論文の内容の要旨

Photocatalytic Alkylation of Carbonyls via sp^3 C-H Bond Activation

（光触媒を用いた sp^3 C-H 結合のカルボニル化合物 への付加反応の開発）

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Introduction

The carbonyl compound holds a prominent position in chemistry and biology and plays a ubiquitous role on important synthetic chemical reactions in both academic and industrial fields. Conventional alkylation of carbonyls via two electron mechanism, including Aldol reaction, Grignard reaction, Wittig reaction, and Nozaki-Hiyama-Kishi, not only requires pre-functionalization but also shows low functional group tolerance.[1] On the other hand, organic radicals can be generated directly from stable and readily-available molecules and are generally compatible with multiple functional groups.[2]

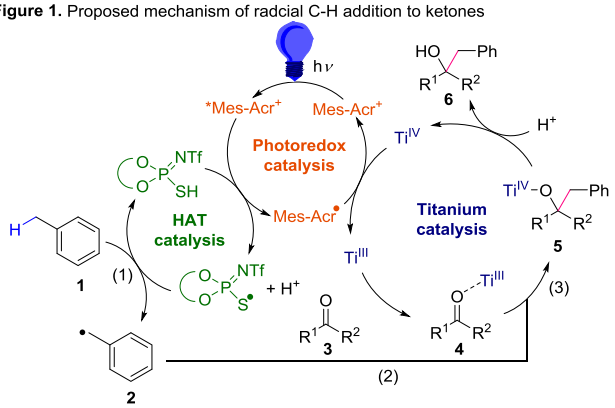
However, radical addition to carbonyl groups is a thermodynamically uphill process: the resulting alkoxy radical easily undergoes β-fragmentation to afford starting materials, especially for intermolecular radical addition to ketones.[3] Fostered by the rapid development of photoredox catalysis, photocatalytic carbonyl addition has been well developed and realized various transformations.[4] Compared to photocatalytic alkyl radical addition to aldehydes, radical addition to ketones is challenging with only a handful reported methods. Despite the progress, there is no example of introducing C-H bond of hydrocarbon feedstocks to both aldehydes and ketones with good functional group tolerance. Hydrogen atom transfer (HAT) can be a considerable method to activate inert sp^3 C-H bond under mild condition. Therefore, in this research we developed two types of C-H addition reactions to carbonyls combining photoredox HAT catalysis and metal catalysis, which can directly utilize chemically inert organic molecules and complex molecules, like drugs and their derivatives.

Results and Discussion

1. Tertiary alcohol synthesis by C-H addition to ketones promoted by acridinium/thiophosphoric imide (TPI)/titanium ternary hybrid catalysis

The synthesis of tertiary alcohols is one of the most fundamental and important reactions in organic chemistry because they are key compounds in pharmaceuticals, natural products, and functional materials. However, traditional syntheses of these alcohols have faced several challenges including the use of functionalized reactive reagents, undesirable side reactions and decomposition of the alcohol products under harsh conditions. Compared to these precedents, direct radical addition to ketones would be applicable to a wider range of tertiary alcohols. Therefore, we designed a ternary hybrid catalysis

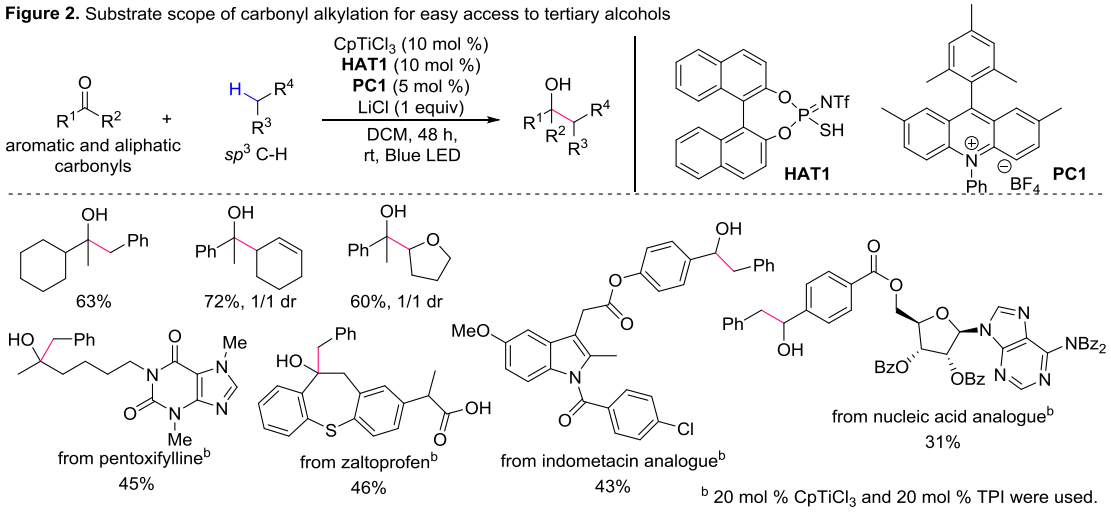
Figure 1. Proposed mechanism of radcial C-H addition to ketones



