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Energy Transfer

Harnessing Energy-Transfer in N-Centered Radical-Mediated Synthesis of Pyrrolidines

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Dedicated to Professor R.M. Kellogg on the occasion of his 80th birthday.

Abstract: Atom transfer radical addition (ATRA), cyclization (ATRC), and polymerization (ATRP) are valuable synthetic methods for the functionalization of olefins. With the advent of photoredox catalysis, visible-light became a popular tool for the initiation of these reactions. We have developed a protocol that enables easy access to distally functionalized pyrrolidines employing blue-light mediated atom transfer radical [3+2] cyclization. The reaction is scalable, proceeds at very mild conditions. tolerates various functional groups, and provides the corresponding products in good to excellent yields. If rigid olefins are utilized as the reaction partners, the products can be isolated as single diastereomers. The mechanistic investigations provide strong support for an energy-transfer mechanism.

Introduction

Atom transfer radical addition (ATRA), cyclization (ATRC),[1] and polymerization (ATRP)[2] are valuable synthetic methods for the functionalization of olefins.[3] Since the introduction in 1945 by Kharasch, Jensen, and Urry,[1] ATRA underwent several notable improvements and modifications. Most recently, the groups of Stephenson[4,5] and Reiser[6] independently reported that photoredox catalysis is a viable activation mode for atom trans-

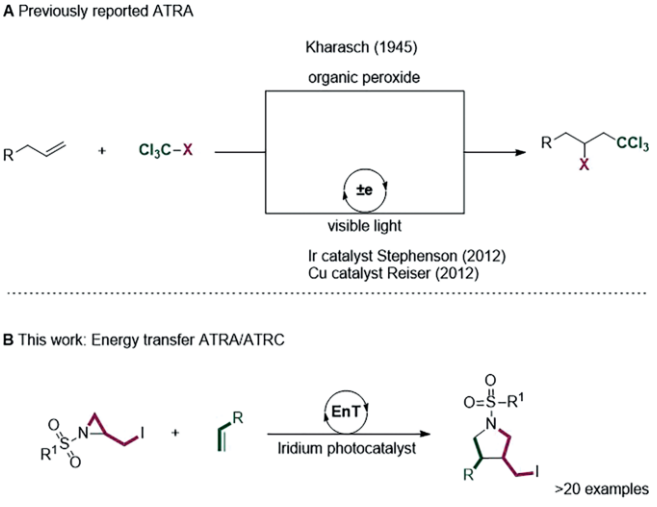

Figure 1. Developments in ATRA. **1A)** Initial development by Kharash and photoredox-catalyzed ATRA developed by Stephenson. **1B)** Energy-transfer ATRA/ATRC reported in this work.

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Peter Fodran *graduated from Comenius University in Bratislava (Slovakia). During his research under the guidance of Prof. Radovan Šebesta, Peter focused on ferrocene-based ligands and Cu-catalyzed tandem reactions. He completed his Ph.D. at the University of Groningen, where under the supervision of Prof. Adriaan Minnaard, he synthesized biologically active lipids. Given Peter's interest in total synthesis, he stayed in the group of Prof. Minnaard as a postdoc working on the total synthesis of enantiopure Methoxy-Mycolic acid. After completing the synthesis, his next stop was the contract-research organization Syncom (Groningen, The Netherlands), where he, together with Dr. Bas Dros, developed synthetic routes to active pharmaceutical ingredients, process impurities, and analogs of biologically active molecules. After securing Carl-Tryggers and Marie-Curie fellowships, Peter moved to the University of Gothenburg (Sweden), where his research in the group of Dr. Carl-Johan Wallentin focused on photoredox catalysis.*

Carl-Johan Wallentin *initiated his academic career in 2004 as a Ph.D. student at the Lund University (Sweden) under the directions of Prof. Kenneth Wärnmark. The main efforts during his time as a Ph.D. student-centered on various aspects of supramolecular chemistry, with particular emphasis on hydrogen bonding and its utilization in the construction of discrete molecular aggregates. In 2011, he joined the research group of Prof. Corey Stephenson, then at Boston University (USA), to explore the upcoming field of photoredox catalysis. Thereafter, he joined the Department of Chemistry and Molecular Biology at Gothenburg University to established his own group active within the fields of method development and sustainable chemistry.*

