C–H Carbonylation

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Atom-Economical Synthesis of Unsymmetrical Ketones through Photocatalyzed C–H Activation of Alkanes and Coupling with CO and Electrophilic Alkenes[**]

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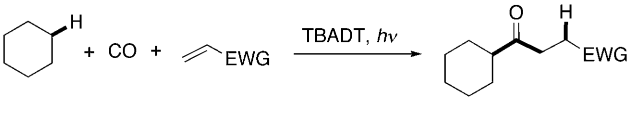
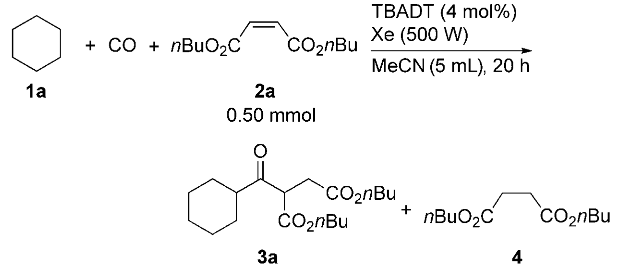
Multicomponent processes are highly desirable in modern organic synthesis because they allow the rapid generation of the targeted compounds.[1] Our research group has previously reported that unsymmetrical ketones can be synthesized by free-radical mediated, three-component coupling reactions of haloalkanes, CO, and electron-deficient alkenes, which employ Group 14 metal hydrides, such as tributyltin hydride[2a] or tris(trimethylsilyl)silane (TTMSS),[2b,c] as radical mediators.[3] We recently reported a related transformation that can be achieved by using tetrabutylammonium cyanoborohydride as an alternative for toxic tin hydride.[2d] A breakthrough would be obtained by replacing haloalkanes with alkanes and by avoiding the use of tin and silicon hydride reagents.[4] Provided that a convenient catalytic activation of the alkane would be available,[5] an atom-economical and eco-friendly process would result.[6] Herein, we report a viable photocatalytic alternative (Scheme 1).



Scheme 1. Atom-economical three-component coupling reactions leading to unsymmetrical ketones. EWG = electron-withdrawing group, TBADT = tetrabutylammonium decatungstate, $(nBu_4N)_4W_{10}O_{32}$.

This process is based on the use of tetrabutylammonium decatungstate (TBADT) as the photocatalyst.[7,8] This species has recently attracted attention because of the high photoactivity in the C–H bond homolytic hydrogen abstraction in alkanes[9] and in other substrates including aldehydes[10] and amides.[11] We supposed that a three-component coupling reaction through alkane C–H cleavage under photocatalysis by TBADT and a radical carbonylation would lead to the desired products. In 1995, Hill and Jaynes reported the 8% formation of cyclohexanecarboxaldehyde by a related photocatalytic reaction of cyclohexane with CO (1 atm).[12] We chose the three-component coupling involving cyclohexane (**1a**), CO, and dibutyl maleate (**2a**) as a model reaction, by using a xenon lamp as the light source and a stainless-steel autoclave equipped with two quartz windows as a pressure-durable apparatus (see the Supporting Information for details). The results are summarized in Table 1. When a solution of **1a**, **2a**, and TBADT (4 mol%) in acetonitrile was irradiated for 20 hours under a CO pressure of 80 atm, the desired reaction proceeded to give the ester-functionalized unsymmetrical ketone **3a** in a modest yield (51%; Table 1, entry 1) because a significant amount of dibutyl succinate **4** was likewise formed. However, the formation of **4** was effectively suppressed by simply changing the quartz liner to a

Table 1: TBADT photocatalyzed three-component coupling reaction of cyclohexane (**1a**), CO, and dibutyl maleate (**2a**).[a]



Entry	**1a** [equiv]	CO [atm]	Conversion [%][b]	Liner	Yield [%][c] **3a**	Yield [%][c] **4**
1	5	80	> 99	quartz	51	10
2	5	80	80	Pyrex	45	2
3	10	80	89	Pyrex	59	2
4	20	80	> 99	Pyrex	77	5
5[d]	20	40	89	Pyrex	60	2

[a] Reaction conditions: **1a** (2.5–10 mmol), **2a** (0.5 mmol), TBADT (4 mol%), CO (80 or 40 atm), MeCN (5 mL), irradiation by 500 W Xenon lamp for 20 h. [b] Determined by ^1H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. [c] Yield of product isolated after flash chromatography on SiO_2. [d] Dibutyl 2-cyclohexylsuccinate was obtained in 8% yield.

