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

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Supporting Information Placeholder

ABSTRACT: A new 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 3º 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 six 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.

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 an increased 3º C–H bond dissociation energy (BDE) of

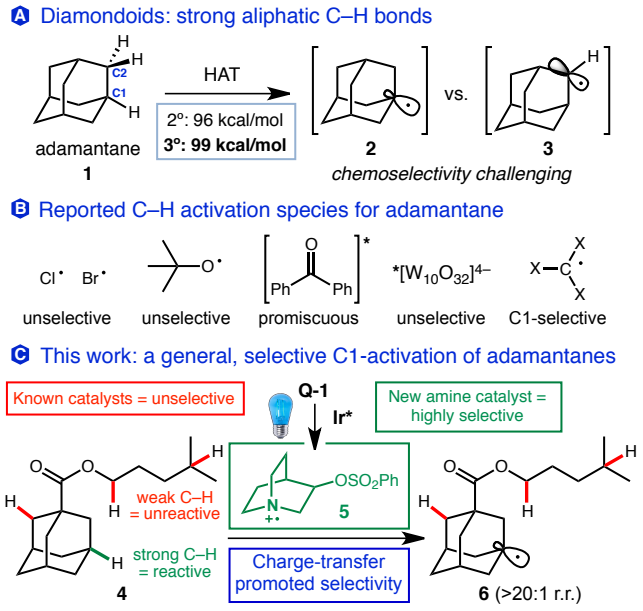


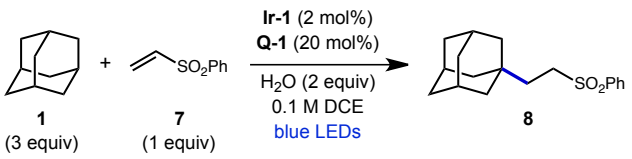
Figure 1. Strong adamantane bonds lead to functionalization challenges: previous methods unselective compared to amine radical cation **5**.

99 kcal/mol, which exceeds the 2º 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 memantine).[7,8] Hydrogen 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.[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] Herein, we report a new 3º amine-based HAT catalyst system that leverages charge-transfer character in the C–H function-

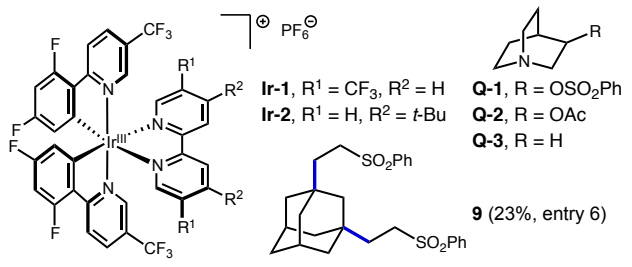
alization step to provide high chemoselectivity independent of significant BDE differences (e.g. **4** → **6**, Figure 1C).[16] This dual catalyst system provides a general platform for the direct functionalization of diamondoids and an unprecedented selectivity profile in polyfunctional substrates.

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 coworkers, we examined the use of quinuclidines as HAT catalysts due to the very strong N–H bond generated (≥ 100 kcal/mol).[14a,18,19,20] 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).[21] The optimized sulfonate derivative **Q-1** is more effective than the previously reported acetate **Q-2** or **Q-3** (Entries 2 and 3). 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 limiting reagent, the reaction proceeds in 55% yield when performed with limiting hydrocarbon (Entry 6). 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 3º (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.[20]

Table 1. Optimization studies of adamantane alkylation[a]



Entry	Variation from "standard" conditions	Conv. (**7**, %)	Yield (**8**, %)
1	none	100	79 (72)
2	**Q-2** instead of **Q-1**	100	74
3	**Q-3** instead of **Q-1**	55	33
4	**Ir-2** instead of **Ir-1**	89	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% **Ir-1**	100	73



