OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Visible Light-Promoted Aliphatic C−H Arylation Using Selectfluor as a Hydrogen Atom Transfer Reagent

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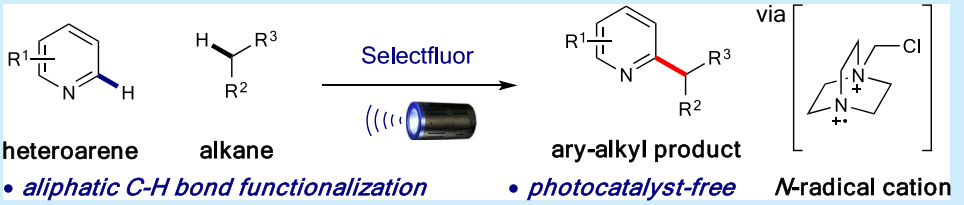
Supporting Information



ABSTRACT: A mild, practical method for direct arylation of unactivated C(sp^3)−H bonds with heteroarenes has been achieved via photochemistry. Selectfluor is used as a hydrogen atom transfer reagent under visible light irradiation. A diverse range of chemical feedstocks, such as alkanes, ketones, esters, and ethers, and complex molecules readily undergo intermolecular C(sp^3)−C(sp^2) bond formation. Moreover, a broad array of heteroarenes, including pharmaceutically useful scaffolds, can be alkylated effectively by the protocol presented here.

Aliphatic C−H bonds are the most abundant moiety but are among the least reactive in organic chemistry. The direct functionalization of sp^3 C−H bonds offers new strategies for constructing organic molecules rapidly.[1] Such reactions could convert bulk chemical feedstocks such as light alkanes to higher-value products and also could introduce more functionality into natural products or pharmaceuticals at late stages.[2] The last two decades witnessed impressive progress in the development of sp^3 C−H functionalization techniques, which could be categorized into three major types: hydrogen atom transfer (HAT), transition metal-catalyzed C−H activation, and carbene/nitrene insertion.[3] Distinct from the other two types, HAT possesses a radical mechanism. In this pathway, a hydrogen atom is abstracted from the C−H bond by a highly reactive radical species, such as a nitrogen, oxygen, sulfur, or chlorine radical.[4] The resulting alkyl radical could then be trapped to form a new C−C or C−X bond (e.g., X = F, N, or O). By accessing open-shell species, the unique HAT strategy enables organic transformations that cannot be accessed through polar pathways. The groups of Baran and Lectka reported the first examples of Selectfluor as a hydrogen atom transfer reagent.[5] Intensive mechanistic experiments suggested that the single-electron transfer (SET) event between the Cu catalyst and Selectfluor furnished an *N*-radical cation, which was responsible for the hydrogen atom transfer from the alkane substrates.[6]

In medicinal chemistry, the alkyl groups have magic effects on drug metabolism and pharmacokinetic profiles.[7] There is a growing demand for the direct introduction of alkyl groups to heteroarenes. The Minisci reaction, featuring a direct addition of the alkyl radical to heteroarenes, has attracted a great deal of attention within modern drug discovery.[8] Prefunctionalized reagents were typically employed as the alkyl radical precursors.[9−18] In a few cases, alkanes were coupled with heteroarenes directly via a dual C−H functionalization way, which represent a more ideal approach to molecule construction.[19] Herein, we describe a mild, practical method for the aliphatic C−H arylation using Selectfluor as a HAT reagent enabled by visible light.

We proposed a radical chain mechanism for aliphatic C−H arylation (Scheme 1). During the initial stage, Selectfluor **1** was activated by visible light irradiation to provide *N*-radical cation **2**. We anticipated that electrophilic *N*-radical cation **2** would abstract a hydrogen atom from alkane **3** to provide ammonium ion **4** and alkyl radical **5**. Once generated, nucleophilic alkyl radical **5** would be intercepted by protonated electron-deficient heteroarene **6** at a rate approaching that of diffusion, although in the presence of Selectfluor, to furnish aminyl radical cation **7**. Deprotonation of the acidic α-C−H bond of **7** would form α-amino radical **8**. The following single-electron transfer from intermediate **8** to Selectfluor would readily occur and, after rearomatization, furnish the desired alkyl−aryl coupling product **9** while regenerating *N*-radical cation **2**.