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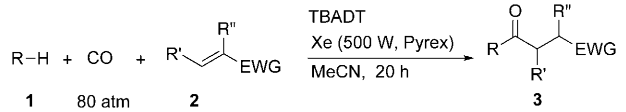
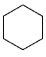
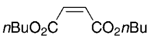
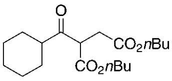
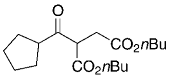
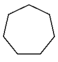
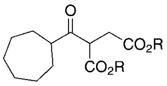
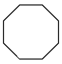
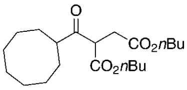
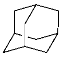
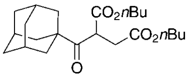
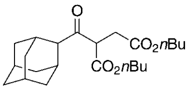
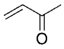
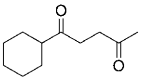
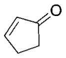
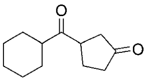
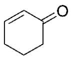
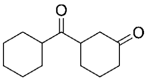
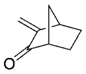
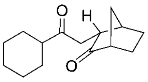
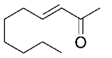
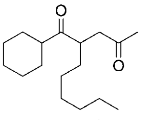
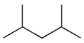
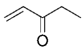
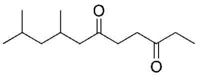
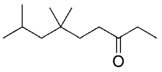
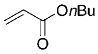
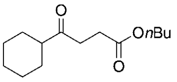
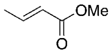
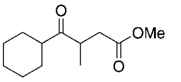
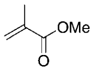
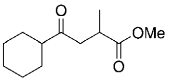
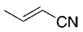
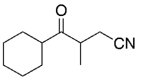
Pyrex-glass liner (Table 1, entry 2). With the use of an excess amount (20 equiv) of cyclohexane (**1a**), the yield of **3a** was increased to 77% (Table 1, entry 4). The reaction under lower CO pressure (40 atm) resulted in a lower yield of **3a** (60%; Table 1, entry 5) because of the competitive formation of the non-carbonylated product dibutyl 2-cyclohexylsuccinate.

Encouraged by the result reported in Table 1, we then applied these reaction conditions to the three-component synthesis of unsymmetrical ketones **3** using a variety of alkanes **1** and alkenes **2** (Table 2). The carbonylation of cyclopentane (**1b**) worked well, and led to the corresponding unsymmetrical ketone **3b** in 68% yield after isolation by chromatography on silica gel (Table 2, entry 2). In a similar manner, cycloheptane (**1c**) and cyclooctane (**1d**) gave good yields of **3c** and **3d**, respectively (60% and 58%; Table 2, entries 3 and 5). The reaction of **1c** with dimethyl maleate (**2a′**) gave the corresponding keto dimethyl ester **3c′** in 74% yield (Table 2, entry 4). The carbonylation of adamantane (**1e**) suffered from poor solubility in acetonitrile. Accordingly, we used a 1:1 mixture of acetonitrile and benzene dissolving 2 equivalents of adamantane (**1e**). This gave a 1:1.3 mixture of the 1- and 2-carbonylated products **3e** and **3e′** in a 35% overall yield (73% based on 48% conversion of **2a**; Table 2, entry 6). Among other electron-deficient alkenes, α,β-unsaturated ketones generally gave good results. For example, methyl vinyl ketone (**2b**), 2-cyclopentenone (**2c**), 2-cyclohexenone (**2d**), 3-methylene-2-norbornanone (**2e**), and *trans*-3-decen-2-one (**2f**) were all used in a three-component coupling reaction with cyclohexane and CO to give the corresponding 1,4-diketones **3f–j** in good yields (Table 2, entries 7–11). The reaction of an acyclic alkane, 2,4-dimethylpentane (**1f**), with CO and ethyl vinyl ketone (**2g**) was not selective, and gave a mixture of several products (Table 2, entry 12). Among them, 1,4-dike-

