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Synthesis of Amino-Diamondoid Pharmacophores via Photocatalytic C–H Aminoalkylation

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We report a direct C–H aminoalkylation reaction using two light-activated H-atom transfer catalyst systems that enable the introduction of protected amines to native adamantane scaffolds with C–C bond formation. The scope of adamantane and imine reaction partners is broad and deprotection provides versatile amine and amino acid building blocks. Using readily available chiral imines, the enantioselective synthesis of the saxagliptin core and rimantadine derivatives is also described.

Chiral amines are an important class of molecules found in bioactive natural products and pharmaceuticals, making them desirable synthetic targets. Many methods have been developed for their synthesis from classical approaches (e.g. Strecker, Ugi reactions[1] to modern stereoselective catalytic strategies.[2] Aminoalkylation reactions that simultaneously introduce a C–C bond and amine are particularly powerful (Figure 1A). Three main strategies for radical-mediated aminoalkylation are commonly used:[3] addition of an alkyl radical to an imine derivative (disconnection i),[4,5,6] radical conjugate addition into an α,β-dehydroamino acid (disconnection ii),[7] or the addition of a captodative α-amino radical to a radical acceptor.[8] The use of imine derivatives as radical acceptors has grown in recent years and typically involves the use an alkyl halide in conjunction with a radical initiator. Improvements on traditional initiators (e.g. Et_3B/O_2, Bu_3SnH/AIBN, etc.) with their associated drawbacks have been reported, such as photoredox activation of organosilicon and organoboron compounds by Molander, Gong and Friestad.[9] The importance of chiral amines highlights an ongoing need for efficient, stereoselective methods for their synthesis.

The direct aminoalkylation of hydrocarbons is an attractive but challenging method for direct C–H functionalization. The high reactivity required to perform H-atom transfer (HAT) of unactivated C–H bonds often leads to incompatibility with redox-sensitive functional groups and site selectivity issues on complex substrates.[10] As a result, most examples have focused on more reactive substrates such as ethers with activated α-heteroatom-C–H bonds that can be selectively targeted.[11] The C–H functionalization of diamondoids is challenging due to unusually high bond dissociation energies (BDEs) of these hydrocarbons (96 and 99 kcal/mol for 2º and 3º C–H bonds, respectively) and potential regioselectivity issues.[12] The aminoalkyl derivatives typified by rimantadine (**2**, Figure 1B) are especially prevalent in a variety of anti-virals,[13] HDAC inhibitors (martinostat)[14] and anti-diabetic agents (saxagliptin **3**),[15a] highlighting the utility of this pharmacophore.[15b] A direct aminoalkylation of diamondoids would provide an ideal method for their synthesis, which often relies on the reductive amination of acyl-derivatives such as **4**, as shown in Figure 1C.[13a] The adamantyl-glycine core of saxagliptin (**3**) has been synthesized

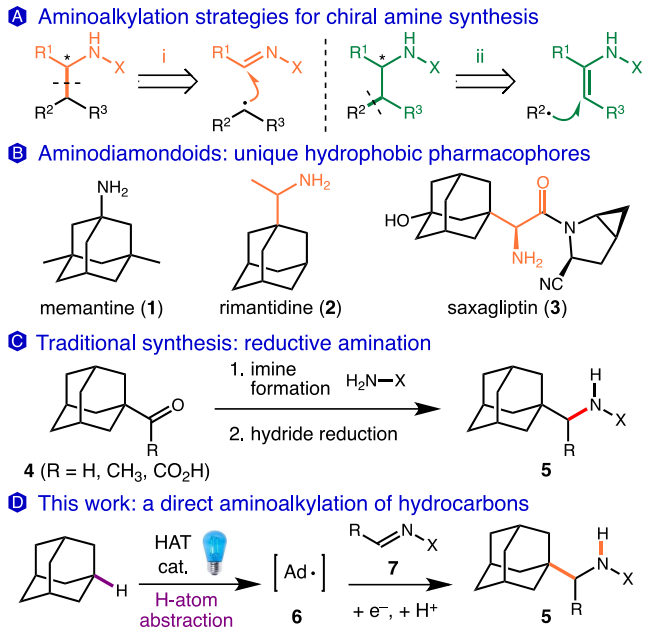

Figure 1. Bioactive aminoadamantanes and synthetic approaches for the preparation of aminoalkylated molecules.

