JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Site-Selective Aliphatic C−H Bromination Using *N*-Bromoamides and Visible Light

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Supporting Information

ABSTRACT: Transformations that selectively functionalize aliphatic C−H bonds hold significant promise to streamline complex molecule synthesis. Despite the potential for site-selective C−H functionalization, few intermolecular processes of preparative value exist. Herein, we report an approach to unactivated, aliphatic C−H bromination using readily available *N*-bromoamide reagents and visible light. These halogenations proceed in useful chemical yields, with substrate as the limiting reagent. The site selectivities of these radical-mediated C−H functionalizations are comparable (or superior) to the most selective intermolecular C−H functionalizations known. With the broad utility of alkyl bromides as synthetic intermediates, this convenient approach will find general use in chemical synthesis.

An important goal of modern chemical synthesis is to develop transformations that achieve the site-selective, intermolecular functionalization of isolated, unactivated aliphatic C−H bonds.[1] The low reactivity and relative ubiquity of these bonds in small organic molecules renders this task a formidable challenge.[2] The transformation of aliphatic C−H bonds to functional groups such as alcohols and alkyl halides is routinely performed in Nature by highly selective enzymes featuring tailored reaction sites and metal−oxo intermediates.[3] Accessing chemical reactions capable of achieving comparable levels of reactivity and selectivity has proven challenging; few examples of the functionalization of unactivated, isolated aliphatic C−H bonds exist that are both efficient and site-selective. While promising transformations involving aliphatic C−H alkylation, amination, or oxidation have been reported, the majority use large excesses of hydrocarbon substrate.[4] This requirement limits the utility of these transformations in contexts involving precious substrates (i.e., late-stage functionalization of complex molecules or pharmaceutical agents). Recently, intermolecular, site-selective oxidations of aliphatic C−H bonds with substrate as limiting reagent have begun to emerge. Foremost among these methods are the reactions of strained electrophilic heterocycles[5] and biomimetic Fe-catalyzed oxidation systems.[6]

Few site-selective methods exist for the intermolecular halogenation of aliphatic C−H bonds.[7] Moreover, existing C−H halogenations of alkanes commonly require an excess of substrate. A number of recent reports have disclosed promising catalytic C−H fluorination systems using substrate as the limiting reagent.[8] However, other practical, intermolecular C−H halogenations (i.e., bromination) are yet to be developed. Alkyl bromides are among the most widely used building blocks in synthetic chemistry and are readily converted to a diverse array of compounds via general methods such as heteroatom alkylation or organometallic cross-coupling.[9]

Hofmann-Löffler-Freytag processes use nitrogen-centered radicals to perform site-selective, intramolecular C−H functionalizations, including C−H halogenations.[10] These processes capitalize on the marked preference for 1,5-H-atom abstraction by heteroatom-centered radicals to achieve high site selectivities. Intermolecular, heteroatom-centered radical-mediated functionalizations of unactivated aliphatic C−H bonds, however, are rarely used in synthesis. Interestingly, there are preliminary reports indicating that site-selective, intermolecular C−H functionalizations using N-centered radicals may be possible,[11] however the use of strong acid as solvent (e.g., H_2SO_4) limits potential synthetic applications of these systems.[11a,b] We hypothesized that the development of a set of simple, stable reagents that deliver an array of unique N-centered radicals could enable a new approach to site-selective, intermolecular C−H halogenation. Tuning the steric and electronic parameters of the reacting species enables reagent-controlled C−H halogenations that override inherent substrate-controlled selectivities. We report herein an intermolecular, aliphatic C−H bromination that uses readily available *N*-bromoamides and visible light to achieve this goal (Figure 1).

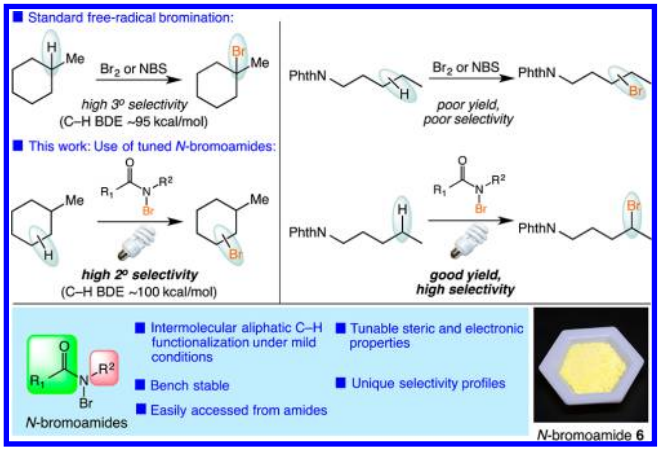
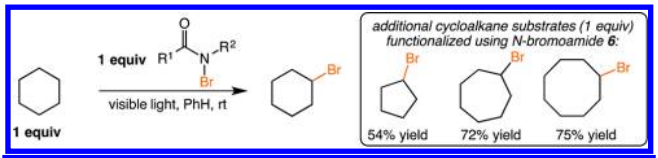