We began our investigation into this aliphatic C−H arylation by subjecting lepidine and cyclohexane to visible light irradiation (Kessil 40 W 427 nm light-emitting diode) with Selectfluor for 16 h (Table 1). To our delight, it afforded the desired aryl−alkyl product **11** in 14% yield (entry 1). Markedly, trifluoroacetic acid (TFA) offered an increase in

Received: May 8, 2019

DOI: 10.1021/acs.orglett.9b01635
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Scheme 1. Possible Mechanism for sp^3 C−H Arylation

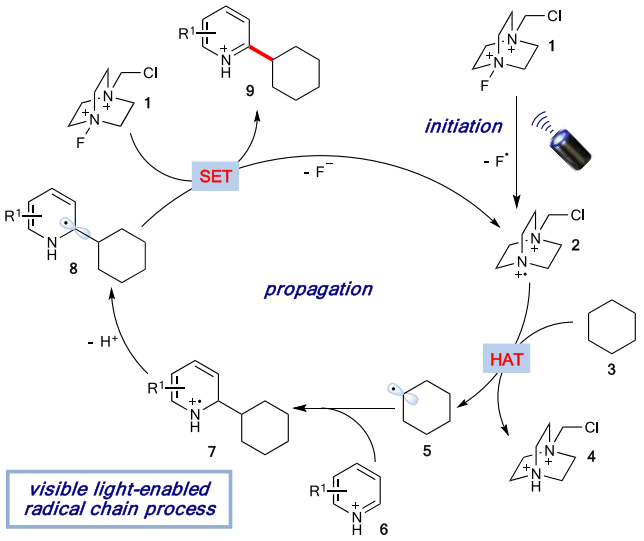
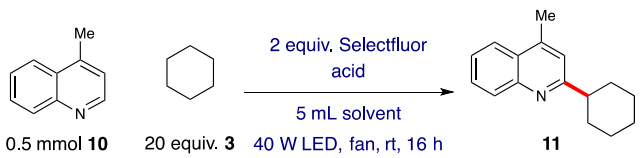


Table 1. Optimization of the sp^3 C−H Arylation[a]



0.5 mmol **10** 20 equiv. **3** 40 W LED, fan, rt, 16 h **11**

entry	solvent	acid	wavelength	yield (%)
1	acetone	none	427 nm	14
2	acetone	1 equiv of TFA	427 nm	33
3	acetone	1 equiv of HCl	427 nm	91
4	acetonitrile	2 equiv of TFA	427 nm	92
5	acetonitrile	2 equiv of HCl	427 nm	84
6	acetone	1 equiv of HCl	440 nm	70
7	acetone	1 equiv of HCl	456 nm	27
8	acetone	1 equiv of HCl	467 nm	39
9	acetone	1 equiv of HCl	dark	0
10	acetone	1 equiv of HCl	dark, 50 °C	0
11[b]	acetone	1 equiv of HCl	427 nm	78
12[c]	acetone	1 equiv of HCl	427 nm	90
13[d]	acetone	1 equiv of HCl	427 nm	0

[a]Yields determined by ^{1}H NMR using 1,3-benzodioxole as the internal standard. [b]One equivalent of Selectfluor used. [c]Reaction performed without N_2 purging. [d]One and one-half equivalents of TEMPO added.

yield (entry 2, 33%), which was consistent with most Minisci-type reactions by making the heteroarene substrates more electron-deficient. Changing the acid to concentrated hydrochloric acid (HCl) dramatically improved the yield to 91% (entry 3). An examination of common solvents showed that the reaction could also be carried out efficiently in acetonitrile with TFA as the superior acid additive (entries 4 and 5). Visible light with longer wavelengths could promote this C−H arylation, although in decreased yields (entries 6−8). Indeed, light plays a critical role in the reaction. There was no desired product in the absence of light, even upon heating to 50 °C (entries 9 and 10). When the equivalent of Selectfluor was reduced to **1**, the C−H arylation protocol still could provide a 78% yield of the alkyl−aryl product (entry 11), while an only minimal amount of fluorocyclohexane was detected by ^{19}F NMR. It is worth mentioning that a small amount of oxygen was well tolerated because the reaction could proceed robustly without nitrogen purging (entry 12). The addition of free radical scavengers could shut down the aliphatic C−H arylation completely, which indicated a radical mechanism (entry 13 and the Supporting Information).