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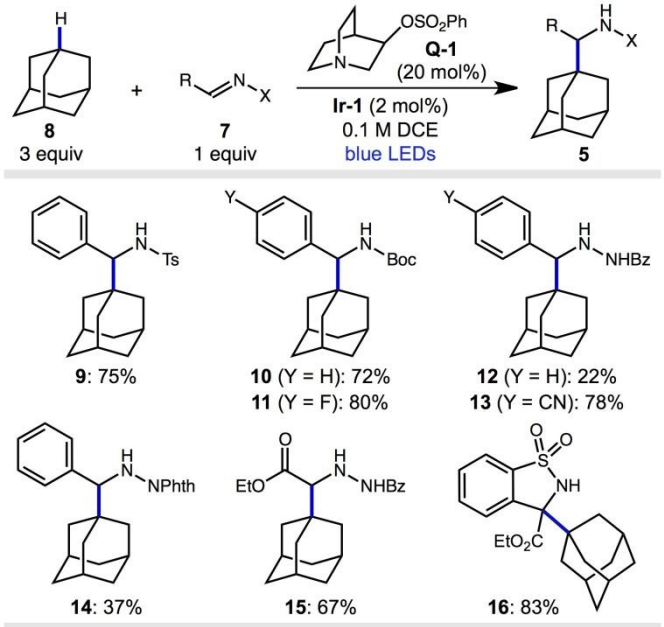
using asymmetric reductive amination or Strecker approaches.[15] This strategy necessitates pre-functionalization of adamantane and complicates the introduction of additional substituents on the adamantane core. Herein, we describe a photocatalytic method enabling the direct aminoalkylation of adamantanes without these drawbacks (Figure 1D).

Key to the efficient substitution of adamantanes is an HAT step that can overcome the strong C–H BDEs while maintaining high chemo- and regioselectivity. We recently reported a method for the alkylation of diamondoids with alkenes using a photoredox/HAT dual catalytic system.[16] This alkylation reaction displays unusual selectivity for the 3º C–H bonds of adamantanes over weaker C–H bonds. Using the combination of an oxidizing photocatalyst ($Ir(dF(CF_3)ppy)_2(d(CF_3)bpy)PF_6$, **Ir-1**) with an electron-deficient quinuclidine catalyst (quinuclidin-3-yl benzenesulfonate, **Q-1**),†[16] we explored the reaction of adamantane with various imine derivatives under blue-light irradiation (Table 1).[17,18] We found that Ts-imines and Boc-imines were efficient coupling partners, giving the aminoalkylated products **9** and **10** in 75% and 72% yield, respectively. Hydrazones were also competent radical acceptors in this reaction, however with lower efficiency (**12** and **14**, 22-37% yield). Substitution of the phenyl ring with an electron-withdrawing substituent such as *p*-F and *p*-CN led to higher yields, as shown for *N*-Boc **11** (80% yield) and *N*-Bz-hydrazide **13** (78% yield), consistent with a LUMO-lowering effect and the nucleophilic character of the adamantyl radical.[19] A Ns-protected imine was less efficient due to competing decomposition pathways (see ESI†). Other imines such as a glyoxalate derivative and a cyclic, trisubstituted sulfonylimine were excellent partners, giving esters **15** and **16** in 67% and 83% yield, respectively. Sulfonamide product **16** has adjacent fully substituted carbons, highlighting the power of radical addition reactions to generate congested C–C bonds.

Table 1. Survey of imine and hydrazone derivatives in aminoalkylation of adamantane.



Notes. Reactions performed on a 0.5 mmol scale using 2 x 40W 456nm lamps over 18-48 h. Reaction temp. maintained at approx. 28 °C with a small cooling fan. See ESI† for structure of **Ir-1**, **Q-1** and details. All yields are isolated yields.

