Intermolecular amination of allenes via twofold photocatalytic nitrene transfer reactions

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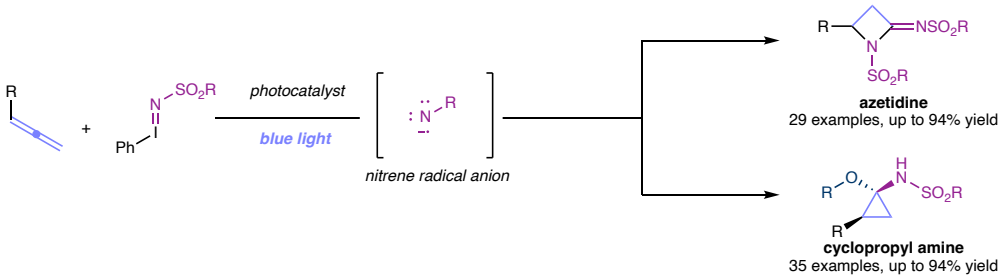


Abstract: The amination with monovalent, nitrogen-based intermediates constitutes an important reaction for the construction of valuable amines. The high basicity of reagents, reaction intermediates or products however poses significant challenges to metal-catalyzed amination through coordination and blocking of catalytically active sites and hampering their efficiency. In this context, high-yielding intermolecular amination reaction of allenes remain an unsolved challenge in organic synthesis and general methods are not available. Herein, we describe a photochemical approach towards the intermolecular amination of allenes via free nitrene radical anions as the key reactive intermediate. This reaction proceeds without the participation of catalyst-bound nitrogen species and can thus overcome current limitations. We report on the application in the amination of allenes to give azetidine and cyclopropyl amines with a broad and general substrate scope. Experimental and theoretical studies were performed to provide an understanding of the reaction mechanism and rationalize the high efficiency of this photocatalytic approach.

Introduction

Amines constitute a key structural feature in the design and development of active ingredients in agrochemical and pharmaceutical research.[1,2] The introduction of an amine functional group – an amination reaction – is commonly achieved by textbook S_N type reactions or by cross-coupling reactions in the presence of precious metal catalysts that often requires pre-functionalized building blocks, forcing reaction conditions and careful separation of trace impurities of the metal catalyst. The direct amination reaction at room temperature with reactive nitrogen-based intermediates, such as nitrogen-based radicals[3,4] or nitrenes,[5–9] is one of the main strategies to overcome these fundamental challenges. However, the basic nature of amines comprises one of the main drawbacks in the development of such reactions and can easily lead to complexation of metal catalysts resulting in reduced catalytic efficiency or even catalyst poisoning.[5,10,11] Metal-catalyzed nitrene transfer reactions thus mainly focus on the amination of reactive substrates, such as olefins, sulfides or activated C-H bonds in the presence of Rh, Ag or Cu catalysts among others.[8,12] These catalysts however prove inefficient in a generalized amination reaction of allenes and current methods remain strictly limited (Figure 1a).[13,14] The only high-yielding approach lies within the development of intramolecular, oxidative amination reactions as demonstrated independently by the Blakey,[15,16] Robertson,[17] and Schomaker[18–21] groups using Rh(II) or Ag(I) catalysts (Figure 1b). The intermolecular nitrene transfer reaction with allenes is however much more challenging.[11,22–24] Early reports significantly lack synthetic utility and, for example, the reaction of ethoxy carbonylnitrene with allenes yields only 14% of a spirocyclic diaziridination product.[24] More recently, Maseras, Díaz-Requejo and Pérez reported on the reaction of iminoiodinanes in the presence of a Ag(I)Tp^x (hydrotrispyrazolyborate) complex that gave an intriguing azetidine albeit only a single example with a synthetically useful yield of >50% is reported.[11] Despite of this important recent advancement, the intermolecular amination reaction of allenes remains a significant challenge.

We hypothesized that the unfavorable reaction efficiency of metal-catalyzed amination reactions of allenes may be reasoned by the strong coordinating properties of basic nitrogen species along the reaction pathway that in turn would result in reduced reaction yield. Indeed, multiple key reaction steps in the silver-catalyzed intermolecular amination reactions of allenes involve an energetically unfavorable cleavage of the silver catalyst. We therefore considered that a photochemical approach should be ideally suited to overcome these limitations (Figure 1c).[25] Photochemical conditions allow the access of monovalent nitrogen-based intermediates to either access light-assisted metal-catalyzed amination reactions via metal nitrene intermediates[26–29] or – in the absence of conventional metal catalysts – allow to access amination reactions with free nitrene or nitrene radical anion intermediates.[30,31] The latter approach should now circumvent unfavorable, catalytic reaction pathways as substrate inhibition of the catalyst by basic intermediates cannot occur. As a net result, the reaction of a free nitrene species under catalyst-free conditions may be suitable to overcome above limitations and provide a high-yielding approach towards intermolecular nitrene transfer reactions with allenes.

