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Catalyst-Controlled C–H Functionalization of Adamantanes using Selective H-Atom Transfer

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ABSTRACT: A method for the direct functionalization of diamondoids has been developed using photoredox and H-atom transfer catalysis. This C–H alkylation reaction has excellent chemoselectivity for the strong 3° C–H bonds of adamantanes in polyfunctional molecules. In substrate competition reactions, a reversal in selectivity is observed for the new H-atom transfer catalyst reported here when compared to five known photochemical systems. Derivatization of a broad scope of diamondoids and adamantane-containing drugs highlights the versatility and functional group tolerance of this C–H functionalization strategy.

KEYWORDS: photoredox catalysis, H-atom transfer, C-H functionalization, drug derivatization, adamantane

The direct functionalization of aliphatic C-H bonds is critical to the large-scale processing of hydrocarbon feedstocks and its inherent chemical difficulty has inspired the development of new methods that push the frontiers of reactivity and selectivity in organic synthesis. In particular, the selective functionalization of one type of C-H bond in the presence of a variety of different C-H bonds represents a long-standing challenge.¹ Many successful strategies employ a directing group to guide a metal catalyst to the desired site of reactivity, while others rely on the innate reactivity of weak C-H bonds such as those at tertiary, benzylic or heteroatom-substituted positions (Figure 1A).^{2,3,4} New methods that bypass such activated positions in favor of unactivated aliphatic C-H bonds would significantly broaden the potential applications of direct C-H functionalization.1 A difficulty for the selective activation of strong alkane C-H bonds is the high kinetic barrier associated with their cleavage. Intermediates capable of activating these bonds often do so at the expense of selectivity, limiting applications in complex molecules due to poor functional group compatibility.

The diamondoids are a compelling substrate class for the investigation of selective C–H functionalization due

to the unusually high C–H bond strengths.⁵ The rigid caged structure of adamantane (1, Figure 1A) results in





Figure 1. Strong adamantane bonds lead to functionalization challenges: previous methods unselective compared to amine radical cation **5**.

an increased 3° C-H bond dissociation energy (BDE) of 99 kcal/mol, which exceeds the 2° C-H BDE of 96 kcal/mol and most other hydrocarbons.⁶ The unique structure and chemical properties of diamondoids have led to many applications in nanoscale frameworks, optical materials and clinically approved drugs (e.g. anti-dementia).7,8 Hydrogen memantine. atom abstraction methods that directly generate the adamantyl radical include halogen and alkoxyl radicals, as well as catalytic hydrogen atom transfer (HAT) species such as diarylketone and decatungstate photocatalysts (Figure 1B).⁹ The high reactivity of these abstractors results in variable, often low selectivity between different types of C-H bonds, rendering them impractical for many applications.^{10,11} We sought to overcome previous limitations through the systematic study of adamantanes to identify a catalyst system that can target strong C-H bonds in the presence of weaker activated bonds. Recent reports have highlighted the power of HAT to activate a range of C–H bonds using photoredox catalysis.^{12,13,14,15} In particular, MacMillan and coworkers have combined a quinuclidine-mediated HAT cycle with several C–C bond forming processes.14 Herein, we report a new 3° amine-based HAT catalyst system that leverages chargetransfer character in the C–H functionalization step to provide high chemoselectivity independent of significant BDE differences (e.g. $4 \rightarrow 6$, Figure 1C).¹⁶ This dual catalyst system provides a general platform for the direct functionalization of diamondoids and an unprecedented selectivity profile in polyfunctional substrates.

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We began our studies by examining the reaction of adamantane with phenyl vinyl sulfone (7, Table 1).¹⁷ Inspired by reports of C-H functionalization reactions via heteroatom-stabilized radicals by MacMillan and others, we examined the use of quinuclidines as HAT catalysts due to the very strong N–H bond generated (\geq 100 kcal/mol).14,15lmn,18,19 We identified optimal conditions using the highly oxidizing photocatalyst $Ir(dF(CF_3)ppy)_2(d(CF_3)bpy)PF_6$ (Ir-1) and newly designed sulfonylated quinuclidinol Q-1 to provide alkylated product 8 in 79% yield by GC (72% isolated yield, Entry 1).²⁰ The optimized sulfonate derivative Q-1 is more effective than the previously reported acetate Q-2 or Q-3 (Entries 2 and 3) in terms of yield and reaction rate. A synergistic effect between the two catalysts was observed, as shown by the improved performance of Q-3 when paired with Ir-2 (66%, Entry 5 vs 3 and 4). While optimal yields are obtained with the alkene as Table 1. Optimization studies of adamantane alkylation^a

