Carbonylation of Alkyl Radicals Derived from Organosilicates through Visible-Light Photoredox Catalysis

Alex Cartier*, Etienne Levernier*, Vincent Corcé, Takahide Fukuyama,* Anne-Lise Dhimane, Cyril Ollivier,* Ilhyong Ryu,* and Louis Fensterbank*

Abstract: Primary, secondary, and tertiary alkyl radicals formed by the photocatalyzed oxidation of organosilicates underwent efficient carbonylation with carbon monoxide (CO) to give a variety of unsymmetrical ketones. This study introduces the possibility of radical carbonylation under a photooxidative regime.

Visible-light photoredox catalysis now holds a privileged position in modern radical chemistry.[1-3] Visible-light irradiation of several families of alkyl radical precursors, such as alkyl carboxylates,[3] alkyl trifluoroborates,[4] and alkyl sulfinate salts,[5] is known to promote the efficient formation of alkyl radical species under photooxidation conditions. Recently, alkyl bis(catecholato)silicates[6] were introduced by our Paris group[7] and later by Molander and co-workers[8] and others[9] to allow for the smooth generation of a variety of alkyl radicals, including unstable primary radicals, and this enhancement applies to visible-light photoredox-catalyzed conditions with RuII or IrIII photoactive complexes and even with the organic dye 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).[7b,10] The generated alkyl radical species can be promptly trapped by activated alkenes, allylsulfones,[7a] and imines.[11]

Radical multicomponent processes are in great demand, as they allow a reduction in the number of steps required to obtain targeted compounds.[12] In this regard, carbon monoxide (CO) is effective as a donor/acceptor-type radical C1 synthon similar to isonitriles.[13] Carboxylative coupling reactions for the formation of ketones or esters by radical sources, including unstabilized primary radicals, and this enhancement applies to visible-light photoredox-catalyzed conditions (previous studies) and photooxidative conditions.[7b,10] Several groups have applied successful photoredox conditions to aryl radical carbonylation through a reductive photoredox pathway by using aryl diazonium salts as aryl radical precursors. For example, Gu et al., Majek and Jacobi von Wangelin, and Xiao and co-workers independently reported that ketones and esters can be formed by the photoredox carbonylation of an aryl ring by using CO either in the presence of eosin Y[14] or fluorescein as a photocatalyst (Scheme 1, type A).[15,16]

Visible-light photoredox catalysis now holds a privileged position in modern radical chemistry.[1-3] Visible-light irradiation of several families of alkyl radical precursors, such as alkyl carboxylates,[3] alkyl trifluoroborates,[4] and alkyl sulfinate salts,[5] is known to promote the efficient formation of alkyl radical species under photooxidation conditions. Recently, alkyl bis(catecholato)silicates[6] were introduced by our Paris group[7] and later by Molander and co-workers[8] and others[9] to allow for the smooth generation of a variety of alkyl radicals, including unstable primary radicals, and this enhancement applies to visible-light photoredox-catalyzed conditions with RuII or IrIII photoactive complexes and even with the organic dye 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).[7b,10] The generated alkyl radical species can be promptly trapped by activated alkenes, allylsulfones,[7a] and imines.[11]

Radical multicomponent processes are in great demand, as they allow a reduction in the number of steps required to obtain targeted compounds.[12] In this regard, carbon monoxide (CO) is effective as a donor/acceptor-type radical C1 synthon similar to isonitriles.[13] Carboxylative coupling reactions for the formation of ketones or esters by radical sources, including unstabilized primary radicals, and this enhancement applies to visible-light photoredox-catalyzed conditions (previous studies) and photooxidative conditions.[7b,10] Several groups have applied successful photoredox conditions to aryl radical carbonylation through a reductive photoredox pathway by using aryl diazonium salts as aryl radical precursors. For example, Gu et al., Majek and Jacobi von Wangelin, and Xiao and co-workers independently reported that ketones and esters can be formed by the photoredox carbonylation of an aryl ring by using CO either in the presence of eosin Y[14] or fluorescein as a photocatalyst (Scheme 1, type A).[15,16]

Ryu and co-workers previously reported three-component processes to form unsymmetrical ketones in which alkyl halides, CO, and alkenes were typically treated with tributyltin hydride[10] or tri(triethylsilyl)silane (TTMS)[20] as a radical mediator.[21] We considered the use alkyl bis(catecholato)silicates as new substrates in this reaction. These compounds are readily prepared from the corresponding alkoxydimethanes and trichlorosilanes in a one-pot reaction (see the Supporting Information for more details). They can be conserved for weeks on the bench in contact with ambient air.[12] They also exhibit relatively low oxidation potentials (<1 V vs. SCE). Herein we report the first example of an oxidative photocatalyzed carbonylative coupling reaction as a novel three-component carbonylation route to unsymmetrical ketones under mild visible-light photoredox conditions.