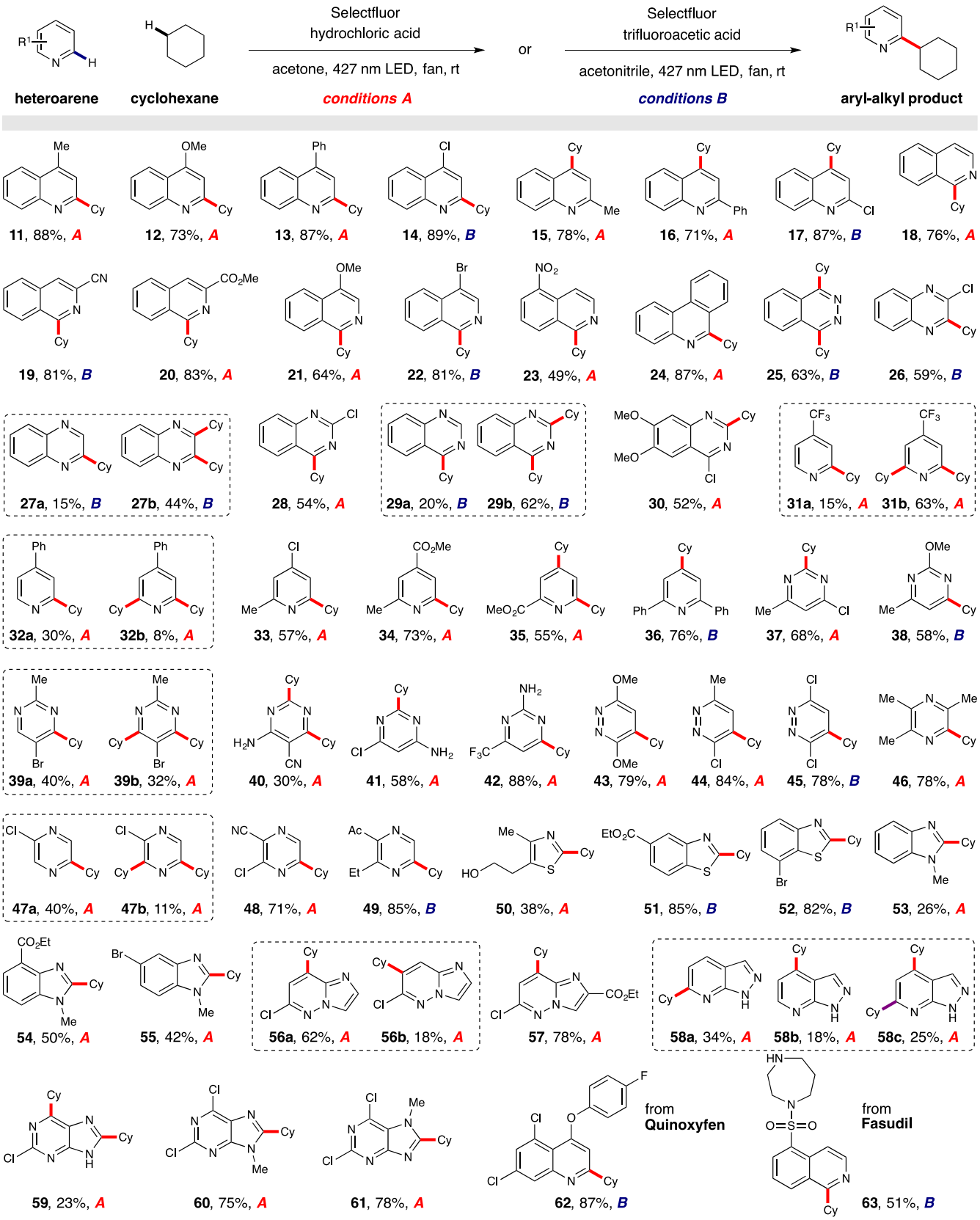
With the optimal conditions in hand, we began to evaluate the generality of this aliphatic C−H arylation transformation. As shown in Scheme 2, a diverse range of heteroarenes were alkylated with cyclohexane effectively under the identified conditions A (with HCl in acetone) and B (with TFA in acetonitrile). Quinolines with a variety of substituents (such as methyl, methoxy, phenyl, and chloro groups) were functionalized in good to excellent yields (**11**−**17**, 71−89% yields).

