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論文名 Visible-light photoredox catalyzed multicomponent carbonylation of alkyl radical precursors via the action of carbon monoxide as carbonylative agent
可視光レドックス触媒による一酸化炭素をカルボニル源としたラジカル前駆体の多成分カルボニル化反応

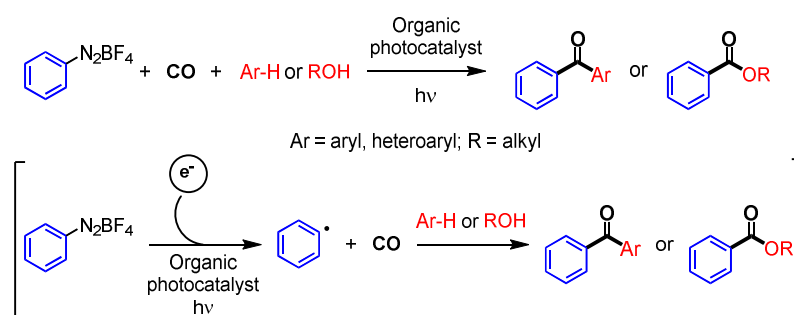
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Visible-light photoredox catalyzed multicomponent carbonylation of alkyl radical precursors *via* the action of carbon monoxide as carbonylative agent

This thesis describes the development of novel photoredox catalyzed alkyl radical carbonylation of organosilicates to form unsymmetrical ketones and aliphatic amides.

1. General Introduction to Photocatalyzed Carbonylation

CO is an abundant gas and is already widely used as a carbonylative agent in organic chemistry. Historically, transition-metal catalyzed carbonylation has been the most intensively studied method of carbonylation. But more recently, it has been discovered that CO is also effective as a donor/acceptor-type radical C1 synthon that can be involved in radical carbonylation chemistry. Thus, it was intensively studied by Ryu and coworkers to form a variety of carbonyl compound.¹ On the other hand, visible-light photoredox catalysis has experienced a significant increase of popularity among organic chemists during the last decade, as it often require very mild reaction conditions under visible light as energy source while providing as good results as more classic organic chemistry. However, until this day, photoredox catalyzed carbonylation syntheses were not yet extensively investigated and only three groups published a result of photoredox catalyzed carbonylation of aryl diazonium salt under *photoreductive* conditions (Scheme 1).²

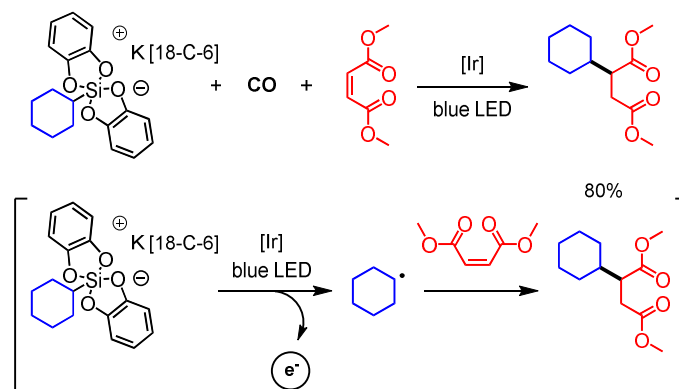


Scheme 1. Photoreductive catalyzed carbonylations using diazonium salt as an aryl radical precursor.²

Meanwhile, new class of radical precursors were also investigated and recently, Fensterbank, Ollivier and Goddard elaborated a new type of organosilicates compounds that promote alkyl radicals under *photooxidative* conditions, even unstabilized primary alkyl radical, due to their low oxidation potential (<1 eV vs. SCE).³ They showed that in the presence of an activated iridium photocatalyst through the illumination by blue LED lamp, radicals can be formed from

alkyl bis(catecholato)silicates and then trapped by an activated unsaturated double bond to perform an intermolecular addition (scheme 2).³

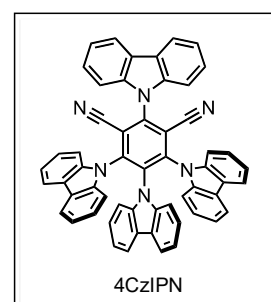
During my Ph-D course, I dedicated my time to expand the scope of photoredox photocatalyzed carbonylative protocols for alkyl substrates. To obtain ultimately unsymmetrical aliphatic ketones and aliphatic amides in mild conditions under blue LED light, using original organosilicate radical precursors.



