

# Uranyl-catalyzed C-H Alkynylation and Olefination

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## Article

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# Abstract

Uranyl cation ( $\text{UO}_2^{2+}$ ) has been identified as highly oxidizing agent to abstract hydrogen atoms from C-H bonds for the formation of carbon-centered radicals. This work described a photocatalytic strategy to utilize uranyl peroxo complexes for direct alkynylation and olefination of  $\text{C}(\text{sp}^3)$  aliphatics. Crystallographic analysis revealed that the in situ generated uranyl peroxide accelerated the reaction.

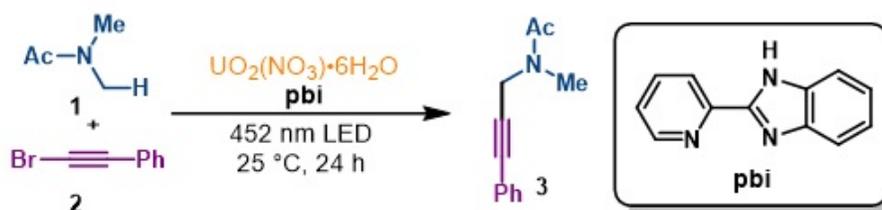
## Introduction

Uranium is a substantial unexploited resource with crustal abundance of  $2.3 \times 10^{-4} \%$ <sup>1</sup>. After separation of its fissile isotope  $^{235}\text{U}$  for power generation and nuclear weaponry, 99.3% of non-fissile isotope  $^{238}\text{U}$  was wasted in magnitude of two million tons globally<sup>2</sup>. As the dominant form of uranium in the environment<sup>3</sup>, the  $[\text{U}^{\text{VI}}\text{O}_2]^{2+}$  cation has been noticed for its unique photon properties<sup>4-6</sup>. Under the irradiation of blue light (450–495 nm), the uranyl cation possesses a highly oxidizing excited state via the ligand-to-metal charge transfer (LMCT)<sup>7</sup>. The single electron shifts from O to U in the  $\text{O}=\text{U}=\text{O}$  group forms a  $\text{U}^{\text{V}}$  center and an oxygen radical. This oxidizing species is prone to abstract hydrogens from C-H bonds to generate carbon-centered radicals. Meanwhile, the excited state of uranyl undergoes hydrogen evolution to generate uranyl peroxide<sup>8</sup>. Furthermore, the U center is found capable of rapid electron transfer and ligand exchange<sup>9</sup> (Fig. 1A). Despite these distinctive reactivities, the chemistry of the uranyl cation was underdeveloped until in recent years, direct functionalizations of the U-activated carbon radicals, such as oxidation<sup>9,10</sup>, fluorination<sup>11</sup>, cyanation<sup>12</sup>, and Giese reaction<sup>13</sup> have been reported. Nevertheless, uranyl cation promoted cross-coupling has not yet been disclosed.

Alkynes are versatile intermediates for diverted transformations<sup>14-16</sup> and broadly employed in fuel industry<sup>17</sup>, material science<sup>18</sup>, chemical biology<sup>19</sup> and drug discovery<sup>20</sup>. The Sonogashira reaction was the most renowned approach to access substituted alkynes from various organic halides<sup>21-23</sup>. To avoid halogenated alkyl sources, the direct C-H alkynylation of hydrocarbons has been developed with the assistance of pre-installed directing groups<sup>24-33</sup>. However, modification of the hydrocarbons and use of expensive catalysts inevitably restricts the application of such strategies. Recently, prefunctionalized alkynyl reagent such as sulfones or hypervalent iodines were employed in Giese-type reactions for radical alkynylation<sup>34-37</sup> (Fig. 1B). We envisioned that the direct  $\text{sp-sp}^3$  cross-coupling could be achieved by ubiquitous C-H sources and alkynyl halides. In this context, a highly oxidizing species is required for the continuous generation of  $\text{sp}^3$  carbon radicals and captured by alkyne reagents. Based on the recently discovery on the uranyl peroxide complex for photoinduced hydrogen evolution and subsequent mechanistic studies<sup>38</sup>, we have designed a uranyl peroxide catalyzed C-H alkynylation reaction using readily available aliphatics (Fig. 1C). Initially, hydrogen evolution of uranyl catalyst under blue-light irradiation gives the uranyl peroxide, which would abstract hydrogens from C-H bonds to generate alkyl radicals. The radical could be trapped by electrophilic bromoalkynes and gives bromoalkenyl radical. Subsequently, desired alkynylated products could be furnished by cleavage of the C-Br bond.