Scheme 1. Photocatalyzed radical carbonylation under photoredox conditions (previous studies and photooxidative conditions (this study). EWC — electron-withdrawing group.

[6] A. Cartier,[1] Prof. T. Fukuyama, Prof. I. Ryu Department of Chemistry, Graduate School of Science Osaka Prefecture University Sakai, Osaka 599-8531 (Japan)
E-mail: fukuyama@cc.osakafu-u.ac.jp
ryu@cc.osakafu-u.ac.jp
E. Levernier,[1] Dr. V. Corcé, Dr. A.-L. Dhiman, Dr. C. Ollivier, Prof. L. Fensterbank Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire 4 Place Jussieu, CC 229, 75252 Paris Cedex 05 (France)
E-mail: cyril.ollivier@sorbonne-universite.fr
louis.fensterbank@sorbonne-universite.fr
Prof. I. Ryu Department of Applied Chemistry, National Chiao Tung University Hsinchu (Taiwan)

[7] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.201811858.
that require no traditional radical mediators (Scheme 1, type B). As ketones are ubiquitous and important in organic chemistry owing to their polyvalent reactivity, the development of new methods for their synthesis is still very useful.[25]

As a model, we first tested a three-component coupling reaction between bis(catecholato)cyclohexylsilicate (1a), CO, and dimethyl maleate (2a; Table 1). The experiment was carried out in a stainless-steel autoclave equipped with two quartz glass windows that served as a pressure-resistant apparatus during light irradiation (15 W blue LEDs, see the Supporting Information for details). When a solution of 1a, 2a, [Ir(dF(CF3)ppy)2(bpy)](PF6)2 (1 mol%), and KH2PO4 (0.36 mmol), CO (80 atm), DMF (10–13 mL), irradiation with a blue LED lamp (425 nm) for 24–48 h. [b] Yield of the isolated product. [c] The product ratio was determined by GC of the crude mixture. [d] [Ir(dF(CF3)ppy)2(bpy)](PF6)2 (2 mol%).

Table 1: Optimization of the reaction conditions.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>( [2a] [\text{mol}] )</th>
<th>( \text{time}[\text{h}] )</th>
<th>Yield 3a [%]</th>
<th>3a/4a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Ir]</td>
<td>0.15</td>
<td>24</td>
<td>28</td>
<td>92.8</td>
</tr>
<tr>
<td>2</td>
<td>4CzIPN</td>
<td>0.15</td>
<td>24</td>
<td>69</td>
<td>93.7</td>
</tr>
<tr>
<td>3</td>
<td>none</td>
<td>0.15</td>
<td>24</td>
<td>13</td>
<td>75.25</td>
</tr>
<tr>
<td>4</td>
<td>4CzIPN</td>
<td>0.02</td>
<td>24</td>
<td>49</td>
<td>97.3</td>
</tr>
<tr>
<td>5</td>
<td>4CzIPN</td>
<td>0.04</td>
<td>24</td>
<td>65</td>
<td>97.3</td>
</tr>
<tr>
<td>6</td>
<td>4CzIPN</td>
<td>0.09</td>
<td>24</td>
<td>71</td>
<td>94.6</td>
</tr>
<tr>
<td>7</td>
<td>4CzIPN</td>
<td>0.09</td>
<td>48</td>
<td>85</td>
<td>95.5</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: potassium [18-Crown-6] bis(catecholato)cyclohexylsilicate (1a, 0.3 mmol, 1 equiv), dimethyl maleate (2a, 2 equiv), photocatalyst (1–2 mol%), KH2PO4 (0.36 mmol), CO (80 atm), DMF (10–13 mL), irradiation with a blue LED lamp (425 nm) for 24–48 h.