Ir-1 (2 mol%) Q-1 (20 mol%) H₂O (2 equiv) 'SO₂Ph 0.1 M DCE 8 7 blue LEDs (3 equiv) (1 equiv) Variation from Entry Conv. (7, %) Yield (8, %) "standard" conditions 1 none 100 79 (72) 2 Q-2 instead of Q-1 100 74 3 Q-3 instead of Q-1 55 33 89 4 Ir-2 instead of Ir-1 16 5 Ir-2 + Q-3 instead of Ir-1 + Q-1 100 66 6^b 1 (1 equiv) and 7 (2 equiv) 94 55 7 0.5 mol% lr-1 100 73 PF_6^{Θ} Ir-1, $R^1 = CF_3$, $R^2 = H$ Q-1, R = OSO₂Ph \mathbb{R}^2 Ir-2, $R^1 = H$, $R^2 = t$ -Bu Q-2, R = OAc Q-3, R = H SO₀Ph 9 (23%, entry 6) SO₂Ph

^aReaction performed on 0.5 mmol scale with 2 x 40W blue LED lamps. Conversion of **7** determined after 8h by ¹H NMR with internal standard. Yield of **8** determined by GC with internal standard. Isolated yield in parentheses. ^bConversion of **1** after 24h by GC with internal standard.

limiting reagent, the reaction proceeds in 55% yield when performed with limiting hydrocarbon (Entry 6), giving 23% of dialkylated product **9** as the major sideproduct. In addition, reducing the **Ir-1** loading to 0.5 mol% maintains high conversion and good yield (73%, Entry 7). In all cases, we observed complete selectivity for the 3° (C1) position of adamantane and detected no C2 products.11 Control reactions demonstrate that the iridium catalyst, quinuclidine catalyst and light are all necessary for this direct C–H alkylation process.19

With optimal catalytic conditions in hand, we investigated the scope of the alkylation reaction of adamantane (Table 2). A number of alkenes with different electron-withdrawing groups including sulfones, nitriles, ketones and esters are effective partners, giving a single regioisomer of product (8, 10-14, 57–91% yield).²¹ Ethyl acrylate was successfully employed in this chemistry using catalysts Ir-2/Q-3 to facilitate the more challenging reduction step of the catalytic cycle (see 52, Scheme 2).²² A dehydroalanine derivative was an excellent substrate in this C-H alkylation, delivering amino acid derivative 15 in 89% yield.²³ Olefins with two electron-withdrawing groups were particularly effective, including 1,2-disubstituted and trisubstituted variants (16-20, 82-94% yield). Adjacent tertiary and quaternary centers are forged, highlighting the power of radical chemistry to generate highly congested centers.²⁴

We also investigated the scope of adamantane coupling partners. As shown in Table 2, a broad range of substituents at the 1-position including alkyl, aryl, OH, halides and nitriles were well tolerated, providing the corresponding 3-alkylated products in 64-72% yield (21–26). Selected examples using only 1.5 equivalents of adamantane are shown in parentheses with a modest decrease in yield. Electron-deficient 2-adamantanone and 1-acetyladamantane could be alkylated in 60% and 75% yield, respectively. Direct comparison of sulfonate catalyst Q-1 and acetoxy Q-2 again shows that the more electron-deficient catalyst leads to a faster and highervielding reaction with several electron-withdrawn adamantanes (e.g. product 25: 42% (with O1) vs 24% (with Q2) at an early time point; see Table S13).19 Diamantane, the simplest higher order diamondoid, gave the corresponding sulfone product 29 in 62% yield and succinate product **30** in 65% yield as a 1.1–1.2:1 mixture of regioisomers. This implies a moderate inherent selectivity (\sim 3:1) for the apical position.²⁵ We also investigated the alkylation of clinically approved drug derivatives such as N-Boc-amantadine (31, 63% yield). N-Boc-memantine was alkylated with good efficiency

ACS Catalysis

using it as the limiting reagent to give tetrasubstituted adamantane **32** in 74% yield. A precursor to the antiacne medication differin underwent alkylation at the 3° position without significant interference of the electronrich aryl and methoxy groups (33, 51% yield). The success of this HAT strategy in medicinally relevant substrates

Table 2. Scope of direct alkylation of substituted adamantanes and diamantanes with electron deficient alkenes.^a



^aReaction performed on 0.5 mmol scale with 2 x 40W blue LED lamps, standard conditions, typically 8–48 h. All yields are isolated yields. ^bYield in parentheses with 1.5 equiv adamantane partner, determined by GC with internal standard. ^cReaction performed using **Ir-2** and **Q-3**. ^dSolvent is CH₃CN. ^eReaction temperature approximately 38 °C. ^fRegioisomeric ratio (r.r.) was determined by ¹H NMR of the purified product. Major isomer shown, minor site of reaction highlighted. ^g1 equiv *N*-Bocmemantine, 2 equiv 7.

demonstrates a level of versatility and predictability that is necessary for late-stage functionalization applications.