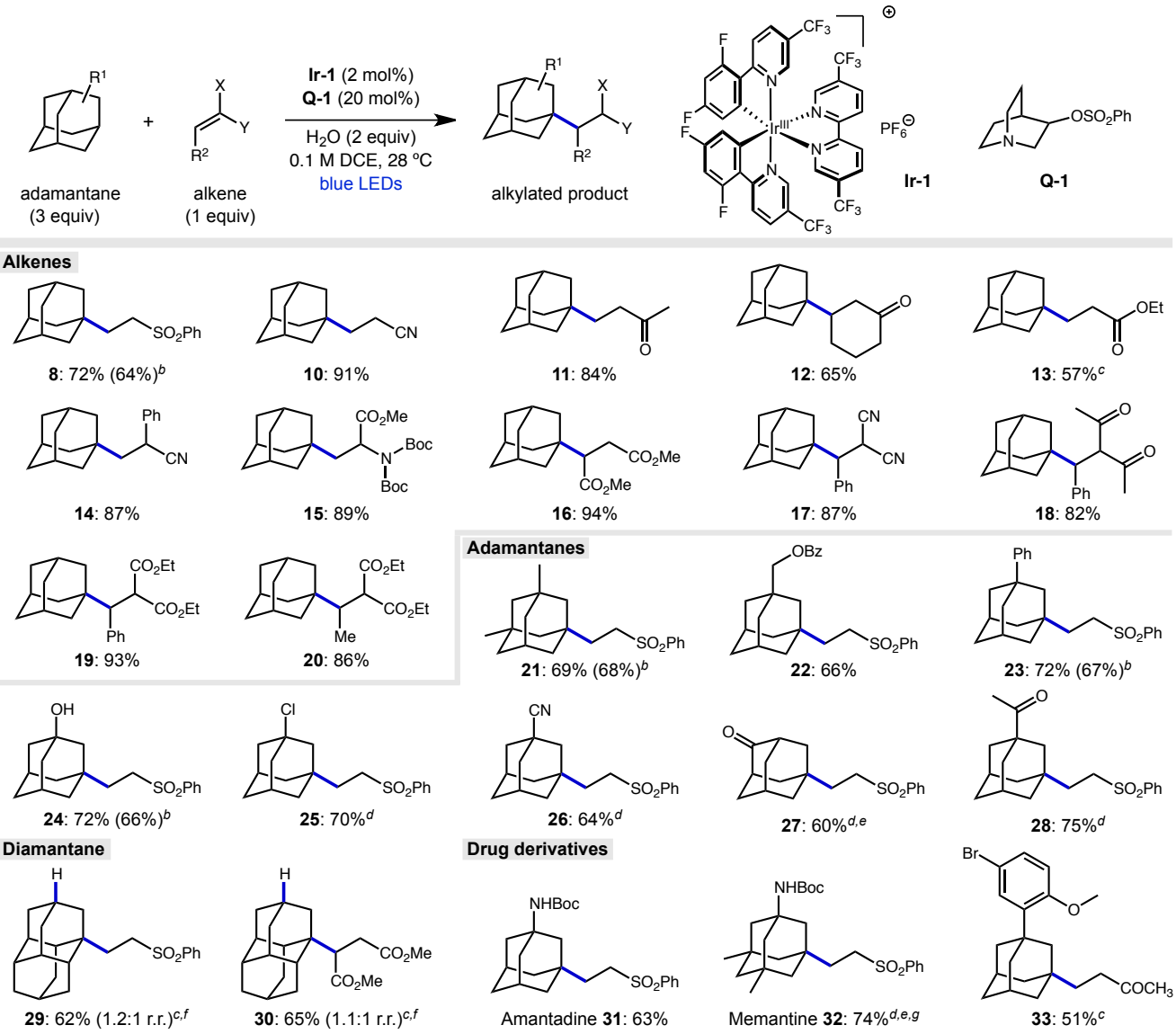
[a]Reaction performed on 0.5 mmol scale with 2x456 nm LED lamps. Conversion of **7** determined after 8h by ^{1}H NMR with internal standard. Yield of **8** determined by GC with internal standard. Isolated yield in parentheses. [b]Conversion of **1** after 24h by GC with internal standard.

