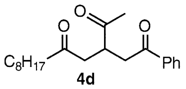
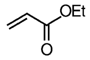
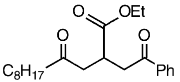
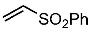
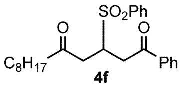
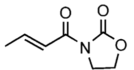
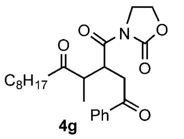
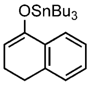
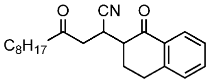
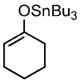
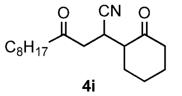
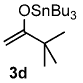
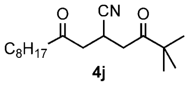
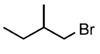
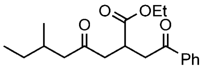
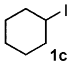
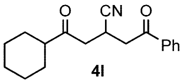
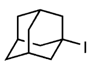
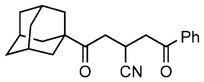
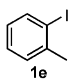
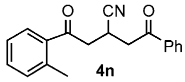
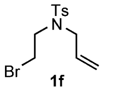
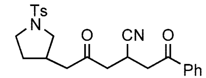
Table 1: Tin enolate mediated carbonylative four-component coupling reactions.[a]

Entry	1	2	3[b]	4	Yield [%][c]
1	**a**	 **2b**	**a**	 **4d**	74
2	**a**	 **2c**	**a**	 **4e**	80
3	**a**	 **2d**	**a**	 **4f**	50
4	**a**	 **2e**	**a**	 **4g**	64 (d.r. 50:50)[d]
5	**a**	**a**	 **3b**	 **4h**	92 (d.r. 60:40)[d]
6[e]	**a**	**a**	 **3c**	 **4i**	56 (d.r. 57:43)[d]
7[f]	**a**	**a**	 **3d**	 **4j**	56
8	 **1b**	**c**	**a**	 **4k**	73 (d.r. 50:50)[d]
9	 **1c**	**a**	**a**	 **4l**	71
10	 **1d**	**a**	**a**	 **4m**	76
11	 **1e**	**a**	**a**	 **4n**	72
12	 **1f**	**a**	**a**	 **4o**	88 (d.r. 50:50)[d]

[a] Conditions: **1** (0.5 mmol), **2** (0.6 mmol), **3** (1 mmol), AIBN (0.2–0.4 equiv), benzene (20 mL), CO (80–85 atm), 90 °C, 8 h. [b] **3a**: *O*-Sn/*C*-Sn = 26:74; **3b**: *O*-Sn/*C*-Sn = 99:1; **3c**: *O*-Sn/*C*-Sn = 99:1; **3d**: *O*-Sn/*C*-Sn = 1:99. [c] Yields of products isolated by flash chromatography on SiO_2. Products **4d**, **4f**, **4g**, and **4i** were further purified by preparative HPLC. [d] Determined by ^1H NMR spectroscopy. [e] **3d**: 3 equiv. [f] **3c**: 6 equiv. AIBN = 2,2′-azobisisobutyronitrile; Ts = *para*-toluenesulfonyl.

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