

Photo-Induced Pyridylic C(sp³)-H Alkylation with Unactivated Alkenes Enabled by Hydrogen Atom Transfer/Lewis Acid Co-Catalysis

Yusuke Kuroda,* Hikaru Saito, Tsukasa Tawatari, Kiyosei Takasu*

Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan.

Hydroalkylation, Pyridines, Photoreaction, Lewis acid catalysis, Hydrogen Atom Transfer, Radical Addition

ABSTRACT: Radical hydroalkylation of alkenes represents an ideal approach for C(sp³)-C(sp³) bond formation. However, radical precursors have been substantially limited due to the sluggish nature of less electrophilic carbon-centered radicals to participate in addition step toward unactivated alkenes. Herein, we demonstrate that this inherent limitation can be overcome by the use of a Lewis acid catalyst. This co-catalytic system enables the hitherto elusive radical C(sp³)-C(sp³) bond formation between pyridylacetates and unactivated alkenes to generate medically relevant valuable products. Computational studies support that the formation of a Lewis pair with the substrates is crucial to lower the energy of the transition state for the rate-determining radical addition step.

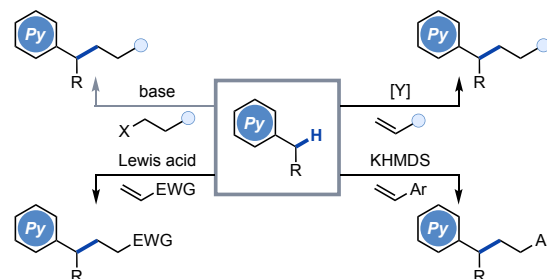
INTRODUCTION

Pyridines are among the most prevalent motifs in a wide array of biologically active molecules.¹ In fact, the pyridine core represents the most frequently employed nitrogen heterocycle among all U.S. FDA approved small-molecule drugs reported between 2015 and 2020.^{1a} To meet the growing demand for sp³-enriched drug candidates,² methods that enable direct introduction of alkyl groups to pyridylic C(sp³)-H bonds are highly sought after in the medicinal chemistry community.³ In this context, hydroalkylation of alkenes, involving the net addition of C(sp³)-H bonds across alkenes,⁴ presents a competent alternative to conventional S_N2-type alkylation with alkyl halides (Scheme 1A, top-left) as it allows for the use of abundant and stable alkenes as alkyl halide replacements. Over the past decade, several elegant strategies for pyridylic C(sp³)-H alkylation with alkenes have developed.⁵⁻⁷ For example, Matsunaga, Kanai and co-workers reported a Lewis-acid catalyzed addition reaction of 2-alkylpyridines to α,β-unsaturated enones (Scheme 1A, bottom-left).^{5a} Hou and co-workers developed a rare-earth catalyzed benzylic C(sp³)-H alkylation of 2,6-disubstituted alkylpyridines (Scheme 1A, top-right).^{6a} More recently, Guan and co-workers demonstrated that alkylpyridines can directly undergo addition reaction to styrene derivatives upon deprotonation by a strong base (Scheme 1A, bottom-right).^{7a} As a notable example, Bower and co-workers reported an Ir-catalyzed branch-selective hydroalkylation of alkenes with 2-pyridylacetates.^{6f} Despite these advances, a strategy for pyridylic C(sp³)-H alkylation with unactivated aliphatic alkenes that exhibits broad functional group compatibility remains virtually elusive.

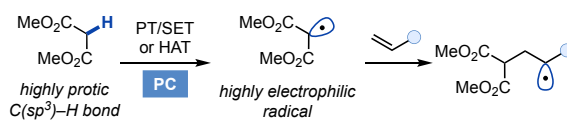
In recent years, photochemical methods have been utilized to achieve radical hydroalkylation via the generation of electrophilic carbon-centered radicals from substrates bearing protic C(sp³)-H bonds (Scheme 1B).^{4c,8-10} For instance, Yamashita, Kobayashi and co-workers reported an addition reaction of malonyl radicals via single electron transfer (SET) oxidation of lithium malonate enolates by a photoredox catalyst.^{8a} As an

Scheme 1. Research Overview

A. Prior art of pyridylic C(sp³)-H alkylation with alkenes



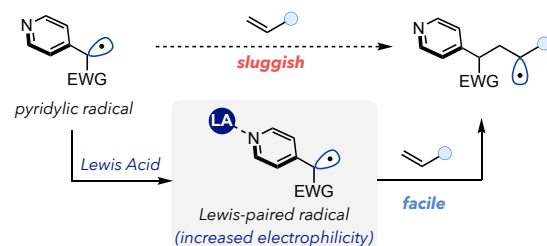
B. Photocatalytic radical hydroalkylation of unactivated alkenes



challenges:

- generation of radicals from less protic C(sp³)-H bonds
- radical addition of less electrophilic C-centered radicals

C. This work: Radical hydroalkylation with pyridylic C(sp³)-H bonds



alternative strategy for generating electrophilic carbon-centered radicals, Funes-Ardoiz, Ye and co-workers demonstrated that

an amine-borane can function as a nucleophilic hydrogen atom transfer (HAT) catalyst upon SET oxidation by a photocatalyst.^{8b} A key challenge in the radical hydroalkylation of unactivated aliphatic alkenes lies in the fact that the range of C(sp³)-H bonds amenable to these methodologies remains predominantly confined to highly protic substrates such as dimethyl malonate. This limitation can be attributed to the necessity of multiple strong electron-withdrawing groups (EWGs) for 1) facilitating the initial proton transfer (PT) or polarity-matched hydrogen atom transfer (HAT)¹¹ process by enhancing the acidity of C(sp³)-H bonds, thereby enabling easier access to electrophilic radicals, and 2) promoting radical addition to less-reactive aliphatic alkenes by lowering the SOMO energy of the resultant carbon centered-radical, which enhances favorable frontier molecular orbital interactions.¹² With these challenges in mind, we sought to develop a distinct catalytic system that would enable the radical alkylation of pyridylic C(sp³)-H bonds with unactivated aliphatic alkenes.

