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Iron-Catalyzed Site-Selective Bromination of Benzylic C(sp^3)−H Bonds

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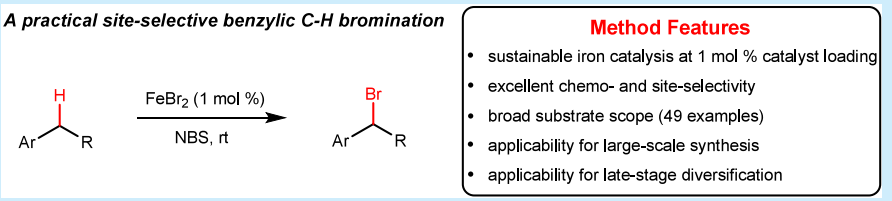

ABSTRACT: An iron-catalyzed chemo- and site-selective benzylic C−H bromination has been described. The practical approach uses the C−H substrate as the limiting reagent and commercially available iron(II) bromide at a loading of 1 mol % as the catalyst without the involvement of any extrinsic ligand. The simple and mild reaction can be readily scaled up to gram quantity with good functional group tolerance, offering a convenient route for the late-stage diversification of complex bioactive natural products and pharmaceutical molecules through sequential benzylic C−H bromination.

Benzylic bromides are key intermediates for synthesizing numerous organic compounds through carbon−carbon and carbon−heteroatom bond formation reactions.[1] Therefore, late-stage site-selective bromination of benzylic C−H bonds represents a promising tool to quickly diversify a given molecule containing substituted benzyl structures for the expansion of the accessible chemical space.[2] To our surprise, a practical and effective site-selective benzylic C−H bromination approach has scarcely been reported.[3] Traditional preparative chemistry typically relies on the direct employment of liquid bromine or generation of bromine *in situ* by oxidation of hydrogen bromide or alkali-metal bromide (Figure 1A).[4] The toxicity and corroding properties together with poor functional group tolerance prevent the development of an efficient late-stage bromination approach. The Wohl−Ziegler bromination using relatively safe and user-friendly *N*-bromosuccinimide (NBS) as a brominating agent in the presence of potentially explosive radical initiators such as benzoyl peroxide or UV or visible light often remains the method of choice for the purpose (Figure 1B).[5] However, this protocol still suffers from inferior chemoselectivity, generating undesired benzylic dibromination and arene C(sp^2)−H bromination byproducts together with inapplicability for large-scale synthesis.[6] The development of a practical, sustainable, and readily scalable site-selective benzylic C−H bromination for late-stage functionalization would be highly desired.

Iron is the second most abundant metal in the Earth's crust. The low cost, environmental friendliness, and biocompatible nature of iron make this metal particularly attractive for the development of sustainable catalytic protocols.[7] Herein, we disclose an iron/NBS-mediated site-selective benzylic C−H bromination (Figure 1C). The practical and simple approach

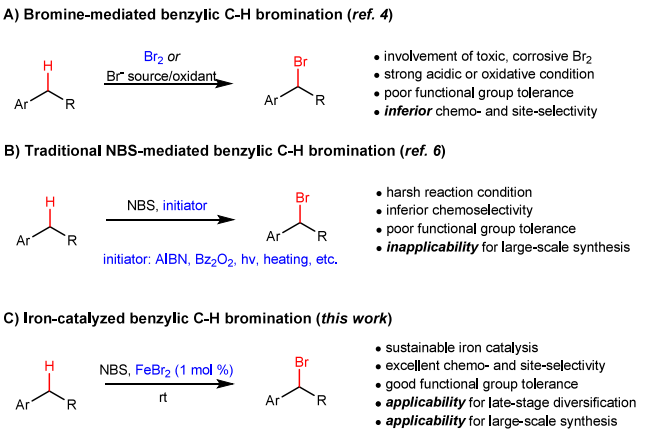

Figure 1. Overview of the existing methods for benzylic C−H bromination. (A) Benzylic bromination mediated by liquid bromine or bromine generated *in situ*. (B) Benzylic bromination mediated by NBS and various radical initiators. (C) Iron-catalyzed benzylic bromination.

