Photoreactions Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 7873–7879
International Edition: doi.org/10.1002/anie.202016156
German Edition: doi.org/10.1002/ange.202016156

Visible-Light-Induced 1,3-Aminopyridylation of [1.1.1]Propellane with *N*-Aminopyridinium Salts

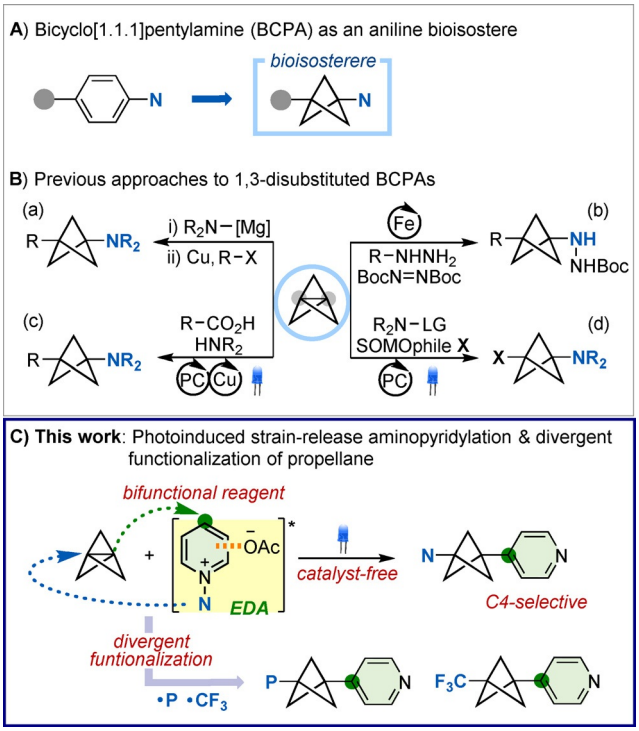
*Sanghoon Shin, Seojin Lee, Wonjun Choi, Namhoon Kim, and Sungwoo Hong**

Dedicated to Professor Phil Ho Lee on the occasion of his 60th birthday

Abstract: *Through the formation of an electron donor–acceptor (EDA) complex, strain-release aminopyridylation of [1.1.1]propellane with N-aminopyridinium salts as bifunctional reagents enabled the direct installation of amino and pyridyl groups onto bicyclo[1.1.1]pentane (BCP) frameworks in the absence of an external photocatalyst. The robustness of this method to synthesize 1,3-aminopyridylated BCPs under mild and metal-free conditions is highlighted by the late-stage modification of structurally complex biorelevant molecules. Moreover, the strategy was extended to P-centered and CF_3 radicals for the unprecedented incorporation of such functional groups with pyridine across the BCP core in a three-component coupling. This practical method lays the foundation for the straightforward construction of new valuable C4-pyridine-functionalized BCP chemical entities, thus significantly expanding the range of accessibility of BCP-type bioisosteres for applications in drug discovery.*

Introduction

The strategic replacement of an aromatic ring with unconventional structural bioisosteres can provide unique opportunities in pharmaceutical chemistry to enhance the physicochemical properties of drug candidates while maintaining comparable levels of activity.[1] Recently, a strained bicyclo[1.1.1]pentane (BCP) scaffold has received increased attention in medicinal chemistry as a nonclassical bioisostere of arenes and internal alkynes due to its unique structural and conformational rigidity.[2] Importantly, the isosteric replacement strategy is of significant interest for circumventing deleterious metabolic processes of an aniline moiety.[3] Accordingly, bicyclo[1.1.1]pentylamine (BCPA) has been extensively targeted as a prominent aniline bioisostere by creating unexplored druglike chemical space with varying levels of synthetic utility (Scheme 1 A).[4] From a synthetic point of view, propellane can be efficiently aminated by ring-opening functionalization at the BCP bridgehead positions, where the internal central C–C bond of [1.1.1]propellane[5] can be readily cleaved under an anionic strain-release approach[6] and, more recently, a radical pathway affording the requisite substituted BCPA compounds (Scheme 1 B).[7] Baran et al. disclosed the strain-release amination of propellane by employing deprotonated dialkyl amines to access monosubstituted BCPAs.[6a,b] The Gleason group has extended this approach to the synthesis of 1,3-disubstituted BCPAs by trapping alkyl electrophiles with in situ generated metalated intermediates (a).[6c] Despite the advances, this protocol is limited to benzylic amines as the source of N-nucleophiles because BCP-Grignard reagents have to be accumulated before trapping with electrophiles. Uchiyama and co-workers achieved iron-catalyzed radical carboamination of propellane using azodicarboxylate as a radical acceptor to access 1,3-disubstituted BCP-hydrazines (b).[7a] Recently, the MacMillan group reported the elegant three-component radical coupling of propellane, where BCP radical intermediates were intercepted by amine nucleophiles under dual photoredox/copper



Scheme 1. A) Bioisosteric replacement of aniline. B) Strategies for the formation of 1,3-disubstituted BCPAs. C) Design plan: A single-step approach to 1,3-aminopyridylated BCPs using *N*-aminopyridinium salts as bifunctional reagents and divergent functionalization.