Isoquinolines were amenable to the protocol (**18**−**23**, 49−83% yields), as well as phenanthridines, phthalazines, quinoxalines, and quinazolines (**24**−**30**, 52−87% yields). Notably, pyridine derivatives could be alkylated in good yields (**31**−**36**, 38−78% yields). Substituted pyrimidines provided the alkylated products in useful yields, including those with free amine substituents (**37**−**42**, 30−88% yields). Pyridazines and pyrazines were competent substrates for the aliphatic C−H arylation protocol (**43**−**49**, 51−85% yields). It is important to note that a variety of five-membered heteroarenes performed well in this reaction. (Benzo)thiazoles reacted at the C2 position regioselectively (**50**−**52**, 38−85% yields) as well as benzoimidazoles (**53**−**55**, 26−50% yields). Imidazo[1,2-*b*]-pyridazines underwent aryl−alkyl coupling smoothly (**56** and **57**, 80% and 78% yields, respectively). 1*H*-Pyrazolo[3,4-*b*]pyridine was successfully used to deliver mono- and bis-alkylated products in 77% total yield (**58**). Moreover, the aliphatic C−H arylation could be applied to purine derivatives (**59**−**61**, 23−78% yields). Finally, it turned out that this photocatalyst-free protocol was compatible with the late stage functionalization of agrochemical and pharmaceutical agents (**62** and **63**, 87% and 51% yields, respectively).

Next, we explored the scope of the C−H arylation method with regard to the aliphatic C−H component (Scheme 3). Including but not limited to alkanes, a broad array of organic frameworks with sp^3 C−H bonds readily participated in the C−H arylation reaction. While simple cycloalkanes afforded a single arylation product for each case (**64**−**67**, 67−90% yields), substituted cycloalkanes might be arylated at different sites to afford regioisomers. More specifically, *trans*- and *cis*-1,4-dimethylcyclohexanes could react at either secondary or tertiary C−H bonds (**68** and **69**, 60% yield each). Not surprisingly, quaternary products **68b** and **69b** turned out to be the same compound because they had exactly the same alkyl radical intermediate. It is noted that norbornane reacted at the ethylene bridge only while the other strained C−H bonds were left untouched (**70**, 87% yield). Acyclic alkanes were likewise successful in the protocol with a greater-than-statistical preference for position C2 due to the bond strength and steric effect (**71** and **72**, 70% and 61% yields, respectively). Imparted by the electrophilic nature of *N*-radical cation **2**, ketones and esters were functionalized distal to the electron-withdrawing groups (**73**−**77**, 50−81% yields). Furthermore, various cyclic ethers were regioselectively arylated in good to high yields at the α-C−H position (**78**−**83**, 47−86% yields).[20] As an exception, the arylation of bridged ether 1,4-epoxycyclohexane occurred only on the ethylene bridge but the bridgehead strained α-C−H bonds were left out (**84**, 90% yield). Due to the electron-withdrawing effect, the α-oxy position of propyl acetate was no longer the dominant site for

DOI: 10.1021/acs.orglett.9b01635
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope of the Heteroarenes[a]