## Results

**Reaction optimization.** To confirm our hypothesis, we evaluated the conditions for this alkynylation reaction after a survey (see Supplementary Information) and found out in the presence of Uranyl nitrate hexahydrate catalyst (8 mol%) and 2-(2-pyridyl)benzimidazole (pbi) (10 mol%) with (bromoethynyl)benzene (0.2 mmol) in the solvent of N,N-dimethylacetamide (2 mL) at ambient temperature, the desired C-H alkynylation product was obtained in 98% yield under irradiation of 452 nm LEDs (Table 1, entry 1). Control experiment showed a decreased yield (73%) without adding ligand (entry 2). The uranyl catalyst and light were proven necessary (entries 3,4). The use of other HAT photocatalysts such as benzophenone or tetrabutylammonium decatungstate (TBADT) did not lead to any products (entries 5,6). The reaction proceeded slowly with benzene as solvent and 5 equiv. of N,N-dimethylacetamide (32%, entry 7). Even after 72 h the yield was only 62% (entry 8).

**Table 1. Condition Control Experiment.**

Entry	Deviation from the reaction conditions	Yield <sup>b</sup> [%]
1	N/A	98
2	w/o pbi	73
3	w/o UO <sub>2</sub> (NO <sub>3</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	-
4	in darkness	-
5	TBADT (2 mol%) instead of [UO <sub>2</sub> ]	-
6	Ph <sub>2</sub> CO (10 mol%) instead of [UO <sub>2</sub> ]	-
7 <sup>c</sup>	5 equiv. of <b>1</b>	32
8 <sup>c</sup>	5 equiv. of <b>1</b> , 72 h	62

<sup>a</sup> All reactions were carried out with **1** (2 mL), **2** (0.2 mmol, 1 equiv.), UO<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (8 mol %), pbi (10 mol %), 25 °C, 452 nm Kessil Lamp (60 W), 24 h. <sup>b</sup> Yields were determined by GC-FID using cyclododecane as internal standard. <sup>c</sup> 1 mL of benzene was added.

**Substrate scope with respect to the C(sp<sup>3</sup>)-H sources and the alkynyl bromides.** With the optimized reaction conditions, we examined the substrate scope for this C(sp<sup>3</sup>)-H alkylation (Figure 2A). Linear amides (**3** & **7**) and imide (**6**) are tolerated to access propargyl amides. The alkylation of DMF resulted in two isomers in 52% and 29% isolated yield (**4** & **5**). Secondary amide could also be converted to the product (**8**) with moderate yield. Interestingly, the alkylation of N-methyl pyrrolidone occurred on the methylene instead of methyl substitution (**9**). Pivaloyl piperidine (**10**) resulted in the alkynylated product in 48% yield. For the urea derivative and the phosphoric amide, alkylation proceeded efficiently (**11**, **12**). Notably, chiral proline derivative could also convert to the corresponding product in which the trans

diastereomer was dominant (**13**). Furthermore, ethers were also found suitable for this transformation (**14-18**). Unfortunately, the previously reported simple alkanes<sup>9-13</sup> such as cyclohexane and adamantane proceeded slowly and could not be tolerated. The alkylation of cyclooctane generated the desired products in good yield after long reaction time (**19**).

We next employed N,N-dimethylacetamide to examine the scope of alkynyl bromides (Figure 2B). Both alkyl group and halogen substituted substrates were tolerated under the same condition (**20-24**). Electron-withdrawing ester group led to moderate yield (**25**). The dibromoethynyl substrate furnished a mixture of mono- and di-substituted products in 52% and 45% isolated yields (**26, 27**). Besides, the alkynylsilane and the aliphatic alkyne transformed into the corresponding products in good yields (**28, 29**). Pharmaceutical Ethisterone and herbicide Clodinafop-propargyl were also subjected to the standard conditions to furnish the propargylic derivatives in 61% and 49% yields (**30, 31**).

**Substrate scope for C(sp<sup>3</sup>)-H alkenylation and allylation.** Furthermore, we expanded the scope of this radical C-H functionalization to olefination. By using alkenyl or allyl bromides, we were delighted to discover that C(sp<sup>3</sup>)-C(sp<sup>2</sup>) and C(sp<sup>3</sup>)-C(sp<sup>3</sup>) coupling products (**32 & 39**) were readily furnished under the same conditions (Figure 3). Unsaturated bromides bearing halogen (**33, 40**), trifluoromethoxy (**34**), methoxy (**35**), acetoxy (**36**), thiophene (**37**), naphthyl (**41**) substitutions were tolerated under the conditions. Disubstituted ethylene bromide was applicable for generating the desired products in good yields (**38**). For 2,3-dibromo-1-propene, the reaction only occurred on the allylic site (**42**). The bromo-Carvone was also successfully converted into the corresponding derivative in 55% yield (**43**).

**Synthetic applications.** In order to simplify the procedure, bromoalkyne could be prepared in situ from terminal alkyne and the coupling product could be afforded in single operation (Figure 4A). Considering dibromoethene as key intermediate in Corey-Fuchs reaction for converting aldehydes to alkynes<sup>39</sup>. Previous procedures<sup>36,40,41</sup> employed strong base to transfer dibromoethene (**46**) into the terminal alkyne (**48**) and three-step transformation to access propargyl amide (**47**). Following our uranyl-catalytic protocol, **47** could be conveniently obtained in 65% yield in single step (Figure 4B).