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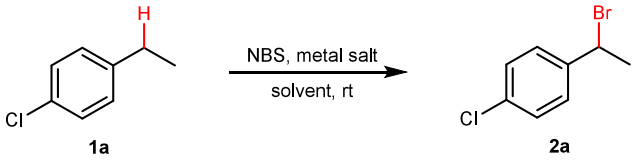
employs the C−H substrate as the limiting reagent and commercially available iron(II) bromide at a loading of 1 mol % as the catalyst without the involvement of any extrinsic ligand, allowing the reaction to be readily scaled up to gram quantity with good functional group tolerance. Application in the late-stage bromination of complex bioactive molecules is also demonstrated.

We initially investigated benzylic C−H bromination of 1-chloro-4-ethylbenzene (**1a**) using NBS as a brominating agent for the search of a suitable iron catalyst (Table 1). A series of

Table 1. Reaction Condition Optimization[a]



1a **2a**

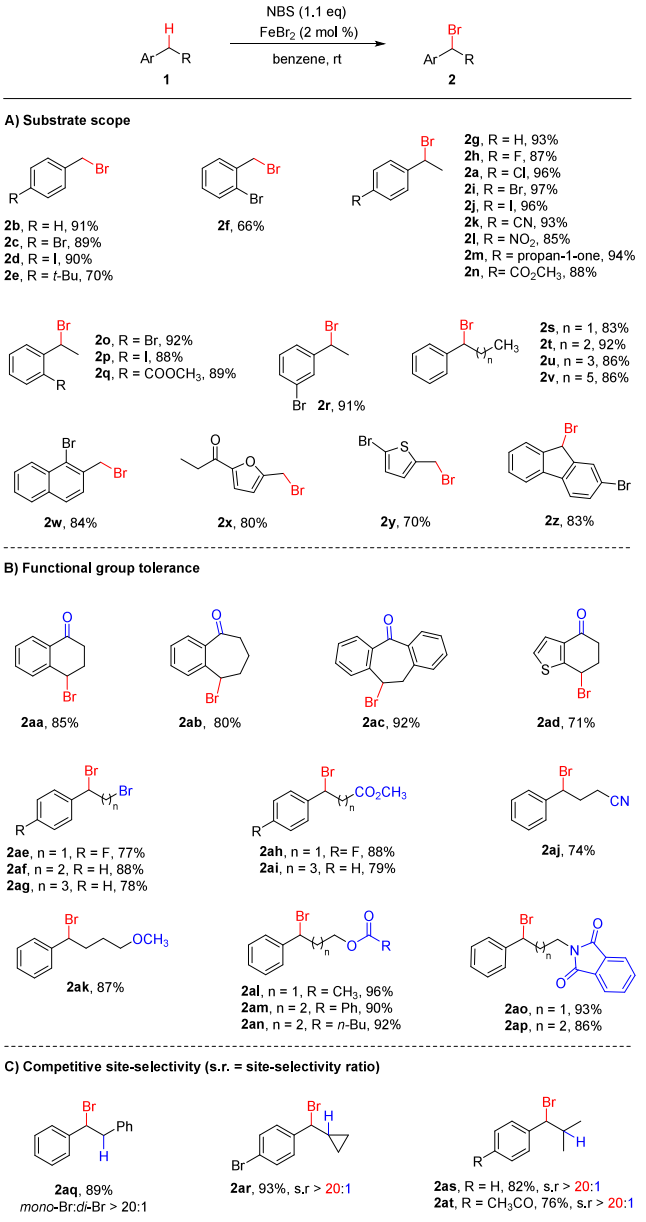
entry	catalyst	solvent	yield (%)[b]
1	$Fe(OAc)_2$	*n*-hexane	25
2	FeC_2O_4	*n*-hexane	36
3	$Fe(OTf)_2$	*n*-hexane	60
4	$Fe(acac)_2$	*n*-hexane	55
5	$FeCl_2$	*n*-hexane	43
6	$FeBr_2$	*n*-hexane	88
7	$FeBr_2$	cyclohexane	61
8	$FeBr_2$	THF	33
9	$FeBr_2$	CH_3NO_2	62
10	$FeBr_2$	$ClCH_2CH_2Cl$	64
11	$FeBr_2$	CH_2Cl_2	93
12	$FeBr_2$	benzene	98
13[c]	$FeBr_2$	benzene	96

[a]Reaction conditions: **1a** (0.2 mmol), NBS (0.22 mmol), and a catalyst (5 mol %) in a solvent (1.0 mL) at rt for 12 h. [b]Yield of the isolated product. [c]$FeBr_2$ (2 mol %) as the catalyst at rt for 24 h.

commercially available iron salts containing different counterions were evaluated, and $FeBr_2$ was identified to be optimal in terms of the reaction yield (entries 1−6). Solvent optimization studies identified CH_2Cl_2 and benzene as the most effective choices with 93% and 98% yields, respectively (entries 6−12). No obvious loss of reaction yield was observed when the loading of $FeBr_2$ was decreased from 5 to 2 mol %, though a prolonged reaction period was required (entry 13).