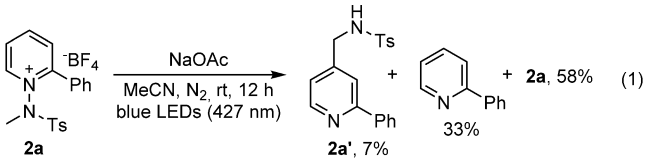
[*] S. Shin, S. Lee, W. Choi, Dr. N. Kim, Prof. Dr. S. Hong
Department of Chemistry
Korea Advanced Institute of Science and Technology (KAIST)
Daejeon 34141 (Republic of Korea)
and
Center for Catalytic Hydrocarbon Functionalizations
Institute for Basic Science (IBS)
Daejeon 34141 (Republic of Korea)
E-mail: hongorg@kaist.ac.kr
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.202016156.

catalysis (c).[7b] In addition, the photocatalytic strategy used for N-centered radical addition to propellane was first demonstrated by the Leonori group, in which a range of external SOMOphiles, such as halide, sulfur, and selenium, could be efficiently installed on the BCPA building blocks (d).[7c]

Considering the utility of BCPA and pyridyl groups in the pharmaceutical industry,[3,4,8] the development of a method for the efficient synthesis of 1,3-aminopyridyl-functionalized BCP scaffolds is highly demanded for the rapid construction of complex and druglike BCP targets. In general, the preparation of heteroaryl-functionalized BCPAs requires further elaboration of BCPA-halide intermediates with prefuntionalized heteroarenes,[9] thus limiting their wide application to lead optimization in medicinal chemistry. In this context, the goal of this work is to develop a new strategy to efficiently access 1,3-aminopyridylated BCP scaffolds from the direct transformation of propellane in a controllable and selective manner. In previous work, our laboratory has demonstrated that *N*-aminopyridinium salts can be efficiently leveraged as bifunctional reagents[10] in a visible-light-enabled platform for the difunctionalization of alkenes to directly access amine- and pyridine-containing molecules.[11] In view of our previous experience on the use of pyridinium salts and the susceptibility of propellane to radical opening, we were intrigued by the possibility of embracing the intrinsic reactivity of the strained C–C bond in propellane by using *N*-aminopyridinium salts in strain-release settings (Scheme 1C). We speculated that the reaction could proceed through the generation of an amidyl radical[12,13] and subsequent BCP radical trapping of a pyridyl ring at the C4 position[14,15] to yield complex 1,3-aminopyridylated BCP products through a radical-chain propagation pathway. Recently, strategies exploiting electron donor–acceptor (EDA) complexes have been widely explored to drive a new pattern of visible-light-induced transformations without requiring an external photocatalyst.[16] We reasoned that the photochemically formed amidyl radical by the single-electron transfer (SET) process of the EDA complex[17] could readily engage in the cross-coupling process with propellane. We speculated that the resulting BCP radical would trap a pyridine group over another propellane if the cross-coupling process between BCP radical and *N*-aminopyridinium salt could be fast. Here, we report a strategy for the visible-light-driven 1,3-aminopyridylation of propellane employing various *N*-aminopyridinium salts as bifunctional reagents under photocatalyst-free conditions, which allows the direct introduction of amide and pyridyl functionality across the BCP core. Furthermore, this strategy could be extended to a divergent functionalization with P-centered and CF_3 radicals through three-component cascade reactions, thereby enabling the diversification of synthetically valuable 1,3-disubstituted BCP-building blocks.

Results and Discussion

Before starting the optimization of the postulated strategy, we decided to evaluate the behavior of *N*-aminopyridinium salt **2a** on an EDA complex for the one-step, modular construction of 1,3-aminopyridylated BCP products. Under these settings, our initial studies surveyed various anions to determine the abilities to promote photolysis of pyridinium salts (for the screens of various wavelengths, the Supporting Information for details). Upon addition of sodium acetate to pyridinium salt **2a** in acetonitrile, a photolytic pyridine product was observed, indicating that the photoinduced SET took place between **2a** and acetate anions to trigger the amidyl radical. We observed that **2a** could be photoreduced by the addition of acetate anions under visible light irradiation (427 nm), leading to the generation of 2-phenylpyridine and **2a′**. The formation of **2a′** indicated that the amidyl radical was readily generated by photolysis and underwent the 1,2-hydrogen atom transfer (HAT) process[18] that was intercepted by the pyridinium segment [Eq. (1)]. The addition of more soluble additives such as tetrabutylammonium bromide (TBAB) and tetrabutylammonium acetate (TBAOAc) exhibited a dramatic enhancement in the absorption (Figure 1) and led to substantial decomposition of **2a** (see Scheme 5e). Considering the radical chain propagation pathway, less soluble inorganic base (NaOAc) in acetonitrile solution is most suitable for the proposed EDA-complex-driven transformation with only minimal sacrifice of starting substrate **2a**.



(1)

Based on the observation of our initial studies, the reaction was next optimized by monitoring the reactivity of propellane **1** and *N*-aminopyridinium salt **2a** under light irradiation at room temperature, as shown in Table 1. After screening the parameters, the desired product **3a** was successfully produced in an acetonitrile solvent system with sodium acetate as a base under blue LED irradiation in the absence of an external photocatalyst, thus indicating that the overall proposed process was effectively operating (entry 1). Other electron donors, such as bromide, show diminished

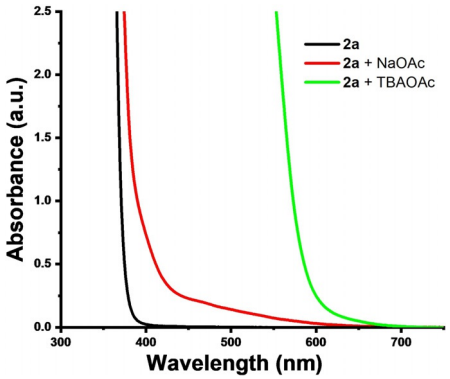
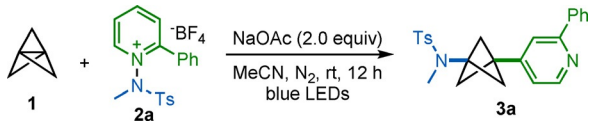


Figure 1. Absorption spectra of **2a** and mixtures of **2a** and additives.