Table 2. Scope of imine and hydrazone derivatives in aminoalkylation of adamantanes.

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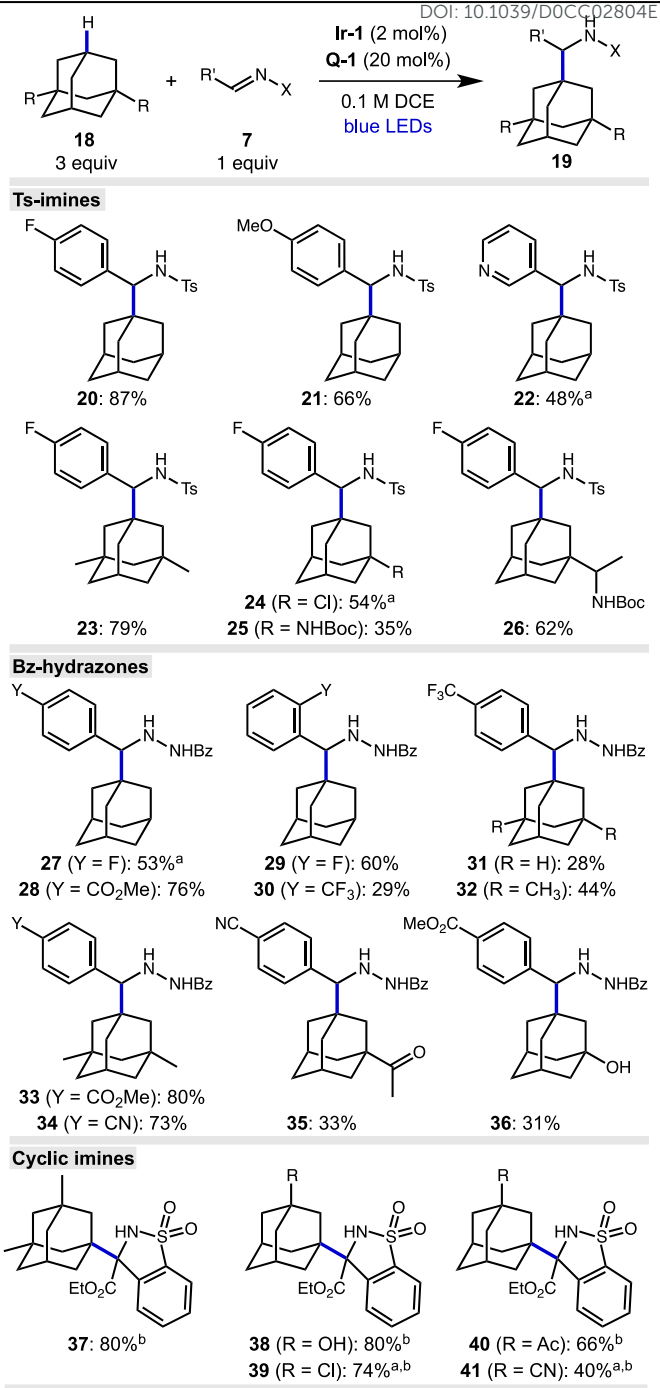


Notes. Reactions performed on a 0.5 mmol scale using 2 x 40W 456nm lamps over 24-72 h. All yields are isolated yields. [a]Solvent is CH_3CN. [b]2 equiv H_2O added.

We next explored the scope of imine and adamantane partners. As shown in Table 2, both electron-deficient and electron-rich Ts-imines are coupled with moderate to high yield. A pyridine substituent was tolerated with some substrate degradation observed (**22**, 48% yield). Electron-rich adamantanes were high yielding while electron-withdrawn adamantanes with a chloro and NHBoc substituent were incorporated with lower efficiency. The scope of hydrazide products

was broad, provided an electron-withdrawing substituent was present on the aryl group. Both *ortho*- and *para*-substitution was tolerated. The highest yields were achieved with electron-rich adamantanes and yields were diminished for acetyl- and hydroxyadamantane substrates (compare **34** and **35**, **28** and **36**). In general, the reaction rate was slower for hydrazone substrates. The scope of cyclic, alpha-3º amine products was also broad. Electron-rich and moderately electron-deficient adamantanes led to the highest yields for **37–39** (74–80% yield) while acetyl- and cyano-substituents showed more significant decreases (66% for **40**, 40% for **41**).