The scalability of this reaction was also evaluated, we chose bromo-Ethisterone (**51**) as substrate and achieved 1.06 g of substituted progesterone (**30**) (Figure 4C). In order to further improve the reaction efficiency, we applied continuous flow technique to this transformation<sup>42-44</sup>. (Bromoethynyl)benzene (0.1 M DMAc solution), uranyl nitrate (0.008 M DMAc solution) and ligand (0.01 M DMAc solution) were mixed thoroughly and pumped into the flowing reactor in 0.33 mL/min of current velocity under blue LED illumination. The propargyl amide was furnished in 26 mmol L<sup>-1</sup> h<sup>-1</sup> (51 % yield) within 2 h and 11 mmol L<sup>-1</sup> h<sup>-1</sup> (97 % yield) in 9 h. Further studies on the reaction rate demonstrated that continuous flow technique distinctly accelerated the process comparing with the batch reaction (98%, 24 h, see Supplementary Information for details).

**Mechanistic investigation.** In order to investigate the reaction mechanism, the control experiments have been performed. We exposed a solution of uranyl nitrate hexahydrate with the same mole of 2-(2-

pyridyl)benzimidazole (pbi) in acetone to 452 nm LED for 1 h under ambient conditions. Single crystals of the uranyl nitrate peroxide complex  $[\text{UO}_2(\text{pbi})(\text{NO}_3)]_2(\text{O}_2) \cdot 2\text{Me}_2\text{CO}$  (**52**) were formed (Figure 5A). The crystallographic analysis of **52** revealed two symmetrically distinct and nearly linear  $(\text{UO}_2)^{2+}$  uranyl ions with  $\text{U}=\text{O}$  bond lengths in the range of 1.75(5)–1.78(3) Å. These uranyl ions are bridged by a  $\mu\text{-}\eta^2\text{:}\eta^2$  peroxo ligand that has an O–O bond length of 1.55(2) Å. The U–O<sub>2</sub>–U dihedral angle is 148°, consistent with those found in a variety of uranyl peroxides<sup>8</sup>. Each uranyl ion is further coordinated by a bidentate nitrate group, and two N atoms of 2-(1H-benzimidazole-2-yl)pyridine ligands, together resulting in a hexagonal bipyramidal coordination geometry about the  $\text{U}^{\text{VI}}$  cation. Using the isolated uranyl peroxide crystals **52** as the photocatalyst, the same alkynylated product **3** could be generated with a yield of 95% in 16 h (Figure 5B).

## Discussion

The control experiments demonstrated that the product could be generated without pbi ligands and the reaction could proceed with uranyl cation by itself. When adding the ligand, uranyl peroxide was smoothly formed under the irradiation. Based on the above results and previous studies on uranyl cations<sup>13</sup> and uranyl peroxides<sup>38</sup>, a plausible mechanism is proposed (Fig. 6). In the absence of ligands (Fig. 6A), photoinduced LMCT of  $\text{U}^{\text{VI}}$  catalyst (**56**) generates  $\text{U}^{\text{V}}$  centered oxygen radical (**53**), which extracts C–H of dimethylacetamide (**1**) to give  $\text{sp}^3$ -carbon radical (**57**) that trapped by electrophilic bromoalkynes (**2**). The cleavage of bromoalkenyl radical (**58**) gives the desired products (**3**) and bromine radicals.  $\text{U}^{\text{VI}}$  catalyst can be regenerated by SET and deprotonation from the  $\text{U}^{\text{V}}$  intermediate **54**. With pbi ligands (Fig. 6B), the hydration of uranyl nitrate (**59**) furnishes a hydroxo-bridged diuranyl complex (**60**). Under visible light irradiation, the LMCT from oxygen to uranium gives an oxygen radical (**61**) and intramolecular HAT furnishes the intermediate **62**. The following hydrogen evolution of **62** furnishes the uranyl peroxide **52**. Subsequently, complex **52** can either undergo homolysis of O–O bond to give diradical **63**, or photoinduced LMCT of U–O bond to generate oxygen radical **64** and the following hydrogen abstraction of dimethylacetamide **1** gives the alkyl radical **57**. Overall, this uranyl peroxide catalytic process accelerated the formation of alkyl radicals.

In summary, we have developed a uranyl-catalyzed alkynylation reaction of  $\text{C}(\text{sp}^3)\text{-H}$  bonds. The photoexcitation of uranyl cations provides a feasible strategy to generate a range of carbon-centered radicals, which can be successfully applied in cross-coupling reaction with a broad range of bromoalkynes. Under the same protocol, the alkenylation and allylation have also been achieved. Crystallographic analysis demonstrated that the uranyl peroxides were generated in situ from uranyl cations and suitable ligands. The mechanistic studies revealed that the uranyl peroxide accelerated the hydrogen abstraction from various substrates and promoted the alkynylation.