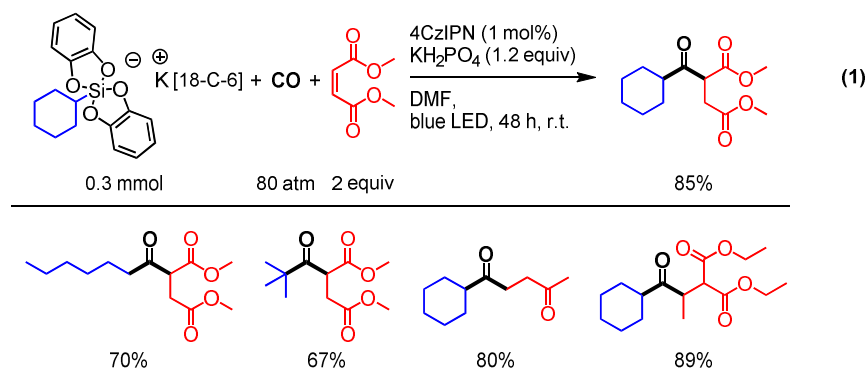
Scheme 2. Photooxidative catalyzed radical addition of organosilicate to radical acceptors³

2. Synthesis of Unsymmetrical Ketones through Photooxidative Carbonylation

Ryu and co-workers already reported a 3-component formation of unsymmetrical ketones from alkyl halides, CO, and alkenes in the presence of radical mediators.⁴ Alkyl bis(catecholato)silicates were considered as alkyl radical precursors, for their convenience for laboratory work and to avoid the use of any radical mediators. The reaction of cyclohexylsilicate, CO, dimethyl maleate and a weak acid was studied as a model (Scheme 3, eq 1). Optimized conditions were obtained with organic dye 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene 4CzIPN as photocatalyst.

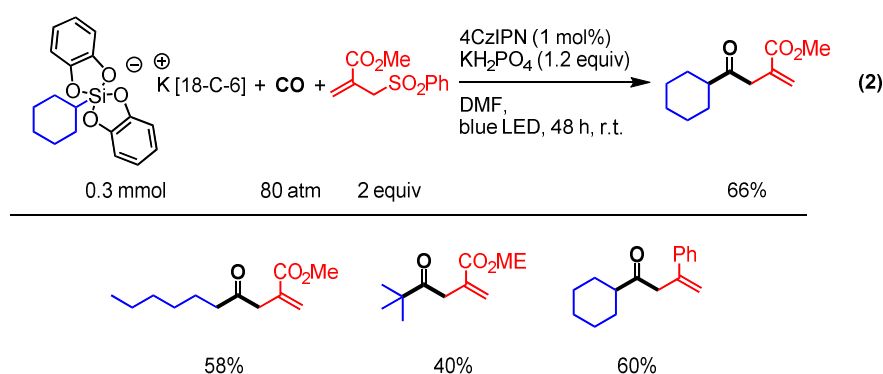


A large scope of primary, secondary and tertiary silicates was tested, then many unsaturated alkenes to *in fine* synthesize 20 unsymmetrical ketones, from 34% to 89% yield (Scheme 3, eq 1).



Scheme 3. Synthesis of asymmetrical ketones under *photooxidative* conditions.

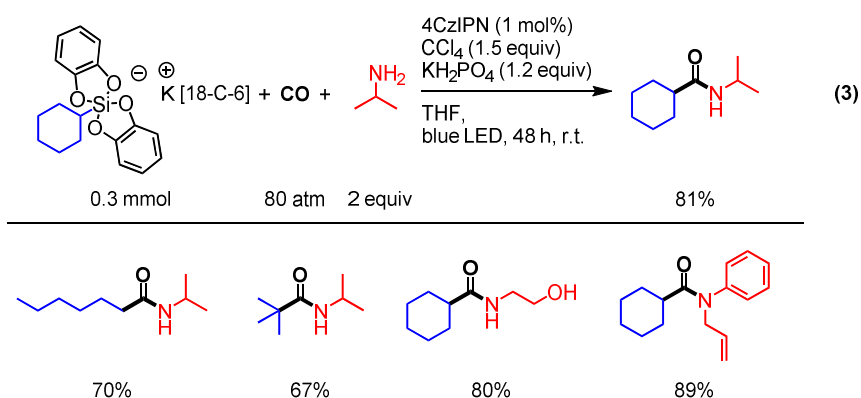
In addition, carbonylative radical allylation was also supported by various silicates, giving the desired product in moderate to good yield (Scheme 4, eq 2). This was the first example of metal-free *oxidative* photoredox catalysis, combined with radical carbonylation chemistry as discussed in the chapter entitled *Synthesis of Unsymmetrical Ketones through Photooxidative Carbonylation*.