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fer transformations. (Figure 1A). Currently, these initiation protocols are broadly exploited in numerous photoredox mediated processes.[3,7–14]

In contrast to the electron-transfer ATRA, energy-transfer[15–20] based ATRA received significantly less attention. This discrepancy can be explained by the difference in the physical data required for the rational design of the corresponding processes. While the collection of electrochemical data and construction of the Stern-Volmer plots of the reagents required for electron-transfer processes are straightforward, the photoacoustic calorimetry or transient absorption spectroscopy, which are necessary for obtaining triplet states energy (TSE) necessary for the Dexter-type energy-transfer are not commonly found in the organic laboratories. This downside is partially remedied by an approximation, which utilizes the triplet-state energy of photosensitizers and bond-dissociation energy of the quencher. In a pioneering report the group of Melchiorre reported that 20 mol-% of *p*-anisaldehyde, together with a stoichiometric amount of 2,6-lutidine, constitute a competent system for an energy transfer-based ATRA between electron-deficient haloalkanes and electron-rich alkenes.[21]

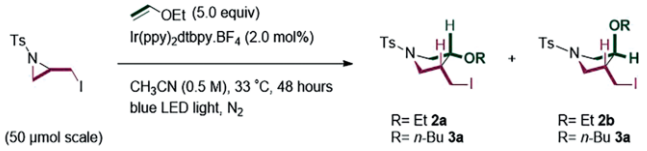
Strain-release promoted processes are frequently exploited in radical chemistry. For example, the well-documented behavior of substituted cyclopropyl methyl radicals serves as a radical clock[22] and as verification of intermediacy of radicals. The corresponding heterosubstituted small rings as aziridines[23,24] and oxiranes[25] have received less attention in the context of radical chemistry. Aziridines have been applied in photoredox catalysis, but mainly in the generation of C-centered radicals,[26] which could be harnessed in various transformations. However, the application of aziridines in the generation of heteroatom-centered radicals is rare and typically limited to intramolecular reactions.[27]

Taguchi has reported an interesting ATRA/ATRC,[28,29] where the authors utilized aziridinylmethyl iodides as precursors of azahomoallyl radicals in the synthesis of pyrrolidines. The optimized conditions required either relatively high loading (20 mol-%) of toxic $(Bu_3Sn)_2$ or superstoichiometric amounts of Et_3B (1.5 equiv.) in oxygen atmosphere. These reaction conditions demonstrated a relatively narrow scope, moderate yields, and the authors reported explosions. Given that radical chemistry without the use of tin was proclaimed as one of the key green chemistry areas,[30] we aimed to develop a practical tin-free [3+2] approach to pyrrolidines.

Results and Discussion

Our initial efforts towards the development of visible-light mediated [3+2]-cycloaddition protocol involved tosyl iodomethyl aziridine **1** and ethyl vinyl ether as model substrates (Table 1). A comprehensive screening of photocatalysts, solvents, and stoichiometry of the reagents (see supporting information) identified $Ir(ppy)_2dtbpy.BF_4$ (2.0 mol-%) as the competent catalyst and CH_3CN (0.5 M) as the optimal solvent. These conditions yielded the corresponding pyrrolidine derivative in 96 % (approx. 1:1 *d.r.*) upon 36 hours of blue-light (460 nm) irradiation (entry 1). Control experiments (entries 2 and 3) confirmed that light and photocatalyst are essential for the reaction. In their absence, we did not observe any formation of products and no conversion of **1**.

Table 1. Optimization of the conditions and control experiments.