Figure 1. Radical-mediated aliphatic C−H brominations using *N*-bromoamides offer both high steric and electronic selectivities, enabling C−H brominations inaccessible using standard protocols.

Received: August 18, 2014

   dx.doi.org/10.1021/ja508469u | *J. Am. Chem. Soc.* XXXX, XXX, XXX−XXX

Table 1. Bromination of Cycloalkanes with *N*-Bromoamide Reagents Using Substrate as Limiting Reagent[a]



entry	reagent	yield (%)[b]
1	**1**: R^1 = Ph; R^2 = H	25
2	**2**: R^1 = Ph; R^2 = *t*Bu	44
3	**3**: R^1 = Ph; R^2 = CH_2CF_3	52
4	**4**: R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = CH_2CF_3	57
5	**5**: R^1 = 4-$NO_2C_6H_4$; R^2 = *t*Bu	65
6	**6**: R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = *t*Bu	70
7[b]	**6**: R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = *t*Bu	68

[a]Reactions were performed in PhH at rt under Ar using visible light irradiation with 1 equiv of substrate and *N*-bromoamide. Yields were determined by GC analysis. [b]Reaction performed under air atmosphere using commercial, unpurified reagents.

Table 2. Sterically Dictated Site Selectivities in the Bromination of Methylcyclohexane[a]

entry	reagents	% 2° Br	% 3° Br	$k_{secondary}/k_{tertiary}$
1	NBS, AIBN, 60 °C (neat in **8**)	37.8	62.2	0.06
2	Mn(TPP)Cl/NaOBr	79.8	20.2	0.40
3	bromoamide **1**	40.2	59.8	0.07
4	bromoamide **2**	98.1	1.9	5.2
5	bromoamide **3**	77.6	22.4	0.35
6	bromoamide **4**	79.8	20.2	0.40
7	bromoamide **5**	98.3	1.7	5.8
8	bromoamide **6** (1 equiv)	98.5 (75% yield)	1.5	6.6

[a]See Table 1 for conditions. Reaction yields and selectivities were determined by GC analysis.

Initially, we pursued the C−H bromination of simple cycloalkanes with substrate as limiting reagent. While there are reports of aliphatic C−H bromination using excess alkane substrate,[7] the only studies with substrate as limiting reagent that proceed with practical yields (i.e., >50%) require highly reactive superacids and are not suitable for general applications in synthesis.[12] We began with the bromination of cyclohexane (1 equiv) using a number of *N*-bromoamide reagents (**1**−**6**) (Table 1). These *N*-bromoamides are stable solids that are easily accessed from their parent amides.[13] The hindered, electrophilic *N*-bromoamide **6** provided cyclohexyl bromide in the highest yield of the reagents studied (70%, entry 6). Notably, these experiments were performed on the benchtop with common 100 W household bulbs (23 W fluorescent bulbs provided equivalent yields) and are complete in <30 min. While we typically perform these reactions under Ar using purified reagents and solvents; there is only a minor decrease in yield when the reaction is run in air with undistilled reagent-grade chemicals (68% vs 70%, entry 7). Stoichiometric reactions with other cyclic hydrocarbons proceeded with similar efficiencies. Dihalogenation was not observed in any appreciable amounts in these reactions. We attribute this to the electronic deactivation of the bromoalkane products.

In order to gain insight regarding the mechanism of the C−H halogenation, we determined the deuterium kinetic isotope effect by the competition reaction between cyclohexane and d_{12}-cyclohexane using reagent **6**. The observed primary kinetic isotope effect of k_H/k_D = 5.8 is consistent with irreversible hydrogen atom abstraction. Under identical conditions, neither Br_2 nor *N*-bromosuccinimide delivered more than a trace amount of product. This is consistent with an amidyl radical C−H abstraction step in our approach, as further demonstrated by the site selectivity studies below.

