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Tandem Visible Light-Mediated Radical Cyclization–Divinylcyclopropane Rearrangement to Tricyclic Pyrrolidinones

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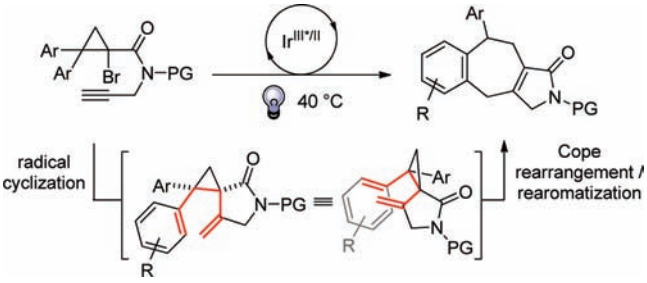
ABSTRACT



Visible light promoted single electron reduction of bromocyclopropyl cyclization scaffolds enabled by photoredox catalysis initiates a novel tandem radical cyclization/sigmatropic rearrangement to generate tricyclic pyrrolidinones having considerable molecular complexity from simple, readily available starting materials. Furthermore, subtle variations to substrate structure afford a wide array of reaction diversity.

Visible light photoredox catalysis is emerging as a powerful tool in organic reaction development.[1] In particular, the single electron transfer (SET) processes enabled by metal polypyridyl catalysts[2,3] have recently found application in a variety of mild oxidation and reduction reactions.[4–7] Specifically, we have demonstrated that photoredox catalysis can serve as a more environmentally friendly alternative to typical reaction systems which

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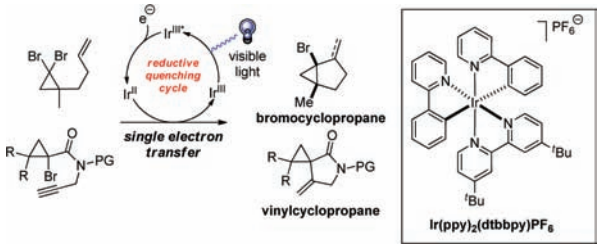
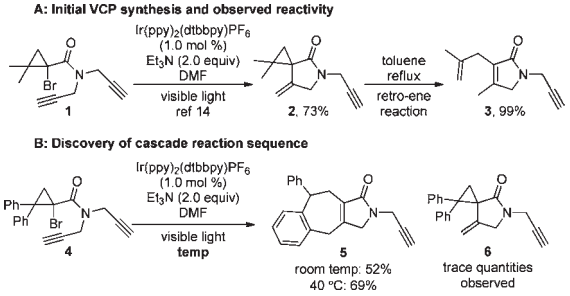
generate alkyl free radical intermediates.[8,9] Visible light-mediated photoredox catalysis is particularly attractive as the reaction occurs under mild conditions, requiring low catalyst loadings, and offering good functional group tolerance and chemoselectivity. In addition, the synthetic community has long recognized the importance of accessing significant molecular complexity in a single step from relatively simple starting materials.[10] One means of accomplishing this goal is through thoughtful design of substrates and the use of cascade reactions. Herein, we report the application of photoredox catalysis to afford fused tricyclic molecular architectures from simple, functionalized cyclopropane starting materials.

Scheme 1. Photoredox Catalysis: Rapid Generation of Platforms for Diversity and Reaction Discovery



We have recently reported the development of a general radical cyclization reaction, wherein an alkyl radical is generated via the single electron reduction of alkyl halides. In this work, we observed efficient formation of compounds which we hypothesized had great potential for use as a platform for molecular diversity and reaction discovery,[11] in particular bromocyclopropanes and vinylcyclopropanes (VCPs) (Scheme 1).[12,13] With this in mind, we observed that heating of **2**[14] in toluene induced a retro-ene fragmentation of the cyclopropane ring to afford **3** in 99% yield (Scheme 2A).[15] This type of reaction profile is typical of alkyl substituted VCPs and is often encountered as an undesired transformation, particularly in the VCP/cyclopentene rearrangement.[16] Therefore, we synthesized **4** in an effort to suppress this retro-ene pathway. Upon subjecting **4** to the photoredox cyclization conditions, including irradiation by a household compact fluorescent lamp (CFL) at room temperature, we observed only trace amounts of the corresponding VCP product (**6**). Instead,