Next we investigated the selectivity of amine catalyst **Q-1** in polyfunctional substrates with multiple C_{sp}^3 -H bonds (Scheme 1). Boc-protected **34** derived from antiviral drug rimantadine was monoalkylated in 68% yield at the 3° position. We did not observe functionalization at the α -amino methine position, which is electronically activated but sterically hindered.14 An adamantane ester substrate bearing an additional tertiary site undergoes alkylation on the adamantane group (**35**, 70% yield, >20:1 r.r.). Aldehyde product **36** was formed in 70% yield with only 3% ketone product resulting from activation of the weak aldehyde C–H bond. Notably, Glorius and coworkers described a carboxyl radical HAT system that shows the opposite selectivity

in closely related substrates, favoring activation of the weaker aldehyde and 3° C–H bonds.15^{c,g,k} As a result, these methods represent *complementary* strategies for targeted C-H functionalization.

To assess the limits of the observed selectivity, we performed intermolecular competition experiments with prototypical substrates for HAT methodologies including alkanes, ethers, aldehydes, alcohols and amides.4·14·15 In all cases, the reactivity of adamantane was dominant and 46–80% of alkylation product **8** was obtained. Other tertiary C–H bonds such as those in norbornane and 2,2,4-trimethylpentane were virtually unreactive.²⁶ Only octanal, THF and isopropanol, having very electronically activated C–H bonds, gave significant amounts of product (14–27%), but adamantane **8** was still the major product.²⁷ We then

performed a competition with polyfunctional natural products and observed high chemoselectivity. Menthol was essentially unreactive, providing only 4% of the corresponding product **45** along with 75% of adamantane **8**. Progesterone, limonin and sclareolide (not shown) were also tested and no alkylation products were identified using catalyst **Q-1**, instead affording only adamantane product **8**.19 The wide range of C–H bond types that remain untouched in favor of adamantanes is a remarkable demonstration of the

• Polyfunctional substrates



Scheme 1. Competition experiments demonstrating the selective functionalization of adamantanes in the presence of activated C–H bonds.

chemoselectivity that is unique to the quinuclidine catalyst system reported here.

To further demonstrate this, we compared the chemoselectivity of amine **Q-1** for the strong C–H bonds of adamantane to several previously reported photocatalytic HAT systems (Table 3).9·12^c.15 While the amine-based catalyst system provided 4.5:1 selectivity for adamantane over octanal (Entry 1), all other catalysts investigated were either poorly selective (e.g. 1:2 for quinone photocatalysts) or favored functionalization of the weaker C–H bond (Entries 2– 6).19 The decatungstate photocatalyst and carboxyl radical gave moderate yields but a 1:5 ratio favoring octanal.²⁸ Similar trends were observed with THF competitions (Table S12), highlighting the unique selectivity profile of the 3° amine-based quinuclidine catalysts and the complementarity of substrate selectivity through proper catalyst selection.

In order to shed light on this new photoredox catalyzed reaction, we performed a series of mechanistic experiments. The alkylation reaction is inhibited by radical scavengers BHT and TEMPO. Stern–Volmer luminescence studies showed no quenching by adamantane or phenyl vinyl sulfone, however HAT catalyst **O-1**

 Table 3. Comparison of catalyst systems for C-H bond selectivity^a

	+ H_{6}^{O} + $cataly$	$r SO_2 Ph$ $r SO_2 Ph$ r S	+ _{C7} H ₁₅	SO ₂ Ph
3 equiv	3 equiv h ^r	v		42
Entry	Catalyst system	Yield 8	Yield 42	Selectivity
1	Ir-1, Q-1	63%	14%	4.5:1
2	2-CI-AQ ^b	11%	24%	1:2.2
3	PT⊄	13%	26%	1:2
4	TBADT ^d	8%	41%	1:5.1
5	Ir-2 , NBu₄OBz	7%	34%	1:4.9
6	Acr ^e , HPO ₄ ^{2–}	7%	7%	1:1
7	Ir-2, Q-3	55%	13%	4.2:1

^aReactions performed under standard conditions; see SI for catalyst structures and light source information. ^b2-Chloroanthraquinone. ^c5,7,12,14-Pentacenetetrone. ^d(Bu₄N)₄(W₁₀O₃₂). ^eNicewicz acridinium photocatalyst, see SI.