Entry	Deviation from the optimized conditions[a]	Conversion **1**[b]	yield **2a** + **2b**[b,c]
1	No deviation	100%	96%
2	No light	0%	0%
3	No catalyst	0%	0%
4	5.0 equiv. of *n*-butyl vinyl ether as reaction partner[d]	100%	96% **3a** + **3b**
5	2.0 equiv. of *n*-butyl vinyl ether[d]	100%	95% **3a** + **3b**
6	1.0 M concentration	50%	45%
7	0.1 M concentration	84%	75%

[a] Optimized conditions: 50 µmol scale with $Ir(ppy)_2dtbpy{\cdot}BF_4$ (2.0 mol-%), 5.0 equiv. of *n*-butyl vinyl ether irradiated for 24–36 h in CH_3CN (0.5 M). [b] Determined by ^1H NMR using dimethyl sulfone as the internal standard. [c] Combined yield of both stereoisomers. [d] 24 hours reaction time.

Given the low boiling point of ethyl vinyl ether (bp 33 °C), it is expected that a considerable amount of this reagent will be allocated to the headspace of the reaction vessel. Consequently, we reasoned that a vinyl ether with a higher boiling point would allow us to decrease its stoichiometry. In line with this argument, we subjected the less volatile *n*-butyl vinyl ether (bp 94 °C) to the reaction conditions, which indeed provided the product in an excellent 96% yield using only 2 equivalents (entry 5) of olefin in just 24 hours. Both increase (entry 6) and decrease (entry 7) in the concentration was detrimental to the yield. An increase to 1.0 M led to a drop in the yield to 45% and incomplete, 50% conversion. A decrease in concentration to 0.1 M led to a decrease in the reaction rate, with incomplete, 84 % conversion after 48 h.

With the optimized conditions established, we explored the scope of the reaction (Figure 2). Given that the substituents on the *N*-arylsulfonyl groups can modulate the electrophilicity of the generated N-centered radicals (see supporting information), we first examined their influence on the reactivity. In general, *N*-arylsulfonyl groups substituted with electron-donating substituents, e.g., 4-methyl and 4-methoxy, provided the [3+2] adducts **3** and **4** in the highest isolated yields – 87% and 85%, respectively. Unsubstituted *N*-arylsulfonyl such as phenyl and fused polycyclic aromates such as 2-naphthyl provided the corresponding products **5** and **6** in lower yields – 65% and 66%, respectively. Substitution of the *N*-arylsulfonyl group with electron-withdrawing groups such as 4-bromo and 4-cyano led to lower but still synthetically useful yields of the corresponding cycloadducts **7** and **8**–58% and 50%, respectively. The aryl group can also bear two substituents – the 2,4-dimethoxyphenyl sulfonyl-substituted aziridine, provided **9** in 54% yield. The arylsulfonyl group can be replaced with an alkylsulfonyl group. The corresponding mesyl-substituted aziridine provides the desired product **10** in 63% yield, albeit with longer reaction

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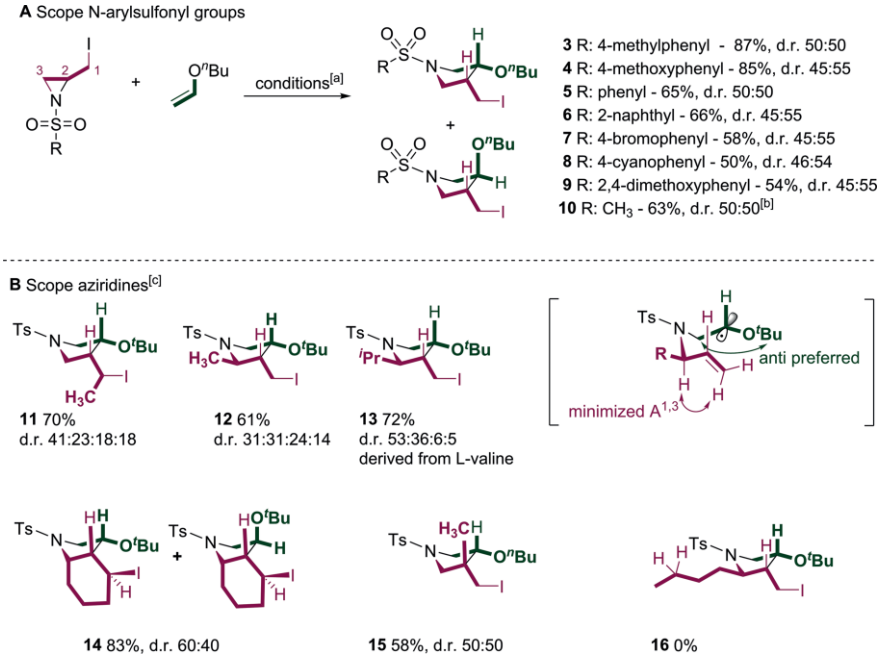