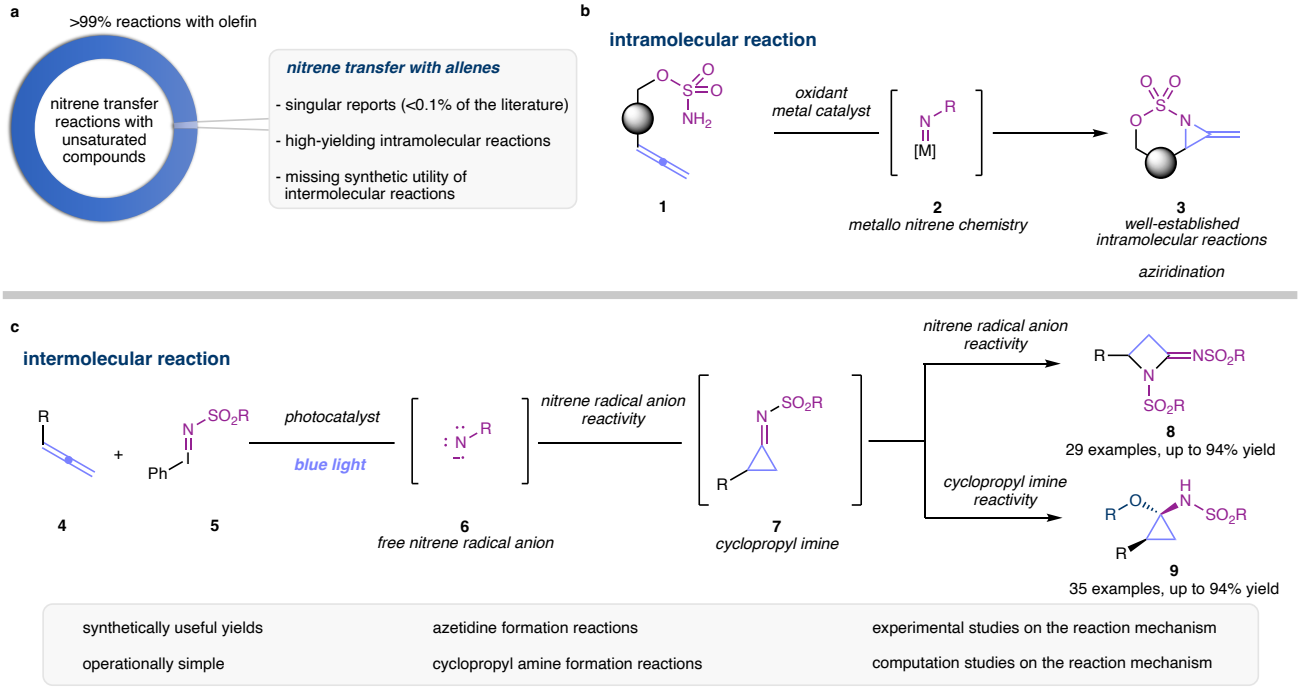
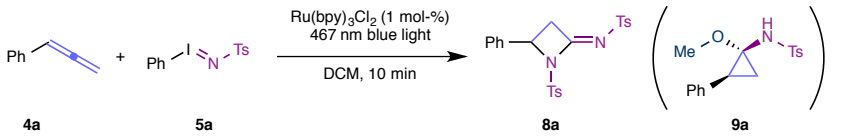


Figure 1. a Reaction of unsaturated compounds in nitrene transfer reactions. **b** Previous attempts at intramolecular amination reactions of allenes. **c** This work: photocatalytic twofold amination reaction of allenes via nitrene radical intermediates.

Results and discussion

To access a monovalent nitrene intermediate under catalyst-free conditions, we turned our attention to the photocatalytic reaction of iminoiodinanes, which gives upon reductive quenching a highly nucleophilic nitrene radical anion (Table 1).[7] In the presence of $Ru(bpy)_3Cl_2$ as photocatalyst, the reaction of phenyl allene and iminoiodinane gave the desired azetidine in excellent yield within only 10 minutes reaction time using 5 equivalents of phenyl allene. A short survey of solvents, light sources and stoichiometry quickly led to the optimized conditions, which now allows intermolecular nitrene transfer reactions to allenes in excellent yield (for a complete survey of optimization, see Table S1). Notably, this reaction needs to be carried out in halogenated solvents. Only trace amounts of the reaction product were observed in aromatic, THF or acetonitrile solvent. In methanol solvent, cyclopropyl amine **9a** was obtained instead in high yield, which corresponds to a trapping reaction of an intermediated cyclopropyl imine. In further control reactions without catalyst, we could show that a photochemically generated triplet nitrene intermediate can also serve as a viable reactive intermediate in this reaction. However, only after prolonged reaction time (60 minutes) a significantly reduced yield of the azetidine was observed, which suggest that direct photolysis of iodinane **5a** can serve as an alternative yet less efficient pathway. We then performed control reactions under metal-free reaction conditions. No reaction occurred in the absence of light as well as under oxidative conditions to access the nitrene precursor similar to intramolecular amination reactions of allenes.

