How to cite: *Angew. Chem. Int. Ed.* **2024**, *63*, e202406485
doi.org/10.1002/anie.202406485

C-H Halogenation

Site-Selective Distal $C(sp^3)$–H Bromination of Aliphatic Amines as a Gateway for Forging Nitrogen-Containing sp^3 Architectures

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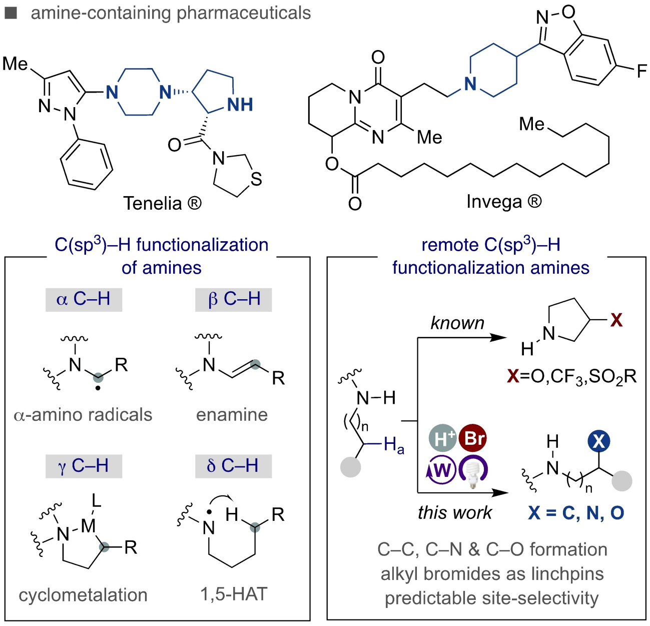
Abstract: Herein, we disclose a new strategy that rapidly and reliably incorporates bromine atoms at distal, secondary $C(sp^3)$–H sites in aliphatic amines with an excellent and predictable site-selectivity pattern. The resulting halogenated building blocks serve as versatile linchpins to enable a series of carbon-carbon and carbon-heteroatom bond-formations at remote $C(sp^3)$ sites, thus offering a new modular and unified platform that expedites the access to advanced sp^3 architectures possessing valuable nitrogen-containing saturated heterocycles of interest in medicinal chemistry settings.

A close inspection into the literature data reveals that 82 % of the top 200 small molecule prescription medicines by 2022 global sales contain at least an amine moiety or a nitrogen-containing heterocycle (Scheme 1, *top*).[1] Driven by this observation, the recent years have witnessed remarkable levels of sophistication for preparing amine architectures.[2] Among different conceivable scenarios, the ability to rapidly and reliably access advanced amine analogues by site-selective $C(sp^3)$–H functionalization[3] of pre-existing aliphatic amines or nitrogen-containing heterocycles might offer the advantage to implement late-stage diversification of advanced synthetic intermediates,[4] thus streamlining the synthesis of lead candidates while accelerating structure–reactivity relationships (SAR) explorations.[5] While the ubiquity of multiple, yet similar, $C(sp^3)$–H linkages in amine-containing architectures might render site-selectivity a challenging endeavor, a series of elegant disclosures have offered α-functionalizations adjacent to nitrogen with superbases,[6] oxidative processes,[7] or β-functionalization scenarios via imine-enamine equilibriums.[8] On the other hand, catalytic functionalization of aliphatic amines at remote $C(sp^3)$–H sites can be promoted by metal-catalyzed strategies using transient or native directing groups,[9] 1,5 hydrogen atom transfer (HAT) strategies aided by the intermediacy of amidyl radicals[10] or at terminal $C(sp^3)$–H sites by means of Ir-catalyzed borylation events,[11] among others (Scheme 1, *bottom left*). Alternatively, the utilization of ammonium salts derived from alkyl amines has offered new pathways for bond-forming reactions at remote sp^3 sites, including $C(sp^3)$–H oxygenation, trifluoromethylation or sulfonylation (*bottom right*), with site-selectivity being dictated by either bond-dissociation energies or by the presence of a transition metal.[12] Despite the inherent potential of these techniques to access reaction vectors left unexplored by conventional synthetic methods, the design of a modular and general blueprint that incorporates with equal ease carbon-carbon or carbon-heteroatom bonds at remote $C(sp^3)$–H sites of unprotected alkyl amines with a predictable site-selectivity pattern still represents a worthwhile endeavor for chemical invention. If successful, such a strategy would provide a



Scheme 1. Remote $C(sp^3)$–H functionalization of unprotected amines.