With the optimized conditions in hand, we next explored the scope of $FeBr_2$-catalyzed benzylic C−H bromination (Scheme 1A). In general, a wide variety of substrates containing substituted benzyl structures participate in the mild bromination reactions in high efficiency without any dibromination or arene C(sp^2)−H bromination byproducts observed. For example, a set of substituted toluenes bearing both electron-donating and electron-withdrawing groups at different positions is well tolerated, as demonstrated by the generation of expected **2b**−**2f** in good to excellent yields. Furthermore, a range of electronically varied arylethanes **1g**−**1r** with diverse substituents at the *ortho*, *meta*, and *para* positions are suitable components. In addition, phenyl-substituted alkanes with various alkyl chains are also viable substrates (**1s**−**1v**). In addition to simple aryl rings, more complicated rings, such as 2-naphthyl (**1w**), heteroaryls like furanyl (**1x**) and thienyl (**1y**), and fluorenyl (**1z**), are compatible with the reaction.

Scheme 1. Scope of Iron-Catalyzed Benzylic Bromination[a,b]



[a]Reaction conditions: **1** (0.2 mmol), NBS (0.22 mmol), and $FeBr_2$ (2 mol %) in benzene (1.0 mL) at rt for 24 h. [b]Isolated yield.

The mild protocol exhibits good functional group tolerance (Scheme 1B). For instance, a range of ketones (**1aa**−**1ad**), alkyl bromide (**1ae**−**1ag**), carboxylic esters (**1ah** and **1ai**), cyano (**1aj**), ether (**1ak**), acetates (**1al**−**1an**), and amides (**1ao** and **1ap**) are well tolerated with good yields. The site selectivity of the bromination reaction was further examined for substrates bearing a competitive reaction site (Scheme 1C). The reaction for **1aq** bearing two equivalent benzylic sites proceeds smoothly, furnishing monobrominated **2aq** in 89% yield without any dibenzylic bromination product. Moreover, this iron-catalyzed reaction supports benzylic bromination in good yield and selectivity, with benzylic:tertiary ratios of >20:1 for **1ar**−**1at**.

The synthetic application of the mild protocol in late-stage site-selective bromination was next evaluated (Scheme 2A). Benzylic bromination of Celestolide proceeds, giving expected

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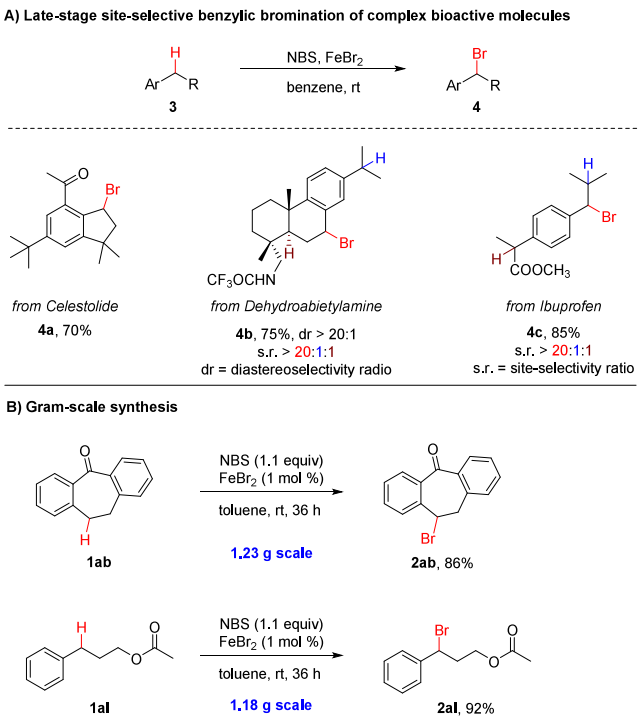
Scheme 2. Applications in Late-Stage Site-Selective Bromination and Large-Scale Synthesis