Table 1. Reaction Optimization.



Entry	Changes from above	%yield 8a
1	-	85
2	1 equiv / 2 equiv / 10 equiv of allene	32 / 45 / 85
3	4-CzIPN / $Ir(ppy)_3$ / $Ru(bpz)_3(PF_6)_2$	58 / 39 / 57
4	370 nm / 525 nm	trace / n. R.
5	1,2-DCE / $CHCl_3$ as solvent	58 / 55
6	Toluene / MeCN / dmso as solvent	n. R.
7	MeOH as solvent / 5 eq. MeOH	40 (**9a**) / 77 (**9a**)
8	No catalyst	60
9	No light	n. R.
10	$PhI(OAc)_2$ + $TsNH_2$ + MgO instead of **5a** in the dark	n. R.

Reaction conditions: 0.2 mmol **5a** and **4a** (5 equiv and catalyst (1 mol-%) were dissolved in 2.0 mL DCM. The mixture was irradiated with the light source indicated for 10 min from 5 cm distance at room temperature.

Studies on the reaction mechanism.

For further understanding of the high reaction efficiency, we next examined the reaction mechanism by theoretical and experimental studies (Figure 2). A first on/off experiment revealed that light is required for the reaction to proceed and that no hidden chain processes are at place (Figure 2b). In a next set of studies, we examined pathways that might be accessed from the photoexcited state of the photocatalyst. Stern-Volmer studies show fluorescence quenching of the photoexcited state by both reagents near the diffusion limit (PhINTs: $k_q = 12.3 \times 10^{-8}$ M^{-1} s^{-1}; allene: $k_q = 8.5 \times 10^{-8}$ M^{-1} s^{-1}, see Figure 2c and Figure S6 and Table S7). To distinguish between electron or energy transfer we conducted cyclic voltammetry, which shows a facile reduction of iodinane **5a**. The allene can indeed be oxidized, yet significantly higher potentials are required to access electron transfer (E_{Ox} = +1.11 V vs. S.C.E., Figure 2d). This data is backed up by theoretical calculations (Figure 2a and S12-S15). These suggest an unfavored single electron transfer reaction of the allene ($\Delta G^{\ddagger}_{SET}$ = 31.4 kcal mol^{-1}), while energy transfer and triplet sensitization is marginally disfavored ($\Delta G^{\ddagger}_{ET}$ = 1.7 kcal mol^{-1}). On the contrary, reduction of iodinane **5a** occurs almost spontaneously with an activation free energy of only 0.5 kcal mol^{-1} for the single electron transfer reduction.[30] The reduction gives a nitrene radical anion that in turn can add to the allenic carbon with an activation free energy of 16.8 kcal mol^{-1}. Addition reactions to the terminal or benzylic carbon atom are energetically disfavored and do not account to the reaction mechanism

(for details, see Figure S12 and S13). Further oxidation and cyclization leads to formation of the cyclopropyl imine intermediate, which can react in a second catalytic cycle with another nitrene radical anion near the diffusion limit ($\Delta G^{\ddagger}$ = 9.0 kcal mol^{-1}).[32] This step proceeds with concomitant ring opening of the cyclopropane ring and formation of an acyclic intermediate **7** that undergoes oxidation followed by cyclization to give the azetidine product **8a**. The high reactivity of the cyclopropyl imine intermediate **7** prompted us to examine alternative reaction pathways that may rationalize azetidine formation with different aminating agents. We examined the addition of iodinane **5a** in either singlet or triplet state and the addition of a free triplet nitrene, yet in all cases the amination of cyclopropyl imine occurs via energetically unfavorable transition states.

It is important to note that the second addition event of a nitrene radical anion occurs with a lower activation free energy as compared to the initial addition to the allene ($\Delta G^{\ddagger}$ = 16.8 vs. 9.0 kcal mol^{-1}). This can reason the rapid formation of the azetidine product from the intermediate cyclopropyl imine that remains elusive for analysis. The experimental data, however suggests that the cyclopropyl imine can be trapped by methanol solvent. In this case, the analysis of the computational data suggest that methanol addition becomes suitable and competitive, when three explicit methanol molecules are considered ($\Delta G^{\ddagger}$ = 14.8). Taking the excess of methanol and the low concentration of the nitrene radical anion in the reaction mixture into account, this data suggests that methanol should undergo favorable addition reactions to give the cyclopropyl amine product **9a**.