Figure 2. Scope of photoredox catalyzed [3+2] cycloaddition. **A)** Scope in *N*-arylsulfonyl groups. **B)** Scope in aziridines. Conditions: [a] 200 µmol scale with $Ir(ppy)_2dtbpy{\cdot}BF_4$ (2 mol-%), 2.0 equiv. of *n*-butyl vinyl ether irradiated for 48 h in CH_3CN (0.5 M), yield refer to isolated products; [b] irradiated for 72 h; [c] 5.0 equiv. of olefin was used.

time (72 h). In summary, we observed that the N-substitution influences the yield, but it does not have any effect on the diastereoselectivity.

Next, we focused our attention on the scope of aziridines, which were obtained by modification of the existing methods.[31,32] We evaluated the reactivity of aziridines together with the *tert*-butyl vinyl ether because the corresponding products display singlets in the ^1H NMR. Thus, the evaluation of the diastereomeric ratios is convenient and precise. The substitution patterns of the aziridines can easily be recognized in the corresponding pyrrolidine products. The substituent introduced to position 1 (arbitrary numbering, see Figure 2A) is reflected as an additional exocyclic stereogenic center, as evident in **11**. All four diastereomers of **11** were detected in the reaction mixture in the ratio 41:23:18:18. The introduction of a methyl substituent at position 3 also leads to the formation of all four diastereomers of **12** in the ratio 31:31:24:14 and 52% yield. When increasing the steric demand of the substituent going from methyl to isopropyl as represented by product **13**, changes the ratio to 53:36:6:5. While the diastereomers were inseparable, their structures can be assigned on several assumptions, observations, and experiments. First of all, the reaction proceeds via the early Beckwith–Houk type transition state, where the substituents try to adopt pseudoequatorial conformation.[33,34] In this conformation, the $A^{1,3}$ strain in the aziridine-derived portion (purple) of the molecule is minimal, and the *tert*-butoxy group is *anti* to the sulfonamide to minimize the torsional strain in the vinyl ether derived portion (green) of the molecule. Given that the transition-state is early, the eclipsing interaction between the *tert*-butoxy substituent and the olefinic moiety is insignificant. Elimination of HI with DBU (1.0 equiv.) in DMF from **12** and **13** provides the corresponding 3-methylenepyrrolidines in identical 40:60 *cis*/*trans* ratio, which roughly corresponds to the *syn*/*anti* conformational preference of the *tert*-butoxy substituent in the ring-closing event. This preference is further corroborated by the bicyclic example **14** (Figure 2B), where the aziridine-derived portion of the molecule is rigid, resulting in two stereoisomers of **14** also obtained in 60:40 *d.r.*

The influence of the $A^{1,3}$ strain is notable in the proportion of the major diastereomers in **12** and **13**. The increase of the steric demand in going from methyl to isopropyl leads to an increase in the proportion of the presumed all-pseudoequatorial major stereoisomer (as depicted in Figure 2) from 31% to 53%. Worth mentioning is that since **13** is a derivative of *l*-valine, our protocol can be utilized in the synthesis of enantiomerically pure, highly substituted pyrrolidines.