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).[22] Ethyl acrylate was successfully employed in this chemistry using catalysts **Ir-2**/**Q-3** to facilitate the more challenging reduction step. 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. 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 (~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 using it as the limiting reagent to give tetrasubstituted adamantane **32** in 74% yield. A precursor to the anti-acne medication differin underwent alkylation at the 3º position without significant interference of the electron-rich aryl and methoxy groups (**33**, 51% yield). The success of this HAT strategy in medicinally relevant substrates 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

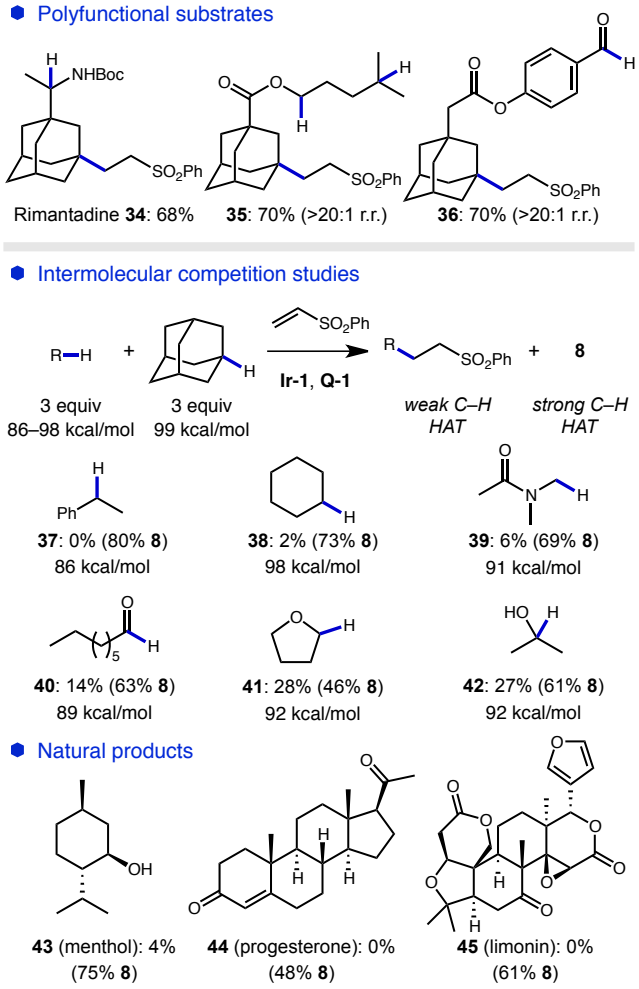
Table 2. Scope of direct alkylation of substituted adamantanes and diamantanes with electron deficient alkenes.[a]



[a]Reaction performed on 0.5 mmol scale with 2x456 nm LED lamps, standard conditions, typically 8–48 h. All yields are isolated yields. [b]Yield in parentheses with 1.5 equiv adamantane partner, determined by GC with internal standard. [c]Reaction performed using **Ir-2** and **Q-3**. [d]Solvent is CH_3CN. [e]Reaction temperature approximately 38 ºC. [f]Regioisomeric ratio (r.r.) was determined by ^{1}H NMR of the purified product. Major isomer shown, minor site of reaction highlighted. [g]1 equiv *N*-Boc-memantine, 2 equiv **7.**

at the 3º position. We did not observe functionalization at the α-amino methine position, which is electronically activated but sterically hindered.[18] 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 bonds.[14d,g,j] As such, 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. In all cases, the reactivity of adamantane was dominant and 46–80% of alkylation product **8** was obtained. 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. We then performed a competition with polyfunctional natural products and observed high chemoselectivity. Menthol (**16**) was essentially unreactive, providing only 4% of the corresponding product 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**.[20]



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

We compared the remarkable chemoselectivity of amine **Q-1** for the strong C–H bonds of adamantane to several previously reported photocatalytic HAT systems.[9,14,15] While the amine-based catalyst system provided 4.5:1 selectivity for adamantane over octanal (Scheme 1), all other catalysts investigated were either poorly selective (e.g. 1:2 for quinones) or favored functionalization of the weaker C–H bond (Table S#).[20] The decatungstate photocatalyst and carboxyl radical gave moderate yields but a 1:5 ratio favoring octanal. Similar trends were observed with THF competitions, highlighting the unique selectivity profile of the 3° amine-based catalyst **Q-1** 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 **Q-1** resulted in a dramatic decrease in luminescence.[20] 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 CH_3CN)[14b] is a sufficiently strong oxidant to generate the radical cation from quinuclidine **Q-1** ($E_{1/2}^{red}$ = +1.41 V vs SCE in CH_3CN).[20] Similarly, photocatalyst **Ir-2** is well matched with quinuclidine **Q-3**.[26,19] 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) and intermolecular competition experiments in parallel reactions (k_H/k_D = 1.3) indicate that the HAT process is likely not the turnover-limiting step in the catalytic cycle.[27] 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.[14a,28]