Table 1: Strain-release aminopyridylation of [1.1.1]propellane.[a]



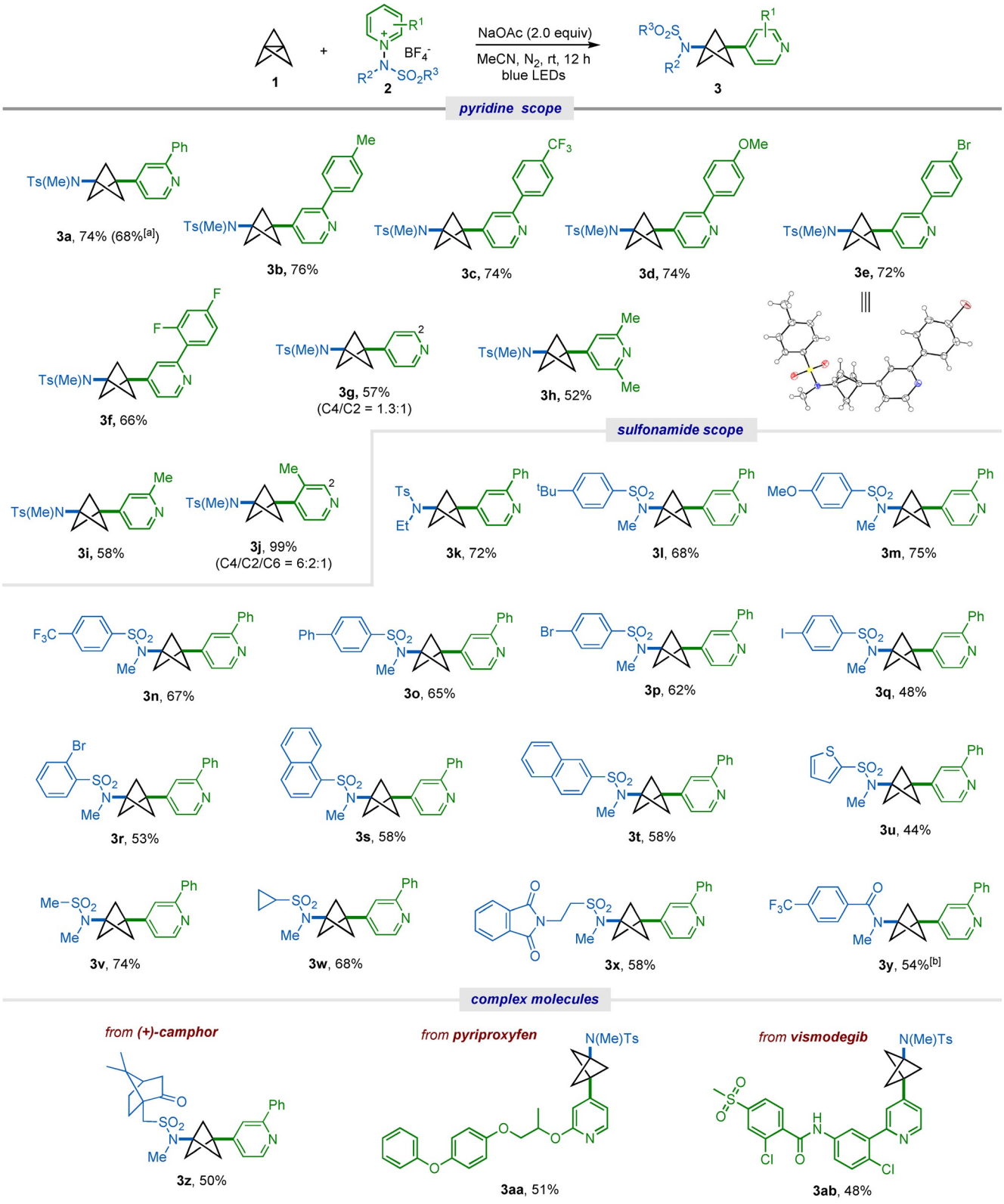
Entry	Change from standard conditions	Yield [%][b]
1	none	75 (74)[c]
2	TBAB instead of NaOAc	17
3	TBAOAc instead of NaOAc	29
4	without base	trace
5	MeCN instead of pentane stock	trace
6	benzene instead of pentane stock	70
7	467 nm instead of 427 nm	50
8	525 nm instead of 427 nm	13
9	dark	0
10	with TEMPO (2.0 equiv)	0

[a] Reactions were performed by using **1** (0.05 mmol in 0.4 M pentane solution), **2a** (2.0 equiv) and NaOAc (2.0 equiv) in MeCN (0.5 mL) under irradiation using blue LEDs (427 nm, 40 W) at room temperature for 12 h under N_2. [b] Yields were determined by ^{1}H NMR spectroscopy. [c] Yield of the isolated product. TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