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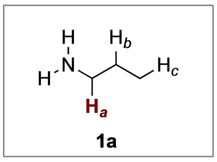
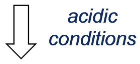
useful entry point to currently inaccessible advanced amine scaffolds, thus streamlining the access to molecules of interest in medicinal chemistry settings. As part of our ongoing interest in $C(sp^3)$–H functionalization,[13] we hypothesized that the site-selective installation of a versatile halogenated linchpin at remote $C(sp^3)$–H sites in *unprotected* primary or secondary aliphatic amines would offer a new gateway for downstream applications. Herein, we report the successful realization of this goal, culminating in a highly versatile and broadly applicable $C(sp^3)$–H bromination that streamlines the access to advanced sp^3 architectures with an aliphatic amine core (Scheme 1, *bottom*). The implications of these findings might impact both academic and industrial laboratories, not only by accelerating SAR explorations but also offering a rapid and reliable access to lead candidates with amine functions in drug discovery campaigns.

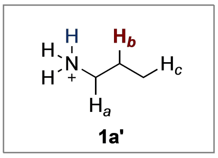
We began our investigations by evaluating the $C(sp^3)$–H bromination of *n*-propyl amine (**1a**) with an appropriate bromine source in an acidic media (Scheme 2). Given that protonation of the amine effectively inhibits hydrogen-atom transfer (HAT) at proximal $C(sp^3)$–H bonds,[14] bromination is expected to occur at remote $C(sp^3)$–H bonds with an appropriate electrophilic brominating source, with site-selectivity being likely dictated by a subtle combination of electronic effects and bond-dissociation energies at different $C(sp^3)$–H sites. As expected, density functional theory (DFT) calculations univocally revealed that $C(sp^3)$–H bonds adjacent to the nitrogen atom are electronically perturbed upon protonation of the amine function.[15] This notion gained credence by the calculated bond-dissociation energies and natural population analysis (NPA) of the molecular orbitals for both *n*-propyl amine **1a** and its protonated congener **1a′** (Scheme 2, *left*). A simple comparison at the bond-dissociation energies of H*a*–H*c* in **1a′** indicated that H*b* abstraction would be expected to be more facile than H*a* and H*c*. As clearly shown in Scheme 2 (*right*), this turned out to be the case, and a protocol consisting of $HClO_4$, 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as bromine source and tetra-*n*-butylammonium decatungstate (TBADT) as photocatalyst (entry 1) under 390 nm irradiation cleanly delivered **2a′**:**2a″** in high yield and with an excellent regioselectivity pattern, favoring the corresponding C–Br bond-forming reaction at the β $C(sp^3)$–H site. As anticipated, traces of $C(sp^3)$–H bromination were found in the absence of $HClO_4$ or photocatalyst, thus standing as a testament to the impact that these two parameters have on the reaction outcome (entry 2). As shown in entries 3–6, subtle modifications of the decatungstate core or the utilization of acridinium photocatalysts instead had a deleterious impact on reactivity,[16] whereas bromination at the primary $C(sp^3)$–H site was predominantly observed with



1a

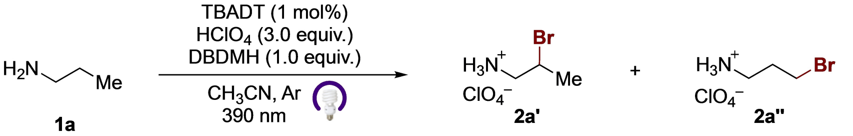
	H_a	H_b	H_c
NPA	0.167	0.189	0.197
BDE	91.9	97.4	101.3