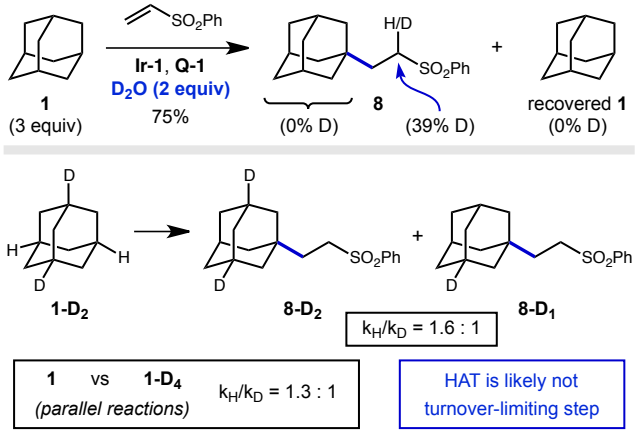
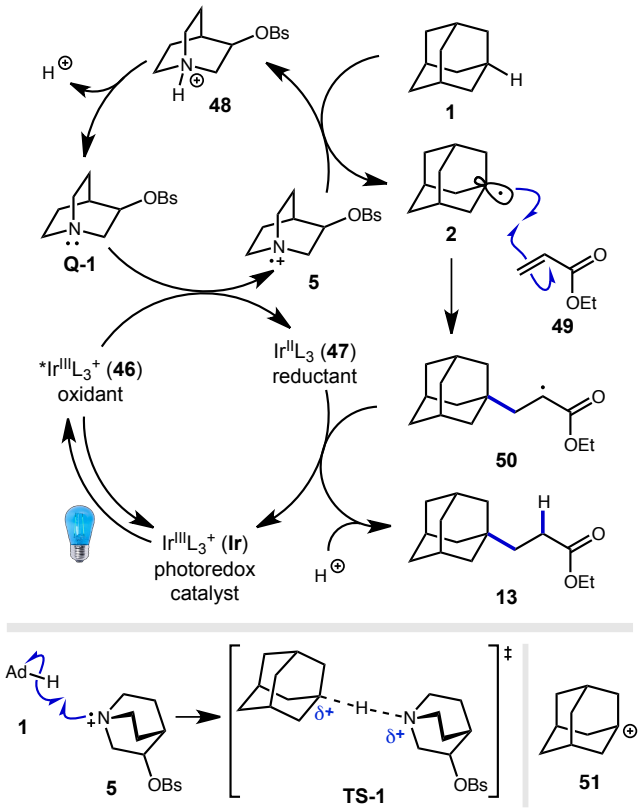


Figure 2. Deuterium labeling experiment and kinetic isotope effect experiments.

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 **48** and adamantyl radical **2**, which rapidly adds to the electron-deficient olefin **49** to generate α-acyl radical **50**.[17] Reduction of radical **50** ($E_{1/2}^{red}$ = –0.66 V vs SCE in CH_3CN)[29] 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 CH_3CN)[26,14b] and protonation by quinuclidinium **48** (or water as a proton shuttle) provides the final product **13** and closes both catalytic cycles.

The optimal performance of quinuclidine **Q-1** is in part because the electron-withdrawing substituent leads to an increase in the ammonium N–H BDE and the driving force for HAT.[19] Furthermore, HAT is known to be highly influenced by polar effects and radical cation **5** is the only species examined that is positively charged.[14a,16,18] This suggests that the high chemoselec-



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

tivity of **Q-1** can be attributed to increased charge-transfer character in the HAT transition state **TS-1**.[16] Increased positive charge development on adamantane is favorable due to the high stability of the 3°-adamantyl carbocation **51**.[6] This model also explains the superior C1/C2 selectivity compared with other protocols using neutral, oxygen-centered radicals as HAT species and contributes to the remarkable selectivity for adamantanes over substrates with weaker C–H bonds.

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 adamantyl amines. The demonstration 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, ^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

No competing financial interests have been declared.

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