Scheme 2. Access to VCPs and Observed Reactivity



the fused tricyclic pyrrolidinone was generated as the major product in 52% yield after 12 h. When the reaction was run at elevated temperature, 40 °C, the yield of the tricycle improved to 69% (Scheme 2B). In this case, heating of the reaction medium required only surrounding the reaction vessel and CFL with aluminum foil and relying on the light source to heat the medium.[17] Furthermore, it is noteworthy that this transformation results in the generation of two new ring structures bearing valuable chemical motifs, specifically a diarylmethane[18] and fused pyrrolidinone.[19]

The substrate scope of this transformation is quite broad, as demonstrated in Table 1. The reaction is insensitive to substitution about the aryl ring. Both electron-rich and -deficient aromatic rings undergo the tandem reaction sequence efficiently. In addition, utilization of *trans*-1,2-diaryl substituted cyclopropanes allows access to the complementary regioisomer of the tricyclic product (Table 1, entries 6–8). Furthermore, tertiary amides having one propargyl group afforded the rearranged compound in low yields, due to the inability of one of the conformational isomers to undergo the initial cyclization (entry 9). Finally, diastereomerically pure substrates having differentially substituted aromatic rings provided a 1:1 mixture of the constitutional isomers of the rearranged product (entry 10). This is a reflection of the lack of diastereoselectivity of the radical cyclization step.

In addition to this observed reactivity, subtle structural changes to the reaction scaffold afforded varied types of transformations. For instance, an interesting mode of reactivity was observed when subjecting the corresponding secondary amide, **7a**, and propargyl ester, **7b**, to the optimized reaction conditions. Compounds of this type have a thermodynamic bias to adopt the (*Z*) conformation about the amide/ester bond.[20] As a result, they are less

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(17) See the Supporting Information for details.
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Table 1. Radical Cyclization/Cope Rearrangement[a]

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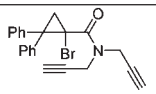
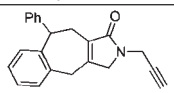
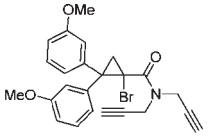
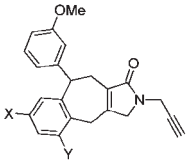
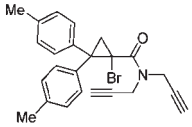
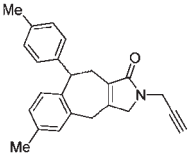
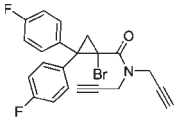
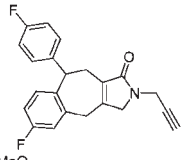
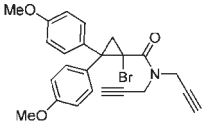
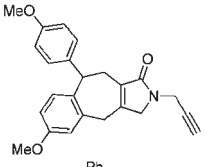
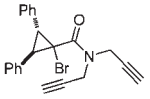
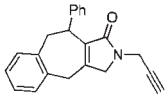
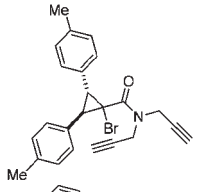
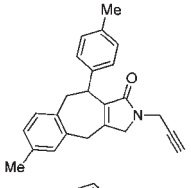
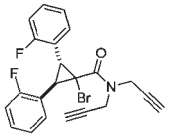
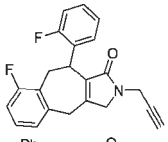
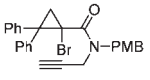
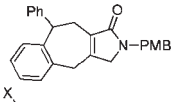
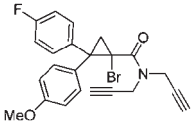
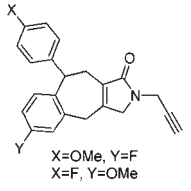
1			69
2		 X=OMe, Y=H X=H, Y=OMe	80[c]
3			91
4			89
5			79
6			85
7			82
8			88
9			32[d]
10		 X=OMe, Y=F X=F, Y=OMe	66[c]