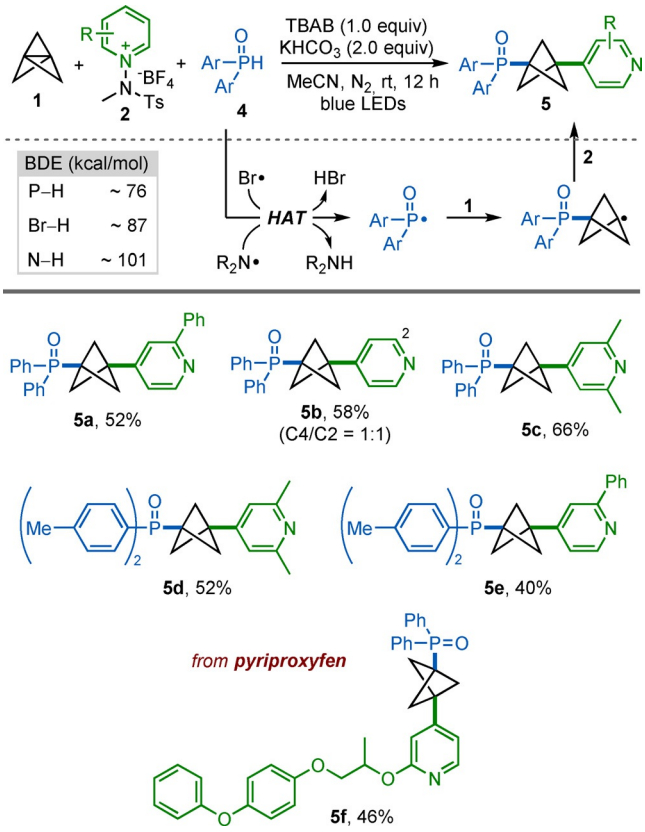
yield (entry 2), probably because of the side reaction between a bromo radical and **1**. Among the solvents screened, acetonitrile and pentane cosolvent systems were optimal (entries 5 and 6). We next investigated the influence of the light source, and blue LEDs (427 nm, 40 W) gave the highest yield. The longer wavelength under green LED irradiation also resulted in product **3a**, albeit in diminished yield (entries 7 and 8). As expected, control experiments confirmed that visible light is critical for this transformation (entry 9). The reaction was completely terminated using the radical scavenger TEMPO, supporting the radical-mediated mechanism (entry 10).

With the optimized reaction conditions for strain-release aminopyridylation, we set out to investigate the generality of this protocol, as summarized in Scheme 2. First, a series of pyridinium substrates with various substituents (methyl, trifluoromethyl, methoxy, bromo, and fluoro group) on the phenyl rings reacted well to furnish the 1,3-aminopyridylated BCP products with excellent C4-selectivity (**3b**–**3f**).[13,14] Importantly, the bromide group was tolerable under the standard reaction conditions to provide product **3e**,[19] thus providing an opportunity for further functionalization. Further exploration demonstrated that pyridine-, picoline-, and lutidine-substituted BCPAs (**3g**–**3j**) were readily produced with similar reactivity under the reaction conditions. In general, C2-substituted *N*-aminopyridinium salts give C4 products exclusively whereas substrates bearing no C2 substituent provide a modest preference (**3g** and **3j**). We next investigated the utility of our method by exploring other heteroarenes such as quinolinium salts. Unfortunately, only trace amounts of desired products (< 5 %) were observed. Considering the importance of sulfonamide in medicinal chemistry and materials science, we next assessed the applicability of this method with respect to the *N*-sulfonamide unit, and we found that a broad range of sulfonamide groups could be incorporated into the propellane substrate to afford valuable BCP building blocks. Specifically, substrates bearing both electron-rich and electron-deficient substituents in the aryl group were suitable to yield the desired products (**3l**–**3o**). Halogen-substituted substrates were tolerated in reaction conditions, thus enabling further synthetic functionalization at various positions (**3p**–**3r**). The applicability of the current protocol to other arenes, such as naphthyl and thiophenyl scaffolds, was also examined, and the desired products were produced in a similar fashion (**3s**–**3u**). Notably, this method could be expanded to substrates containing alkylsulfonyl amides, such as methyl, cyclopropyl, and phthalimide groups, to generate synthetically valuable BCPA building blocks (**3v**–**3x**). Given the importance of the carboxamide group for diverse structures of BCPA moieties, the suitability of this transformation was subsequently investigated to further expand scope generality. We were pleased to find that the carboxamide group was well tolerated under our standard reaction conditions, affording corresponding product **3y**. The applicability of the current method is further highlighted by late-stage modifications of pharmaceutically relevant molecules. Pleasingly, structurally complex substrates camphor (**3z**) and pyridine-based drugs, such as pyriproxyfen (**3aa**) and vismodegib (**3ab**), were rapidly modified with propellane to deliver new drug derivatives with excellent regioselectivity, demonstrating broad functional group tolerance.