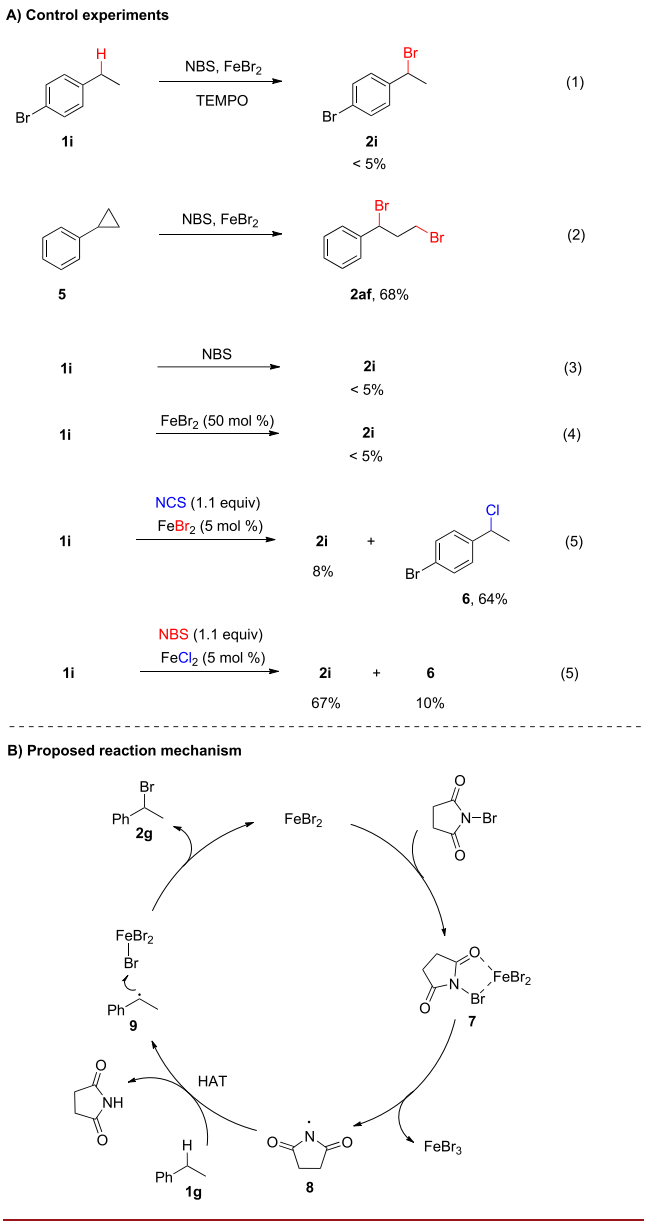


product **4a** in 70% yield. More complex molecules containing multiple reactive C−H bonds also proved to be effective. For example, dehydroabietylamine derivative **3b** undergoes site-selective C−H bromination at the cyclic secondary benzylic position over acyclic tertiary benzylic and cyclic tertiary ones with excellent diastereoselectivity. In addition, bromination of ibuprofen methyl ester (**3c**) proceeds with overwhelming site selectivity at the less sterically hindered secondary benzylic C−H bond.

The applicability of the method in a large-scale synthesis was then demonstrated (Scheme 2B). Benzylic bromination of **1ab** and **1al** proceeds without obvious loss of reaction yields. The catalyst loading of $FeBr_2$ can be decreased to 1 mol % for these gram-scale reactions. Notably, a scalable protocol for benzylic C−H bromination remains extremely lacking.[6] It has been known that benzylic bromides can participate in a wide variety of subsequent substitution reactions.[1] Take benzylic bromide **2s**, for example. The C−Br bond in **2s** is readily transformed into new C−C,[8a−e] C−N,[8f−h] C−S,[8i] C−O,[8j] C−F,[8k] and C−P[8l] bonds with varied substituent patterns. Therefore, this simple and scalable $FeBr_2$-catalyzed method would provide a democratized platform for late-stage diversification of complex bioactive molecules through site-selective benzylic C−H bromination followed by subsequent diverse substitution.