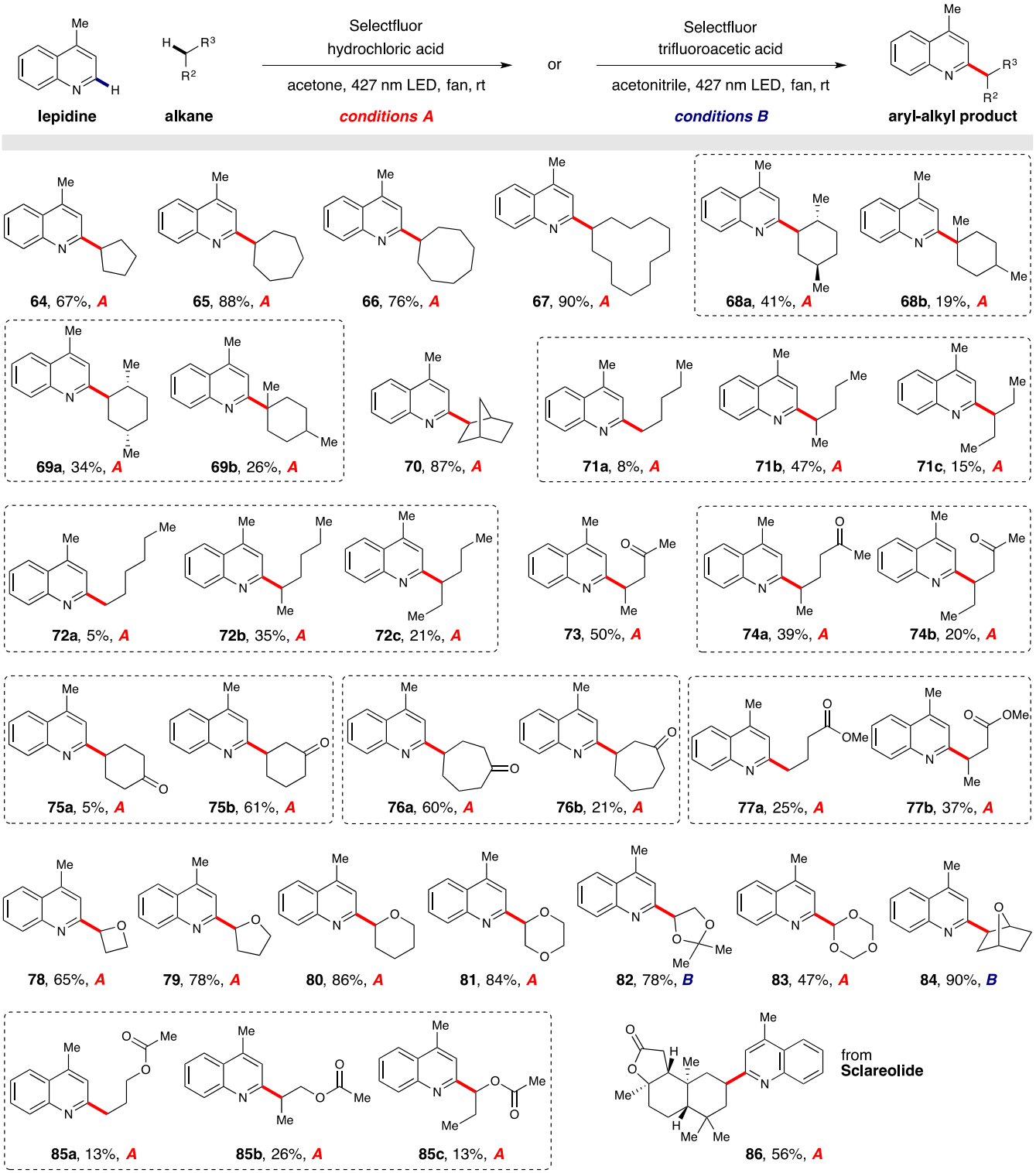


[a]Isolated yields. See the Supporting Information for experimental details.

the arylation, and other regioisomers were also obtained (**85**, 52% yield). Toward that end, Sclareolide, a sesquiterpene lactone natural product, was subjected to the reaction conditions for late stage functionalization (**86**, 56% yield),

DOI: 10.1021/acs.orglett.9b01635
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of the Aliphatic C−H Components[a]



[a]Isolated yields. See the Supporting Information for experimental details.

showcasing the preparative potential of the arylation protocol toward the rapid construction of molecular complexity.

In conclusion, we have developed a mild and operationally simple method for the construction of C(sp^3)−C(sp^2) bonds from alkanes and heteroarenes.[21] Aliphatic C−H arylation shows a broad scope with respect to both alkane and heteroarene substrates. Remarkably, the results presented above demonstrate that Selectfluor can be enabled by visible light as a powerful hydrogen atom transfer reagent to convert unactivated alkanes to high-value products in the context of late stage functionalization of medicinal agents. As such, we expect that the pharmaceutical sector will find this new transformation to be of utility in medicinal chemistry studies.

DOI: 10.1021/acs.orglett.9b01635
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01635.

General experimental procedures, characterization data, spectra for all key compounds, and mechanistic studies (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the "Thousand Plan" Youth program, the Chinese Academy of Sciences, the Shanghai Institute of Organic Chemistry, and the CAS Key Laboratory of Synthetic Chemistry of Natural Substances.

■ REFERENCES

(1) (a) Hartwig, J. F. Evolution of C-H Bond Functionalization from Methane to Methodology. *J. Am. Chem. Soc.* **2016**, *138*, 2−24. (b) Hartwig, J. F.; Larsen, M. A. Undirected, Homogeneous C-H Bond Functionalization: Challenges and Opportunities. *ACS Cent. Sci.* **2016**, *2*, 281−292. (c) Davies, H. M. L.; Morton, D. Recent Advances in C-H Functionalization. *J. Org. Chem.* **2016**, *81*, 343−350. (d) Davies, H. M. L.; Morton, D. Collective Approach to Advancing C−H Functionalization. *ACS Cent. Sci.* **2017**, *3*, 936−943. (e) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C-H Bonds. *Chem. Rev.* **2017**, *117*, 8754−8786. (f) Tang, X.; Jia, X.; Huang, Z. Challenges and Opportunities for Alkane Functionalisation Using Molecular Catalysts. *Chem. Sci.* **2018**, *9*, 288−299.