We next explored the potential for site-selective C−H functionalization. The ability to differentiate sites of functionalization on both steric and electronic bases (multidimensional selectivity) is paramount. Classical radical-mediated C−H brominations are often selective for tertiary C−H sites.[14] In addition, the preference for tertiary C−H functionalization is also characteristic of the majority of known polar or metal-catalyzed C−H functionalizations.[4e,15] We hypothesized that tuning the steric and electronic parameters of the putative amidyl radical involved in our system could offer the potential to overcome this inherent reactivity profile.

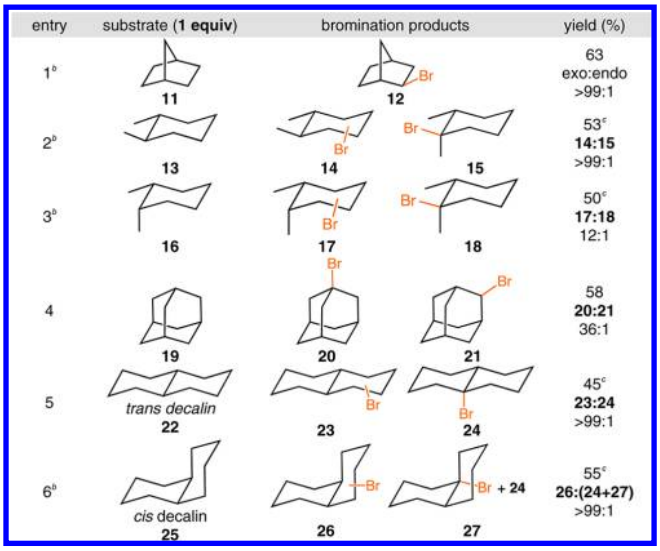
We began with the selective functionalization of methylcyclohexane (**8**) to survey the selectivity of secondary (desired) versus tertiary (undesired) C−H functionalization (Table 2). The bromination of methylcyclohexane using common reagent NBS (*N*-bromosuccinimide, entry 1) requires a large excess of substrate to deliver greater than a trace amount of product, and therefore was performed neat in methylcyclohexane. As expected, this reaction greatly favored halogenation at the tertiary C−H site after correcting for the number of tertiary (1) and secondary (10) sites available ($k_{secondary}/k_{tertiary}$, k_s/k_t = 0.06). Bromination using a biomimetic Mn-porphyrin system[7a] (entry 2) also favored tertiary halogenation (k_s/k_t = 0.40). The photochemical C−H bromination using bromoamide **1** proceeded with a k_s/k_t selectivity comparable to NBS (0.07, entry 3), while the reactions of *N*-bromoamides **3** and **4** were comparable to the Mn-porphyrin system (entries 5 and 6). However, the use of bulky *N*-*t*Bu reagents **2**, **5**, and **6** led to a marked increase for methylene functionalization, with bromoamide **6** providing >98% selectivity and k_s/k_t = 6.6 (entry 6). This level of methylene selectivity in the functionalization of a simple cyclic hydrocarbon is unmatched by any known system for aliphatic C−H halogenation.

A particularly intriguing aspect of these results is the ability to alter the site selectivity through changing the N-substituent of the reagent used. While N−H and *N*-trifluoroethyl *N*-bromoamides **1**, **3**, and **4** favor functionalization of the weakest C−H bond (tertiary), *N*-*t*Bu reagents **2**, **5** and **6** strongly favor functionalization at the less sterically hindered secondary sites. The ability to overcome inherent substrate dictated selectivity in intermolecular, aliphatic C−H functionalization is a notable goal,[6b] and the use of easily tuned radicals such as those presented herein offers an attractive solution to this problem.