Our reaction design drew inspiration from early reports on the effect of Lewis acids in radical reactions, wherein Lewis acids are believed to enhance the electrophilicity of a radical intermediate through complexation with a Lewis-basic functionality in a substrate.¹³ More recently, Lewis acid co-catalysis has proven a powerful tool in photochemical transformations to activate Lewis basic substrates.¹⁴ On this basis, we hypothesized that the electrophilicity of a pyridylic radical intermediate could be enhanced by a Lewis acid co-catalyst upon coordination, thereby facilitating the otherwise sluggish radical addition to less-reactive aliphatic alkenes.¹⁵ Herein, we report the successful implementation of this idea, employing a merger of HAT and Lewis acid catalysis, to establish a mild catalytic system for pyridylic C(sp³)-H alkylation with a wide array of unactivated alkenes (Scheme 1C).

RESULTS AND DISCUSSION

We commenced our investigation by identifying a Lewis acid co-catalyst that works in synergy with a HAT catalyst to facilitate the desired hydroalkylation of 4-phenyl-1-butene (**2a**) with ethyl 4-pyridylacetate (**1a**) (Table 1). After an extensive screening of various conditions (see the SI for details), we identified the optimized conditions as shown in entry 1, employing 20 mol% Y(OTf)₃ as a Lewis acid catalyst, 2.5 mol% bis(2,4,6-triisopropylphenyl) disulfide [(TRIPS)₂] as a HAT catalyst in MeCN at 60 °C under irradiation with 440 nm LEDs, providing the desired hydroalkylation product **3aa** in 87% NMR yield (84% isolated yield). It is worth noting that the reaction proceeds without a photocatalyst, which contrasts sharply with previous radical hydroalkylation methods under photocatalysis,^{8,9} suggesting an alternative mechanism driven solely by irradiation. As shown in entry 2, the use of 5.0 mol% [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (**PC1**) improved the reaction efficiency, affording **3aa** in a comparable yield (91%) within 24 h. Screening of Lewis acid co-catalysts revealed that other Lewis acids resulted in lower yields, with Sc(OTf)₃ providing the highest yield (80%) among them (entries 3-5). Utilizing diphenyl disulfide as a HAT catalyst instead of (TRIPS)₂ led to a diminished yield due to a competing thio-ene reaction (entry 6).¹⁶ Control experiments established that the combination of a Lewis acid co-catalyst, a HAT catalyst and light irradiation is essential for obtaining the desired hydroalkylation product (entries 7-9). Notably, this alkylation can be performed on 1 mmol scale without loss in efficiency (entry 10).

Table 1. Optimization of Reaction Conditions^a

entry	deviations from the standard conditions	yield (%) ^b
1	none	87 (84) ^c
2	with 5 mol% PC1 for 24 h	91 (91) ^c
3	Sc(OTf) ₃ instead of Y(OTf) ₃	80
4	Mg(OTf) ₂ instead of Y(OTf) ₃	74
5	Cu(MeCN) ₄ BF ₄ instead of Y(OTf) ₃	<5
6	(PhS) ₂ instead of (TRIPS) ₂	42
7	without Lewis acid	<5
8	without (TRIPS) ₂	<5
9	no light	<5
10	none (1.0 mmol scale)	(94) ^c

(TRIPS)₂

[Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (**PC1**)

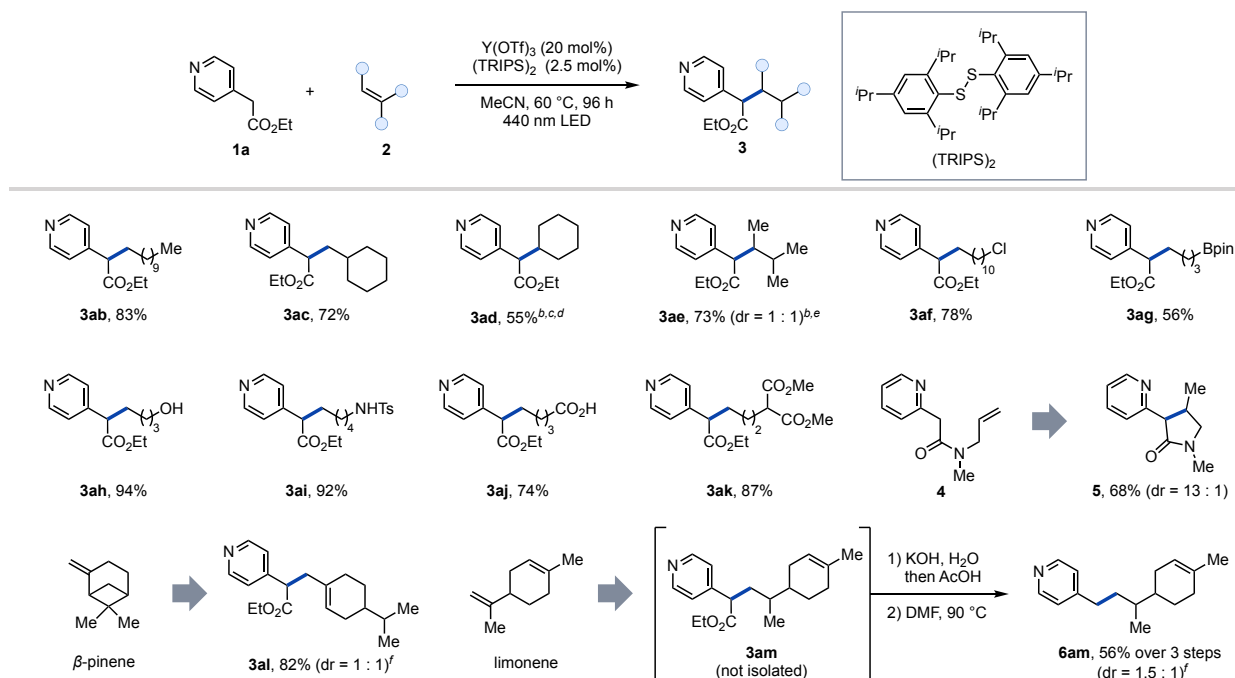
^aReaction conditions: **1a** (0.20 mmol), **2a** (0.6 mmol), Lewis acid (20 mol%), (TRIPS)₂ (2.5 mol%), 440 nm irradiation in MeCN (0.4 mL) at 60 °C. ^bYields determined using ¹H NMR analysis with triphenylmethane as an internal standard. ^cIsolated yield in parentheses.