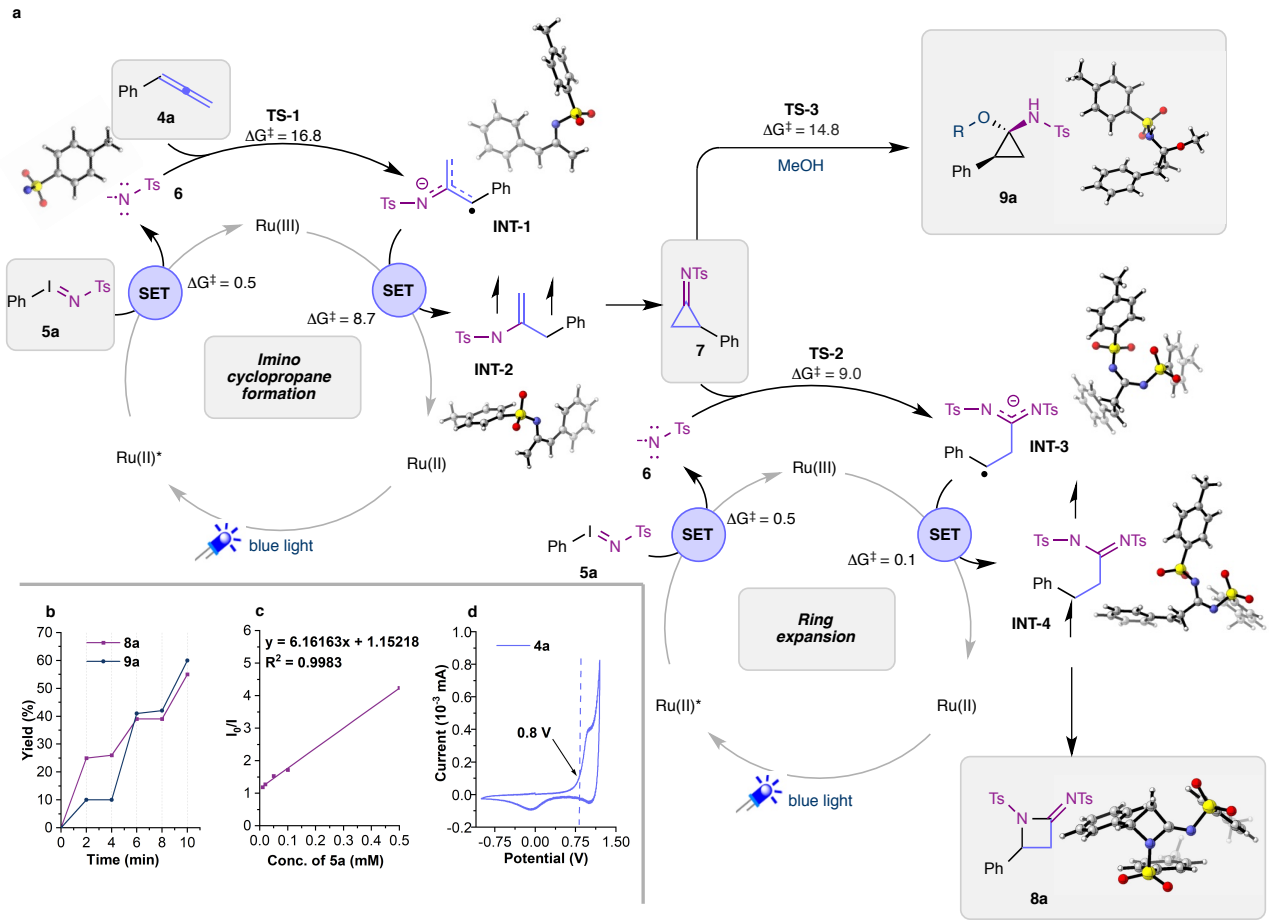


Figure 2. a. Reaction mechanism of allene and cyclopropyl amine formation. Calculations were performed at the SMD(DCM)-(U)M06-2X-D3/ def2-TZVPP // (U)M06-2X-D3/def2-SVP(def2-TZVP) level of theory, energies are given in kcal mol^{-1} **b.** On/Off Experiment **c.** Stern Volmer experiments of **5a d.** Cyclic voltammetry of allene **4a**.