A methyl substituent at position 2 of the aziridines leads to the formation of **15** bearing an all-carbon quaternary stereocenter in 58% yield with a 50:50 *d.r.* Extension of the alkyl substituent at the 3-position to *n*-butyl leads to a competing intramolecular 1,5-hydrogen atom abstraction of the nitrogen-centered radical, which ultimately suppresses the formation **16**.

After exploring the scope in aziridines, we turned our attention to the evaluation of different olefins (Figure 3A). Ethyl vinyl ether and *tert*-butyl vinyl ether provided the corresponding products **2** and **17** in similar yields (83 % vs. 76 %) with a diastereomeric ratio of 50:50 and 60:40 respectively. In the case of **17**, the sterically more hindered *cis* isomer is the major isomer, which is again consistent with the Beckwith–Houk model.[33–35] It is noteworthy that in a related [3+2] cycloaddition reported by Tsuritani, Shinokubo, and Oshima,[36] the authors reported a 68:32 *d.r.* in a similar reaction albeit with a considerable lower yield of 28%. The cyclohexyl-substituted vinyl ether provided

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18 in 55% yield and 50:50 *d.r.* The halogen-substituted (2-chloroethoxy)ethene is also a viable substrate providing **19** in moderate 41% yield and 50:50 *d.r.*, illustrating that the reaction conditions tolerate potential synthetic handles on the vinyl ether. Comparing various steric demands of the alkyl groups of vinyl ethers (**3**, **17**–**19**), it is evident that the bulk of the alkoxy group effects the yield and has a modest influence on the diastereoselectivity of the reaction. More sterically demanding groups (larger A-values) on the oxygen atom provide the pyrrolidines in lower yields, but in slightly higher *d.r.*

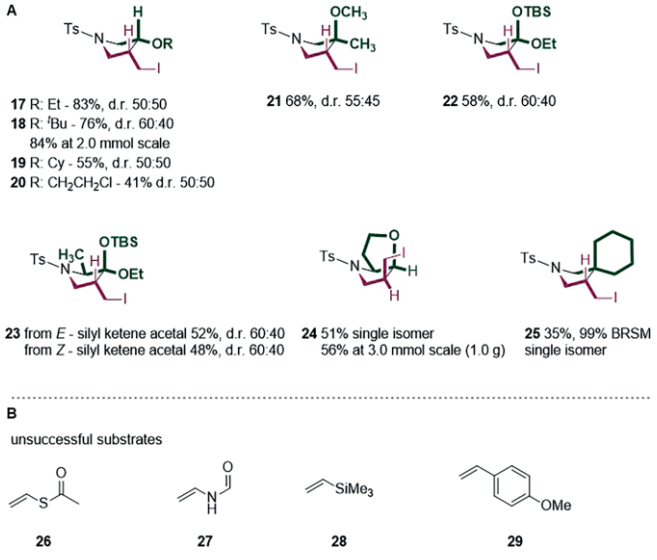

Figure 3. Scope of photoredox catalyzed [3+2] cycloaddition. **A)** Scope in olefins. **B)** Unsuccessful substrates. Conditions: 200 µmol scale with $Ir(ppy)_2dtbpy{\cdot}BF_4$ (2 mol-%), 3.0 equiv. of vinyl ether irradiated for 48 h in CH_3CN (0.5 M) yield refer to isolated products.

Next, we explored 2-substituted vinyl ethers. The commercially available 2-methoxyprop-2-ene provided the corresponding tertiary ether **20** in a reasonable 68% with 55:45 *d.r.* Readily available[37] silyl ketene acetal 1-ethoxy-1-(TBS)ethene provided the cycloadduct **21** in 58% yield with a *d.r.* of 60:40. The homologous *E*-silyl ketene acetal and *Z*-silyl ketene acetal provide product **22** in identical *d.r.* and almost identical yields (48% vs. 52% yield), which suggests that this [3+2] addition is a stepwise process. Although silyl ketene acetals are rarely used in radical reactions, they are suitable partners in our [3+2] conditions,[38] thus providing a smooth entry into valuable 3-oxopyrrolidines.[39,40]