Examination of the steric-based selectivity of our approach continued with a number of hydrocarbon substrates used as benchmarks for site-selective aliphatic C−H functionalization (Table 3). In each case, the C−H bromination proceeded with excellent levels of steric selectivity. The bromination of norbornane occurs exclusively on the *exo* face of the bicyclo[2.2.1]heptane framework (entry 1). The functionalization of *trans*-1,2-dimethylcyclohexane proceeds only at the

dx.doi.org/10.1021/ja508469u | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 3. Sterically Selective Aliphatic C−H Bromination of Diverse Hydrocarbons with Bulky *N*-Bromoamide 6[a]



[a]See Table 1 for conditions. Yields and selectivities were determined by GC analysis. For details regarding product distributions, see the Supporting Information. [b]Reaction performed using 1.5 equiv of **6**. [c]^{1}H NMR yield.

methylene sites (entry 2). The more challenging *cis*-1,2-dimethylcyclohexane contains a relatively unhindered tertiary equatorial C−H bond that is prone to react owing to the release of 1,3-diaxial strain.[16] Using **6**, the bromination remains selective for the methylene positions of the carbocycle (k_s/k_t = 3.0, entry 3). This remarkable level of methylene selectivity of aliphatic C−H halogenation with this substrate is higher than any other C−H functionalization method previously reported.[6,17]

The halogenation of adamantane proceeds with modest site selectivity with common radical halogenating agents (e.g., Br_2 and NBS), yet favors the less encumbered tertiary sites with sterically selective reagents.[18] The reaction of adamantane with *N*-bromoamide **6** was highly selective for the tertiary site (k_t/k_s >100), consistent with previous studies of amidyl radical selectivity (entry 4).[11c] The bromination of *trans*-decalin proceeds with excellent methylene site selectivity using **6** (>99%, entry 5). *Cis*-Decalin is a more challenging substrate for methylene-selective functionalization, and only modest 2°/3° selectivity has been achieved to date, owing to the presence of a reactive equatorial 3° C−H bond.[4d,19] With reagent **6**, the bromination of *cis*-decalin is also highly selective for methylene functionalization (>99%, entry 6), further demonstrating the unique levels of steric selectivities obtained using our system.

Next we surveyed the potential for electronic site selectivity in the C−H halogenation using methyl hexanoate as a test substrate (Table 4). The Mn-porphyrin-catalyzed bromination[7a] of this substrate is highly selective for the δ and γ sites, although there is little discrimination between these two positions (entry 1). Functionalization using *N*-haloamide **6** (2 equiv) leads to a δ-selective process, favoring functionalization of the methylene position furthest removed from the electron-withdrawing ester group (entry 2). We also observe γ-functionalization, but bromination with reagent **6** provides good selectivity between the δ and γ sites (δ:γ = 3.2:1).

Our studies of electronic selectivity continued with a set of linear functionalized hydrocarbons as substrates (Table 4, entries 3−6). The functionalization of phthalimide-protected pentyl-

Table 4. Studies of the Electronic Site Selectivity of the Aliphatic C−H Bromination with *N*-Bromoamide 6[a]

entry	reagents	% selectivity of bromination α	β	γ	δ	ω
		$MeO_2C-CH_2-CH_2-CH_2-CH_2-CH_3$				
1	Mn(TPP)Cl/ NaOBr	—	7.7	44.2	45.9	2.2
2	bromoamide **6**	5.2	10.1	18.1	58.8 (56% combined yield)	7.8

entry	substrate (1 equiv)	% selectivity of bromination α	β	γ	δ	ω	combined yield (%)
		EWG $-CH_2-CH_2-CH_2-CH_2-CH_3$					
3	PhthN **29**	—	—	6.5	81.8	11.7	56
4	NC **30**	3.2	2.7	11.6	68.3	14.2	50
5	**31**	13.3	8.3	16.2	53.8	8.4	72
6	F_3C **32**	—	3.6	13.4	66.6	16.4	73
7	**33**			30.1	58.7	11.2	66 (92)[b]
8	NPhth **34**	NPhth **35** 46.1 dr = 80:20		NPhth **36** 45.4 dr = >95:5[c]		+ 8.5% **C2**	61

[a]Reactions were performed in PhH at rt using visible light with 1 equiv of substrate and 2 equiv **6**. Yields and selectivities were determined by GC analysis. [b]Reaction yield using 5 equiv of substrate and 1 equiv **6**. [c]The dr was determined by ^{1}H NMR analysis.