Control experiments were conducted to obtain a preliminary understanding of the reaction mechanism (Scheme 3A). First, the bromination reaction of **1i** was completely inhibited when a stoichiometric amount of TEMPO was added (Scheme 3A, eq 1). Moreover, a radical clock experiment of phenylcyclopropane **5** furnished dibrominated ring-open **2af** (Scheme 3A, eq 2). The observations suggest that benzylic bromination may proceed through a radical mechanism.[9] Second, no reaction was observed in the absence of either NBS or $FeBr_2$, implying the importance of both components (Schemes 3A, eqs 3 and 4). Third, crossover experiments using combinations

Scheme 3. Mechanistic Studies and Proposed Catalytic Cycle



of NCS with $FeBr_2$ and NBS with $FeCl_2$ were next performed (Scheme 3A, eqs 5 and 6). For the former condition, a mixture of brominated **2i** in 8% yield and chlorinated **6** in 64% yield was isolated; for the latter, a mixture of brominated **2i** in 67% yield and chlorinated **6** in 10% yield was obtained. The results indicate that benzylic bromination might occur through halogen atom transfer from the iron species to the benzyl radical.

Based on the above control experiments, a plausible reaction pathway is suggested in Scheme 3B. Iron(II) bromide might activate NBS through chelation, giving N-centered succinimide radical **8** and $FeBr_3$. Then a hydrogen atom transfer (HAT) from substrate **1g** to radical **8** furnishes the benzylic carbon radical.[10] The alkyl radical abstracts a bromine atom from $FeBr_3$ through halogen atom transfer through **9**, providing brominated **2g** together with regeneration of $FeBr_2$ for the catalytic cycle.[3a,11]

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In summary, a practical iron-catalyzed site-selective benzylic C−H bromination has been disclosed. The protocol employs the C−H substrate as the limiting reagent and commercially available $FeBr_2$ at a loading of 1 mol % as the catalyst without any extrinsic ligand. The simple and mild reaction can be readily scaled up to gram quantity with good functional group tolerance. Late-stage site-selective bromination has also been demonstrated. We envision that the method outlined herein would provide a democratized platform for late-stage diversification of complex bioactive molecules through site-selective benzylic C−H bromination followed by subsequent diverse substitution.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c00864.

Experimental procedures, characterization data, and ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) March, J. *Advanced Organic Chemistry: Reactions, Mechanism and Structure*, 4th ed.; John Wiley & Sons: New York, 1992. (b) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (c) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed.; Wiley-VCH: New York, 1999. (d) Dagani, M. J.; Barda, J. H.; Benya, T. J.; Sanders, D. C. *Ullmannas Encyclopedia of Industrial Chemistry: Bromine Compounds*; Wiley-VCH: Weinheim, Germany, 2002. (e) Lu, W.; Zhou, L. *Oxidation of C-H Bonds*; John Wiley & Sons, Inc.: Hoboken, NJ, 2017.

(2) (a) Ackermann, L. Carboxylate-assisted transition metal-catalyzed C−H bond functionalizations: mechanism and scope. *Chem. Rev.* **2011**, *111*, 1315−1345. (b) McMurray, L.; O'Hara, F.; Gaunt, M. J. Recent developments in natural product synthesis using metal-catalysed C−H bond functionalization. *Chem. Soc. Rev.* **2011**, *40*, 1885−1898. (c) Wencel-Delord, J.; Glorius, F. C−H bond activation enables the rapid construction and late-stage diversification of functional molecules. *Nat. Chem.* **2013**, *5*, 369−375. (d) Wang, F.; Chen, P.; Liu, G.-S. Copper-catalyzed radical relay for asymmetric radical transformations. *Acc. Chem. Res.* **2018**, *51*, 2036−2046. (e) Aynetdinova, D.; Callens, M. C.; Hicks, H. B.; Poh, C. Y. X.; Shennan, B. D. A.; Boyd, A. M.; Lim, Z. H.; Leitch, J. A.; Dixon, D. J. Installing the "magic methyl" − C−H methylation in synthesis. *Chem. Soc. Rev.* **2021**, *50*, 5517−5563. (f) Shabani, S.; Wu, Y.-Z.; Ryan, H. G.; Hutton, C. A. Progress and perspectives on directing group-assisted palladium-catalysed C−H functionalisation of amino acids and peptides. *Chem. Soc. Rev.* **2021**, *50*, 9278−9343. (g) Lasso, J. D.; Castillo-Pazos, D. J.; Li, C.-J. Green chemistry meets medicinal chemistry: a perspective on modern metal-free late-stage functionalization reactions. *Chem. Soc. Rev.* **2021**, *50*, 10955−10982. (h) Holmberg-Douglas, N.; Nicewicz, D. A. Photoredox-catalyzed C−H functionalization reactions. *Chem. Rev.* **2022**, *122*, 1925−2016. (i) Wang, C.; Qi, R.-P.; Wang, R.; Xu, Z.-Q. Photoinduced C(sp^3)−H functionalization of glycine derivatives: preparation of unnatural α-amino acids and late-stage modification of peptides. *Acc. Chem. Res.* **2023**, *56*, 2110−2125. (j) Ali, W.; Oliver, G. A.; Werz, D. B.; Maiti, D. Pd-catalyzed regioselective activation of C(sp^2)−H and C(sp3)−H bonds. *Chem. Soc. Rev.* **2024**, *53*, 9904−9953.

