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Stereospecific Assembly of Fused Imidazolidines via Tandem Ring Opening/Oxidative Amination of Aziridines with Cyclic Secondary Amines Using Photoredox Catalysis

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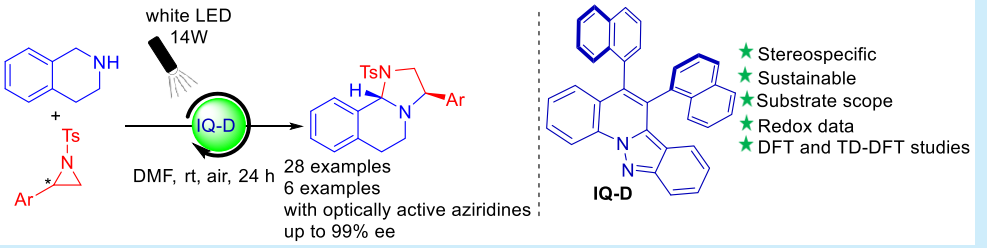
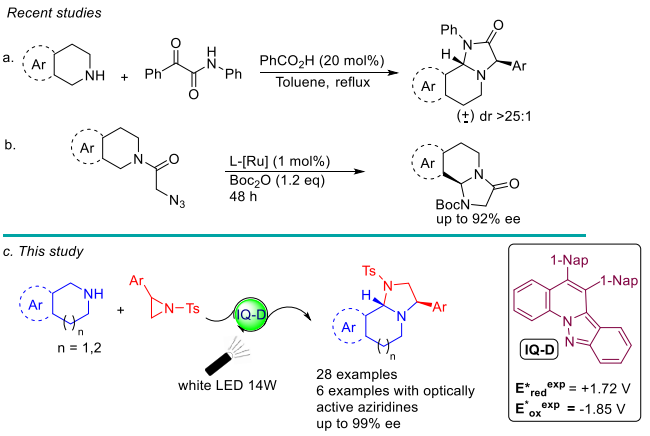
Supporting Information



ABSTRACT: Sustainable assembly of imidazolidines is accomplished via a sequential stereospecific ring opening and C−H amination using aziridines with secondary cyclic amines under visible light mediated indazoloquinoline photoredox catalysis at ambient conditions. Optically active aziridines are coupled with high enantiomeric purities. The computational studies provide insights on the redox properties of the catalysts as well as a profile of the reaction.

Visible-light photoredox catalysis affords a powerful synthetic tool for the sustainable construction of carbon−carbon and carbon−heteroatom bonds.[1] In particular, organo photoredox catalysis is a vibrant field, providing an effective synthetic strategy for the conversion of the simple substrates into complex molecules with structural diversity.[2] Ideally, these catalysts are attractive, as they are cheap, are less toxic, and have comparable redox potential as that of the metal-based systems.[3] However, synthetic application of the organic dyes is still fairly limited, as few catalyst choices are available. Development of organic photoredox catalysts with broad redox competencies is thus valuable.[4,5] Indazoloquinolines (IQ) are widely utilized as the organic light emitting diodes (OLED).[6] These robust fluorescent frameworks can offer a unique stance to alter the redox properties by installing diverse functional groups. In addition, fused imidazolines are often found in natural products and bioactive compounds.[7] Efforts are thus made on the development of synthetic methods to construct these scaffolds.[8] Recently, Seidel and co-workers reported a benzoic acid catalyzed redox-neutral annulation of amine with ketoamides (Scheme 1a),[8f] while Meggers and co-workers demonstrated a chiral Ru-catalyzed C−N cyclization of tetrahydroisoquinoline with 2-azidoacetamides with up to 92% ee (Scheme 1b).[8g] Herein, we present a stereospecific assembly of imidazolidines via a tandem ring opening and an oxidative amination of aziridines with cyclic secondary amines utilizing quinoline based **IQ-A-E** photoredox catalysts in visible light (Scheme 1c). Optically active aziridines can be reacted with 94−99% ee. Computational studies (DFT and TD-DFT) afford insight of the redox properties of the catalysts. To the best of our knowledge, this is the first example available using IQ photoredox catalysis.

Scheme 1. Outline of this Work



Rh-catalyzed regioselective C−H functionalization of 2-aryl-2*H*-indazoles with alkynes produced indazoloquinolines **IQ-A-**

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Org. Lett. XXXX, XXX, XXX−XXX

D and indazolonaphthyridine **IQ-E** in 56−74% yields (Figure 1). Upon visible light irradiation, **IQ-A-E** showed a nano-