comprising a photoredox catalyst, an HAT catalyst, and a titanium complex catalyst, which can realize the addition of feedstock organic molecules to various ketones, including aliphatic ketones (Figure 1).[5] The reaction mechanism involves: (1) hydrogen atom transfer from organic molecules, generating carbon-centered radicals, (2) addition of carbon-centered radicals to ketones and (3) concomitant single-electron reduction of the intermediate alkoxy radical by catalytically generated titanium(III) species.[6] The proposed mechanism has been confirmed by both experimental study and DFT calculation. First, radical clock experiment and carbanion generation system have excluded the possibility of radical-radical coupling or carbanion generation pathway. Then UV-Vis measurements and Stern-Volmer experiment well supported our proposed direct radical addition mechanism by confirming that photoredox catalyst was firstly irradiated to excited state by blue LED, and then this excited state specie was reductively quenched by HAT catalyst (RSH). After the single electron oxidation of RSH, a sulfur-centered radical (RS•) was generated which can work as an active hydrogen atom abstract species. We also confirmed the generation of benzyl radical which was formed by a hydrogen atom transfer from toluene by radical trapping experiment. DFT calculation results showed direct radical addition proceeded with a slight free energy change. Based on all the results, it is likely that the reaction proceeds via the proposed mechanism in Figure 1.

In optimizing the reaction conditions, the combination of $CpTiCl_3$ as a transition metal catalyst, thiophosphoric imide (**HAT1**) as an HAT catalyst, and acridinium photoredox catalyst (**PC1**) in the presence of 1 equiv LiCl under 430 nm visible light irradiation at room temperature was found to be optimal (Figure 2). Due to the mild reaction conditions and unique mechanism, the present method can be applied to a wider range of substrates compared to previously reported methods, and to late-stage modifications of bioactive molecules and drugs. Especially, this is the first hybrid system comprising an HAT catalysis and Ti(IV)/Ti(III) catalysis. I believe that these advances will stimulate further applications in catalysis, green chemistry, material science, and pharmaceuticals.

Figure 2. Substrate scope of carbonyl alkylation for easy access to tertiary alcohols



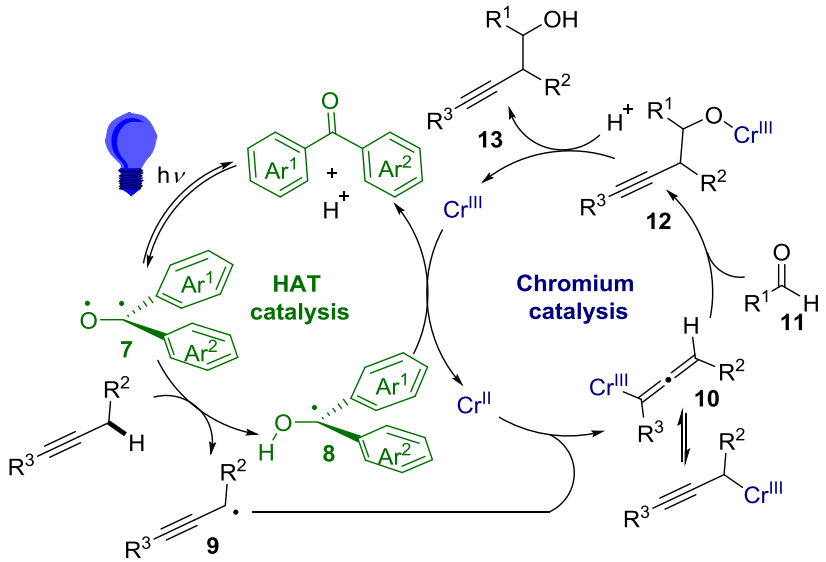
2. Diaryl ketones/chromium dual catalysis for carbonyl propargylation with simple alkynes

Carbonyl propargylation has been established as the most straightforward strategy to construct versatile homopropargyl alcohols. One of the most well established methods is the catalytic Nozaki-Hiyama-Kishi (NHK) reaction, which utilizes propargyl halides in combination with an excess of manganese as a terminal reductant of chromium(III). From a strategic and atom economic viewpoint, the direct functionalization of more readily available propargylic C-H bonds in a catalytic redox-neutral process would therefore be highly desirable, but to the best of our knowledge it remains a challenge in literatures. Current methods required harsh conditions or were limited to specific substrate scope.