resulted in a dramatic decrease in luminescence.19 This is consistent with the redox potentials of these species; the excited photocatalyst Ir-1* ($E_{1/2}^{red}$ (*Ir^{III}/Ir^{II}) = +1.68 V vs saturated calomel electron (SCE) in CH₃CN)15^a is a sufficiently strong oxidant to generate the radical cation from quinuclidine Q-1 ($E_{1/2}^{red} = +1.41$ V vs SCE in CH₃CN).19 Similarly, photocatalyst Ir-2 is well matched with quinuclidine Q-3.29,18 The direct oxidation of adamantane by the photocatalyst or quinuclidine radical cation is not favorable ($E_{1/2}^{red}$ = +2.72 V vs SCE in CH₃CN), rendering a direct oxidation/deprotonation mechanism unlikely.10^{d,30} We also performed deuterium labeling experiments to investigate the HAT step (Figure 2). No incorporation of deuterium into the starting material or adamantyl C-H bonds of the product was observed, suggesting that HAT is irreversible. Small kinetic isotope effect (KIE) values obtained from an intramolecular competition experiment with $1-D_2$ (k_H/k_D = 1.6)

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ACS Catalysis



Figure 2. Deuterium labeling experiment and kinetic isotope effect experiments.



Scheme 2. Proposed mechanism of dual catalytic alkylation process and charge transfer model for selectivity.

and intermolecular competition experiments in parallel reactions ($k_{\rm H}/k_{\rm D} = 1.3$) indicate that the HAT process is likely not the turnover-limiting step in the catalytic cycle.³¹ These data are consistent with HAT as an irreversible, exergonic process with an early transition state, although other mechanistic possibilities cannot be ruled out at this point.14^a

Based on this evidence, the proposed mechanism begins with excitation of the photocatalyst followed by oxidation of quinuclidine **Q-1** to yield the radical cation **5** (Scheme 2). Subsequent HAT gives the corresponding ammonium **50** and adamantyl radical **2**, which rapidly adds to the electron-deficient olefin **51** to generate α acyl radical **52**.17 Reduction of radical **52** ($E_{1/2}^{red} = -$ 0.66 V vs SCE in CH₃CN)³² by iridium(II) intermediate **47** ($E_{1/2}^{red}$ (Ir^{III}/Ir^{II}) = -0.69 V for **Ir-1** and -1.37 V for **Ir-2** vs SCE in CH₃CN)29^{,15a} and protonation by quinuclidinium **50** (or water as a proton shuttle) provides the final product **13** and closes both catalytic cycles.

The optimal selectivity of quinuclidine Q-1 for C1 of adamantane over other "activated" substrates is proposed to result from enhanced polar effects. HAT is known to be highly influenced by polar effects and radical cation 5 is the only species examined that is positively charged, compared to neutral, oxygencentered radicals as H-atom abstractors in other protocols.9,14,16 This suggests that the high reactivity and selectivity of Q-1 can be attributed to increased charge-transfer character in the HAT transition state TS-1 that is further enhanced by the electron-withdrawing substituent.16 Increased positive charge development on adamantane is favorable due to the high stability of the 3°-adamantyl carbocation 53.6 Stabilization of this transition state does not depend on significant rehybridization of the sp³ carbons, which is unfavorable in the rigid cage structure of the diamondoids compared to competing substrates. Finally, while the electronwithdrawing substituent (OBs) on guinuclidine does not significantly change the reaction selectivity (Entries 1 and 7, Table 3), it generally increases the reaction rate and product yield. This effect is attributed to an increase in the driving force for HAT by strengthening the N-H bond of ammonium **50**.18

In summary, we have reported a highly selective C-H functionalization strategy for the direct alkylation of adamantanes in the presence of weaker alkyl and α heteroatom C-H bonds. A synergistic effect between the photocatalyst and electron-deficient quinuclidine HAT catalyst was observed for the first time, providing an unprecedented selectivity profile based on polar effects. New quinuclidine catalyst Q-1 enables a broad substrate scope with respect to alkenes, substituted adamantanes, diamantane and derivatives of clinically approved amines. The demonstration adamantyl of the accelerating effect induced by electron-withdrawing groups will benefit the design of stronger HAT catalysts based on the quinuclidine scaffold. We anticipate that this catalytic strategy will be amenable to other direct C-H functionalization reactions of adamantanes and higher order diamondoids and will greatly expand synthetic access to these fascinating molecules.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, ¹H and ¹³C NMR spectra of all new compounds (PDF)

Page 6 of 10

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Notes

No competing financial interests have been declared.

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