Table 2: TBADT photocatalyzed, three-component coupling reactions comprised of R–H **1**, CO, and electron deficient alkenes **2**.[a]



Entry	Alkane		Alkene		Product		Yield [%][b]
1	**1a**		**2a**		**3a**		77
2	**1b**		**2a**		**3b**		68
3	**1c**		**2a**		**3c**[c]		60
4[d]	**1c**		**2a′**		**3c′**[e]		74
5	**1d**		**2a**		**3d**		58[f]
6[g]	**1e**		**2a**[h]		**3e**		35[i]
					3e′		
7	**1a**		**2b**		**3f**		58
8	**1a**		**2c**		**3g**		62
9	**1a**		**2d**		**3h**		61
10	**1a**		**2e**		**3i**		61 (endo)
11[d]	**1a**		**2f**		**3j**		60
12[d,j]	**1f**		**2g**		**3k**		13
					3k′		10
13	**1a**		**2h**		**3l**		35
14[d]	**1a**		**2i**		**3m**		67
15[d]	**1a**		**2j**		**3n**		58
16[d]	**1a**		**2k**		**3o**		55

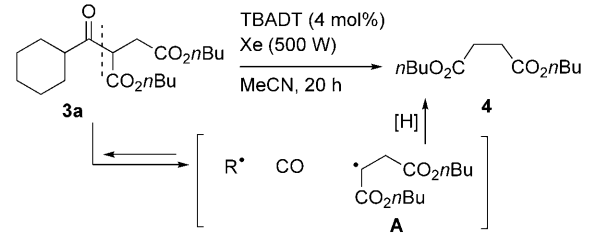
[a] Reaction conditions: **1** (10 mmol), **2** (0.5 mmol), TBADT (4 mol%), CO (80 atm), MeCN (5 mL), irradiation by 500 W Xenon lamp for 20 h. [b] Yields of product isolated after flash chromatography on SiO_2. [c] R = *n*Bu.[d] The reaction was carried out for 30 h. [e] R = Me. [f] Dibutyl 2-cyclooctylsuccinate was likewise obtained in 9% yield. [g] The reaction was carried out using 2 equiv of **1e** in C_6H_6/MeCN (1:1, 5 mL). [h] 48% conversion of **2a**. [i] **3e**/**3e′** = 1:1.3. [j] 40 equiv of **1f** was used.

tone **3k**, which was formed through carbonylation at primary C–H bonds, and the noncarbonylated product **3k′**, formed through a tertiary C–H cleavage, were isolated as the main products.[13]

In the reaction of butyl acrylate (**2h**) with **1a**, the yield of ketoester **3l** was rather low and we observed the formation of appreciable amounts of polyacrylate, (Table 2, entry 13). When methyl crotonate (**2i**) and methyl methacrylate (**2j**) were used, however, the expected products **3m** and **3n** were obtained in 67% and 58% yield, respectively (Table 2, entries 14 and 15). The reaction with crotonitrile (**2k**) gave ketonitrile **3o** in 55% yield (Table 2, entry 16). The reaction of **1a** with 1-undecene or ethyl vinyl ether did not give the corresponding three-component coupling products. These results may be rationalized by the well-established nucleophilic character of the acyl radical intermediates.[14]

The formation of dibutyl succinate (**4**; Table 1) conceivably arises from the photodecomposition of the initially formed product **3a** through a Norrish I cleavage of the weak bond between the acyl and the carboxyl-substituted methine carbon atoms. Thus, the photoirradiation of isolated **3a** was examined under different reaction conditions (Table 3).