(2) (a) Newhouse, T.; Baran, P. S. If C-H Bonds Could Talk: Selective C-H Bond Oxidation. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362−3374. (b) White, M. C. Adding Aliphatic C−H Bond Oxidations to Synthesis. *Science* **2012**, *335*, 807−809. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C-H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009. (d) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-like Molecules. *Chem. Soc. Rev.* **2016**, *45*, 546−576. (e) Karimov, R. R.; Hartwig, J. F. Transition-Metal-Catalyzed Selective Functionalization of C(sp^3)-H Bonds in Natural Products. *Angew. Chem., Int. Ed.* **2018**, *57*, 4234−4241. (f) White, M. C.; Zhao, J. Aliphatic C-H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 13988−14009.

(3) Chu, J. C. K.; Rovis, T. Complementary Strategies for Directed C(sp^3)-H Functionalization: A Comparison of Transition-Metal-Catalyzed Activation, Hydrogen Atom Transfer, and Carbene/Nitrene Transfer. *Angew. Chem., Int. Ed.* **2018**, *57*, 62−101.

(4) (a) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 2056−2071. (b) Bietti, M. Activation and Deactivation Strategies Promoted by Medium Effects for Selective Aliphatic C-H Bond Functionalization. *Angew. Chem., Int. Ed.* **2018**, *57*, 16618−16637.

(5) (a) Michaudel, Q.; Thevenet, D.; Baran, P. S. Intermolecular Ritter-Type C-H Amination of Unactivated sp^3 Carbons. *J. Am. Chem. Soc.* **2012**, *134*, 2547−2550. (b) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. A Polycomponent Metal-Catalyzed Aliphatic, Allylic, and Benzylic Fluorination. *Angew. Chem., Int. Ed.* **2012**, *51*, 10580−10583.

(6) Pitts, C. R.; Bloom, S.; Woltornist, R.; Auvenshine, D. J.; Ryzhkov, L. R.; Siegler, M. A.; Lectka, T. Direct, Catalytic Monofluorination of sp^3 C-H Bonds: A Radical-Based Mechanism with Ionic Selectivity. *J. Am. Chem. Soc.* **2014**, *136*, 9780−9791.

(7) (a) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215−5246. (b) Schönherr, H.; Cernak, T. Profound Methyl Effects in Drug Discovery and a Call for New C-H Methylation Reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256−12267.

(8) Duncton, M. A. J. Minisci Reactions: Versatile CH-Functionalizations for Medicinal Chemists. *MedChemComm* **2011**, *2*, 1135−1161.

(9) (a) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. Nucleophilic Character of Alkyl Radicals−VI: A New Convenient Selective Alkylation of Heteroaromatic Bases. *Tetrahedron* **1971**, *27*, 3575−3579. (b) Mai, D. N.; Baxter, R. D. Unprotected Amino Acids as Stable Radical Precursors for Heterocycle C-H Functionalization. *Org. Lett.* **2016**, *18*, 3738−3741. (c) Cheng, W.-M.; Shang, R.; Fu, Y. Photoredox/Brønsted Acid Co-Catalysis Enabling Decarboxylative Coupling of Amino Acid and Peptide Redox-Active Esters with N-Heteroarenes. *ACS Catal.* **2017**, *7*, 907−911. (d) Cheng, W.-M.; Shang, R.; Fu, M.-C.; Fu, Y. Photoredox-Catalysed Decarboxylative Alkylation of N-Heteroarenes with *N*-(Acyloxy)phthalimides. *Chem. - Eur. J.* **2017**, *23*, 2537−2541. (e) Garza-Sanchez, R. A.; Tlahuext-Aca, A.; Tavakoli, G.; Glorius, F. Visible Light-Mediated Direct Decarboxylative C-H Functionalization of Heteroarenes. *ACS Catal.* **2017**, *7*, 4057−4061. (f) Wang, J.; Li, G.-X.; He, G.; Chen, G. Photoredox-Mediated Minisci Alkylation of N-Heteroarenes using Carboxylic Acids and Hypervalent Iodine. *Asian J. Org. Chem.* **2018**, *7*, 1307−1310. (g) Genovino, J.; Lian, Y.; Zhang, Y.; Hope, T. O.; Juneau, A.; Gagné, Y.; Ingle, G.; Frenette, M. Metal-Free-Visible Light C-H Alkylation of Heteroaromatics via Hypervalent Iodine-Promoted Decarboxylation. *Org. Lett.* **2018**, *20*, 3229−3232. (h) Zhang, X.-Y.; Weng, W.-Z.; Liang, H.; Yang, H.; Zhang, B. Visible-Light-Initiated, Photocatalyst-Free Decarboxylative Coupling of Carboxylic Acids with *N*-Heterocycles. *Org. Lett.* **2018**, *20*, 4686−4690. (i) Li, Z.; Wang, X.; Xia, S.; Jin, J. Ligand-Accelerated Iron Photocatalysis Enabling Decarboxylative Alkylation of Heteroarenes. *Org. Lett.* **2019**, DOI: 10.1021/acs.orglett.9b01439.