(3) For isolated practical site-selective benzylic C−H chlorination, see: (a) Lopez, M. A.; Buss, J. A.; Stahl, S. S. Cu-catalyzed site-selective benzylic chlorination enabling net C−H coupling with oxidatively sensitive nucleophiles. *Org. Lett.* **2022**, *24*, 597−601. (b) Maity, S.; Lopez, M. A.; Bates, D. M.; Lin, S.-S.; Krska, S. W.; Stahl, S. S. Polar heterobenzylic C(sp^3)−H chlorination pathway enabling efficient diversification of aromatic nitrogen heterocycles. *J. Am. Chem. Soc.* **2023**, *145*, 19832−19839. (c) Golden, D. L.; Flynn, K. M.; Aikonen, S.; Hanneman, C. M.; Kalyani, D.; Krska, S. W.; Paton, R. S.; Stahl, S. S. Radical chlorination of non-resonant heterobenzylic C−H bonds and high-throughput diversification of heterocycles. *Chem.* **2024**, *10*, 1593−1605.

(4) (a) Mestres, R.; Palenzuela, J. High atomic yield bromine-less benzylic bromination. *Green Chem.* **2002**, *4*, 314−316. (b) Raju, T.; Kulangiappar, K.; Kulandainathan, M. A.; Muthukumaran, A. A simple and regioselective α-bromination ofalkyl aromatic compounds by two-phase electrolysis. *Tetrahedron Lett.* **2005**, *46*, 7047−7050. (c) Jiang, X.-F.; Shen, M.-H.; Tang, Y.; Li, C.-Z. Chemoselective monobromination of alkanes promoted by unactivated MnO_2. *Tetrahedron Lett.* **2005**, *46*, 487−489. (d) Manabe, Y.; Kitawaki, Y.; Nagasaki, M.; Fukase, K.; Matsubara, H.; Hino, Y.; Fukuyama, T.; Ryu, I. Revisiting the Bromination of C−H bonds with molecular bromine by using a photo-microflow system. *Chem. - Eur. J.* **2014**, *20*, 12750−12753. (e) Ni, S.; El Remaily, M. A. E. A. A. A.; Franzén, J. Carbocation catalyzed bromination of alkyl arenes, a chemoselective sp^3 vs. sp^2 C−H functionalization. *Adv. Synth. Catal.* **2018**, *360*, 4197−4204. (f) Zhao, M.-D.; Lu, W.-J. Catalytic bromination of alkyl sp^3 C−H bonds with KBr/air under visible light. *Org. Lett.* **2018**, *20*, 5264−5267. (g) Zhao, M.-D.; Li, M.-Q.; Lu, W.-J. Visible-light-driven oxidative mono- and dibromination of benzylic sp^3 C−H bonds with potassium bromide/oxone at room temperature. *Synthesis* **2018**, *50*, 4933−4939.

(5) (a) Liu, P.-N.; Chen, Y.-C.; Deng, J.-G.; Tu, Y.-Q. An efficient method for the preparation of benzylic bromides. *Synthesis* **2001**, *2001*, 2078−2080. (b) Amijs, C. H. M.; van Klink, G. P. M.; van Koten, G. Carbon tetrachloride free benzylic brominations of methyl aryl halides. *Green Chem.* **2003**, *5*, 470−474. (c) Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, j. Visible light induced 'on water' benzylic bromination with N-bromosuccinimide. *Tetrahedron Lett.* **2006**, *47*, 1097−1099. (d) Shibatomi, K.; Zhang, Y.-H.; Yamamoto, H. Lewis acid catalyzed benzylic bromination. *Chem. - Asian J.* **2008**, *3*, 1581−1584.