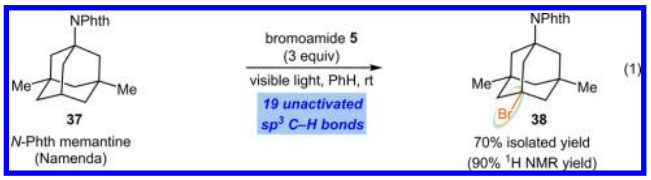
amine using reagent **6** proceeded with even greater site selectivity than methyl hexanoate, with a remarkable 81.8% selectivity for the δ site (entry 3). No α or β functionalization was observed, clearly indicating the excellent potential for electronically dictated site selectivity using protected primary amines. The functionalizations of both hexanenitrile and heptan-2-one also proceeded with good δ selectivities (68.3% and 53.8%, respectively, entries 4 and 5). The promising level of δ selectivity with heptan-2-one is intriguing given the known protocols for the α-halogenation of ketones using simple brominating agents (e.g., NBS) and visible light.[20] The reaction of pentyl trifluoroacetate also displayed good δ selectivity (66.6%, entry 6). Bromination of *n*-hexane was 58.7% δ selective, indicating the possibility of a minor steric component in reactions of linear substrates (entry 7). A minor amount of dihalogenation of *n*-hexane was observed; therefore, a reaction using an excess of substrate was performed to determine the site selectivity. While further studies will seek reagents with improved selectivities, the efficiency of these reactions already positions this method as a practical (>50% yield) approach to C−H bromination.

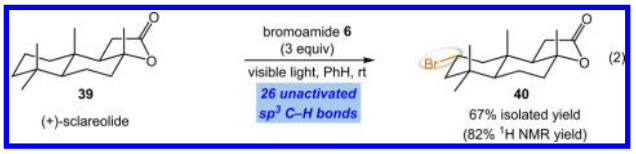
We also examined the site selectivity using a functionalized cycloalkane substrate, phthalimide-protected cyclohexylamine (entry 8). The C−H bromination favored reaction at the C3 and C4 positions (91.5%), with only a minor amount (8.5%) of the C2 product detected. The C3 bromination delivered the 1,3-*cis* product as a single diastereomer, and the C4 bromination proceeded diastereoselectively to yield two products with a 80:20 dr favoring functionalization *trans* to the phthalimide group. The potential for diastereoselective methylene C−H halogenation is

dx.doi.org/10.1021/ja508469u | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

intriguing and is a useful complement to C−H oxidation approaches which typically deliver sp^2-hybridized ketone products at methylene sites.

We have also begun an initial survey of more complex substrates (eqs 1 and 2). Amino-adamantanes are found in a large





number of pharmaceuticals, typified by the anti-Alzheimer's drug Namenda. The functionalization of the adamantane core is usually achieved via electrophilic bromination using excess bromine (~10 equiv).[21] This strategy has not been successful using nitrogen- or oxygen-substituted adamantanes; the simple electrophilic halogenation of amino-adamantanes is unknown. The site-selective C−H bromination using *N*-bromoamides proved to be an excellent solution. Functionalization of the *N*-phthalimide derivative of memantine (**37**) using *N*-bromoamide **5** delivered tertiary bromination product **38** in good isolated yield (70%), with complete site selectivity. As observed in the reaction of adamantane (**19**, see Table 3), the amidyl radical favors C−H abstraction at the less-hindered tertiary C−H site.

The terpenoid natural product (+)−sclareolide (**39**) contains 26 aliphatic C−H bonds, with diverse steric and electronic control elements, and has recently been studied using a number of C−H functionalization methods.[6a,7a,d,8] The functionalization of **39** using reagent **6** under visible light irradiation at room temperature provides the C2-equatorial bromination product **40** in 67% isolated yield as a single regio- and stereoisomer. Notably, as with all C−H brominations reported herein, the substrate is the limiting reagent, and no recycling of unreacted starting material is required. For comparison, the only other reported C−H bromination of (+)-sclareolide involves a large excess of substrate and proceeds with <5% conversion to a mixture of brominated derivatives.[7d]

In conclusion, we have developed a site-selective, intermolecular bromination of unactivated, aliphatic C−H bonds using *N*-bromoamides and visible light. The high efficiency of this radical-mediated process permits the use of hydrocarbon as limiting reagent in all examples, which is critical to future applications in complex synthesis. These reactions proceed with site selectivities that rival the most selective intermolecular C−H functionalizations known. Expansions of this approach to site selective C−H functionalization to other classes of small molecules and synthetic transformations are currently underway, with the ultimate goal of developing a set of easily accessed reagents capable of practical, predictable, and site-selective C−H functionalizations by way of tuned heteroatom-centered radicals.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by UNC Chapel Hill, a Venable Fellowship (V.A.S.) and an NSF graduate fellowship (R.K.Q).

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