We also explored cyclic olefins as possible reaction partners. Commercially available 2,3-dihydrofuran yielded a medicinally relevant[41] bicyclic product **23** as a single stereoisomer, which demonstrates that our protocol provides access to tri-substituted pyrrolidines in synthetically useful yields and stereoselectivities if the olefinic partner is rigid. 1D and 2D NMR spectroscopy confirmed the stereochemistry of **23**, which is in agreement with the stereoelectronic requirements of radical bicyclizations.[42] Alkenes such as methylene cyclohexane participate in the reaction affording spirocyclic pyrrolidone **24** in relatively modest yield (35%) after an increase in the catalyst loading (7.5 mol-%). Further expanding the scope beyond vinyl ethers, we next pursued a variety of other olefinic substrates. To our dismay, substrates such as vinyl thioethers **25**, enamines **26**, vinylsilanes **27**, and styrenes **28** (Figure 3B) did not afford any [3+2] cycloadducts. However, many of these substrates were reported unreactive towards the addition of *N*-sulfonamidyl radicals.[43]

In addition to investigating the scope using a substrate derivative library, Glorius and co-workers recently formalized means to assess the robustness of novel methods by evaluating the outcome of a reaction in the presence of various additives.[44] Accordingly, we selected and subjected ten different additives (1.0 equivalent) to the optimized reaction conditions. Subsequently, we followed the yield of **17** and the recovery of the additive. The results are summarized in Figure 4. The reaction conditions tolerate esters (ethyl benzoate), diaryl sulfides (diphenyl sulfide), sulfonamides (tosylamide), electron-poor heterocycles (pyrimidine) and halogenated anisoles. In these cases, the additive did not affect the yields, and the recovery of additive was > 90% in all cases. In the presence of decanal, the yield of **17** decreased to 79%, but the recovery of the additive was complete (100%). In the case of benzyl alcohol, the yield of **17** was 75% yield, but the recovery of benzyl alcohol was only 47%. It is noteworthy that a mixed benzyl-*tert*-butyl acetal formed as a by-product in significant amounts (50%). Submission of 4-*tert*-butylphenylacetylene in the optimized conditions resulted in a decrease of the yield of **17** to 48%, but a significant amount (75%) of the additive could be recovered. Electron-rich heterocycles as Boc protected indole and dimethylaniline result in a further decrease in the yield. Submitting *N*-Boc-indol led to a 25% yield of **17** and mediocre recovery (52%). *N*,*N*-dimethylaniline halts the reaction completely, but almost all of it (90%) can be recovered.

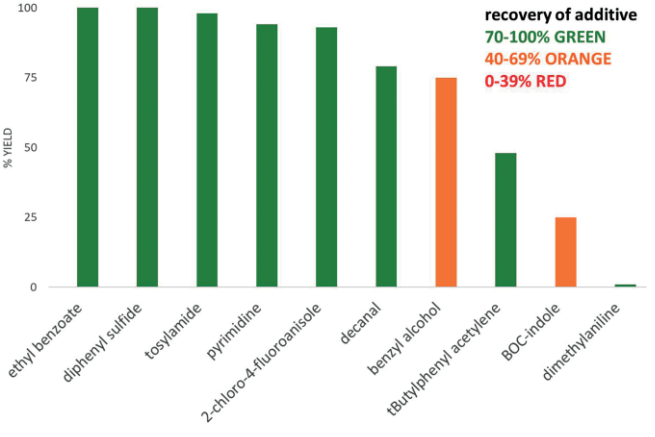

Figure 4. Robustness of the reaction. Conditions[a] 200 µmol scale with $Ir(ppy)_2dtbpy{\cdot}BF_4$ (2 mol-%), 2.0 equiv. of *tert*-butyl vinyl ether and 1.0 equiv. of additive irradiated for 48 h in CH_3CN (0.5 M).