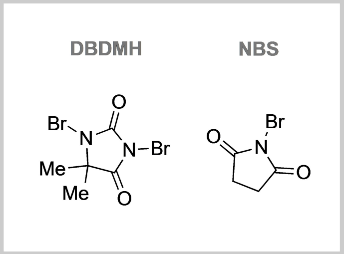


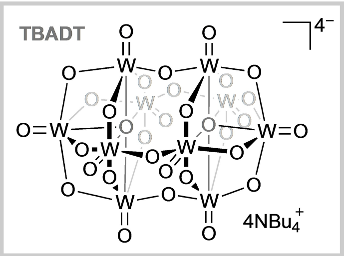
1a′

	H_a	H_b	H_c
NPA	0.220	0.208	0.207
BDE	102.9	97.8	102.3



entry	deviation standard conditions	2a'(%)[a]	selectivity(%)[b]
1	none	80	89
2	no TBADT or $HClO_4$	trace	-
3	using (Mes-Acr-Ph)BF_4	0[c]	-
4	using NCS, CCl_3Br	4[d]	31
5	*n*-Bu_3BnNDT as PC	72	89
6	Ph_4PDT as PC	76	89
7	Br_2 instead of DBDMH	11	61
8	NBS instead of DBDMH	54	83
9	HCl instead of $HClO_4$	21	88
10	H_2SO_4 instead of $HClO_4$	11	65
11	TfOH instead of $HClO_4$	11	58
12	CH_3CO_2H instead of $HClO_4$	0	-
13	$H[BArF]_4$ instead of $HClO_4$	0	-
14	$BF_3\cdot Et_2O$ instead of $HClO_4$	0	-
15	CH_3CN:H_2O (10:1) as solvent	21	64