(6) For an isolated protocol of scalable benzylic bromination of substituted toluenes relying on a flow reactor, see: Cantillo, D.; de Frutos, O.; Rincon, J. A.; Mateos, C.; Kappe, C. O. A scalable procedure for light-induced benzylic brominations in continuous flow. *J. Org. Chem.* **2014**, *79*, 223−229.

(7) (a) Sherry, B. D.; Fürstner, A. The promise and challenge of iron-catalyzed cross coupling. *Acc. Chem. Res.* **2008**, *41*, 1500−1511. (b) Morris, R. H. Asymmetric hydrogenation, transfer hydrogenation and hydrosilylation of ketones catalyzed by iron complexes. *Chem. Soc. Rev.* **2009**, *38*, 2282−2291. (c) Shang, R.; Ilies, L.; Nakamura, E. Iron-catalyzed C−H bond activation. *Chem. Rev.* **2017**, *117*, 9086−9139. (d) Liu, Y.-G.; You, T.-J.; Wang, H.-X.; Tang, Z.; Zhou, C.-Y.; Che, C.-M. Iron- and cobalt-catalyzed $C(sp^3)$−H bond functionalization reactions and their application in organic synthesis. *Chem. Soc. Rev.* **2020**, *49*, 5310−5358. (e) Rana, S.; Biswas, J. P.; Paul, S.; Paik, A.; Maiti, D. Organic synthesis with the most abundant transition metal−iron: from rust to multitasking catalysts. *Chem. Soc. Rev.* **2021**, *50*, 243−472. (f) Mo, J.-Y.; Messinis, A. M.; Li, J.-L.; Warratz, S.; Ackermann, L. Chelation-assisted iron-catalyzed C−H activations: scope and mechanism. *Acc. Chem. Res.* **2024**, *57*, 10−22.

(8) (a) Binder, J. T.; Cordier, C. J.; Fu, G. C. Catalytic enantioselective cross-couplings of secondary alkyl electrophiles with secondary alkylmetal nucleophiles: Negishi reactions of racemic benzylic bromides with achiral alkylzinc reagents. *J. Am. Chem. Soc.* **2012**, *134*, 17003−17006. (b) Jiang, S.-P.; Dong, X.-Y.; Gu, Q.-S.; Ye, L.; Li, Z.-L.; Liu, X.-Y. Copper-catalyzed enantioconvergent radical Suzuki−Miyaura $C(sp^3)$−$C(sp^2)$ cross-coupling. *J. Am. Chem. Soc.* **2020**, *142*, 19652−19659. (c) Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. A general asymmetric copper-catalysed Sonogashira $C(sp^3)$-C(sp) coupling. *Nat. Chem.* **2019**, *11*, 1158−1166. (d) Li, C.-X.; Zhang, Y.-Y.; Sun, Q.; Gu, T.-N.; Peng, H.-N.; Tang, W.-J. Transition-metal-free stereospecific cross-coupling with alkenylboronic acids as nucleophiles. *J. Am. Chem. Soc.* **2016**, *138*, 10774−10777. (e) Li, C.; Chen, B.; Ma, X.-D.; Mo, X.-L.; Zhang, G.-Z. Light-promoted copper-catalyzed enantioselective alkylation of azoles. *Angew. Chem., Int. Ed.* **2021**, *60*, 2130−2134. (f) Yang, Y.-Z.; Xue, Q.; Xiong, Z.-Q.; Li, Y.; Ouyang, X.-H.; Hu, M.; Li, J.-H. Divergent [2 + n] heteroannulation of β-CF_3-1,3-enynes with alkyl azides via hydrogen atom transfer and radical substitution. *Org. Lett.* **2024**, *26*, 889−894. (g) Zhang, Y.-F.; Dong, X.-Y.; Cheng, J.-T.; Yang, N.-Y.; Wang, L.-L.; Wang, F.-L.; Luan, C.; Liu, J.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Enantioconvergent Cu-catalyzed radical C−N coupling of racemic secondary alkyl halides to access α-chiral primary amines. *J. Am. Chem. Soc.* **2021**, *143*, 15413−15419. (h) Yu, M.; Stevenson, K.; Zhou, G. N-Alkylation of lactams with secondary heterobenzylic bromides. *Tetrahedron Lett.* **2014**, *55*, 5591−5594. (i) Tian, Y.; Li, X.-T.; Liu, J.-R.; Cheng, J.; Gao, A.; Yang, N.-Y.; Li, Z.; Guo, K.-X.; Zhang, W.; Wen, H.-T.; Li, Z.-L.; Gu, Q.-S.; Hong, X.; Liu, X.-Y. A general copper-catalysed enantioconvergent $C(sp^3)$−S cross-coupling via biomimetic radical homolytic substitution. *Nat. Chem.* **2024**, *16*, 466−475. (j) Tawari, N. R.; Bag, S.; Raju, A.; Lele, A. C.; Bairwa, R.; Ray, M. K.; Rajan, M.; Nawale, L. U.; Sarkar, D.; Degani, M. S. Rational drug design, synthesis and biological evaluation of dihydrofolate reductase inhibitors as antituberculosis agents. *Future Med. Chem.* **2015**, *7*, 979−988. (k) Lai, J.-W.; Xiao, X.; Shao, S.-X.; Wang, S.-P.; Kan, J.; Su, W.-P. Photoinduced transition-metal and external photosensitizer free benzylic fluorination of unactivated alkylarenes. *Chem. - Eur. J.* **2024**, *30*, No. e202401669. (l) Pandey, R. K.; Wakharkar, R. D.; Kumar, P. Wittig−Horner approach for the synthesis of Tamoxifen. *Synth. Commun.* **2005**, *35*, 2795−2800.