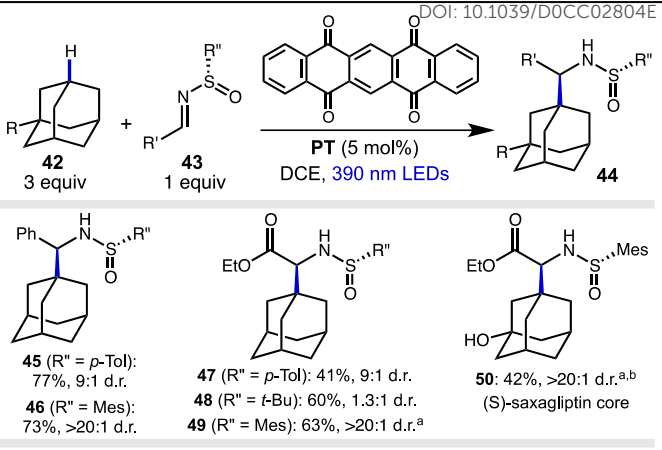
We then turned to the synthesis of enantioenriched α-adamantyl amines using our dual catalytic system in conjunction with chiral *N*-sulfinyl imines. The use of *N*-sulfinyl imines as chiral auxiliaries is a well-established strategy for the asymmetric synthesis of α-branched amines and α-amino acids.[20] There are fewer but nonetheless important examples of stereocontrolled radical additions.[4ab,21] Unfortunately, we found that using our **Ir-1/Q-1** system with a *N*-tolylsulfinimine **43** (R" = *p*-Tol) resulted in poor conversion and some decomposition, therefore we looked for possible alternative catalysts. Kamijo and coworkers have shown that using 5,7,12,14-pentacenetetraone (**PT**) as a photocatalyst provides a viable method for generating the desired 1-adamantyl radical **6**.[22,6e]

Gratifyingly, we found that the use of **PT** with 390 nm LEDs gave benzylic *N*-tolylsulfinamide **45** in good yield with moderate stereoselectivity (9:1 d.r., Table 3). A glyoxalate-derived imine also proceeded with 9:1 d.r., albeit in lower yield (**47**, 41% yield). Only marginal asymmetric induction was observed using the Ellman *N*-*tert*-butylsulfinyl auxiliary (**48,** 1.3:1 d.r.). The stereocontrol was significantly improved by switching to *N*-mesitylsulfinimines, providing **46** and **49** in good yields and >20:1 d.r.. Notably, use of *N*-mesitylsulfinimines provides a direct route to enantiopure adamantyl glycine precursor **49** and the 3-hydroxyadmantyl glycine core of saxagliptin **50** in a direct and highly selective manner, enabling further exploration of these unnatural building blocks.[15]

Next, we explored the performance of the aminoalkylation method with cyclohexane and tetrahydrofuran (Scheme S2†). Using the **PT** system, cyclohexane reacted with an *N*-tosyl imine in 31% yield. Tetrahydrofuran was selectively aminoalkylated at the α-oxy-C–H bond using **Ir-1/Q-1** in 50% yield. While the yields of these reactions are lower than related transformations by Gong[6e] and Dilman's recent report[6d] with a decatungstate HAT catalyst, we have found that TBADT is ineffective for activating adamantanes in this reaction (see ESI† for details). As a result, the catalyst systems described here provide a complementary substrate scope. Efforts to generalize this reaction manifold are ongoing in our laboratory.

Finally, we moved to the deprotection of representative reaction products to provide the free amines (Scheme 1). The use of samarium diiodide allowed efficient cleavage of the N–NHBz bond of **27** to afford free amine **51** (79% yield). Similarly, deprotection of the tosyl group was very efficient (92% yield). Cleavage of the sulfinyl group in sulfinamide **49** proceeded smoothly under acidic conditions to afford the corresponding adamantylglycine ethyl ester **52** in 53% yield.