For further experimental analysis, we performed experiments in the presence of oxidative or reductive quenching agents, which could thus alter reaction pathways (Figure 3a). Importantly, the azetidine product was obtained in high yield, if 4-nitro toluene or sodium persulfate were used as alternative oxidative quenching agents. No reaction was observed in the presence of iron salts, which might be reasoned by formation of iron nitrene intermediates that do not participate in nitrene transfer. Similarly, tertiary amines that can serve as reductive quenching agents, proved incompatible, which may be a result from the formation of amine radical intermediates that in turn inhibit the reaction. However, in the presence of oxalate or ascorbate salts or 4-methyl anisole as alternative reductive quenchers, the reaction smoothly proceeded. The catalytic cycle is thus only marginally affected by the presence of other quenching agents. Importantly, spin trapping agents, such as DMPO, DMPO or DNP, resulted in a complete inhibition of the reaction, which is in line with the above theoretical calculations.

We next embarked on deuterium labeling studies (Figure 3b) using the *bis*-deuterated allene **4a-d$_2$**. The deuterium label could be exclusively found as a dideuterio methylene group for azetidine **8a-d$_2$**

and cyclopropane **9a-d$_2$** without notable loss of the deuterium label, which is supportive of a reaction mechanism that involves addition to the central carbon atom of the allene followed by a cyclization to the cyclopropane ring. As part of these studies, we also examined the kinetic isotope effect, yet no differences in the reaction rate for **4a** and **4a-d$_2$** were observed.

In a last step, we examined the influence of methanol on the reaction outcome and product distribution of azetidine and cyclopropane and we could observe a gradual increase of the cyclopropane product with the equivalents of methanol added. An almost equimolar mixture of both products were obtained when using 2 equivalents of methanol, while a complete shift to the cyclopropane product was only observed when using 5 equivalents of methanol (Figure 3c).

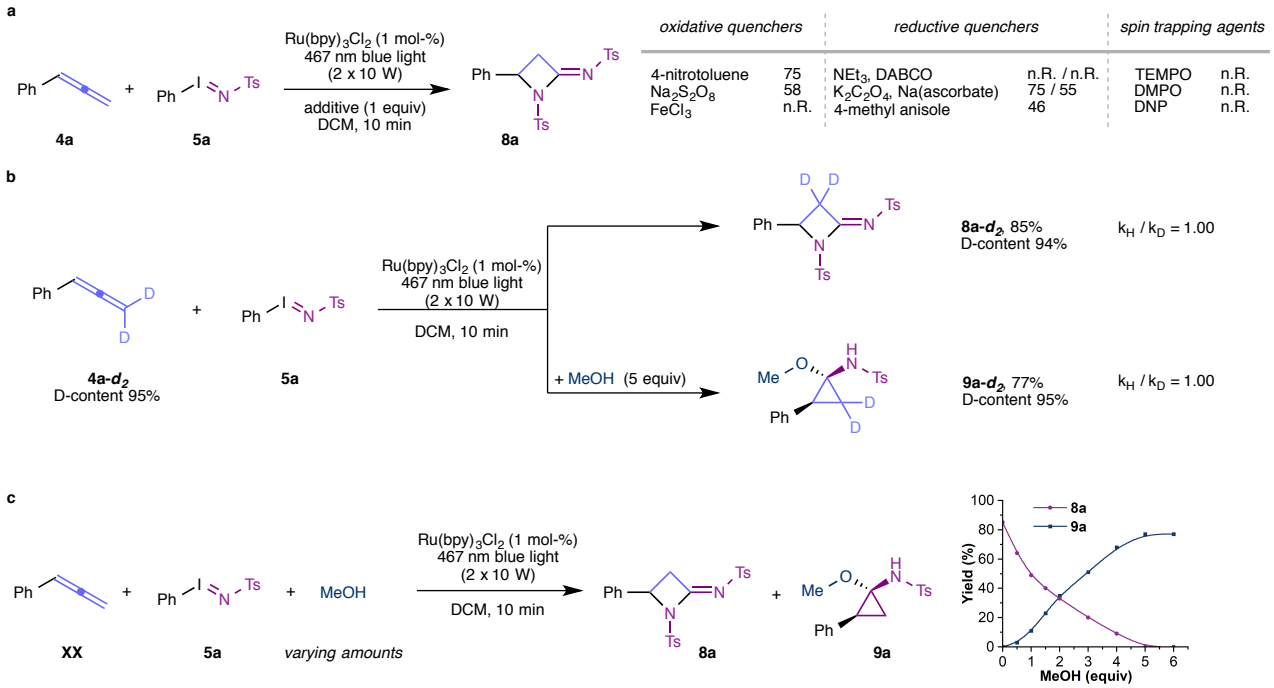


Figure 3. Control experiments on the photocatalytic reaction of allenes with iminoiodinanes: **a.** Reaction in the presence of different oxidative or reductive quenching agents and spin trapping reagents. **b.** Deuterium labeling experiments. **c.** Influence of the amount of alcohol on the reaction pathway.