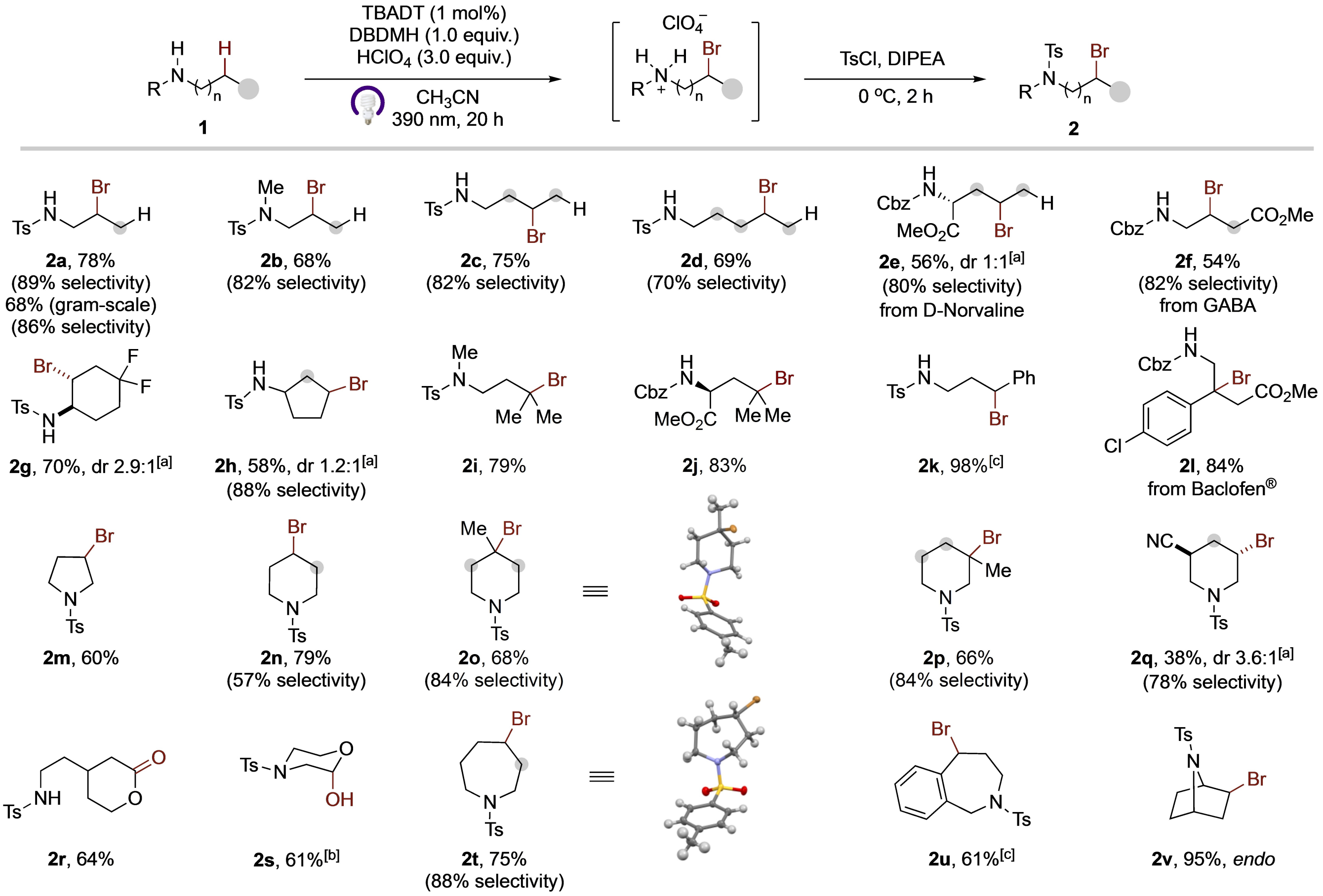




Scheme 2. DFT calculations (left) and Optimization of the reaction conditions (right). Left: Natural Population Analysis (NPA) and bond-dissociation energies (BDE, kcal·mol^{-1}) of C–H bonds for **1a** and **1a′** (B3LYP/6-311++G(d.p)). Lower NPA values indicate a particularly electron-rich C–H site. Right: Optimization of the reaction conditions: **1a** (0.40 mmol), $HClO_4$ (0.60 mmol), TBADT (1 mol%), DBDMH (0.20 mmol) in MeCN (1 mL) under 390 nm for 20 h. [a] ^1H NMR yield utilizing CH_2Br_2 as internal standard. [b] selectivity = (**2a′**/(**2a′**+**2a″**)). [c] **1a** (0.40 mmol), (Mes–Acr–Ph)BF_4 (5 mol%), K_3PO_4 (0.30 mmol), DBDMH (0.20 mmol) in HFIP (1 mL) under 450 nm for 20 h. [d] **1a** (0.40 mmol), NCS (0.20 mmol), $HClO_4$ (0.60 mmol), CCl_3Br (1.0 mmol) in MeCN:H_2O 10:1 (1 mL) under 450 nm for 20 h. TBADT=Tetra-*n*-butylammonium decatungstate. DBDMH = 1,3-dibromo-5,5-dimethylhydantoin. NBS = *N*-bromosuccinimide. NCS = *N*-chlorosuccinimide. BArF=Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate. TfOH=Trifluoromethanesulfonic acid.

N-chlorosuccinimide (NCS) as HAT reagent.[17] The latter finding is particularly noteworthy, revealing that a judicious choice of the HAT reagent is required for the reaction to occur with high levels of regioselectivity. In addition, low yields and site-selectivities were found when utilizing otherwise related Br_2 or *N*-bromosuccinimide (NBS) as bromine sources (entries 7–8). It quickly became apparent that the nature of the Brönsted acid or the photocatalyst had a non-negligible impact in the reaction outcome. Indeed, the utilization of Brönsted acids other than $HClO_4$ displayed markedly lower reactivity, thus suggesting a non-negligible influence of the escorting counterion (entries 9–11) in both reactivity and site-selectivity. This observation was further corroborated by not observing even traces of **2a**′ or **2a**″ when promoting an otherwise identical $C(sp^3)$–H functionalization in AcOH, with Brookhart's acid ($H[BArF]_4$) or with $BF_3\cdot Et_2O$ in lieu of $HClO_4$ (entries 12–14). Note, however, that low site-selectivities were found in the presence of water in the solvent mixture (entry 15).

With optimized conditions in hand, we sought to examine the generality of the remote $C(sp^3)$–H bromination in a series of amine-containing sp^3 architectures. As shown in Scheme 3, a variety of acyclic alkyl amines could be employed as substrates with similar ease, resulting in the targeted *N*-sulfonyl or - benzyloxycarbonyl protected amines upon simple treatment with TsCl/CbzCl with DIPEA to facilitate the isolation of the brominated ammonium salt intermediate (**2a**–**2v**). The subtle control that electronic effects exert on site-selectivity is illustrated in the **2a**–**2d** series: preferential β site-selectivity was observed regardless of whether primary or secondary aliphatic amines were utilized (**2a**, **2b**) whereas γ- and δ- site-selective bromination was observed in structures possessing longer side-chains (**2c**, **2d**), respectively. It is worth noting that 70% selectivity against all other possible regioisomers was observed for **2d**, even in the presence of multiple, yet similar, $C(sp^3)$–H sites. These results indirectly suggest that the electronic influence of the ammonium salt on hydrogen-atom transfer is progressively attenuated at long range and that $C(sp^3)$–H bromination occurs predominantly at the furthest methylene site of the amine substrate, an observation that was corroborated by DFT calculations (see Supporting Information, Table S5–7). As shown for **2e** and **2f**, unprotected amino acids can be directly subjected to the optimized