Table 3: Photodecomposition studies of **3a**.[a]

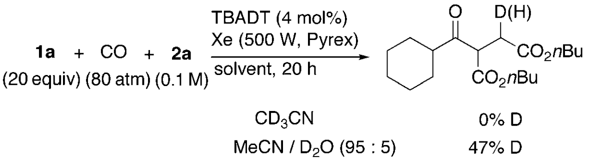


Entry	Liner	CO [atm]	Yield [%][b] 3a	Yield [%][b] 4
1	quartz	0	34%	47%
2	Pyrex	0	59%	13%
3	Pyrex	80	94%	6%

[a] Reaction conditions: **3a** (0.1 mmol), MeCN (5 mL). [b] Determined by NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Our observations are the following: 1) the photodecomposition of **3a** indeed proceeded to give **4**, 2) the use of a Pyrex filter suppressed the photodecomposition channel (Table 3, entry 2), and 3) CO pressures contributed to the slowing of the undesired photodecomposition path (Table 3, entry 3). In the absence of TBADT, the photodecomposition of **3a** resulted in a complex mixture and only a trace amount of **4** was detected. Reasonably, the reduced form of the photocatalyst ($H^+W_{10}O_{32}^{5-}$) present under these conditions delivers a hydrogen atom to the succinate radical **A** to give **4** (Table 3).

Deuterium-labeling experiments were also carried out [Eq. (1)]. Whereas no deuterium incorporation from [D$_3$]acetonitrile was observed, the addition of deuterium oxide resulted in the deuteration at the 3-position with a D/H ratio of 47:53. On the basis of these observations, we proposed a reaction mechanism for the present three-component coupling reaction (Scheme 2), in which the scrambling may be rationalized by assuming a D/H exchange of $H^+W_{10}O_{32}^{5-}$ with D_2O.[9d] This confirmed again that hydrogen was exclusively donated by the reduced photocatalyst, which was thus regenerated, and not by the reaction medium.[15]



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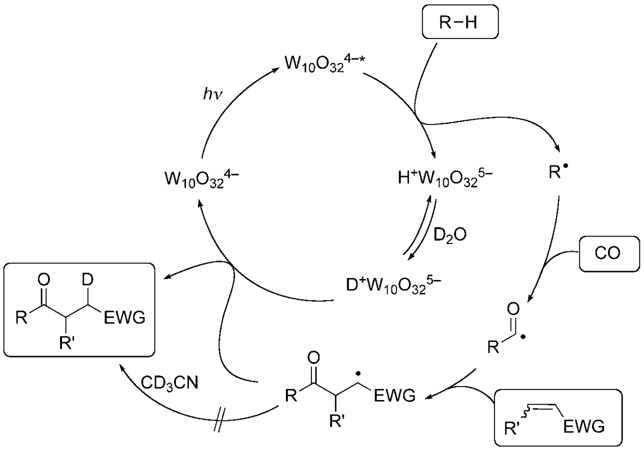

Scheme 2. Proposed reaction mechanism for the photocatalyzed three-component coupling synthesis of ketones. R′ = EWG, H, alkyl group.

Summing up, the carbonylation of unactivated C–H bonds is an important challenge in radical chemistry.[3a] The present reaction protocol, which is based on the use of photocatalyst TBADT and a Pyrex-glass filter, gave access to a variety of functionalized unsymmetrical ketones. This process consists of an atom-economical three-component coupling that uses a smooth reaction occurring at room temperature and potentially abundant feedstocks. We are now exploring other multicomponent processes based on photocatalyzed radical carbonylation reactions.

Experimental Section

Typical synthetic procedure: A magnetic stirring bar, MeCN (5.0 mL), TBADT (tetrabutylammonium decatungstate, $(nBu_4N)_4W_{10}O_{32}$, 66.4 mg, 0.02 mmol), cyclohexane (**1a**, 841.6 mg, 10 mmol), and dibutyl maleate (**2a**, 114.1 mg, 0.5 mmol) were placed in a stainless-steel autoclave for photoreaction equipped with an inserted Pyrex-glass liner. The autoclave was closed, purged three times with carbon monoxide, pressurized with 80 atm of CO and then irradiated by xenon arc lamp (500 W) under stirring for 20 h. After the reaction, excess CO was discharged at RT. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/AcOEt = 10:1) to give **3a** (128.7 mg, 77 %).

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Keywords: carbonylation · C–H activation · multicomponent reactions · photocatalysis · radicals

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