[a] Reaction conditions: cyclopropyl substrate (1.0 equiv), Et_3N (2.0 equiv), $Ir(ppy)_2(dtbbpy)PF_6$ (1.0 mol %), visible light, DMF, 40 °C, 4 to 12 h. [b] Isolated yield after purification by chromatography on SiO_2. [c] Combined yield of regioisomers (1:1). [d] The product of electrocyclic ring opening was isolated in 41% yield (see Figure 1).[17]

likely to undergo the initial cyclization step. Accordingly, the longer lived radical intermediate undergoes an interesting fragmentation process, presumably through a 3π electrocyclic ring opening (Figure 1A).[21] The same cyclopropyl radical fragmentation is observed for the corresponding homopropargylic cyclopropyl ketone, **9**, with the resulting enone undergoing a further conjugate reduction (Figure 1B). In contrast, the dialkyl cyclopropane substrate **11** fails to undergo the same fragmentation process resulting in only the reduction of the bromocyclopropyl moiety (Figure 1C). Furthermore, electron-rich aromatics sufficiently stabilize the allylic radical resulting from the electrocyclic ring opening to promote its efficient dimerization (Figure 1D). Lastly, subjecting compound **15**, having an elongated amide side chain, to the reaction conditions affords a mixture of compounds **16** and **17** (Figure 1E). In contrast to the five-membered ring VCP, **17** does not spontaneously undergo rearrangement under the reaction conditions. In addition, heating this isolated product at 110 °C in DMF afforded no transformation. It is possible that the increased strain of the five-membered VCP allows for the more facile rearrangement.

Several possible mechanisms of this transformation are outlined in Figure 1. The reaction is initiated by a 5-exo-dig radical cyclization and subsequent quenching of the vinyl radical by hydrogen-atom abstraction. The seven-membered ring may then form by a [3,3] sigmatropic rearrangement (Figure 1, path b).[22] Alternatively, it is possible that the same product could be formed via a single electron reduction of the VCP intermediate, followed by a β-scission event and subsequent cyclization and oxidation (Figure 1, path a).[5b] However, when the rearrangement of **4** was carried out on 2.5 mmol scale, small quantities (15 mg, $< 5\%$) of the VCP intermediate **6** were isolated. Mild heating of **6** (40 °C), in DMF in the absence of any redox reaction conditions, cleanly afforded the desired fused tricycle **5** as the sole product. Based on this observation, a thermal sigmatropic rearrangement, presumably driven by the release of the cyclopropyl ring strain, is feasible. However, we cannot exclude the possibility that the rearrangement occurs prior to the quenching of the vinyl radical. In this case, the high energy intermediate may initially cyclize onto the aromatic ring which initiates a β-scission event to form the seven-membered ring (Figure 1, path c).[23] In addition, the inability to isolate any rearranged product from the reaction of compound **15** helps to discount the SET mechanistic pathway.