Table 2. Scope of Pyridines^a

1	2a	3
3ba , 81%	3ca , 49% ^{b,c}	3da , 45% ^{d,e,f}
3ea , 79% ^b	3fa , 19% ^{b,d,g}	3ga , 58% ^{b,f}
3ha , 82% ^{b,f}	3ia , 52% ^b	3ja , 73% ^b
limitations (<20% NMR yield)		

^aReaction conditions: **1** (0.20 mmol), **2a** (0.6 mmol), Y(OTf)₃ (20 mol%), (TRIPS)₂ (2.5 mol%), 440 nm irradiation in MeCN (0.4 mL) at 60 °C for 96 h. Only isolated yields are shown. ^b6.0 equiv. alkene. ^cFor 168 h. ^dWith **PC1** (5.0 mol%). ^e8.0 equiv. alkene. ^fFor 120 h. ^gFor 24 h.

Table 3. Scope of Alkenes^a



^aReaction conditions: **1** (0.20 mmol), **2a** (0.6 mmol), Y(OTf)₃ (20 mol%), (TRIPS)₂ (2.5 mol%), 440 nm irradiation in MeCN (0.4 mL) at 60 °C for 96 h. Only isolated yields are shown. ^b6.0 equiv. alkene. ^cFor 144 h. ^dWith (TRIPS)₂ (10 mol%). ^eFor 168 h. ^fWith **PC1** (5.0 mol%) for 24 h.

With the optimized conditions established, we next sought to examine the generality of the hydroalkylation process. Given that useful product formation can be achieved without an expensive photocatalyst, we employed photocatalyst-free conditions for further studies. As shown in Table 2, a range of structurally and electronically diverse pyridylacetates and pyridylacetamides can be successfully employed as substrates in this radical alkylation protocol. For the 4-pyridyl-based system, both benzyl ester (**3ba**) and secondary *N*-benzyl amide (**3ca**) groups participated effectively in the alkylation reaction. Generally, the photocatalyst-free conditions proved competitive with the photocatalytic reaction; however, the use of **PC1** was essential for the alkylation of 4-pyridylacetonitrile (**1d**). Under the optimal conditions, 2-pyridylacetate **1e** underwent smooth hydroalkylation to afford **3ea** in 79% yield. In addition, a quinoline-type substrate also participated in the reaction to give the desired product **3fa** in 19% yield. Notably, α -methyl pyridylacetate **1g** was a viable substrate with an extended reaction time, giving rise to a quaternary carbon center in synthetically useful yield (**3ga**, 58% yield). Various substituents on the pyridine ring were also well tolerated, and the corresponding alkylation products were obtained in good yields (**3ha**, **3ia** and **3ja**, 52–82% yield). Regarding the limitations of this method, 3-pyridylacetates showed no reactivity, indicating that conjugation of the C=N moiety of the pyridine ring with its pyridylic position is crucial for reactivity. In addition, substrates bearing substituents at the 2-position of a pyridine ring tended to result in low yields (<10%). This failure was likely due to the preclusion of the close contact between the nitrogen atom in a pyridine ring with Y(OTf)₃, which is necessary to form a Lewis acid–base pair. Other *N*-heteroaromatic units such as pyrimidines and

oxazoles also were not competent substrates under current optimal conditions.

Next, we examined the generality of the hydroalkylation protocol concerning the alkene component (Table 3). In addition to terminal monosubstituted alkene (**3ab**), 1,1-disubstituted (**3ac**), 1,2-disubstituted (**3ad**), and trisubstituted (**3ae**) alkenes were all competent reaction partners, providing the desired product in good yields (55–83% yield). Gratifyingly, the developed reaction conditions tolerate a wide range of functional groups that would not be compatible under traditional strong base-mediated alkylation conditions. For example, alkenes containing chloro (**3af**), boronate (**3ag**), hydroxy (**3ah**), tosylamide (**3ai**) and even carboxylic acid (**3aj**) groups were all tolerated, affording the desired products in good to excellent yields (56–94% yield), thus presenting opportunities for subsequent chemical elaboration. Notably, complete regioselectivity was observed for alkylation at the pyridylic C(sp³)–H bond in the presence of the active methine C(sp³)–H bond (**3ak**). When pyridylacetamide **4** bearing an *N*-allylamide moiety was subjected to the optimal conditions, pyrrolidine-2-one **5** was obtained through a 5-*exo*-trig cyclization, indicating the involvement of a radical intermediate. Underscoring the utility of this method, naturally abundant terpenes including β -pinene and limonene readily participated in this hydroalkylation as alkylating reagents, paving a facile way to pyridine-containing unnatural terpenoids (**3al** and **6am**).