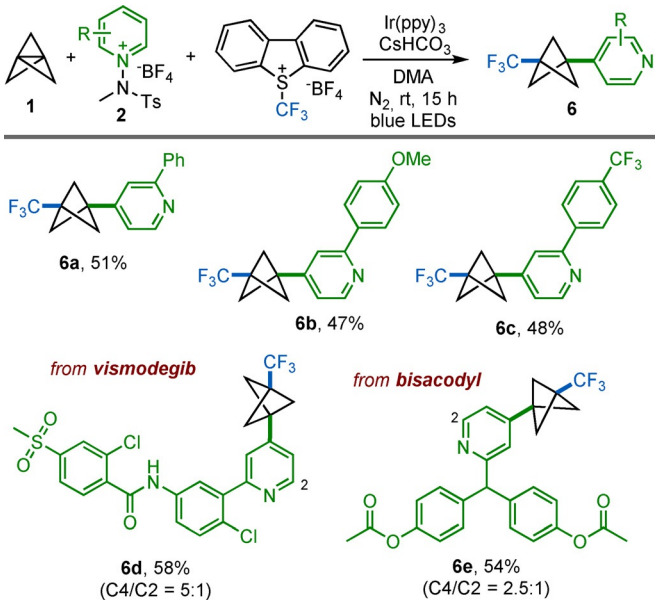
During these investigations, we discovered that an amidyl radical could rapidly engage in intermolecular HAT to form a phosphinoyl radical when diphenylphosphine oxide was added.[20] Therefore, we speculated that the generated phosphinoyl radical could provide a unique opportunity to develop the divergent three-component assembly of 1,3-phosphinoyl and pyridyl-functionalized BCPs, where the extruded amidyl radical serves as an efficient HAT reagent.[13] To corroborate this scenario, we investigated the catalyst-free three-component reaction of propellane by employing pyridinium salt **2** and diphenylphosphine oxide **4** under blue LED irradiation at room temperature, as illustrated in Scheme 3. To our delight, this approach can be successfully applied to cascade phosphinoylation/pyridylation under the slightly modified conditions where TBAB was added as an electron donor to induce the formation of the pyridinium salt–bromide EDA complex. Among the bases screened, $KHCO_3$ was more effective than NaOAc in this reaction (see the Supporting Information for details). Having the optimized reaction condition in hand, we next examined the scope of pyridine derivatives and phosphine oxides to extend the generality of the current three-component phosphorylative pyridylation protocol. A range of *N*-aminopyridinium salts were employed in this transformation and successfully converted to the desired products (**5a**–**5c**). In addition, reactions of tolyl-substituted phosphine oxides smoothly afforded the desired product **5d** and **5e**. Moreover, we observed that pyridine-based drug pyriproxyfen could be successfully employed for the late-stage functionalization with this protocol (**5f**). Notably, phosphinoyl radicals preferentially react with [1.1.1]propellane to install pyridyl and phosphorus groups, and only trace amounts of 1,3-aminopyridylated BCPs were observed under the reaction conditions.



Scheme 2. Substrate scope of strain-release aminopyridylation. Reactions were performed by using **1** (0.1 mmol in 0.4 M pentane solution), **2** (2.0 equiv) and NaOAc (2.0 equiv) in MeCN (1.0 mL) under irradiation using blue LEDs (427 nm, 40 W) at room temperature for 12 h under N_2. Yields are for the isolated product. [a] The reaction was carried out on a 1.0 mmol scale. [b] DMSO was used instead of MeCN; $NaHCO_3$ was used instead of NaOAc.



Scheme 3. Substrate scope of cascade phosphinoylation/pyridylation. Reactions were performed by using **1** (2.0 equiv in 0.4 M pentane solution), **2** (0.1 mmol), **4** (2.0 equiv), TBAB (1.0 equiv) and $KHCO_3$ (2.0 equiv) in MeCN (1.0 mL) under irradiation using blue LEDs (440 nm, 40 W) at room temperature for 12 h under N_2.



Scheme 4. Substrate scope of cascade trifluoromethyl pyridylation. Reactions were performed by using **1** (3.0 equiv in 0.4 M pentane solution), **2** (0.1 mmol), Umemoto reagent (3.0 equiv), $Ir(ppy)_3$ (2.5 mol%) and $CsHCO_3$ (2.0 equiv) in DMA (1.0 mL) under irradiation using blue LEDs (440 nm, 10 W) at room temperature for 15 h under N_2. Yields are for the isolated product.

To further highlight the broad applicability of the present approach, we next explored the compatibility of the method to the trifluoromethylative pyridylation of propellane, as illustrated in Scheme 4. To our delight, the desired trifluoromethylation product **6a** was generated in 43% yield under the slightly altered reaction conditions (see the Supporting Information for details). After evaluating different reaction conditions, the improved result (51%) was obtained when $Ir(ppy)_3$ was added as an external photocatalyst. With the optimal conditions in hand, we next investigate the substrate scope with respect to pyridinium salts to demonstrate the utility of the current method. Specifically, trifluoromethyl pyridylation was successful with several *N*-aminopyridinium salts bearing substituents such as methoxy and trifluoromethyl groups on the aryl ring (**6a**–**6c**). Noteworthily, pyridine-containing drugs, including vismodegib and bisacodyl, underwent the reaction successfully to afford the corresponding products **6d** and **6e**. These results support the potential wide applicability of the divergent method in the construction of synthetically valuable 1,3-functionalized BCP building blocks.