## Methods

### General procedure for C–H Alkynylation, Alkenylation and Allylation.

**Method A (C-H sources as solvent).** Uranyl nitrate hexahydrate (8.0 mg, 8 mol%), 2-(2-pyridyl)benzimidazole (pbi) (3.9 mg, 10 mol%) and the bromide (if solid, 0.2 mmol, 1.0 equiv.) were added into a screw-cap test tube with stirring bar. The alkyl source (2 mL, 0.1 M) was injected into the tube, followed with the bromide (if liquid, 0.2 mmol, 1.0 equiv.). Afterwards, the tube was set between two lamps (10 cm away from the lamp, 60 W each) and stirred at room temperature (with a fan to cool down the reaction) for 24 h. The mixture was diluted with ethyl acetate and washed with saturated NaHCO<sub>3</sub> (10 mL), water (10 mL x 3) and brine (10 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the corresponding product.

**Method B (benzene as solvent).** Uranyl nitrate hexahydrate (8.0 mg, 8 mol%) and 2-(2-pyridyl)benzimidazole (3.9 mg, 10 mol%) were added into a screw-cap test tube with stirring bar. The bromide (0.2 mmol, 1.0 equiv.) and the alkyl source (1 mmol, 5.0 equiv.) were dissolved in benzene (1 mL, 0.2 M) and the solution was injected into the tube. Afterwards, the tube was set between two lamps (10 cm away from the lamp, 60 W each) and stirred at room temperature (with a fan to cool down the reaction) for 24–96 h. The mixture was diluted with ethyl acetate and washed with saturated NaHCO<sub>3</sub> (10 mL), water (10 mL x 3) and brine (10 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the corresponding product.

## Data Availability

The authors declare that the main data supporting the findings of this study, including experimental procedures and compound characterization, are available within the article and its Supplementary Information files. X-ray structural data of compound **52** are available free of charge from the Cambridge Crystallographic Data Center under the deposition number CCDC 2055096. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

## Declarations

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### Author contributions

Y.W. designed and guided this project. Y.M. is responsible for the plan and implementation of the experimental work. S.N. and Y.W. wrote the manuscript. Y.P. was responsible for funding application.

### Competing interests

The authors declare no competing interests.