Scheme 4. Carbonylative allylation under *photooxidative* conditions.

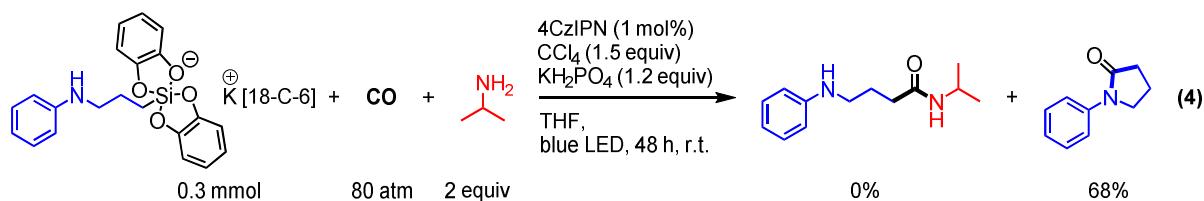
3. Synthesis of aliphatic amides through photooxidative carbonylation

Another *photooxidative* carbonylation reaction to form aliphatic amides was developed using alkyl bis(catecholato)organosilicates as radical precursors, as well as 4CzIPN as photocatalyst, an amine, and carbon tetrachloride CCl_4 as radical mediator (Scheme 4, eq. 1). Literature described carbonylative synthesis of aliphatic amide in a radical/ionic system, in which an alkyl iodide led to the alkyl radical and then to an acyl iodide intermediate. In that case, CCl_4 was added to the mixture as a chlorine donor to form an *in situ* acyl chloride.⁵ A large scope of silicates and primary and secondary amine were tested, and 20 amides were obtained, from 31% to 89% yield (Scheme 5, eq 3).

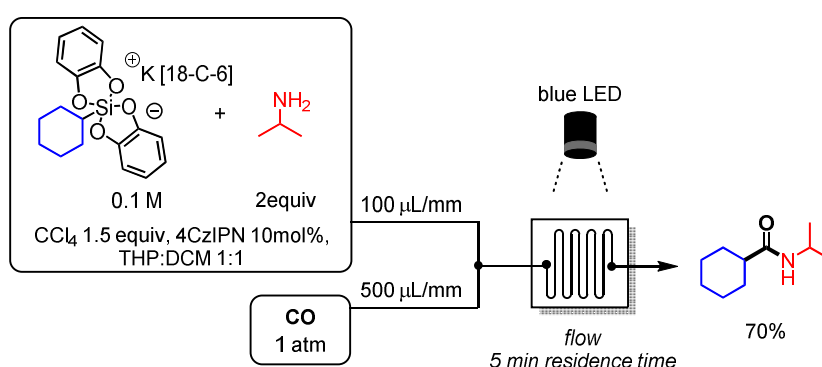


Scheme 5. Synthesis of aliphatic amides under *photooxidative* conditions.

Moreover, when the silicate is bearing an amine function, the intramolecular reaction occurs smoothly, even when in competition with another amine, leading to formation of only one product (eq 4).



Carbonylation reactions are routinely carried out in batch reactor such as a stainless steel autoclave, but a flow apparatus can also be used instead. Flow carbonylation present several advantages over classic batch methods: high mass and energy transfer, and high gas-liquid interfacial area. Therefore, carbonylation reaction can be carried out with a significantly shortened reaction time and reduced amount of toxic CO gas in flow reactor.⁶ Flow version of this reaction presented huge potential, as excellent yields were obtained in much less time, only 5 min the whole under atmospheric pressure of CO (Scheme 6).