An intriguing outcome observed during this study was the unexpected finding that the hydroalkylation, in most cases, proceeds without a photocatalyst under blue LED (440 nm) irradiation. This unprecedented aspect of radical hydroalkylation prompted us to conduct additional experiments to gain insight

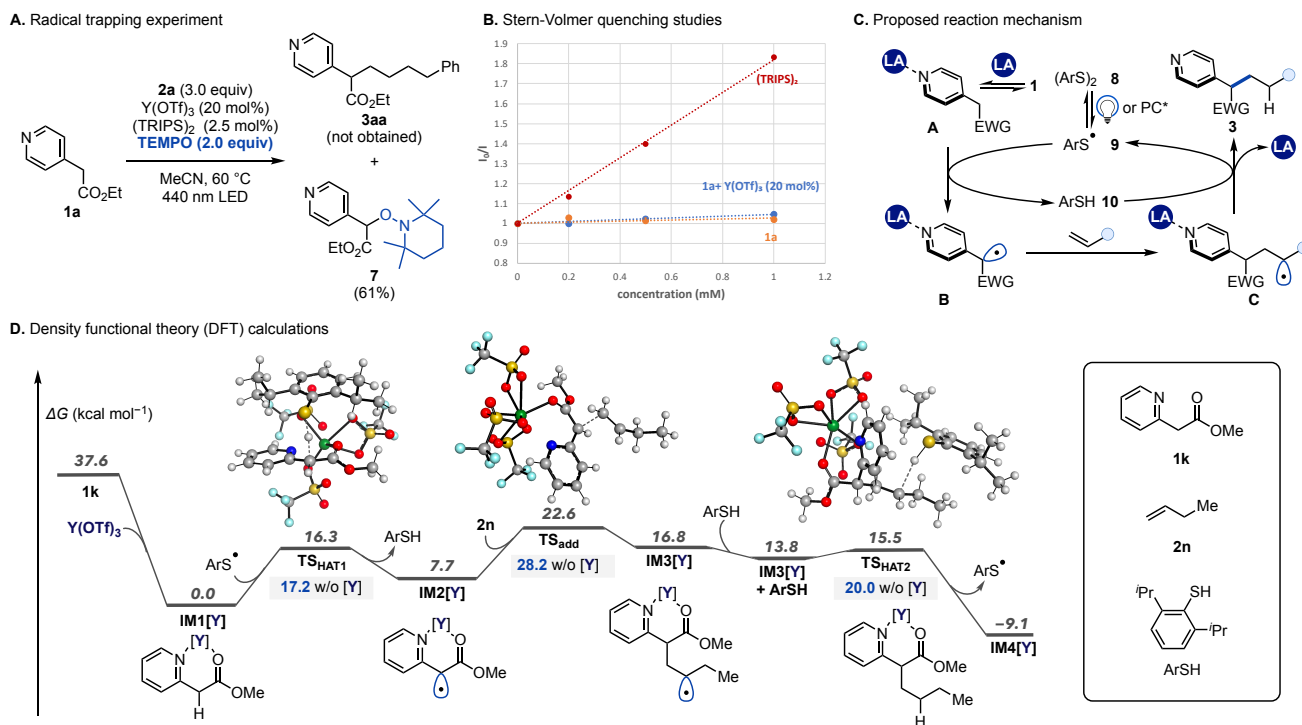


Figure 1. Mechanistic studies. (A) TEMPO trapping experiment. (B) Stern–Volmer quenching studies. (C) Proposed mechanism. (D) Calculated energy diagram for the reaction of pyridylacetate **1k** and 1-butene (**2n**). DFT calculations were conducted at the (U)B3LYP-D3(BJ)/6-311++G(d,p)-SDD/SMD(MeCN) // (U)B3LYP-D3(BJ)/6-31G(d)-LanL2DZ levels of theory.

into the reaction mechanism (Figure 1). First, performing the identical reaction between pyridylacetate **1a** and alkene **2a** in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) resulted in a complete shutdown of the formation of alkylation product **3aa**, and instead the radical adduct **7** was obtained in 61% yield, further supporting the intermediacy of a pyridylic radical (Figure 1A). Second, testing various photocatalysts with different properties revealed that the yield of **3aa** strongly correlated the intrinsic triplet energy of photocatalysts (see the SI for the details), suggesting that a triplet-triplet energy transfer (EnT) mechanism might be operative in this hydroalkylation reaction. Moreover, Stern–Volmer luminescence quenching experiments demonstrated that the luminescence emission of **PC1** was quenched more efficiently by (TRIPS)₂ than by pyridylacetate **1a**, in the presence or absence of Y(OTf)₃ (Figure 1B), indicating that higher efficiency of the hydroalkylation observed in the presence of **PC1** was due to facile access to the thiyl radical via a triplet-triplet EnT process.¹⁷ Although the detailed mechanism remains to be elucidated, a plausible mechanism is proposed based on our mechanistic studies (Figure 1C). Consistent with existing precedent,¹⁸ (ArS)₂ **8** undergoes photolytic homolysis upon blue LED irradiation to generate thiyl radical **9**. The resulting electrophilic radical undergoes HAT with the pyridylic C(sp³)–H bond of Lewis acid-base complex **A** to afford carbon-centered radical **B** and thiol **10**. The resulting electrophilic radical reacts with an alkene to form carbon-centered nucleophilic radical **C**, which rapidly engages in a polarity-matched HAT event with thiol **10** to yield hydroalkylation product **3** and thiyl radical **9**.