### Additional information

**Supplementary information** accompanies this paper at <https://doi.org/10.1038/xxxx>.

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# Figures

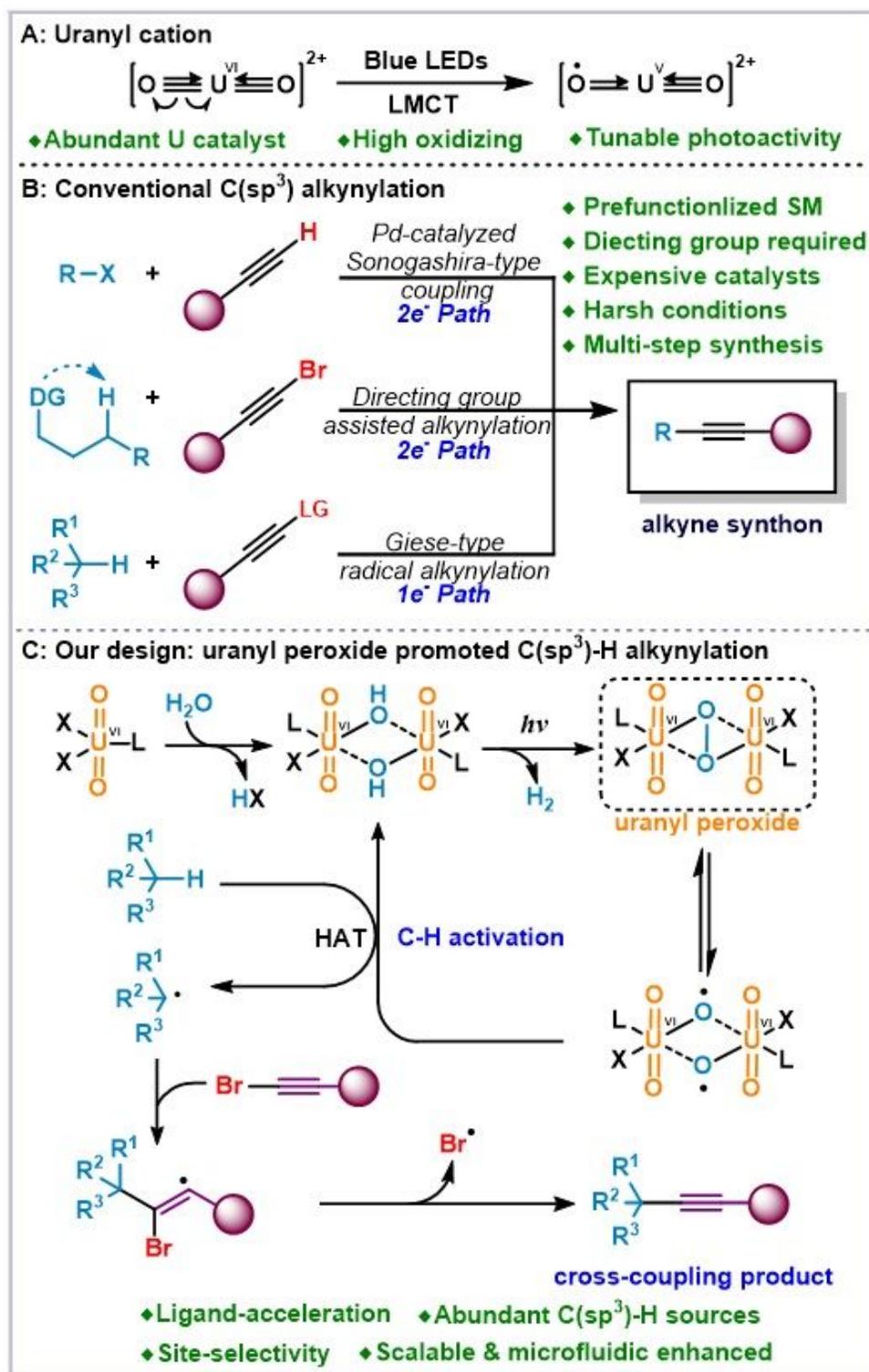
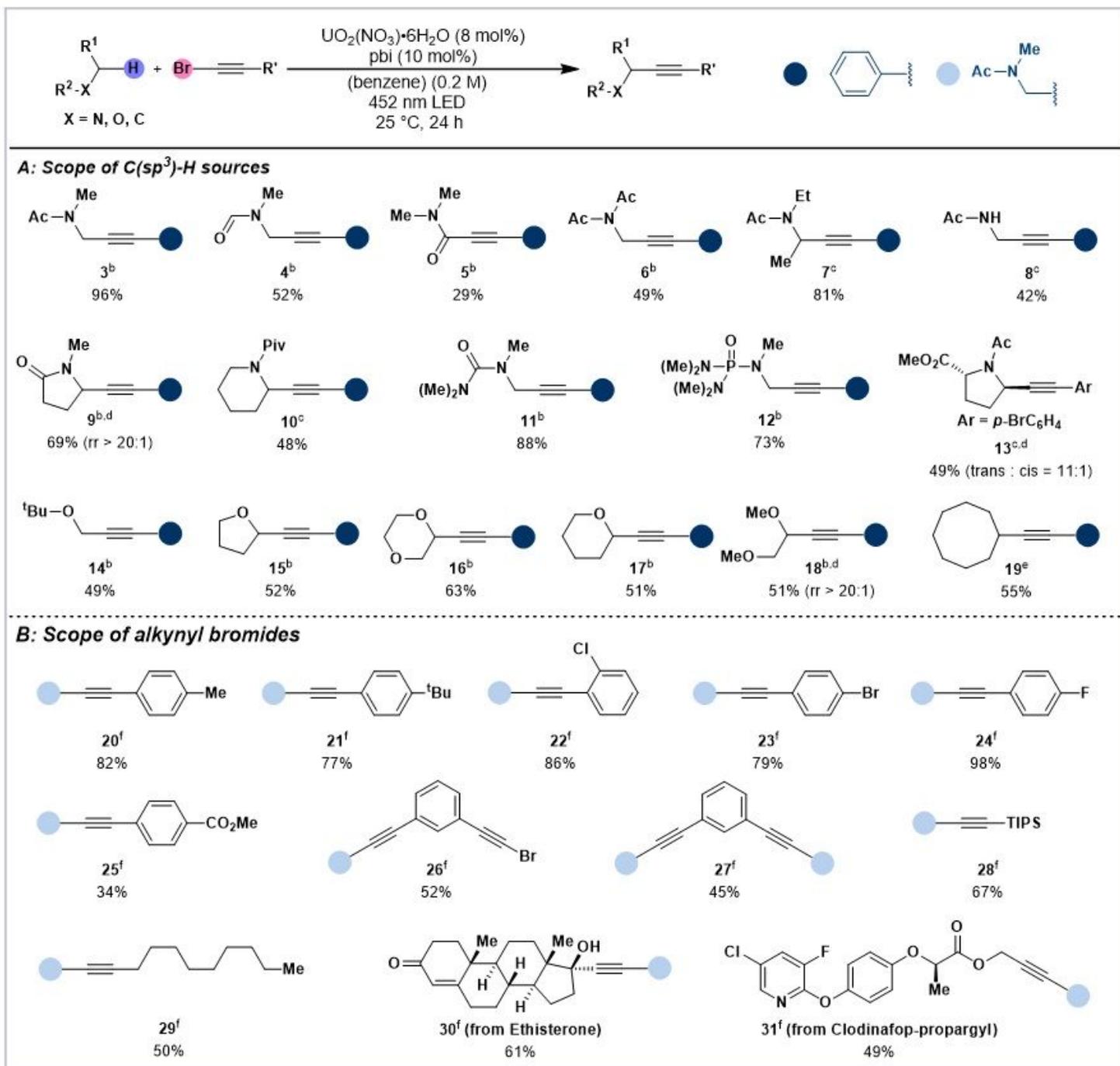