Applications

Finally, we studied the application in intermolecular nitrene transfer reactions. Remarkably, a variety of different N-protecting groups were as well as aromatic, terminal allenes were well tolerated and we could obtain the azetidine products in consistently high yield (Figure 4). Only in the case of an ortho-substituted N-arylsulfonyl group, the yield of the azetidine product dropped significantly. For the allene, different aliphatic, halogen, electron-donating and electron-withdrawing substituents were tolerated in all positions of the aromatic ring – including ortho substitution. Limitations of the present method lie within the use of substituted aromatic allenes. Both 1,1-disubsitution or 1,3-disubsitution

led to a significant reduction of product yield, which both proved as unreactive substrates under silver-catalyzed conditions.[11] Aliphatic allenes reacted only in moderate yield to the azetidine product under photocatalytic conditions. It is important to note that such aliphatic allenes gave a conventional aziridine product under silver-catalyzed reaction conditions.[11] As part of these studies, we also examined two examples of allenes bearing a pendant biologically relevant building block and to our delight the azetidine product could be obtained in high yield in both cases.

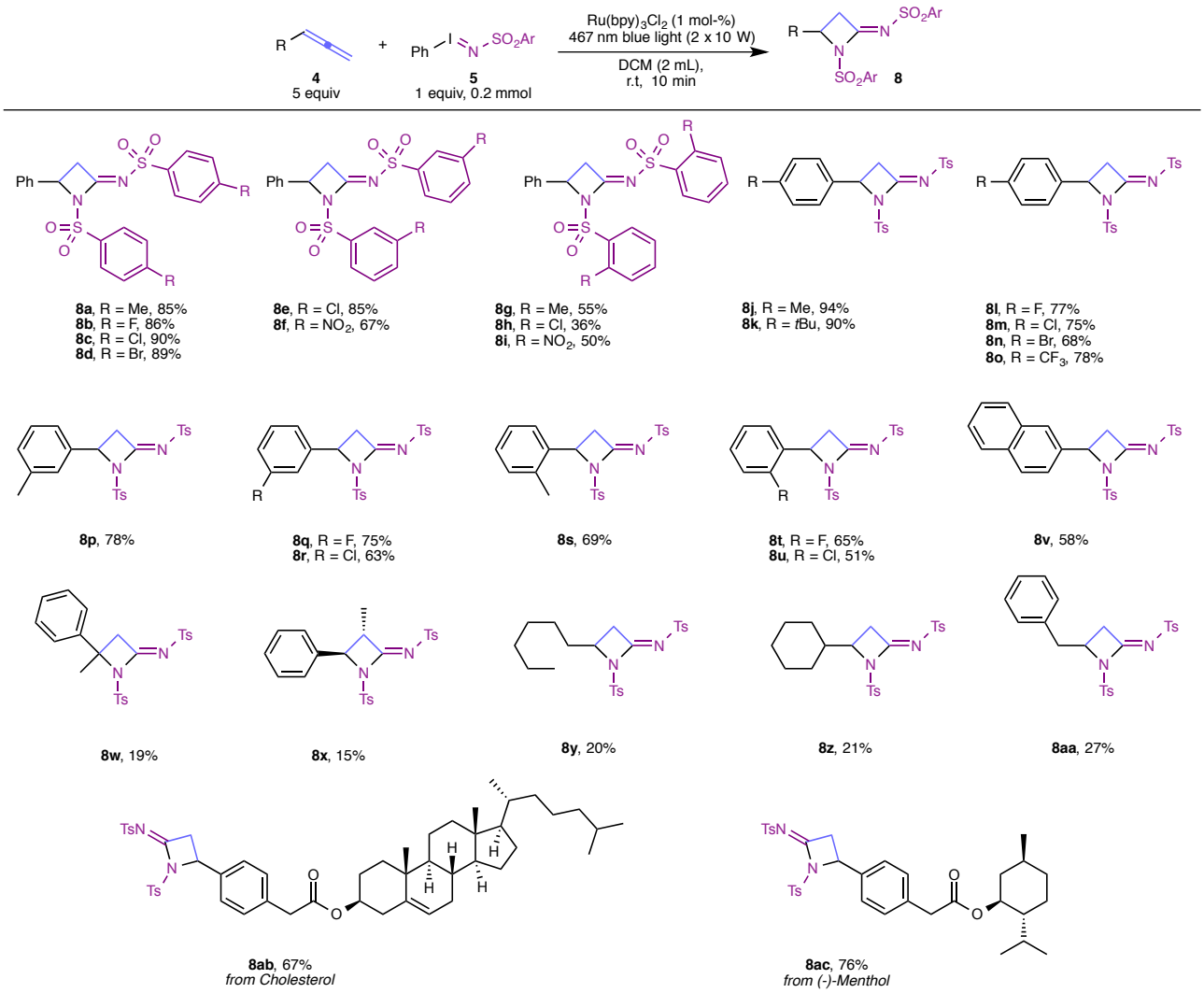


Figure 4. Substrate scope of photocatalytic, intermolecular amination reaction of allenes.