To further elucidate the mechanism and the role of the Lewis acid co-catalyst, we conducted density functional theory (DFT) calculations for the reaction between pyridylacetate **1k**¹⁹ and 1-

butene (**2n**) (see the SI for the details). For computational efficiency, 2,6-diisopropylthiophenol was employed as a model for TRIPSH. As shown in Figure 1D, our calculations predict that a polarity-mismatched HAT event between **IM1[Y]** and a thiyl radical (TS_{HAT1}) is kinetically feasible (16.3 kcal mol^{−1}),²⁰ affording carbon-centered radical **IM2[Y]**. Notably, the Lewis acid co-catalyst Y(OTf)₃ decreases the activation energy of this step by 0.9 kcal mol^{−1}. The subsequent radical addition to 1-butene (**2n**) (TS_{add}) is predicted to be the rate-determining step with 22.6 kcal mol^{−1}. Consistent with the experimental observation, the presence of Y(OTf)₃ effectively lowers the activation energy by 5.6 kcal mol^{−1}. At the HAT event of **IM3[Y]**, a radical chain propagation with **1k** is predicted to be disfavored by 16.4 kcal mol^{−1} compared to the thiol-mediated HAT event (TS_{HAT2}), which was experimentally corroborated by the measured quantum yield ($\Phi = 0.00048$) and a light on/off experiment (see the SI for the details).

CONCLUSIONS

In summary, we have demonstrated that the use of a Lewis acid co-catalyst facilitates the otherwise sluggish addition of pyridylic radicals to unactivated alkenes, thereby enabling the development of a photo-induced pyridylic C(sp³)–H alkylation. Unlike previously described radical hydroalkylation methods, this co-catalytic system operates without the need for photoredox catalysts. The reaction proceeds through a thiol-catalyzed hydrogen atom transfer mechanism under mild conditions with a broad functional group tolerance. We anticipate that this reaction will be beneficial to the medicinal chemistry community in meeting the growing demand for sp³-enriched drug candidates.

METHODS

Representative Procedure for Hydroalkylation of Unactivated Alkenes with Pyridylacetates: To a screw capped test tube equipped with a stir bar were added $\text{Y}(\text{OTf})_3$ (40.0 μmol , 21.4 mg, 20 mol%) and bis(2,4,6-triisopropylphenyl) disulfide $[(\text{TRIPS})_2]$ (5.0 μmol , 2.4 mg, 2.5 mol%). The test tube was then brought into N_2 -filled glovebox, where MeCN (0.40 mL), **1a** (0.20 mmol, 30 μL , 0.20 mmol) and 4-phenyl-1-butene (**2a**) (90 μL , 0.60 mmol, 3.0 equiv) were added. The test tube was sealed with a cap and removed from the glovebox. The reaction mixture was then irradiated with 440 nm LEDs in an oil bath heated to 60 °C. After stirring for 72 h, the reaction was quenched with sat. NaHCO_3 aq. (1 mL), and the aqueous phase was extracted with EtOAc (1 mL $\times$ 5). The combined organic layers were concentrated under reduced pressure, and the residue was purified by column chromatography (SiO_2 , 80/20 to 50/50 hexanes/EtOAc) to provide **3aa** as a yellow oil (49.9 mg, 84%).

AUTHOR INFORMATION

Corresponding Authors

Yusuke Kuroda – Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan.

E-mail: kuroday@pharm.kyoto-u.ac.jp

Kiyosei Takasu – Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan.

E-mail: takasu.kiyosei.6r@kyoto-u.ac.jp

Authors

Hikaru Saito – Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan.

Tsukasa Tawatari – Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan.

Author Contributions

Y.K. discovered the reaction and directed the project with K.T. Y.K. and H.S. performed and analyzed the experiments. T.T. conducted quantum chemical calculations. Y.K. prepared the manuscript with input from all authors.

Notes

The author declares no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data (PDF)

ACKNOWLEDGMENT

This study was supported by a JSPS KAKENHI (Grant Numbers 23H02604, K.T. and Y.K.), the MEXT Leading Initiative for Excellent Young Researchers (Y.K.), MEXT KAKENHI (JP21H05211, K.T.) in Digi-TOS, BINDS from AMED (22ama121042j0001 and 22ama121034j0001, K.T.). Parts of this study we conducted using the supercomputer of ACCMS at Kyoto University.

REFERENCES

(1) (a) Bhutani, P.; Joshi, G.; Raja, N.; Bachhav, N.; Rajanna, P. K.; Bhutani, H.; Paul, A. T.; Kumar, R. U. S. FDA Approved Drugs from 2015–June 2020: A Perspective. *J. Med. Chem.* **2021**, *64*, 2339–2381. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of

the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals: Mini-perspective. *J. Med. Chem.* **2014**, *57*, 10257–10274.

(2) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752–6756. (b) Lovering, F. Escape from Flatland 2: Complexity and Promiscuity. *Med. Chem. Commun.* **2013**, *4*, 515–519.

(3) For a recent review on benzylic $\text{C}(\text{sp}^3)\text{--H}$ functionalization of heterocycles, see: Kaur, M.; Van Humbeck, J. F. Recent Trends in Catalytic $\text{Sp}^3\text{ C--H}$ Functionalization of Heterocycles. *Org. Biomol. Chem.* **2020**, *18*, 606–617.