Next, we investigated the suitability of a variety of activated alkenes 2a–k as radical acceptors in the three-component transformation (Scheme 2). Access to 1,4-dicarbonyl derivatives still remains challenging.[26] Gratifyingly, methyl vinyl ketone (2b) was successfully used in the three-component reaction with CO and bis(catecholato)cyclohexylsilicate (1a) to give the corresponding 1,4-diketone 3j in 80% yield. By contrast, reactions of vinyl sulfone 2c and methyl acrylate (2d) gave the carbonylation products 3k and 3l in rather moderate yields (42 and 34%, respectively). When we used acrylonitrile, the expected product 3m was obtained in excellent yield (81%). Compound 3n, obtained from N,N-dimethylacrylamide (2f), was isolated in a 60% yield. The use of 2-cyclopentenone (2g) led to the formation of diketone 3o in 53% yield. Interestingly, \( \beta \)-alkyl-substituted, \( \beta, \beta \)-unsaturated carbonyl compounds efficiently underwent the present transformation. Thus, methyl crotonate (2h) gave the corresponding 4-keto ester 3p in 78% yield. The reaction of diethyl 2-ethylidenemalonate (2j) gave the expected product 3q in 89% yield, and the reaction of butyl organic dye we observed a better yield of 69% with similar ratios of 3a and 4a (93:7; Table 1, entry 2). When the reaction was tested without the use of a photocatalyst, the yield dropped dramatically to 13% (Table 1, entry 3). Next, we decreased the concentration of 2a from 0.15 to 0.02 and 0.04 M. At a lower concentration (0.02 M), the reaction became sluggish, and the yield of 3a decreased to 49% (Table 1, entry 4). With 2a at 0.04 M, the yield reached 65% (Table 1, entry 5). In these two cases, the ratio remained excellent (97:3). When the reaction was carried out with 0.09 M of 2a, we observed an increase in the yield of product 3a to 71% with a slightly decreased product ratio of 94:6 (Table 1, entry 6). Since the reaction under these conditions (entry 6) remained slow, we extended the reaction time to 48 h, and were able to isolate 3a in 85% yield (Table 1, entry 7). We applied these optimized conditions to the three-component synthesis of a series of unsymmetrical ketones 3 by using a variety of alkyl bis(catecholato) silicates as substrates (Scheme 2). The carbonylation of the cyclopentyl derivative proceeded well and led to the corresponding unsymmetrical ketone 3b in 68% yield. Primary radicals furnished the products in good yields, irrespective of whether they were linear (product 3c, 70%) or branched alkyl radicals (product 3d, 65%). The reaction of a tertiary alkyl silicate also gave ketone 3e in 67% yield. Interestingly, the reaction was compatible with a rather sensitive level of functionality, such as with an oxirane, and gave the desired product 3f in 79% yield. Product 3g with an oxabicycloheptyl moiety was obtained in 80% yield, albeit with an extended reaction time of 72 h. The carbonylated adduct 3h, bearing an acetate, appeared unstable and could not be isolated, although it was identified by \(^1\)H NMR spectroscopy in the crude reaction mixture (50%). The use of the 5-hexenyl derivative 1i was expected to provide insight into the rate of carbonylation under these conditions. Interestingly, under the employed conditions, we obtained an almost equimolar mixture of unycyclized 3i and cyclized 3f in 34% yield, with a crude NMR spectrum that suggested other by-products had formed by carbonylation.[29]
methacrylate (2j) gave the corresponding 4-keto ester 3r in 54% yield. The reaction of 1a with CO in the presence of disulfonylethene 2k gave the noncarbonylated adduct 4s in 76% yield. Disulfonylethene 2k is such a good radical acceptor that the direct addition of cyclohexyl radical occurred.

We proposed the overall mechanism illustrated in Scheme 3. In the first step, the photocatalyst is excited under visible-light irradiation. Single-electron-transfer (SET) oxidation of the alkyl bis(catecholato)silicate 1 by the excited *4CzIPN[10] leads to the reduced species [4CzIPN] and to formation of the alkyl radical A through homolytic cleavage of the C–Si bond of the silicate radical.[7–9] Alkyl radical A reacts with CO to form the acyl radical B,[14] which adds to the acceptor alkene 2 to provide adduct radical C. The latter is reduced by [4CzIPN] to afford the stabilized carbanionic species D and regenerate the photocatalyst in its ground state, thus closing the catalytic cycle and ensuring its propagation. Finally, protonation of D by KH₂PO₄ yields the final product 3.

To support this hypothetical mechanism, we conducted several experiments (see the Supporting Information for details). Fluorescence quenching studies of *4CzIPN with silicate 1a in the absence of CO showed a decrease in the fluorescence intensity upon the gradual addition of 1a. The quenching rate constant kq from the Stern–Volmer equation was determined to be 1.37 × 10⁻⁸ mol⁻¹ L·s⁻¹ (in DMF), a value consistent with its determination in DMSO (kq = 2.5 × 10⁻⁷ mol⁻¹ L·s⁻¹) by Molander and co-workers.[27] The difference in redox potential between *4CzIPN (E₁/₂*(4CzIPN*/[4CzIPN]) = +1.59 V vs. SCE)[10b] and silicate 1a (Eox = +0.69 V vs. SCE)[7c] suggests that SET consisting of the reductive quenching of the photoexcited photocatalyst *4CzIPN by silicate 1a is involved. This hypothesis was confirmed by the treatment of cyclohexyl silicate 1a with CO in the presence of TEMPO (2.2 equiv), which led to the exclusive formation of the noncarbonylated TEMPO adduct 5 in 77% yield, thus highlighting the formation of radical intermediates of type A. A “light/dark” experiment was also conducted in the absence of CO, and it appears that product formation occurs only during periods of light irradiation. This result might support the catalytic mechanism shown in Scheme 3.[28] To ensure that no short radical chain occurs, we measured quantum yields of the reaction of silicate 1a with different acceptors in the presence of 4CzIPN. We obtained a quantum yield of 0.066 in the conjugate addition with maleate and 0.33 for the allylation reaction with 2-phenylallyl p-tolyl sulfone with 4CzIPN. These findings show that the present mechanism does not follow a radical chain pathway but most likely a closed photoredox loop, as depicted in Scheme 3.