Scheme 6. Photoredox carbonylation under flow conditions.

In conclusion, multicomponent carbonylation reactions using alkyl substrates can be run smoothly under *photooxidative* conditions, through the action of an inexpensive organic dye as photocatalyst, excited by blue LED lamp. Various asymmetrical ketones and aliphatic amides were synthesized in mild and metal-free conditions.

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List of publications:

- 1) A. Cartier, E. Levernier, V. Corcé, A.-L. Dhimane, T. Fukuyama, C. Ollivier, I. Ryu, L. Fensterbank, *Angew. Chem. Int. Ed.*, 58, 1789-1793 (2019).
- 2) A. Cartier, E. Levernier, A.-L. Dhimane, M. Zhang, S. Ognier, M. Tatoulian, T. Fukuyama, C. Ollivier, I. Ryu, L. Fensterbank, *Submitted* (2020).

Conference proceedings:

A. Cartier, E. Levernier, V. Corcé, A.-L. Dhimane, T. Fukuyama, C. Ollivier, I. Ryu, L. Fensterbank, Carbonylation of Alkyl Radicals Derived from Organosilicates through Visible-Light Photoredox Catalysis. *The 98th CSJ Annual Meeting*, 2018, 7 min oral presentation.

学位論文審査結果の要旨

近年、可視光を用いた光レドックス触媒を用いた分子変換反応の開発が多くの研究グループにより精力的になされている。一方、一酸化炭素は有用な C1 ユニットであり、各種カルボニル化合物の合成に広く用いられてきたが、光レドックス触媒を用いたカルボニル化反応の開発はほとんど進んでおらず、これまでに数例が報告されているのみである。これらの報告例は、芳香族ジアゾニウム塩を基質とした基質への 1 電子還元を鍵とする反応であり、基質への 1 電子酸化を鍵とする光レドックス触媒によるカルボニル化はこれまでに報告例はない。本論文では、光レドックス触媒存在下、有機シリケートを基質として用いることにより 1 電子酸化を鍵としたカルボニル化反応について検討している。論文の内容は以下の通りである。

(1) 有機シリケートを基質とし、一酸化炭素、電子欠損オレフィンとの 3 成分連結反応により非対称ケトンの合成を行っている。本反応では、光レドックス触媒として安価に調製可能な有機色素を用いることで遷移金属錯体非存在下でのカルボニル化を実現している。ラジカルアクセプターとして α,β -不飽和カルボニル化合物を用いると非対称ジアルキルケトンが得られ、ラジカルアクセプターとしてアリルスルホンを用いると、ラジカルが付加脱離を経てアルキルアリルケトンが良好な収率で得られることを見出している。また、反応機構に関する検討も十分になされ、本反応が、励起された光触媒からの 1 電子酸化を鍵としていることを明らかとしている。1 電子酸化を鍵とした光レドックス触媒によるカルボニル化は、本手法が初めての例である。

(2) 有機シリケートと一酸化炭素、アミンとの 3 成分反応によりアミドが良好な収率で得られることを見出している。本反応では四塩化炭素の添加が有効であるが、系中で生成したアシルラジカルの四塩化炭素からの塩素引き抜きにより酸塩化物が生成していることを提唱し、その生成を実験的に確認している。また、分子内にアミノ基を有するシリケートを用いると分子内環化が進行シラクタムが良好な収率で得られることも見出している。本反応は耐圧性のステンレス製反応容器内で実施されるが、80 気圧の一酸化炭素が必要であり、数十時間の反応時間を要した。これらの問題を解決するために光照射効率に優れたフロー型反応装置を用いたフローカルボニル化を検討している。また、フロー系での気-液異相系は気液接触面積が増大することからも反応の効率化が期待できる。検討の結果、1 気圧の一酸化炭素存在下、わずか 5 分で反応が完結することを見出し、反応効率を飛躍的に改善することに成功している。

以上のように本論文では、光レドックス触媒を用いた一電子酸化を鍵とする新規カルボニル化反応の開発に成功している。いずれの反応も合成化学的に有用である。本委員会は本論文の審査、最終試験の結果に基づき、Alex Cartier 氏に博士（理学）の学位を授与することを適当と認める。

学位論文審査委員会

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