Lastly, we explored the scalability of the reaction (Figure 3A). The reaction of **1** with *tert*-butyl vinyl ether could be scaled to 2.0 mmol with a slight increase in the yield of **17** (0.2 mmol – 76%, 2.0 mmol 84%). With 2,3-dihydrofuran, the reaction could be scaled-up to gram scale (3.0 mmol), together with a slight decrease of the catalyst loading (1.5 mol-%) while providing **24** without any notable deterioration of the yield (56%).

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Mechanism

To elucidate the mechanism, we first determined by Stern-Volmer titration (see supporting information) which components of the reaction mixture quench the excited $[Ir(ppy)_2dtbpy]^+$. We observed that the vinyl ether does not quench the photocatalysts excited state, while aziridinylmethyl iodide does with a rather low k_{q1} = 422 M^{-1} s^{-1}. Furthermore, the Stern-Volmer titrations revealed that product **18** is also a quencher, with more than two times larger quenching constant k_{q18} = 1023 M^{-1} s^{-1}. Accordingly, we evaluated the possibility that the product participates in a productive auto-catalytic process. After subjecting a mixture of *cis* and *trans* **17** to the reaction conditions, we did not observe any increase in the rate of the [3+2] cycloaddition. Irradiation of **17**, together with the catalyst and TEMPO, did not lead to the corresponding adducts, suggesting that even if the C-I bond is homolyzed, the recombination of the generated radicals is faster than a potential escape from the solvent cage. Subjecting TEMPO to the reaction conditions did not afford any **17**, but instead yielded 20% of *N*-allyltosylamide, which presumably comes from ring-opening and subsequent HAT of the aza-homoallyl radical. These results suggest that the formation of product in the reaction vessel has a non-productive parasitic effect on the overall reaction.

Next, we evaluated the reduction potentials of aziridinyl iodide **1** and pyrrolidines **18**, and we found that both compounds display irreversible two-electron reductions. The reduction of aziridinylmethyl iodide **1** occurs at –1.88 V vs. SCE (Saturated Calomel Electrode) and the reduction of the products **2a** and **2b** at even lower –2.51 V vs. SCE. Given that the reduction potential of $[Ir(ppy)_2dtbpy]^+$ is $E_{1/2}[*Ir^{III}/Ir^{IV}]$ = -0.96 V vs. SCE in CH_3CN,[45] a possible redox process would be endergonic by more than 21.0 kcal mol^{-1}.

Another observation that indicates the absence of redox events comes from a careful analysis of the reaction mixture. If the reaction was triggered by a single electron reduction of aziridinylmethyl iodide, the oxidatively quenched $[Ir(ppy)_2dtbpy]^{2+}$ would have a sufficient reduction potential $E_{red}[Ir^{III}/Ir^{IV}]$ = +1.21 V vs. SCE in CH_3CN[46] to oxidize the primary radical [$E_{(1/2)}$(prim°/prim$^+$) = 0.99 V vs. SCE] to the corresponding carbocation, which would lead to the formation of a Ritter product.[47] However, we did not detect any Ritter products even after an independent synthesis of the corresponding compound (see supporting information) and spiked them into the crude reaction mixture.

The quantum yield of the reaction determined by the procedure reported by Cismesia and Yoon[48] is $\Phi_{[3+2]}$ = 6.5. A value higher than one is evidence for a productive chain propagation mechanism.

After considering the electrochemical, photophysical, and chemical experiments, we can rule out that a redox process is operating in this [3+2] cycloaddition, and we propose (Figure 5) that the reaction is initiated by an energy-transfer process and mainly propagated by iodine transfer. The initial step is the excitation of $Ir(ppy)_2dtbpy^+$ by a visible-light photon. Upon collision, the energy is transferred via a Dexter mechanism to the aziridinylmethyl iodide **1**, which undergoes homolysis affording iodine radical and aziridinyl methyl radical **II**, which in turn undergoes a rapid ring opening providing azahomoallyl radical **III**. Radical **III** adds to the olefin, providing a translocated radical **IV**, which undertakes a 5-*endo-trig* cyclization yielding **V**.