To investigate the reaction pathway, several control experiments were next carried out, as shown in Scheme 5. First, we observed that the reaction took place selectively at pyridinium salt **2a** to afford BCPA **3a** (Scheme 5a) when both pyridinium salt **2a** and 2-methylpyridine were used as substrates. Next, we observed that four cross-coupled products were produced when two different pyridinium salts **2s** and **2h** were employed as substrates, implying that the reaction pathways proceed in the proposed stepwise process (Scheme 5b). To better understand whether the radical chain process is involved, light/dark experiments were carried out. While a fully dark reaction could not generate the desired product **3a**, product formation occurred by chain propagation under dark conditions after visible-light-induced initiation for 1 h (Scheme 5c). In addition, we observed that the radical reaction occurred in the dark period (Scheme 5d).[21] Next, we evaluated the photolysis of pyridinium salt **2a**, which could be reduced by several electron donor anions under blue LED irradiation to yield a substantial amount of 2-phenylpyridine (Scheme 5e).

Considering the above observations, the plausible mechanism of the current method is shown in Figure 2. Initially, a small quantity of photoexcited EDA complex **I** upon

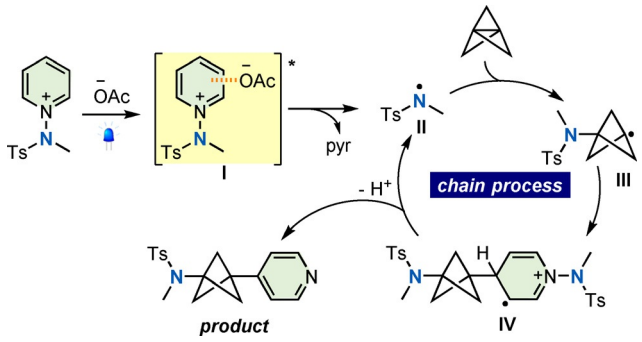
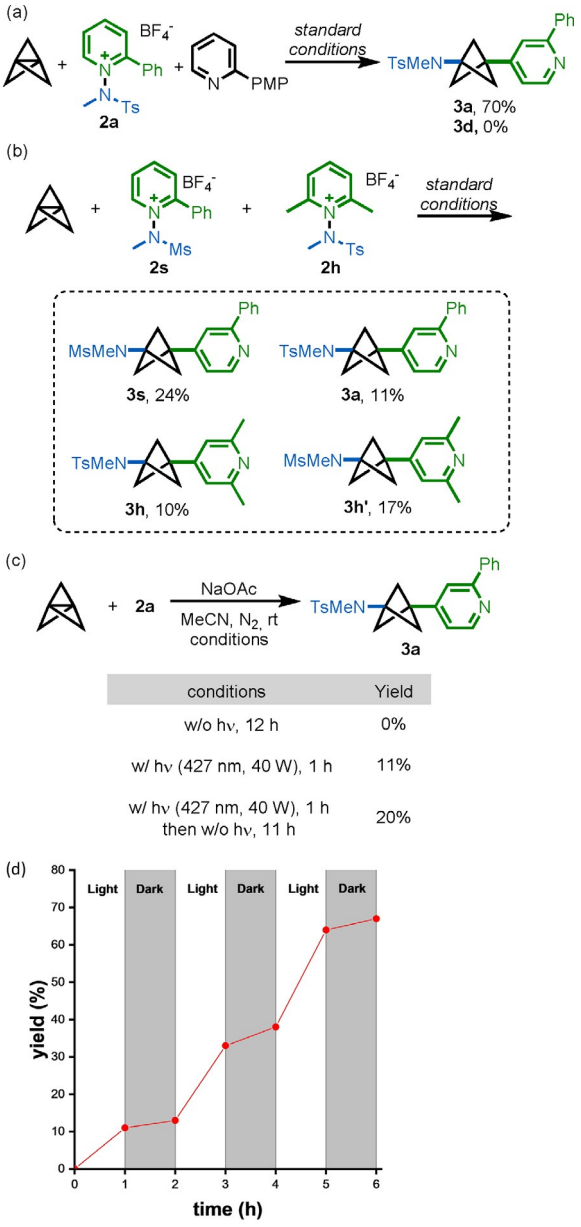
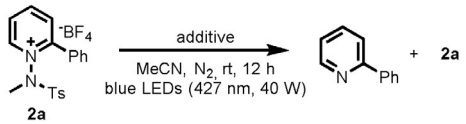


Figure 2. Proposed reaction mechanism.



conditions	Yield
w/o hν, 12 h	0%
w/ hν (427 nm, 40 W), 1 h	11%
w/ hν (427 nm, 40 W), 1 h then w/o hν, 11 h	20%

(e) Photolysis of pyridinium salt[a]



additive (1.0 equiv)	pyridine (%)[b]	2a (%)[b]
none	n.d.	>99
TBAB	50	34
TBAOAc	73	n.d.
NaOAc	33	58

Scheme 5. Control experiments. [a] Reactions were performed by using **2a** (0.05 mmol) and NaOAc (1.0 equiv) in MeCN (0.5 mL) under irradiation with the light source at room temperature for 12 h under N_2. [b] Yields were determined by ^{1}H NMR spectroscopy.

irradiation with blue LEDs undergoes a SET event to yield electrophilic amidyl radical **II**. Subsequently, the resulting amidyl radical adds to the propellane, which cleaves the central σ-bond and provides BCP-radical intermediate **III**. Afterward, the BCP radical **III** is poised for addition to the C4 position of another *N*-aminopyridinium salt. Next, the resulting cationic radical species **IV** undergoes deprotonation followed by cleavage of the N–N bond to afford the final product and amidyl radical **II**. The generated amidyl radical initiates a radical chain process. The measured quantum yield ($\Phi = 2.7$) using **2d** (see the Supporting Information for details), along with a light–dark cycle experiment, supports the radical chain propagation mechanism (see the Supporting Information for details).