As we know, hydrogen atom transfer can be a considerable method to activate inert propargylic sp^3 C-H bond under mild condition. However, alkyne moiety reacts irreversibly with radical species, making it difficult to develop catalysts that can selectively abstract propargylic sp^3 C-H bond. Therefore, the development of a more efficient and functional group compatible protocol for carbonyl propargylation is highly desirable. In this research we realized the direct propargylation of aldehydes by direct activation of C-H bond by a highly active HAT catalyst, 4-4'-di-butylbenzophenone (D^{t}BuBP), which can avoid the undesired radical addition to alkynes.

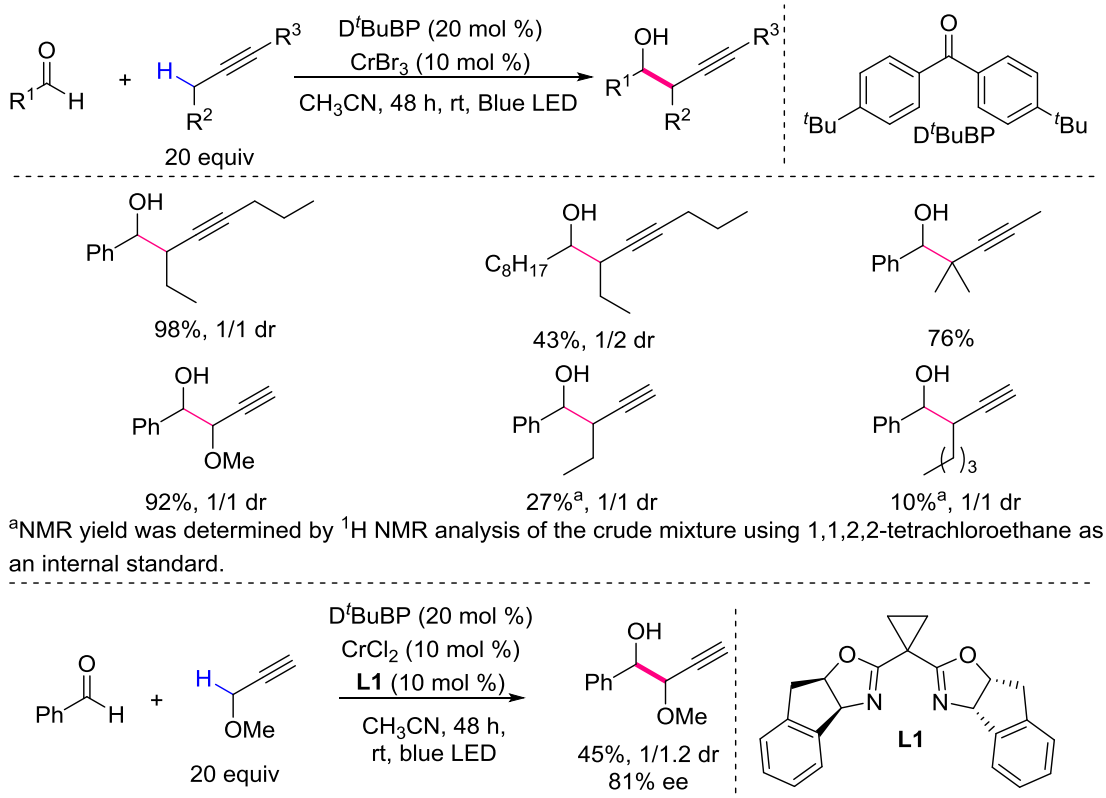
A proposed mechanism is shown in Figure 3.[7] A transient nucleophilic radical **9** would be generated upon HAT from long-lived triplet excited **7** along with the formation of a persistent ketyl radical **8**. Concurrently, **9** would be captured by Cr(II) species and give allenylchromium(III) species **10**. Species **10** would react with aldehyde **11** to produce chromium alkoxide **12**. Protonolysis of **12** by the proton generated in the HAT process should then afford the target product **13** and an oxidized chromium(III) species. The two catalytic cycles could be interfaced by a final SET from **8** to chromium(III) species, thus recovering both the diaryl ketone and chromium(II) catalysts.

Figure 3. Proposed mechanism of carbonyl propargylation



Substrate scopes of alkynes and aldehydes were briefly examined (Figure 4). This protocol can be applied to aliphatic/aromatic aldehydes and internal/terminal alkynes for the synthesis of propargylic alcohols. We applied this reaction to a catalytic asymmetric propargylation of benzaldehyde with Indane-BOX ligand **L1**, and the product was obtained in 45% yield with 81% ee. Further investigation toward improving the reactivity for the asymmetric reaction is ongoing.

Figure 4. Substrate scope of carbonyl propargylation



[a]NMR yield was determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard.

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