(4) For reviews, see: (a) Dénès, F.; Pérez-Luna, A.; Chemla, F. Addition of Metal Enolate Derivatives to Unactivated Carbon–Carbon Multiple Bonds. *Chem. Rev.* **2010**, *110*, 2366–2447. (b) Dong, G.; Lim, H.; Xing, D. Transition-Metal-Catalyzed Ketone α -Alkylation and Alkenylation with Simple Alkenes and Alkynes through a Dual Activation Strategy. *Synlett* **2018**, *30*, 674–684. (c) Yamashita, Y.; Kobayashi, S. Efficient Radical-Mediated Intermolecular α -Alkylation Reactions of Carbonyl Compounds with Nonactivated Alkenes. *Chem. – Asian J.* **2024**, *19*, e202400319.

(5) For selected examples on conjugate addition of pyridylic $\text{C}(\text{sp}^3)\text{--H}$ bonds, see: (a) Komai, H.; Yoshino, T.; Matsunaga, S.; Kanai, M. Lewis Acid Catalyzed Benzylic C--H Bond Functionalization of Azaarenes: Addition to Enones. *Org. Lett.* **2011**, *13*, 1706–1709. (b) Best, D.; Kujawa, S.; Lam, H. W. Diastereo- and Enantioselective Pd(II)-Catalyzed Additions of 2-Alkylazaarenes to N-Boc Imines and Nitroalkenes. *J. Am. Chem. Soc.* **2012**, *134*, 18193–18196. (c) Qian, B.; Shi, D.; Yang, L.; Huang, H. Lewis Acid-Catalyzed Conjugate Addition of $\text{Sp}^3\text{ C--H}$ Bonds to Methylene malononitriles. *Adv. Synth. Catal.* **2012**, *354*, 2146–2150. (d) Fallon, C.; Lam, H. W. Enantioselective Nickel-Catalyzed Michael Additions of Azaarylacetaes and Acetamides to Nitroalkenes. *Chem. – Eur. J.* **2012**, *18*, 11214–11218. (e) Li, H.-Y.; Xing, L.-J.; Xu, T.; Wang, P.; Liu, R.-H.; Wang, B. An Addition of Benzylic $\text{Sp}^3\text{ C--H}$ to Electron-Deficient Olefins. *Tetrahedron Lett.* **2013**, *54*, 858–860. (f) Nageswara Rao, N.; Meshram, H. M. Microwave Promoted Catalyst-Free Benzylic C--H Functionalization of Methyl Quinoline and Michael Addition to Beta-Nitro Styrene. *Tetrahedron Lett.* **2013**, *54*, 1315–1317. (g) Li, T.; Zhu, J.; Wu, D.; Li, X.; Wang, S.; Li, H.; Li, J.; Wang, W. A Strategy Enabling Enantioselective Direct Conjugate Addition of Inert Aryl Methane Nucleophiles to Enals with a Chiral Amine Catalyst under Mild Conditions. *Chem. – Eur. J.* **2013**, *19*, 9147–9150. (h) Lu, B.; Lu, Q.; Zhuang, S.; Cheng, J.; Huang, B. $\text{Bi}(\text{OTf})_3$ -Catalyzed C--H Bond Functionalization of Azaarenes for the Facile Access to Oxindoles Featuring Quaternary Carbon Centers. *RSC Adv.* **2015**, *5*, 8285–8288. (i) Jamal, Z.; Teo, Y.; Wong, L. Functionalization of the Benzylic C--H Bonds in Azaarenes by Cobalt-Catalyzed 1,4-Addition to Enones. *Eur. J. Org. Chem.* **2014**, 7343–7346. (j) Chatterjee, S.; Bhattacharjee, P.; Temburu, J.; Nandi, D.; Jaisankar, P. Indium Trichloride Catalyzed $\text{Sp}^3\text{ C--H}$ Bond Functionalization of 2-Alkyl Azaarenes under Microwave Irradiation. *Tetrahedron Lett.* **2014**, *55*, 6680–6683. (k) Zalznaya, E. V.; Farat, O. K.; Varenichenko, S. A.; Mazepa, A. V.; Markov, V. I. Functionalization of Tetra- and Octahydroacridine Derivatives through Michael Addition. *Tetrahedron Lett.* **2016**, *57*, 3485–3487. (l) Meazza, M.; Tur, F.; Hammer, N.; Jørgensen, K. A. Synergistic Diastereo- and Enantioselective Functionalization of Unactivated Alkyl Quinolines with α,β -Unsaturated Aldehydes. *Angew. Chem. Int. Ed.* **2017**, *56*, 1634–1638. (m) Suzuki, H.; Igarashi, R.; Yamashita, Y.; Kobayashi, S. Catalytic Direct-type 1,4-Addition Reactions of Alkylazaarenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 4520–4524. (n) Rai, P.; Waiba, S.; Maji, K.; Sahoo, D.; Maji, B. Cooperative Lewis Acid Catalysis for the Enantioselective $\text{C}(\text{Sp}^3)\text{--H}$ Bond Functionalizations of 2-Alkyl Azaarenes. *Org. Lett.* **2021**, *23*, 8888–8893.