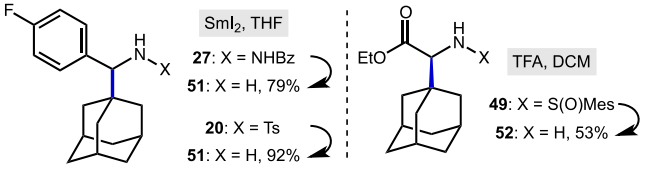
Table 3. Scope of chiral imines acceptors for preparation of enantioenriched amines.



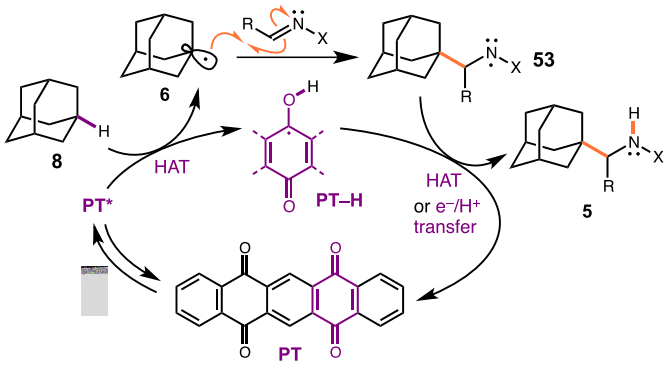
Notes. Reactions performed on a 0.3 mmol scale using 2 x 40W 390nm lamps over 24-48 h. Reaction temperature is approx. 34 °C. All yields are isolated yields. d.r. values obtained via ^{1}H NMR analysis of crude product mixture (see ESI† for details). [a]Reaction performed on a 0.5 mmol scale. [b]Solvent is 1:1 DCE:PhCl.

Based on related mechanistic work, we propose that this transformation parallels the previously reported alkylation reaction via either a direct HAT process for **PT** (Scheme 2) or an indirect HAT process for **Ir-1/Q-1** (Scheme S1†).[16,11b] For the direct HAT process, excitation of **PT** with light generates an excited state capable of H-atom abstraction to give radical **6**.[22] Addition of the radical to the imine or hydrazone gives an N-centered radical **53**. Turnover would either proceed via HAT from semiquinone **PT-H** to aminyl radical **53** or single electron reduction by **PT-H** followed by proton transfer. For the indirect process, excitation of the photocatalyst **Ir-1** followed by oxidation of quinuclidine **Q-1** yields the corresponding radical cation which can undergo HAT to give the adamantyl radical **6**.[16,17] Addition of the radical gives aminyl radical **53**, which can be reduced by Ir(II) to the corresponding anion. Proton transfer from the quinuclidinium ion gives the final product **5** and closes the catalytic cycle. While we cannot rule out an alternative mechanism proceeding via reduction of the imine or hydrazone to a radical anion at this time, the similar efficiency observed for a variety of *N*-substituents (Tables 1 and 3) with a range of reduction potentials is less consistent with literature examples that proceed via this mechanism.[6e,24]

In conclusion, we have described a direct aminoalkylation reaction promoted by selective hydrogen atom abstraction. A dual catalytic system consisting of an Ir-photocatalyst and quinuclidine co-catalyst enables the efficient coupling of diverse imines, hydrazones and adamantane coupling partners with high chemoselectivity. In addition, a quinone catalyst **PT** provides high yields for the enantioselective synthesis of aminoalkylated derivatives of known bioactive molecules and unnatural amino acids. The catalyst systems described tolerate



Scheme 1. Deprotection reactions with SmI_2 and TFA to afford free amines.



Scheme 2. Mechanism of **PT**-catalyzed aminoalkylation reaction.

other substrate classes beyond adamantanes, albeit in lower yield, providing a complementary method to other HAT catalysts. Applications to the synthesis of aminoalkylated analogs of the antiviral rimantadine pharmacophore and amino acid building blocks are under active investigation in our laboratory and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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