Conclusion

In summary, the visible-light-induced strain-release aminopyridylation of propellanes has been developed by employing *N*-aminopyridinium salts as bifunctional reagents under mild reaction conditions. This strategy involves the photoactive formation of EDA complexes between *N*-aminopyridinium salts and acetate anions, enabling the direct incorporation of amino and pyridyl groups onto BCP frameworks without requiring an external photocatalyst. The present procedure exhibits a fairly broad substrate scope and offers a convenient and powerful synthetic tool for accessing 1,3-aminopyridylated BCPs while controlling the C4-selectivity of radical addition to the pyridine ring. Furthermore, this strategy can be extended to P and CF_3 radicals, offering the option of divergence through the three-component assembly of synthetically valuable BCP chemical entities. Overall, this versatile method significantly expands the scope of BCP-type bioisosteres and is expected to stimulate further research endeavors for applications in medicinal chemistry.

Acknowledgements

This research was supported financially by the Institute for Basic Science (IBS-R010-A2). We thank Dr. Dongwook Kim (IBS) for XRD analysis.

Conflict of interest

The authors declare no conflict of interest.

Keywords: bicyclo[1.1.1]pentane · bifunctional reagents · photolysis · pyridinium salts · strained molecules

[1] a) E. M. Carreira, T. C. Fessard, *Chem. Rev.* **2014**, *114*, 8257; b) Y. P. Auberson, C. Brocklehurst, M. Furegati, T. C. Fessard, G. Koch, A. Decker, L. L. Vecchia, E. Briard, *ChemMedChem* **2017**, *12*, 590.

[2] a) G. M. Locke, S. S. R. Bernhard, M. O. Senge, *Chem. Eur. J.* **2019**, *25*, 4590; b) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839; c) N. D. Measom, K. D. Down, D. J. Hirst, C. Jamieson, E. S. Manas, V. K. Patel, D. O. Somers, *ACS Med. Chem. Lett.* **2017**, *8*, 43.