(10) (a) Molander, G. A.; Colombel, V.; Braz, V. A. Direct Alkylation of Heteroaryls Using Potassium Alkyl- and Alkoxymethyltrifluoroborates. *Org. Lett.* **2011**, *13*, 1852−1855. (b) Li, G.-X.; Morales-Rivera, C. A.; Wang, Y.; Gao, F.; He, G.; Liu, P.; Chen, G. Photoredox-Mediated Minisci C-H Alkylation of *N*-Heteroarenes Using Boronic Acids and Hypervalent Iodine. *Chem. Sci.* **2016**, *7*, 6407−6412. (c) Matsui, J. K.; Molander, G. A. Organocatalyzed, Photoredox Heteroarylation of 2-Trifluoroboratochromanones via C-H Functionalization. *Org. Lett.* **2017**, *19*, 950−953. (d) Matsui, J. K.; Primer, D. N.; Molander, G. A. Metal-Free C-H Alkylation of Heteroarenes with Alkyltrifluoroborates: A General Protocol for 1°, 2° and 3° Alkylation. *Chem. Sci.* **2017**, *8*, 3512−3522. (e) Zhang, L.; Liu, Z.-Q. Molecular Oxygen-Mediated Minisci-Type Radical Alkylation of Heteroarenes with Boronic Acids. *Org. Lett.* **2017**, *19*, 6594−6597.

(11) Smith, J. M.; Dixon, J. A.; deGruyter, J. N.; Baran, P. S. Alkyl Sulfinates: Radical Precursors Enabling Drug Discovery. *J. Med. Chem.* **2019**, *62*, 2256−2264.

(12) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. Late-Stage Functionalization of Biologically Active Heterocycles Through Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2014**, *53*, 4802−4806.

(13) (a) Jin, J.; MacMillan, D. W. C. Alcohols as Alkylating Agents in Heteroarene C-H Functionalization. *Nature* **2015**, *525*, 87−90.

(b) Liu, W.; Yang, X.; Zhou, Z.-Z.; Li, C.-J. Simple and Clean Photo-induced Methylation of Heteroarenes with MeOH. *Chem.* **2017**, *2*, 688−702. (c) McCallum, T.; Pitre, S. P.; Morin, M.; Scaiano, J. C.; Barriault, L. The Photochemical Alkylation and Reduction of Heteroarenes. *Chem. Sci.* **2017**, *8*, 7412−7418.

(14) (a) McCallum, T.; Barriault, L. Direct Alkylation of Heteroarenes with Unactivated Bromoalkanes Using Photoredox Gold Catalysis. *Chem. Sci.* **2016**, *7*, 4754−4758. (b) Nuhant, P.; Oderinde, M. S.; Genovino, J.; Juneau, A.; Gagné, Y.; Allais, C.; Chinigo, G. M.; Choi, C.; Sach, N. W.; Bernier, L.; Fobian, Y. M.; Bundesmann, M. W.; Khunte, B.; Frenette, M.; Fadeyi, O. O. Visible-Light-Initiated Manganese Catalysis for C-H Alkylation of Heteroarenes: Applications and Mechanistic Studies. *Angew. Chem., Int. Ed.* **2017**, *56*, 15309−15313. (c) Dong, J.; Lyu, X.; Wang, Z.; Wang, X.; Song, H.; Liu, Y.; Wang, Q. Visible-Light-Mediated Minisci C-H Alkylation of Heteroarenes with Unactivated Alkyl Halides Using O_2 as an Oxidant. *Chem. Sci.* **2019**, *10*, 976−982.