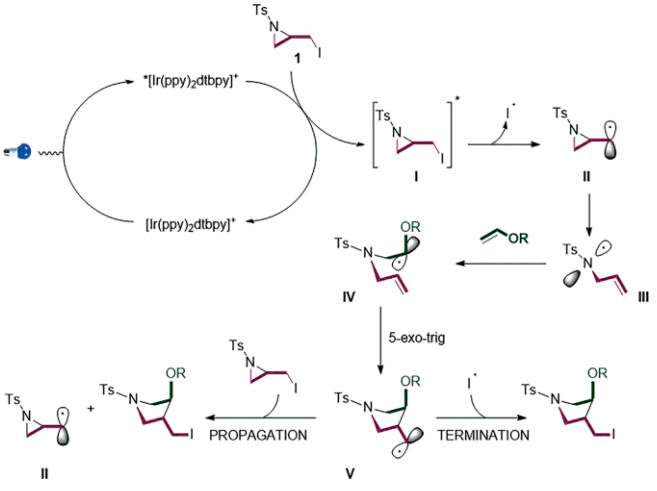

Figure 5. Proposed mechanism.

Radical **V** can recombine with the iodine radical, which leads to termination of the chain process or it can abstract iodine[49] from **1** thus propagating the reaction.

Subjecting commonly utilized photoredox catalysts[46] to the optimized conditions did not reveal any trend between their triplet state energy (TSE) and yield of the [3+2] product **17** (Table 2). $Ir(dF\text{-}CF_3\text{-}ppy)_2dtbpy^+$ with TSE of 60.1 kcal mol^{-1}[46] is frequently utilized in energy-transfer processes. In our [3+2] cycloaddition, this catalyst provided **17** in 54 % yield. $Ir(ppy)_3$[39] is another catalyst with relatively high TSE of 55.8 kcal mol^{-1} but it provided **17** in only 11% yield. $Ru(bpy)_3^{2+}$ with TSE of 45.0 kcal mol^{-1} provided **17** in 44% yield and Eosin Y[50] with slightly lower TSE of 43.6 kcal mol^{-1} provided the products in a 9% yield. $Ir(ppy)_2dtbpy^+$, which was identified as the optimal catalyst, provided the highest, 100% yield in the given set of experiments. These results illustrate that similar processes initiated via energy-transfer are more dependent on matched energy levels between reaction partners rather than the TSE of the photosensitizer and BDE of the homolyzed bond.

Table 2. Influence of TSE on the yield of the [3+2] cycloaddition.

Entry[a]	catalyst	TSE [kcal mol^{-1}]	yield of **17**[a]
1	$Ir(dF\text{-}CF_3\text{-}ppy)_2dtbpy\cdot PF_6$	60.1	54%
2	$Ir(ppy)_3$	55.8[46]	11%
3	$Ir(ppy)_2dtbpy\cdot BF_4$	49.3	100%
4	$Ru(bpy)_3\cdot(PF_6)_2$	45.0	44%
5	Eosin Y	43.6[50]	9%

[a] Determined by calibrated GC/MS analysis using dimethyl sulfone as the internal standard. [a] Conditions 200 µmol scale with catalyst (2 mol-%), 2.0 equiv. of *tert*-butyl vinyl ether irradiated for 48 h in CH_3CN (0.5 M).

Conclusion

In conclusion, we have developed a protocol for the formal [3+2] cycloaddition between aziridinylmethyl iodides and electron-rich olefins. The conditions grant access to all substitution patterns of trisubstituted pyrrolidines. While control of stereo-

chemistry is challenging, we observed that the substitution pattern for the olefins plays a more important role than that of the aziridines. In general, the reaction conditions tolerate a variety of functional groups, and the corresponding products are isolated in useful chemical yields. We have also demonstrated that the energy-transfer triggers the initiation of the reaction and that the operating mechanism is a chain transfer process.

Acknowledgments

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Keywords: ATRA · ATRC · Energy-transfer · Nitrogen heterocycles · Photocatalysis

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