[3] a) J. S. Walsh, G. T. Miwa, *Annu. Rev. Pharmacol. Toxicol.* **2011**, *51*, 145; b) A. S. Kalgutkar, *Curr. Med. Chem.* **2014**, *22*, 438.
[4] T. M. Sodano, L. A. Combee, C. R. J. Stephenson, *ACS Med. Chem. Lett.* **2020**, *11*, 1785.
[5] a) A. J. Sterling, A. B. Dürr, R. C. Smith, E. A. Anderson, F. Duarte, *Chem. Sci.* **2020**, *11*, 4895; b) J. A. Milligan, P. Wipf, *Nat. Chem.* **2016**, *8*, 296; c) K. B. Wiberg, S. T. Waddell, *J. Am. Chem. Soc.* **1990**, *112*, 2194; d) K. B. Wiberg, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312; *Angew. Chem.* **1986**, *98*, 312.
[6] a) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241; b) J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C. M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 3209; c) J. M. E. Hughes, D. A. Scarlata, A. C.-Y. Chen, J. D. Burch, J. L. Gleason, *Org. Lett.* **2019**, *21*, 6800.
[7] a) J. Kanazawa, K. Maeta, M. Uchiyama, *J. Am. Chem. Soc.* **2017**, *139*, 17791; b) X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. C. MacMillan, *Nature* **2020**, *580*, 220; c) J. H. Kim, A. Ruffoni, Y. S. S. Al-Faiyz, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2020**, *59*, 8225; *Angew. Chem.* **2020**, *132*, 8302; d) H. Zhang, M. Wang, X. Wu, C. Zhu, *Chin. J. Org. Chem.* **2020**, *40*, 3431; e) Z. Wu, Y. Xu, J. Liu, X. Wu, C. Zhu, *Sci. China Chem.* **2020**, *63*, 1025; for related a review, see: f) M. M. D. Pramanik, H. Quian, W.-J. Xiao, J.-R. Chen, *Org. Chem. Front.* **2020**, *7*, 2531.
[8] a) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845; b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.
[9] a) J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte, E. A. Anderson, *ACS Catal.* **2019**, *9*, 9568; b) K. Schwärzer, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 20235; *Angew. Chem.* **2020**, *132*, 20412.
[10] For selected examples, see: a) T. M. Monos, R. C. McAtee, C. R. J. Stephenson, *Science* **2018**, *361*, 1369; b) Y. Zhang, H. Liu, L. Tang, H. J. Tang, L. Wang, C. Zhu, C. Feng, *J. Am. Chem. Soc.* **2018**, *140*, 10695; c) H.-M. Huang, M. Koy, E. Serrano, P. M. Pflüger, J. L. Schwarz, F. Glorius, *Nat. Catal.* **2020**, *3*, 393; d) T. Patra, P. Bellotti, F. Glorius, *Angew. Chem. Int. Ed.* **2020**, *59*, 3172; *Angew. Chem.* **2020**, *132*, 3198.
[11] a) Y. Moon, B. Park, I. Kim, G. Kang, S. Shin, D. Kang, M.-H. Baik, S. Hong, *Nat. Commun.* **2019**, *10*, 4117; b) G. R. Mathi, Y. Jeong, Y. Moon, S. Hong, *Angew. Chem. Int. Ed.* **2020**, *59*, 2049; *Angew. Chem.* **2020**, *132*, 2065; c) H. Im, W. Choi, S. Hong, *Angew. Chem. Int. Ed.* **2020**, *59*, 17511; *Angew. Chem.* **2020**, *132*, 17664; d) Y. Kim, K. Lee, G. R. Mathi, I. Kim, S. Hong, *Green Chem.* **2019**, *21*, 2082.
[12] For selected reviews of the generation of an amidyl radical, see: a) T. Xiong, Q. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 3069; b) L. Q. Nguyen, R. R. Knowles, *ACS Catal.* **2016**, *6*, 2894; c) E. C. Gentry, R. R. Knowles, *Acc. Chem. Res.* **2016**, *49*, 1546; d) X.-T. Yu, Q.-Q. Zhao, J. Chen, W.-J. Xiao, J.-R. Chen, *Acc. Chem. Res.* **2020**, *53*, 1066; e) J. Davies, S. P. Morcillo, J. J. Douglas, D. Leonori, *Chem. Eur. J.* **2018**, *24*, 12154; f) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Soc. Rev.* **2016**, *45*, 2044.
[13] S. Jung, H. Lee, Y. Moon, H.-Y. Jung, S. Hong, *ACS Catal.* **2019**, *9*, 9891.
[14] For selected examples of C4-selective functionalization of pyridinium salts, see: a) K. Lee, S. Lee, N. Kim, S. Kim, S. Hong, *Angew. Chem. Int. Ed.* **2020**, *59*, 13379; *Angew. Chem.* **2020**, *132*, 13481; b) N. Kim, C. Lee, T. Kim, S. Hong, *Org. Lett.* **2019**, *21*, 9719.
[15] For selected examples of C2-selective alkylation of pyridine *N*-oxides and pyridinium salts, see: a) W. Jo, J. Kim, S. Choi, S. H. Cho, *Angew. Chem. Int. Ed.* **2016**, *55*, 9690; *Angew. Chem.* **2016**, *128*, 9842; b) C. Hwang, W. Jo, S. H. Cho, *Chem. Commun.* **2017**, *53*, 7573; c) W. Zhou, T. Miura, M. Murakami, *Angew. Chem. Int. Ed.* **2018**, *57*, 5139; *Angew. Chem.* **2018**, *130*, 5233; d) J.-h. Xu, W.-b. Wu, J. Wu, *Org. Lett.* **2019**, *21*, 5321; e) Y. Moon, W. Lee, S. Hong, *J. Am. Chem. Soc.* **2020**, *142*, 12420; f) J. Jeon, Y. He, S. Shin, S. Hong, *Angew. Chem. Int. Ed.* **2020**, *59*, 281; *Angew. Chem.* **2020**, *132*, 287.
[16] For selected reviews of EDA complexes, see: a) S. V. Rosokha, J. K. Kochi, *Acc. Chem. Res.* **2008**, *41*, 641; b) C. G. S. Lima, T. D. Lima, M. Duarte, I. D. Jurberg, M. W. Paixão, *ACS Catal.* **2016**, *6*, 1389; c) A. Postigo, *Eur. J. Org. Chem.* **2018**, 6391; d) G. E. M. Crisenza, D. Mazzarella, P. Melchiorre, *J. Am. Chem. Soc.* **2020**, *142*, 5461.
[17] For selected examples of the use of EDA complexes with pyridinium salts, see: a) V. Quint, F. Morlet-Savary, J.-F. Lohier, J. Lalevée, A.-C. Gaumont, S. Lakhdar, *J. Am. Chem. Soc.* **2016**, *138*, 7436; b) V. Quint, N. Chouchène, M. Askri, J. Lalevée, A.-C. Gaumont, S. Lakhdar, *Org. Chem. Front.* **2019**, *6*, 41; c) S. Jung, S. Shin, S. Park, S. Hong, *J. Am. Chem. Soc.* **2020**, *142*, 11370; d) I. Kim, S. Park, S. Hong, *Org. Lett.* **2020**, *22*, 8730.
[18] a) A. W. Rand, H. Yin, L. Xu, J. Giacoboni, R. Martin-Montero, C. Romano, J. Montgomery, R. Martin, *ACS Catal.* **2020**, *10*, 4671; b) L.-J. Zhong, H.-Y. Wang, X.-H. Ouyang, J.-H. Li, D.-L. An, *Chem. Commun.* **2020**, *56*, 8671; c) J. Zhang, D. Liu, S. Liu, Y. Ge, Y. Lan, Y. Chen, *iScience* **2020**, *23*, 100755.
[19] The C1–C3 bond length of **3e** was found to be 1.858 Å. For the correlation between the C1–C3 non-bonded distance and the field/inductive parameters for substituents, see Ref. [7c]. Deposition Number 2046034 (for **3e**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.
[20] a) I. Kim, G. Kang, K. Lee, B. Park, D. Kang, H. Jung, Y.-T. He, M.-H. Baik, S. Hong, *J. Am. Chem. Soc.* **2019**, *141*, 9239; b) K. Kim, H. Choi, D. Kang, S. Hong, *Org. Lett.* **2019**, *21*, 3417; c) I. Kim, M. Min, D. Kang, K. Kim, S. Hong, *Org. Lett.* **2017**, *19*, 1394.
[21] L. M. Kammer, A. Rahman, T. Opatz, *Molecules* **2018**, *23*, 764.

Manuscript received: December 4, 2020
Accepted manuscript online: January 6, 2021
Version of record online: March 1, 2021