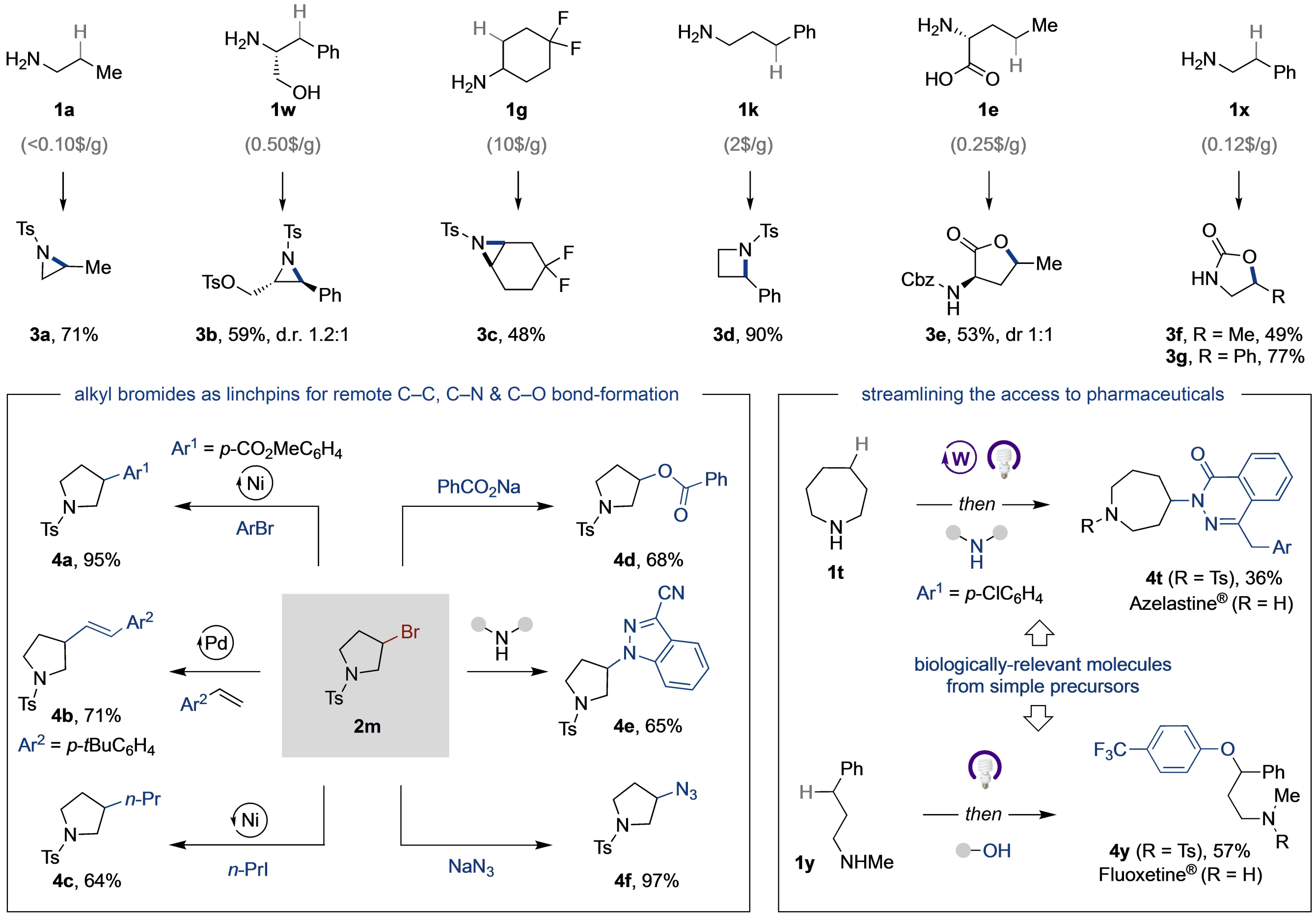
Scheme 3. $C(sp^3)$–H bromination of aliphatic amines and saturated nitrogen-containing heterocycles. Reaction conditions: **1** (0.40 mmol), $HClO_4$ (0.60 mmol), TBADT (1 mol%), DBDMH (0.20 mmol) in CH_3CN (2 mL) under 390 nm for 20 h, then TsCl (0.60 mmol), DIPEA (1.50 mmol) at 0°C for 2 h. See Supporting Information for details; isolated yields, average of at least two independent runs. The selectivity corresponds to the ratio of product to the other regioisomers. [a] dr values refer to the main product. [b] Further oxidation to the lactone was observed in 10% yield. [c] without TBADT.