(6) For selected examples of pyridylic $\text{C}(\text{sp}^3)\text{--H}$ alkylation with unactivated alkenes under transition metal catalysis, see: (a) Guan, B.; Wang, B.; Nishiura, M.; Hou, Z. Yttrium-Catalyzed Addition of Benzylic C--H Bonds of Alkyl Pyridines to Olefins. *Angew. Chem. Int. Ed.* **2013**, *52*, 4418–4421. (b) Luo, Y.; Teng, H.; Nishiura, M.; Hou, Z. Asymmetric Yttrium-Catalyzed $\text{C}(\text{Sp}^3)\text{--H}$ Addition of 2-Methyl

Azaarenes to Cyclopropenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 9207–9210. (c) Sun, Q.; Xie, P.; Yuan, D.; Xia, Y.; Yao, Y. Regioselective Addition of C(sp³)–H Bonds of Alkyl Pyridines to Olefins Catalysed by Cationic Zirconium Complexes. *Chem. Commun.* **2017**, *53*, 7401–7404. (d) Sun, Q.; Chen, P.; Wang, Y.; Luo, Y.; Yuan, D.; Yao, Y. Addition of C–H Bonds of Pyridine Derivatives to Alkenes Catalyzed by Zirconium Complexes Bearing Amine-Bridged Bis(Phenolato) Ligands. *Inorg. Chem.* **2018**, *57*, 11788–11800. (e) Selikhov, A. N.; Boronin, E. N.; Cherkasov, A. V.; Fukin, G. K.; Shavyrin, A. S.; Trifonov, A. A. Tris(Benzhydryl) and Cationic Bis(Benzhydryl) Ln(III) Complexes: Exceptional Thermostability and Catalytic Activity in Olefin Hydroarylation and Hydrobenzylation with Substituted Pyridines. *Adv. Synth. Catal.* **2020**, *362*, 5432–5443. (f) Jing, C.; Mao, W.; Bower, J. F. Iridium-Catalyzed Enantioselective Alkene Hydroalkylation via a Heteroaryl-Directed Enolization–Decarboxylation Sequence. *J. Am. Chem. Soc.* **2023**, *145*, 23918–23924.

(7) For selected examples of pyridylic C(sp³)–H alkylation with unactivated alkenes under strong base-catalysis, see: (a) Zhai, D.; Zhang, X.; Liu, Y.; Zheng, L.; Guan, B. Potassium Amide-Catalyzed Benzylic C–H Bond Addition of Alkylpyridines to Styrenes. *Angew. Chem. Int. Ed.* **2018**, *57*, 1650–1653. (b) Luo, Y.-L.; Liu, Y.-F.; Guan, B.-T. Alkyl Lithium-Catalyzed Benzylic C–H Bond Addition of Alkyl Pyridines to α -Alkenes. *Org. Biomol. Chem.* **2020**, *18*, 6622–6626. (c) Zheng, X.; del Rosal, I.; Xu, X.; Yao, Y.; Maron, L.; Xu, X. Calcium-Mediated C(sp³)–H Activation and Alkylation of Alkylpyridines. *Inorg. Chem.* **2021**, *60*, 5114–5121. (d) Chen, S.; Yang, L.; Shang, Y.; Mao, J.; Walsh, P. J. Base-Promoted Tandem Synthesis of 2-Azaaryl Tetrahydroquinolines. *Org. Lett.* **2021**, *23*, 1594–1599. (e) Li, S.; Xu, X.; Sun, Q.; Xu, X. Organocalcium Hydride-Catalyzed Intramolecular C(sp³)–H Annulation of Functionalized 2,6-Lutidines. *J. Org. Chem.* **2023**, *88*, 1742–1748. (f) Anderson, D. E.; Truong, A. H. N.; Hevia, E. Dual Basicity and Nucleophilicity of Organosodium Reagents in Benzylic C–H Additions of Toluenes to Diarylethenes and Ketones. *Chem. – Eur. J.* **2024**, *30*, e202400492. (g) Zhu, Q.; Long, J.; Song, X.; Wang, K.; Zeng, J.; Fan, Y. KOTBu/DMF-Mediated Hydroalkylation of Alkenes via Benzylic C–H Bond Activation. *J. Org. Chem.* **2024**, *89*, 3726–3731.

(8) For selected examples of photo-induced radical hydroalkylation, see: (a) Yamashita, Y.; Ogasawara, Y.; Banik, T.; Kobayashi, S. Photoinduced Efficient Catalytic α -Alkylation Reactions of Active Methylene and Methine Compounds with Nonactivated Alkenes. *J. Am. Chem. Soc.* **2023**, *145*, 23160–23166. (b) Lei, G.; Xu, M.; Chang, R.; Funes-Ardoiz, I.; Ye, J. Hydroalkylation of Unactivated Olefins via Visible-Light-Driven Dual Hydrogen Atom Transfer Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 11251–11261. (c) Capacci, A. G.; Malinowski, J. T.; McAlpine, N. J.; Kuhne, J.; MacMillan, D. W. C. Direct, Enantioselective α -Alkylation of Aldehydes Using Simple Olefins. *Nat. Chem.* **2017**, *9*, 1073–1077. (d) Qiao, J.; Ci, R.; Gan, Q.; Huang, C.; Liu, Z.; Hu, H.; Ye, C.; Chen, B.; Tung, C.; Wu, L. Amine-Free, Directing-Group-Free and Redox-Neutral α -Alkylation of Saturated Cyclic Ketones. *Angew. Chem. Int. Ed.* **2023**, *62*, e202305679. (e) Hofer, J.; Pecho, F.; Bach, T. Photocatalytic Spirocyclization of 2-Alk- ω -Enyl-Substituted Cycloalkane-1,3-Diones. *Synlett* **2023**, *34*, 1063–1067. (f) Zhang, Y.; Mao, L.-L.; Hu, S.; Luan, Y.; Cong, H. Photo-Induced Anti-Markovnikov Hydroalkylation of Unactivated Alkenes Employing a Dual-Component Initiator. *Chin. Chem. Lett.* **2021**, *32*, 681–684. (g) Tsukamoto, D.; Shiraishi, Y.; Hirai, T. Highly Efficient Methyl Ketone Synthesis with Photoactivated Acetone and Olefins Assisted by Mg(II)-Exchanged Zeolite Y. *J. Org. Chem.* **2010**, *75*, 1450–1457. (h) Shiraishi, Y.; Tsukamoto, D.; Hirai, T. Highly Efficient Methyl Ketone Synthesis by Water-Assisted C–C Coupling between Olefins and Photoactivated Acetone. *Org. Lett.* **2008**, *10*, 3117–3120. (i) Chang, R.; Pang, Y.; Ye, J. Divergent Photosensitizer Controlled Reactions of 4-Hydroxycoumarins and Unactivated Olefins: Hydroarylation and

Subsequent [2+2] Cycloaddition. *Angew. Chem. Int. Ed.* **2023**, *62*, e202309897.