Next, we focused on the behavior of various silicates towards carbonylative radical allylation with allyl sulfones.
Three-component reaction leading to unsaturated ketones 7.

Scheme 4.

6a,b (Scheme 4), for which allyltin was used as a radical acceptor in a previous study.[10] The reaction of 1a with CO and allyl sulfone 6b, which bears a methoxycarbonyl group at the 2-position, returned β,γ-unsaturated ketone 7a in 66% yield. When phenyl allyl sulfone 6b was treated with cyclohexyl silicate 1a and CO, it gave the expected enone 7b in a 60% yield. Again, primary radicals react well the present radical allylation, regardless of whether they are linear alkyl (product 7c, 58%) or branched alkyl radicals (product 7d, 51%). The reaction with a tertiary alkyl silicate gave the desired enone 7e in a 40% yield together with a noncarbonylated addition product. These allylation reactions followed the pattern of the mechanism reported in Scheme 3, in which the photocatalyst was regenerated by reduction of the phenyl sulfonic radical to a phenyl sulfinate anion.[7] The ketones formed herein could be useful scaffolds. For example, 1,4-diketone 3j could be used in a Paal–Knorr reaction for the synthesis of pyrroles or thiophenes. These heteroaromatic systems can be found in many natural products but also in biologically active compounds, such as HMG-CoA reductase inhibitors and hepatitis C virus polymerase inhibitors.[8]

In summary, we have described the first example of oxidative photoredox catalysis combined with radical carbonylation chemistry. The present reaction protocol was based on the use of an inexpensive organic dye, 4CzIPN, as a photocatalyst and a wide range of alkyl bis(catecholato)silicates as alkyl radical precursors under a CO atmosphere. The reaction afforded efficient access to a variety of functionalized unsymmetrical ketones, including β,γ-unsaturated ketones. These results suggest the possibility of other photocatalyzed radical carbonylation reactions under oxidative regimes, which we are now exploring in our laboratory.

Acknowledgements

This research was supported by Grants-in-Aid for Scientific Research (A) (No. 26248031) and (C) (No. 17K05866) from the JSPS, and Scientific Research on Innovative Areas 2707: Middle Molecular Strategy (No. 15H05880) from the MEXT. We thank Sorbonne University, ANR-17-CE07-0018 Hyper-Silite (PhD grant to E.L.).

Conflict of interest

The authors declare no conflict of interest.

Keywords: carbonylation · photocatalysis · radicals · silicates · three-component reactions

How to cite: Angew. Chem. Int. Ed. 2019, 58, 1789–1793
Angew. Chem. 2019, 131, 1803–1807


A. J. Luo, J. Zhang, ACS Catal. 2016, 6, 873–877; for a reevaluation of the reduction and oxidation potentials of the excited state of 4C2IPN, see Ref. [10b].


For practical reasons, the “light/dark” experiment was conducted without CO. We assumed that with or without CO, the reaction would follow the same kind of photocatalysis-catalyzed mechanism. However, the possibility of a radical chain mechanism involving SET between intermediate C and silicate 1 cannot be discarded just from this single experiment; see: M. A. Cismesia, T. P. Yoon, Chem. Soc. Rev. 2015, 45, 5426–5434.


For practical reasons, the “light/dark” experiment was conducted without CO. We assumed that with or without CO, the reaction would follow the same kind of photocatalysis-catalyzed mechanism. However, the possibility of a radical chain mechanism involving SET between intermediate C and silicate 1 cannot be discarded just from this single experiment; see: M. A. Cismesia, T. P. Yoon, Chem. Soc. Rev. 2015, 45, 5426–5434.


For practical reasons, the “light/dark” experiment was conducted without CO. We assumed that with or without CO, the reaction would follow the same kind of photocatalysis-catalyzed mechanism. However, the possibility of a radical chain mechanism involving SET between intermediate C and silicate 1 cannot be discarded just from this single experiment; see: M. A. Cismesia, T. P. Yoon, Chem. Soc. Rev. 2015, 45, 5426–5434.


For practical reasons, the “light/dark” experiment was conducted without CO. We assumed that with or without CO, the reaction would follow the same kind of photocatalysis-catalyzed mechanism. However, the possibility of a radical chain mechanism involving SET between intermediate C and silicate 1 cannot be discarded just from this single experiment; see: M. A. Cismesia, T. P. Yoon, Chem. Soc. Rev. 2015, 45, 5426–5434.