(15) (a) Lo, J. C.; Kim, D.; Pan, C.-M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutiérrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S. Fe-Catalyzed C-C Bond Construction from Olefins via Radicals. *J. Am. Chem. Soc.* **2017**, *139*, 2484−2503. (b) Liang, B.; Wang, Q.; Liu, Z.-Q. A Fe(III)/$NaBH_4$-Promoted Free-Radical Hydroheteroarylation of Alkenes. *Org. Lett.* **2017**, *19*, 6463−6465.

(16) Gutiérrez-Bonet, Á.; Remeur, C.; Matsui, J. K.; Molander, G. A. Late-Stage C-H Alkylation of Heterocycles and 1,4-Quinones via Oxidative Homolysis of 1,4-Dihydropyridines. *J. Am. Chem. Soc.* **2017**, *139*, 12251−12258.

(17) Klauck, F. J. R.; James, M. J.; Glorius, F. Deaminative Strategy for the Visible-Light-Mediated Generation of Alkyl Radicals. *Angew. Chem., Int. Ed.* **2017**, *56*, 12336−12339.

(18) Liu, P.; Liu, W.; Li, C.-J. Catalyst-Free and Redox-Neutral Innate Trifluoromethylation and Alkylation of Aromatics Enabled by Light. *J. Am. Chem. Soc.* **2017**, *139*, 14315−14321.

(19) (a) Deng, G.; Li, C.-J. $Sc(OTf)_3$-Catalyzed Direct Alkylation of Quinolines and Pyridines with Alkanes. *Org. Lett.* **2009**, *11*, 1171−1174. (b) Antonchick, A. P.; Burgmann, L. Direct Selective Oxidative Cross-Coupling of Simple Alkanes with Heteroarenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3267−3271. (c) Quattrini, M. C.; Fujii, S.; Yamada, K.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. Versatile Cross-Dehydrogenative Coupling of Heteroaromatics and Hydrogen Donors via Decatungstate Photocatalysis. *Chem. Commun.* **2017**, *53*, 2335−2338. (d) Hu, A.; Guo, J.-J.; Pan, H.; Zuo, Z. Selective Functionalization of Methane, Ethane, and Higher Alkanes by Cerium Photocatalysis. *Science* **2018**, *361*, 668−672. (e) Li, G.-X.; Hu, X.; He, G.; Chen, G. Photoredox-Mediated Minisci-type Alkylation of *N*-Heteroarenes with Alkanes with High Methylene Selectivity. *ACS Catal.* **2018**, *8*, 11847−11853. (f) Perry, I. B.; Brewer, T. F.; Sarver, P. J.; Schultz, D. M.; DiRocco, D. A.; MacMillan, D. W. C. Direct Arylation of Strong Aliphatic C−H Bonds. *Nature* **2018**, *560*, 70−75.

(20) (a) Correia, C. A.; Yang, L.; Li, C.-J. Palladium-Catalyzed Minisci Reaction with Simple Alcohols. *Org. Lett.* **2011**, *13*, 4581−4583. (b) Jin, J.; MacMillan, D. W. C. Direct α-Arylation of Ethers through the Combination of Photoredox-Mediated C-H Functionalization and the Minisci Reaction. *Angew. Chem., Int. Ed.* **2015**, *54*, 1565−1569. (c) Liu, S.; Liu, A.; Zhang, Y.; Wang, W. Direct Cα-Heteroarylation of Structurally Diverse Ethers via a Mild *N*-Hydroxysuccinimide Mediated Cross-Dehydrogenative Coupling Reaction. *Chem. Sci.* **2017**, *8*, 4044−4050.

(21) (a) A related work was published during the preparation of the manuscript: Niu, L.; Liu, J.; Liang, X.-A.; Wang, S.; Lei, A. Visible-Light-Induced Direct α C−H Functionalization of Alcohols. *Nat. Commun.* **2019**, *10*, 467. (b) A related work was submitted and published after our first submission of the manuscript: Liang, X.-A.; Niu, L.; Wang, S.; Liu, J.; Lei, A. Visible-Light-Induced C(sp^3)−H Oxidative Arylation with Heteroarenes. *Org. Lett.* **2019**, *21*, 2441−2444.

DOI: 10.1021/acs.orglett.9b01635
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