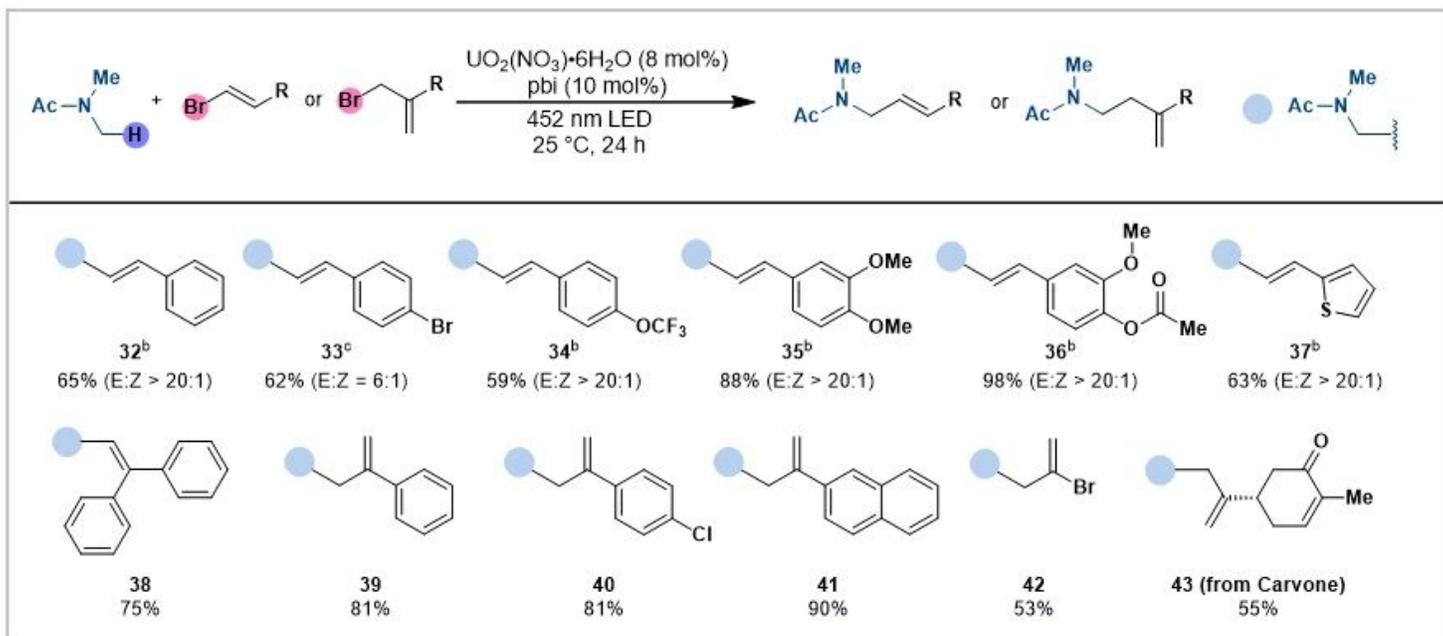
Figure 1

Origin of the Reaction Design.