We then embarked on further investigations of the reaction in MeOH solvent and trapping of the cyclopropyl imine intermediate to give amino cyclopropanes **9** (Figure 5). This reaction proceeded in high yield for a similar range of aryl allene starting materials, disregarding of the substitution pattern at the aromatic ring. This trapping reaction also proved compatible with 1,1-disubstituted allenes to yield the cyclopropyl amine product in good yield, while 1,3-disubsittuted allenes gave only a low yield. Aliphatic allenes similarly reacted to the corresponding cyclopropyl amines in good yield, which contrasts the corresponding metal-catalyzed transformations, which gave the product of conventional

aziridination. As in the case of azetidine formation, allenes with a pendant biologically active compound proved compatible and the corresponding cyclopropyl amines were obtained in high yield.

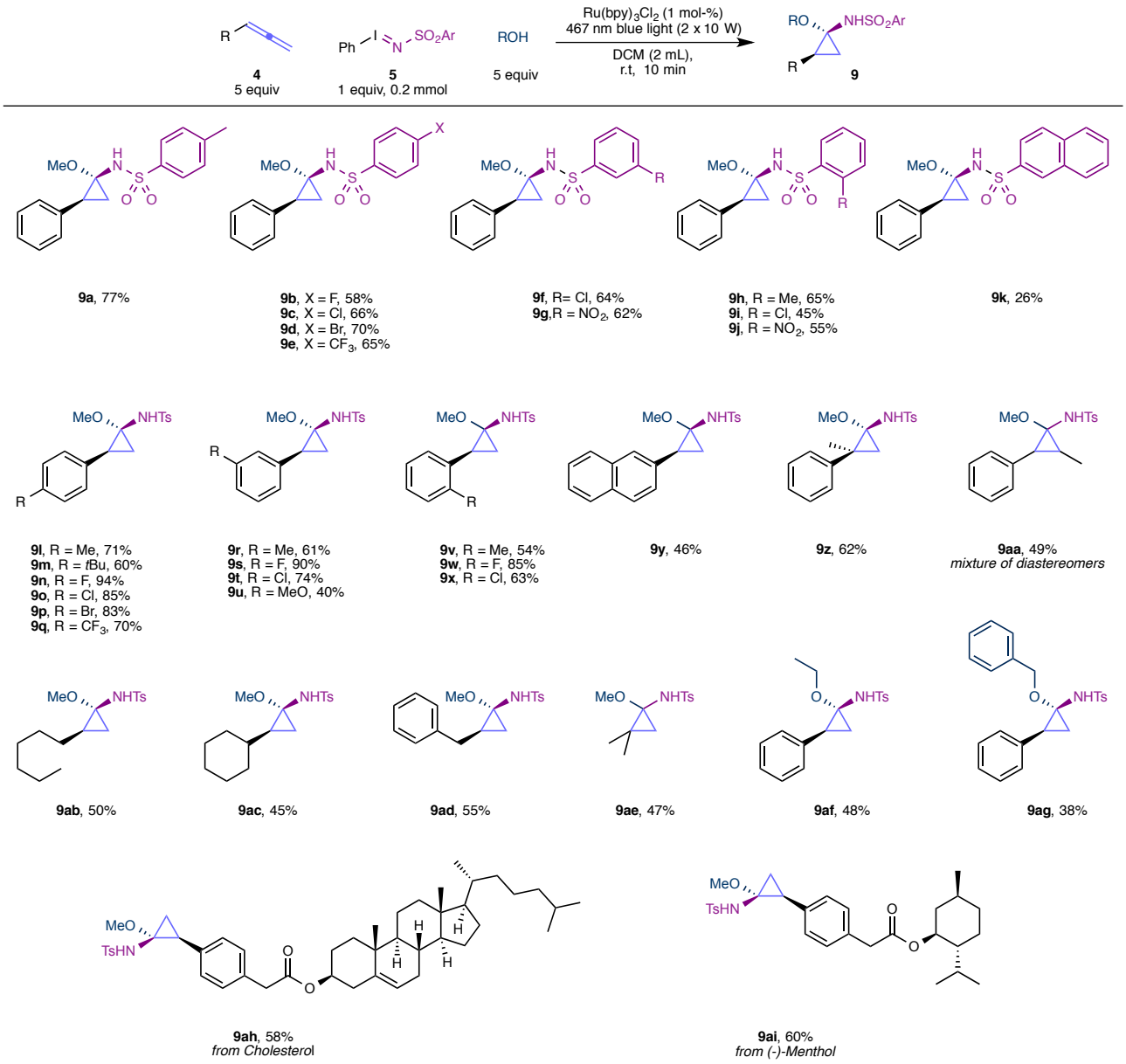


Figure 5. Photocatalytic, intermolecular amination reaction of allenes in the presence of alcohols.