(9) (a) Gieuw, M. H.; Chen, S.-M.; Ke, Z.-H.; Houk, K. N.; Yeung, Y.-Y. Boron tribromide as a reagent for anti-Markovnikov addition of HBr to cyclopropanes. *Chem. Sci.* **2020**, *11*, 9426−9433. (b) Li, Q.-Y.; Cheng, S.; Ye, Z.-Q.; Huang, T.; Yang, F.-X.; Lin, Y.-M.; Gong, L. Visible light-triggered selective $C(sp^2)$-H/$C(sp^3)$-H coupling of benzenes with aliphatic hydrocarbons. *Nat. Commun.* **2023**, *14*, 6366. (c) Xu, Y.-W.; Li, Q.; Ye, R.-Y.; Xu, B.-Y.; Zhou, X.-G. Electrochemical oxidative C−H amination through a Ritter-Type reaction. *J. Org. Chem.* **2023**, *88*, 9518−9522.

(10) (a) McMillan, A. J.; Sieńkowska, M.; Di Lorenzo, P.; Gransbury, G. K.; Chilton, N. F.; Salamone, M.; Ruffoni, A.; Bietti, M.; Leonori, D. Practical and selective sp^3 C−H bond chlorination via aminium radicals. *Angew. Chem., Int. Ed.* **2021**, *60*, 7132−7139. (b) Xiang, M.; Zhou, C.; Yang, X.-L.; Chen, B.; Tung, C.-H.; Wu, L.-Z. Visible light-catalyzed benzylic C−H bond chlorination by a combination of organic dye (Acr+-Mes) and N-chlorosuccinimide. *J. Org. Chem.* **2020**, *85*, 9080−9087.

(11) (a) Shen, C.; Dagnaw, W. M.; Fong, C. W.; Lau, K. C.; Chow, C. F. Selective functionalization of $C(sp^3)$-H bonds: catalytic chlorination and bromination by $iron^{(III)}$-acacen-halide under ambient condition. *Chem. Commun.* **2022**, *58*, 10627−10630. (b) Chen, B.; Fang, C.; Liu, P.; Ready, J. M. Rhodium-catalyzed enantioselective radical addition of CX_4 reagents to olefins. *Angew. Chem., Int. Ed.* **2017**, *56*, 8780−8784. (c) Li, Z.-f.; Zeng, G.; He, Y.-Q.; Zhou, S.; Chen, J.-H.; Chen, Z.-Y.; Chen, J.-X.; Lv, N.-N. Markovnikov hydrochlorination of unactivated alkenes with $FeCl_3$ via a HAT/XAT Sequence. *Org. Lett.* **2024**, *26*, 4813−4817.

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