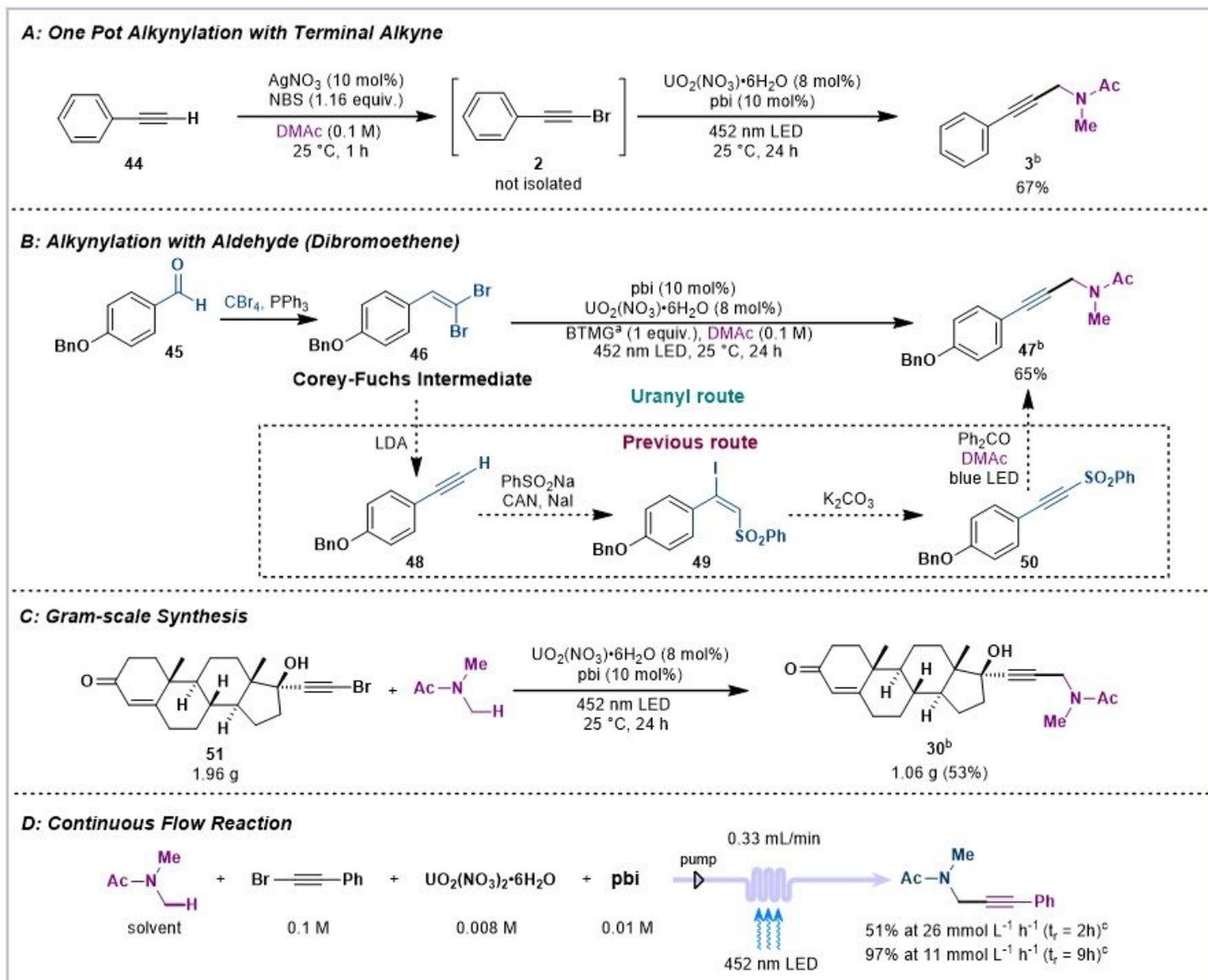
**Figure 2**

Substrate scope for C(sp<sup>3</sup>)-H alkylation. a All reactions were carried out with bromoalkynes (0.2 mmol, 1 equiv.), isolated yields. b 2 mL of alkyl source was used. c 5 equiv. of alkyl source and 1 mL of benzene were used and stirred for 72 h. d Ratio was determined by <sup>1</sup>H NMR. e 40 equiv. of cyclooctane and 1 mL of benzene were used and stirred for 96 h. f N,N-dimethylacetamide (2 mL), bromides (0.2 mmol, 1 equiv.), isolated yields.



**Figure 3**

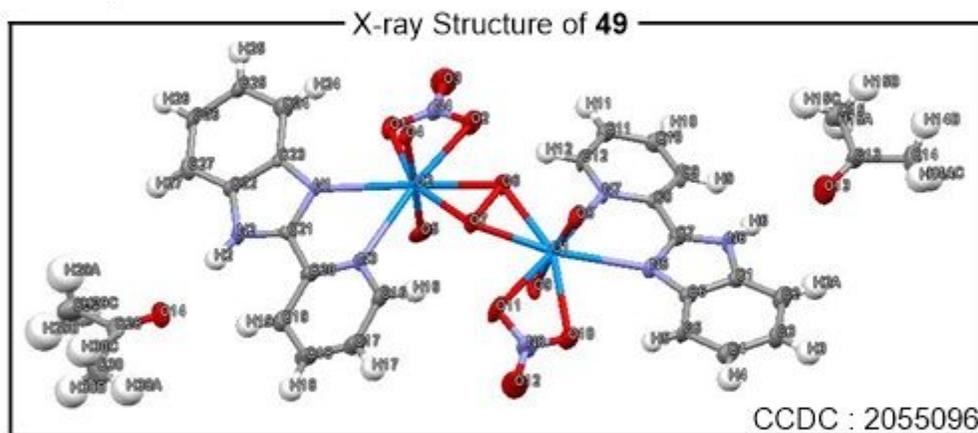
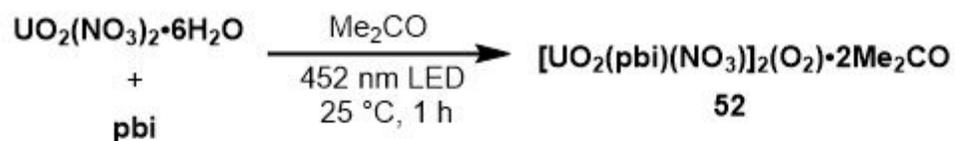
Substrate scope for C(sp<sup>3</sup>)-H alkenylation and allylation. a All reactions were carried out with N,N-dimethylacetamide (2 mL), bromides (0.2 mmol, 1 equiv.), isolated yields. b E/Z ratio was determined by <sup>1</sup>H NMR c E/Z ratio was determined by isolated yields.