reaction conditions to undergo the targeted C(sp^3)–H bromination event. As evident from the results compiled in Scheme 3, the inclusion of functional groups at the side-chain had a non-negligible impact on site-selectivity, probably by changing the electronic properties of all C(sp^3)–H bonds. For instance, γ-bromination was observed for **2e**, whereas β-functionalization was found predominantly in **2f**. A similar behavior was found when promoting the C(sp^3)–H bromination of cyclohexan-1-amines possessing a *gem*-difluorinated backbone, resulting in exclusive β-C(sp^3)–H bromination in good yields (**2g**). Moreover, the absence of electron-withdrawing groups in the cyclopentylamine core resulted in bromination at the most distal methylene position from the protonated ammonium core with an excellent regioselectivity pattern (**2h**). As expected, C(sp^3)–H bromination could be easily conducted at tertiary and benzylic C(sp^3)–H centers (**2i–2l**), even using commercial drugs such as Baclofen® (**2l**) with excellent site-selectivity profile.

Prompted by the ubiquity of piperidine and pyrrolidine heterocyclic scaffolds in several of the top-selling small molecule pharmaceuticals and natural alkaloids, we turned our attention to assess the suitability of promoting a site-selective bromination in these pharmacophores.[18] While β-bromination was exclusively observed for pyrrolidine (**2m**), a site-selectivity switch was observed for larger nitrogen-containing heterocycles such as piperidine and azepane. Although low γ:β selectivity was observed in the former (**2n**, see Supporting Information for an explanation, Table S7), the utilization of the latter resulted in a high γ:β ratio (**2t**, 88 % selectivity). It is worth noting that the inclusion of methyl substituents at the piperidine core delivered preferential bromination at tertiary C(sp^3)–H sites (**2o**, **2p**) whereas the presence of electron-withdrawing nitriles switched the γ-site-selectivity observed for **2n** en route to β-brominated products **2q**. This observation might a priori be attributed to electronic perturbations of the nitrile at the piperidine core. Note, however, that the presence of an ethereal fragment on the side-chain overrides the proclivity for functionalization at tertiary C(sp^3)–H bonds, resulting in lactone **2r** arising from a formal oxidation adjacent to the oxygen atom.[19] Interestingly, preferential formation of hemiacetal **2s** over its oxidized lactone (6:1 ratio) was found for morpholine backbones. Exclusive benzylic C(sp^3)–H bromination was observed for **2u**, while 7-azabicyclo[2.2.1] cores proved to be compatible, resulting in **2v** with exclusive endo selectivity. Taken together, the results compiled in Scheme 3 constitute an opportunity to rapidly and reliably promote site-selective functionalization at remote C(sp^3)–H sites of a series of aliphatic amines and saturated nitrogen-containing heterocycles, thus offering a gateway to access advanced intermediates of interest in medicinal chemistry.

Driven by the wealth of literature data on the utilization of unactivated alkyl halides for downstream applications,[20] we anticipated that our site-selective C(sp^3)–H bromination of unprotected amines might constitute a new gateway to access advanced heterocyclic and amine scaffolds of interest in medicinal chemistry from simple, yet readily available, precursors. In sharp contrast to the venerable Hofmann-Löffler-Freytag (HLF) reaction[21] that ultimately generates either pyrrolidine or piperidine scaffolds from N-halogenated amines via either 1,5- or 1,6-HAT, we anticipated that our site-selective C(sp^3)–H bromination of primary or secondary amines would provide a more customized, flexible and modular strategy to obtain heterocycles with different ring-sizes.[22] As shown in Scheme 4 (*top*), this turned out to be the case. Specifically, aziridines (**3a**-**3c**) or azetidines (**3d**)—heterocycles that are beyond reach in HLF reactions—could be easily prepared from the parent aliphatic amine by a one-pot bromination/C–N bond-formation sequence. The inclusion of carboxylic acids on the side-chain resulted in lactones via C–O bond-forming reaction under otherwise identical reaction conditions (**3e**). The modularity of our protocol is also exemplified in the synthesis of 2-oxazolidones by a tandem site-selective bromination/C–O bond-formation en route to **3f**–**3g**, thus offering the opportunity to access a different set of heterocycles from simple precursors. The potential of our site-selective bromination to rapidly access advanced heterocyclic scaffolds is additionally illustrated in the conversion of pyrrolidine into its corresponding β-substituted analogues **4a**–**4f** via **2m** and subsequent C–C or C-heteroatom bond-formations (*bottom left*). Specifically, Ni-catalyzed cross-electrophile coupling of **2m** with either aryl bromide or alkyl iodide allowed for forging either sp^2-sp^3 or sp^3-sp^3 architectures (**4a**, **4c**)[23] whereas **4b** was obtained by a Pd-catalyzed Heck-type reaction.[24] Moreover, heterocyclic cores possessing oxygen (**4d**) or nitrogen tethers (**4e**, **4f**) could also be within reach by promoting carbon-nitrogen or carbon-oxygen bond-formations with a wide range of nucleophiles. The formal total synthesis of Azelastine® and Fluoxetine® in three-steps from azepine **1t** or *N*-methyl-3-phenylpropan-1-amine **1y** stands as a testament to the synthetic applicability that our protocol might have to access advanced synthetic intermediates from simple, yet commercially available, precursors (*bottom right*).