(9) For examples of photo-induced radical hydroalkylation of more reactive styrene derivatives, see: (a) Baš, S.; Yamashita, Y.; Kobayashi, S. Development of Brønsted Base–Photocatalyst Hybrid Systems for Highly Efficient C–C Bond Formation Reactions of Malonates with Styrenes. *ACS Catal.* **2020**, *10*, 10546–10550. (b) Wang, P.; Bay, A. V.; Farnam, E. J.; Scheidt, K. A. Photocatalyzed Direct α -Alkylation of Esters Using Styrenes. *Adv. Synth. Catal.* **2023**, *365*, 2361–2366.

(10) For a review on photocatalytic generation of carbon-centered radicals from C(sp³)–H bonds, see: O'Brien, T. E.; Morris, A. O.; Villela, L. F.; Barriault, L. Synthetic Applications of Photochemically Generated Radicals from Protic C(sp³)–H Bonds. *ChemCatChem* **2023**, *15*, e202300989.

(11) Roberts, B. P. Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25–35.

(12) (a) Giese, B. Formation of CC Bonds by Addition of Free Radicals to Alkenes. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753–764. (b) Fischer, H.; Radom, L. Factors Controlling the Addition of Carbon-Centered Radicals to Alkenes—An Experimental and Theoretical Perspective. *Angew. Chem. Int. Ed.* **2001**, *40*, 1340–1371. (c) Parsae, F.; Senarathna, M. C.; Kannangara, P. B.; Alexander, S. N.; Arche, P. D. E.; Welin, E. R. Radical Philicity and Its Role in Selective Organic Transformations. *Nat. Rev. Chem.* **2021**, *5*, 486–499.

(13) Renaud, P.; Gerster, M. Use of Lewis Acids in Free Radical Reactions. *Angew. Chem. Int. Ed.* **1998**, *37*, 2562–2579.

(14) (a) Huang, X.; Meggers, E. Asymmetric Photocatalysis with Bis-Cyclometalated Rhodium Complexes. *Acc. Chem. Res.* **2019**, *52*, 833–847. (b) Yoon, T. P. Photochemical Stereocontrol Using Tandem Photoredox–Chiral Lewis Acid Catalysis. *Acc. Chem. Res.* **2016**, *49*, 2307–2315.

(15) For related studies, see: (a) Guo, R.; Adak, S.; Bellotti, P.; Gao, X.; Smith, W. W.; Le, S. N.; Ma, J.; Houk, K. N.; Glorius, F.; Chen, S.; Brown, M. K. Photochemical Dearomative Cycloadditions of Quinolines and Alkenes: Scope and Mechanism Studies. *J. Am. Chem. Soc.* **2022**, *144*, 17680–17691. (b) Treacy, S. M.; Vaz, D. R.; Noman, S.; Tard, C.; Rovis, T. Coupling of α -Bromoamides and Unactivated Alkenes to Form γ -Lactams through EDA and Photocatalysis. *Chem. Sci.* **2023**, *14*, 1569–1574.

(16) Onuska, N. P. R.; Schutzbach-Horton, M. E.; Rosario Collazo, J. L.; Nicewicz, David. A. Anti-Markovnikov Hydroazidation of Activated Olefins via Organic Photoredox Catalysis. *Synlett* **2019**, *31*, 55–59.

(17) Teders, M.; Henkel, C.; Anhäuser, L.; Strieth-Kalthoff, F.; Gómez-Suárez, A.; Kleinmans, R.; Kahnt, A.; Rentmeister, A.; Guldi, D.; Glorius, F. The Energy-Transfer-Enabled Biocompatible Disulfide–Ene Reaction. *Nat. Chem.* **2018**, *10*, 981–988.

(18) Romero, N. A.; Nicewicz, D. A. Mechanistic Insight into the Photoredox Catalysis of Anti-Markovnikov Alkene Hydrofunctionalization Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 17024–17035.

(19) For simplicity of the Lewis acid/substrate coordination mode, we opted for 2-pyridylacetate **1k** that would form a Lewis pair through rigid two-point binding with a Lewis acid.

(20) Related polarity-mismatched HAT at pyridylic C(sp³)–H bonds by electrophilic radicals, see: (a) Cooper, J. C.; Luo, C.; Kameyama, R.; Van Humbeck, J. F. Combined Iron/Hydroxytriazole Dual Catalytic System for Site Selective Oxidation Adjacent to Azaheterocycles. *J. Am. Chem. Soc.* **2018**, *140*, 1243–1246. (b) Bentley, K. W.; Dummit, K. A.; Van Humbeck, J. F. A Highly Site-Selective Radical Sp³ C–H Amination of Azaheterocycles. *Chem. Sci.* **2018**, *9*, 6440–6445.



pyridylic C(sp³)-H alkylation

▪ 23 examples ▪ broad FG tolerance