**Figure 4**

Synthetic applications. a BTMG = 2-(tert-butyl)-1,1,3,3-tetramethylguanidine. b Isolated yields. c Crude yields were determined by GC-FID using cyclododecane as internal standard.

**A: Uranyl Peroxide Complexes**



**B: Uranyl Peroxide Catalyzed Reaction**

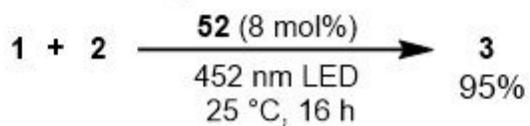


Figure 5

Mechanistic investigation.

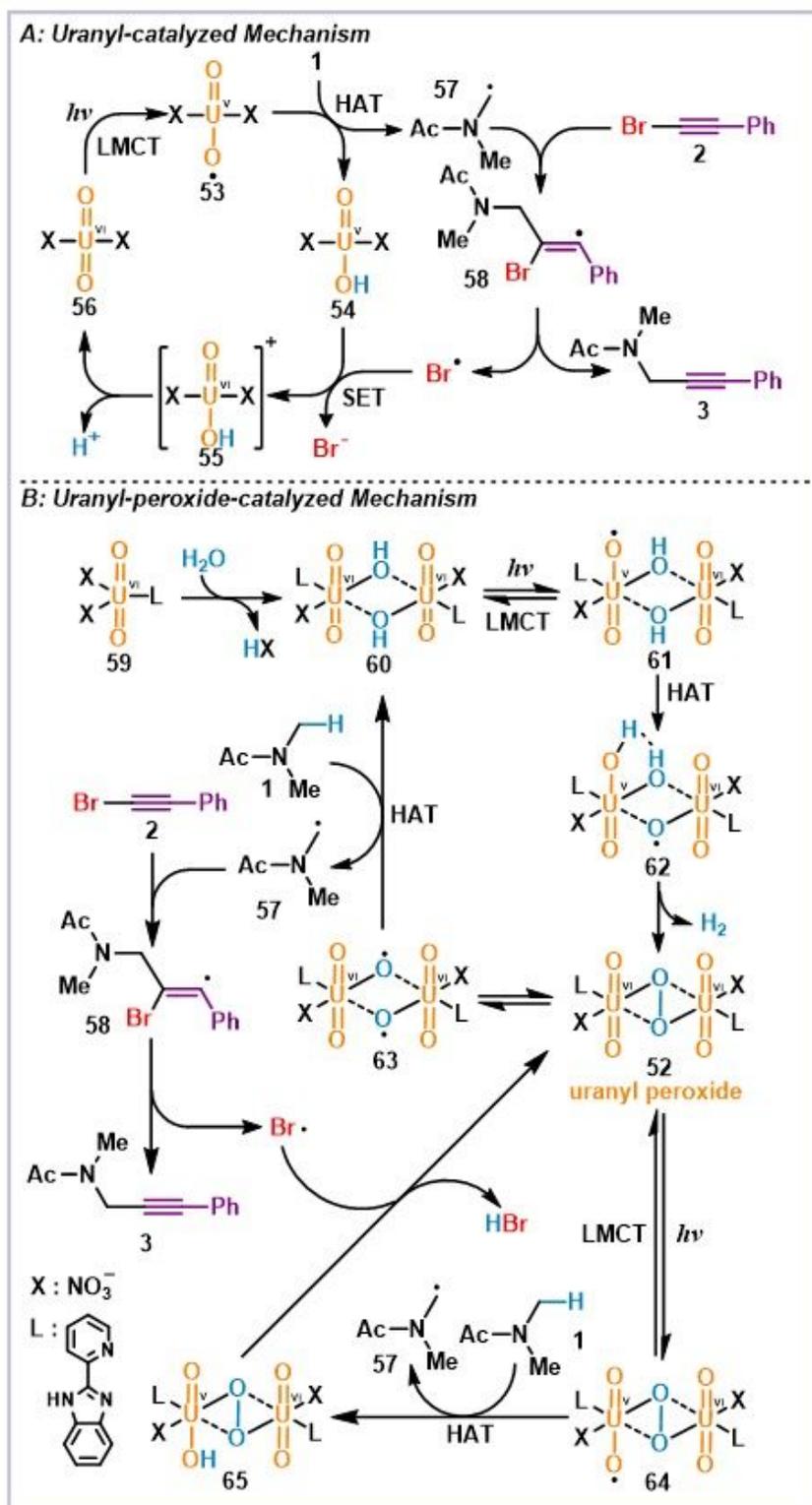


Figure 6

Proposed mechanism.

## Supplementary Files

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