In summary, we have developed a predictable, site-selective light-induced C(sp^3)–H bromination of unprotected primary and secondary amines by a subtle modulation of electronic effects. The transformation is distinguished by its broad applicability and experimental ease across a wide number of acyclic and heterocyclic amine scaffolds. The synthetic applicability of this protocol is illustrated by leveraging the proclivity of the intermediate halogenated compounds as synthons in further transformations, thus offering a valuable entry point to rapidly and reliably diversify medicinally-relevant aminated backbones at remote C(sp^3)–H sites. Given the ubiquity of primary and secondary amines in a myriad of compounds that display important biological properties, we anticipate that the broader consequences of this protocol will foster systematic investigations for streamlining the access to lead candidates in drug discovery campaigns in the context of late-stage diversification.



Scheme 4. Accessing advanced aliphatic amines by levering the potential of remote C(sp^3)–H functionalization *Top:* as for Scheme 2 followed by exposure with base, see Supporting Information for details. *Bottom left:* 1. Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (1 mol%), Ni(dtbbpy)Br$_2$ (2 mol%), methyl 4-bromo benzoate (0.2 mmol), **2m** (0.3 mmol), TTMS (0.2 mmol), Na$_2$CO$_3$ (0.4 mmol), DME (2 mL), blue LED, 14 h. 2. Ni(COD)$_2$ (10 mol%), (*S*)-*i*Pr-Pybox (8 mol%), **2m** (0.2 mmol), 1-iodopropane (0.6 mmol), Zn (0.6 mmol), DMA (1.5 mL), 25 °C, 12 h. 3. Pd(PPh$_3$)$_4$ (5 mol%), dppf (7 mol%), **2m** (0.2 mmol),1-(tert-butyl)-4-vinylbenzene (0.4 mmol), LiI (0.4 mmol), Cy$_2$NMe (0.3 mmol,), PhCF$_3$ (1.0 mL), 110 °C, 36 h. 4. **2m** (0.2 mmol), PhCO$_2$Na (0.60 mmol) and KI (0.22 mmol), DMF (1 mL), 70 °C, 16 h. 5. **2m** (0.2 mmol), 1*H*-Indazole-3-carbonitrile (0.60 mmol), K$_2$CO$_3$ (0.22 mmol), KI (0.22 mmol), DMF (1 mL), 70 °C, 16 h. 6. **2m** (0.2 mmol), NaN$_3$ (1.0 mmol), DMF (1 mL), 80 °C, 18 h. *Bottom right:* as for Scheme 3 followed by exposure with Na$_2$CO$_3$, see Supporting Information for details.

Acknowledgements

The authors thank ICIQ and FEDER/MCI—AEI/PGC2018-096839-B-I00 for financial support. J. C, S. Z. and J. R. thank China Scholarship Council (CSC) and the European Union's research and innovation programme Horizon Europe under the Marie Sklodowska-Curie grant agreement 10115032, respectively. We sincerely thank T. Noël (UvA) and F.-L. Haut for their help assembling the UFO reactor and for Quantum yield measurements, and J. Benet for X-ray crystallographic data.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: C(sp^3)–H functionalization · amine · C–H halogenation · Hydrogen-atom transfer · coupling

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Manuscript received: April 5, 2024
Accepted manuscript online: May 21, 2024
Version of record online: July 4, 2024