In a last step, we examined further applications of this photocatalytic intermolecular amination reaction of allenes with iodinanes (Figure 6). We examined the reaction on 1 mmol scale for the azetidine and cyclopropyl amine product. In both cases, the corresponding amination products were obtained in high yield using either 3 or 5 equivalents of the allene and the majority of unreacted allene could be recovered after the reaction. As examples for applications of the amination products, we examined the reduction of the azetidine with $LiAlH_4$, which furnishes the ring-opened tosyl-protected 1,3-diamine **10** in high yield. As part of these studies, we also examined, if cyclopropyl amine **9a** could be converted to azetidine **8a** in the presence of another equivalent of iminioiodinane **5a**. In this case, we made a surprising observation and could observe the ring opening reaction with concomitant

oxidation and formation of the α,ß-unsaturated tosyl-protected imidate **11**; in the absence of iodinane **5a** – thus only in the presence of Cs_2CO_3 base – ring opening to the saturated imidate **12** occurs.

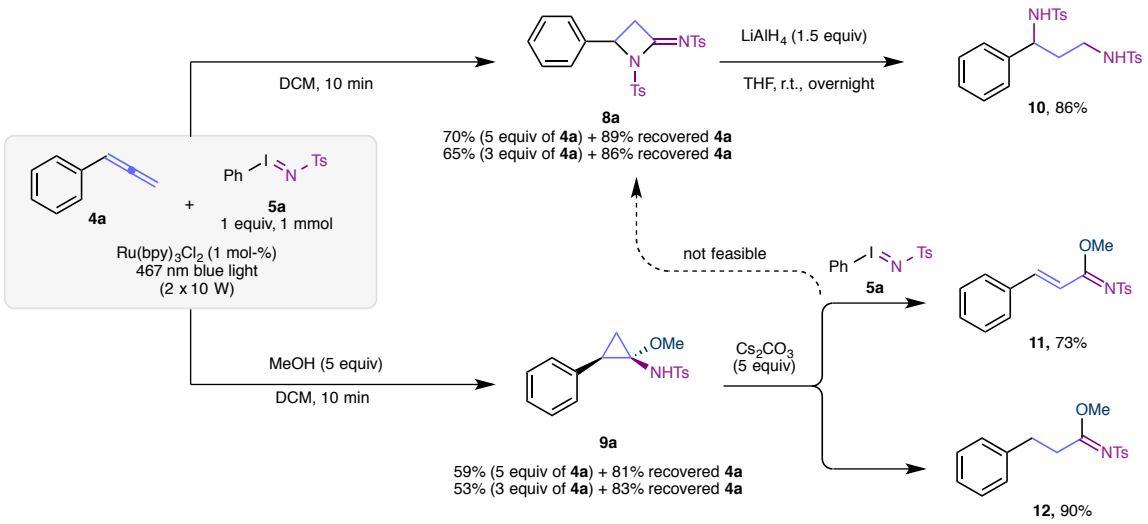


Figure 6. Selected applications.

Conclusion

In summary, we herein report on the photochemical, intermolecular amination reaction of allenes with iodinane reagents. This strategy harnesses the high reactivity of free nitrene radical anions without the need of conventional nitrene transfer catalysts. We could show that nitrene radical anion intermediates can successfully overcome long-standing challenges in chemistry and allow for the development of high-yielding, broadly applicable intermolecular amination reactions of allenes. Depending on the reaction conditions, either an azetidine product is formed via a twofold, photochemical nitrene transfer reactions, or – in the presence of methanol as additive – an aminocyclopropane is formed via trapping of a highly reactive cyclopropyl imine intermediate. We could show the applicability of this approach in a broad substrate scope (64 examples, up to 94% yield). Control experiments, deuterium labeling studies and theoretical calculations provide further support of the reaction mechanism and the relevance of free nitrene radical anions as reactive intermediates in this reaction.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge: Experimental details and spectroscopic data for all products, full Gaussian reference, Cartesian coordinates, electronic and free energies.

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Author Contributions

Y.G., H.F. and S.J. conducted the experiments. C.E. and C.P. performed theoretical calculations. C.E. and R.M.K. wrote the paper. R.M.K. conceived this study. All authors have given approval to the final version of the manuscript.

CONFLICTS OF INTEREST

There is no conflicts of interest to declare.

ACKNOWLEDGMENTS

R.M.K. thanks the German Science Foundation for financial support. Y.G., C.P. and H.F. gratefully acknowledges the China Scholarship Council for generous support. C.E. thanks the Fonds der Chemischen Industrie for a Kekulé Scholarship.

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