Finally, the synthetic utility of this transformation can be broadened by removal of the propargyl group in the products to afford N-unprotected lactams. Treatment of

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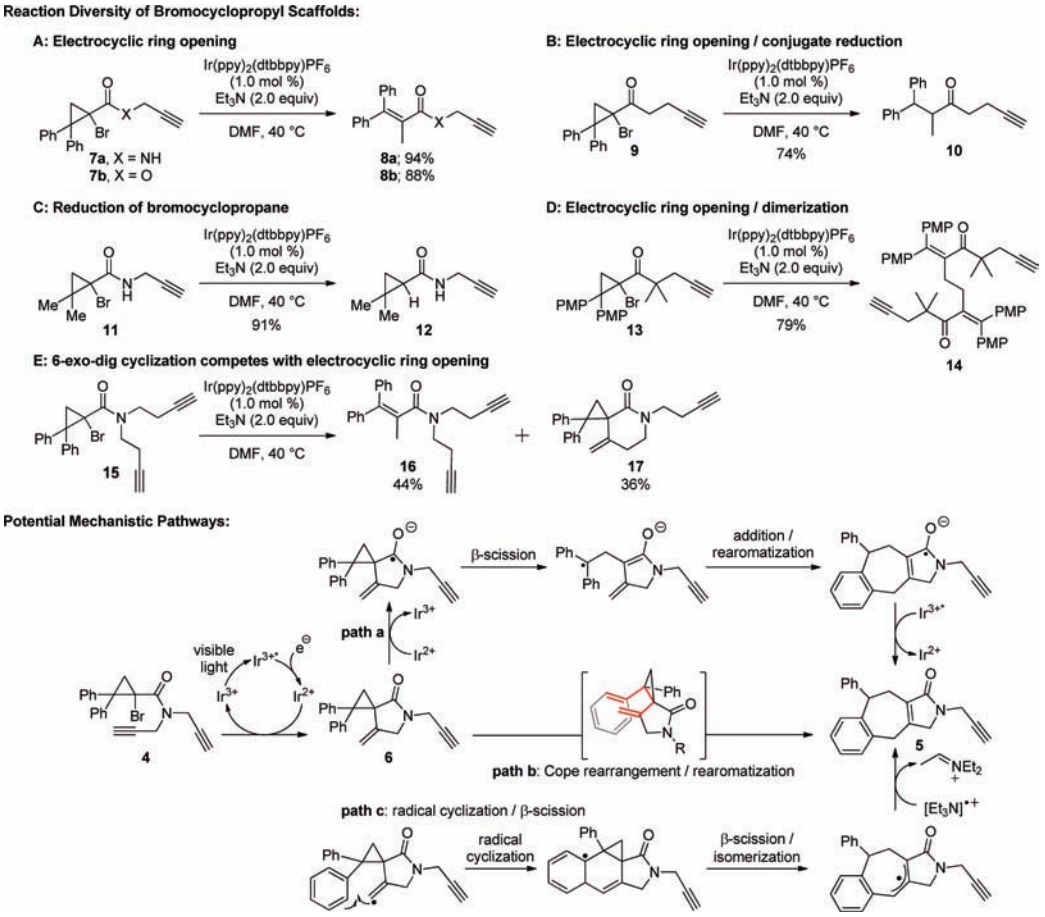
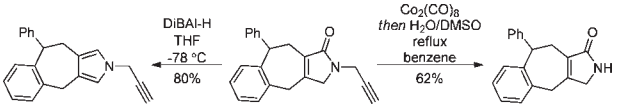


Figure 1. Reaction diversity based upon cyclopropyl substrate and potential mechanistic pathways.

Scheme 3. Elaboration of Rearranged Product



the rearrangement product with $Co_2(CO)_8$ followed by the addition of H_2O and DMSO and heating at reflux affords the secondary amide in good yields.[24] Furthermore, partial reduction by treatment with DIBAL in THF provides the pyrrole in high yields (Scheme 3).

In conclusion, we report the utilization of photoredox catalysis to access, via a cascade reaction sequence, the chemistry of two different valuable synthetic intermediates, alkyl free radicals, and 1,2-divinyl cyclopropanes. By subjecting simple starting materials to these reaction conditions, a significant increase in molecular complexity can be achieved in a single step under mild and operationally simple reaction conditions.

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Supporting Information Available. Experimental procedures, ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.