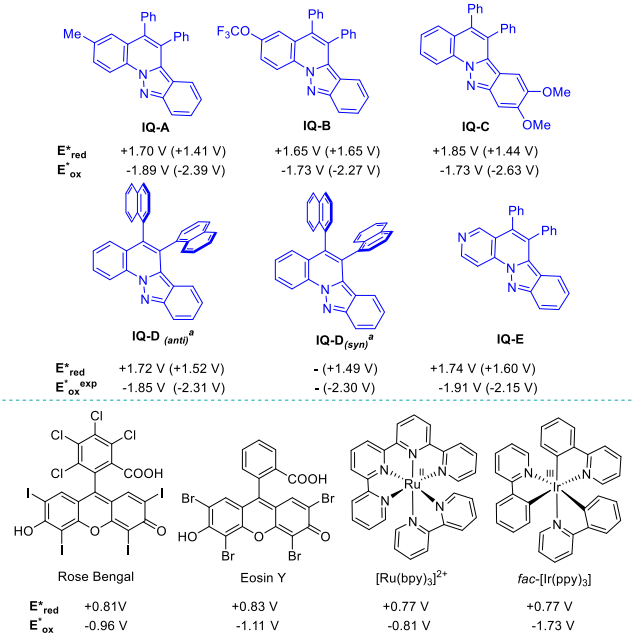
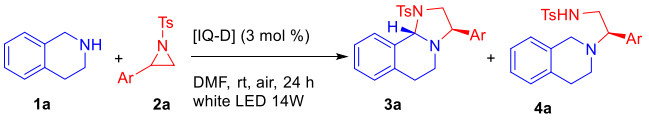


Figure 1. Redox potentials of IQ-A-E with the common catalysts (vs SCE, all potentials mentioned hereafter against SCE). Computed values are given in parentheses. For simplicity, only excited state redox potentials are shown. [a] ^{1}H NMR shows a 10:1 inseparable mixture of rotomers. See SI for more details.

second singlet excited state with the strong oxidative ($E^*_{red}{}^{exp}$ = +1.65 V to +1.85 V, vs SCE and $E^*_{red}{}^{DFT}$ = +1.41 V to +1.65 V, vs SCE) and reductive ($E^*_{ox}{}^{exp}$ = −1.73 V to −1.91 V, vs SCE and $E^*_{ox}{}^{DFT}$ = −2.15 V to −2.62 V, vs SCE) competencies that are comparable/superior to the common photoredox organic dyes and metal complexes (Figure 1 and SI). The electronic properties indicated that the HOMO−LUMO gap of **IQ** (ΔE^{opt} = 2.84 to 2.90 eV, $E_g{}^{exp}$ = 2.48 to 2.84 eV and ΔE^{DFT} = 3.96 to 4.05 eV; see SI) can facilitate the formation of a radical through a single electron transfer (SET). This wide window of strong redox potentials suggests that **IQ-A-E** are most suitable to promote single electron transfer of organic molecules under visible light.

Having the inspired redox results, we initiated the optimization studies for the reaction of tetrahydroisoquinoline **1a** with 2-phenyl-1-tosylaziridine **2a** as the test substrates to examine the feasibility of the hypothesis that can lead to diverse fused imidazolidines (Table 1 and SI: Tables S1 and S2). To our delight, the reaction occurred to produce **3a** in 86% yield when the substrates were stirred with 3 mol % **IQ-D** for 24 h in DMF under white LED 14 W irradiation (entry 1). The reaction of **IQ-A-C** gave 61−72% yields, while **IQ-E** furnished a 55% yield along with **4a** in <31% yield (entries 2−5). These results suggest that the polarizable planar and extended conjugation of **IQ-D** may stabilize the radical anion on the catalyst,[3a] whereas the common photoredox dyes, eosin Y, rose bengal, methylene blue, alizarin red and metal-complexes, $Ru(bpy)_3Cl_2{\cdot}6H_2O$, and *fac*-$Ir(ppy)_3$, yielded inferior results, which may be attributed to their lower redox potential (entries 6−9). Control experiments confirmed that **1a** reacts with **2a** to allow the ring opening of **4a** that leads to

Table 1. Optimization of the Reaction Conditions[a,b]



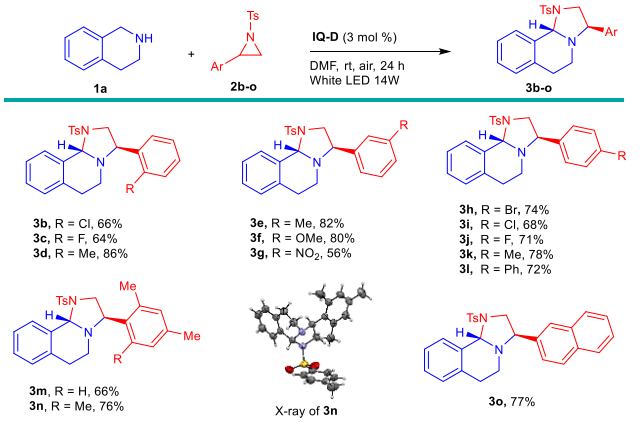
entry	deviation	3a (%)	4a (%)
1	None	86	n.d.
2	**IQ-A** instead of **IQ-D**	69	10
3	**IQ-B** instead of **IQ-D**	61	19
4	**IQ-C** instead of **IQ-D**	72	12
5	**IQ-E** instead of **IQ-D**	55	31
6	Eosin Y instead of **IQ-D**	40	45
7	Rose bengal instead of **IQ-D**	46	33
8	$Ru(bpy)_3Cl_2{\cdot}6H_2O$ instead of **IQ-D**	n.d.	87
9	$Ir(ppy)_3$ instead of **IQ-D**	n.d.	85
10	Without **IQ-D** and light	n.d.	88

[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.25 mmol), [cat.] (3 mol %), DMF (2 mL), air, rt, 24 h. [b]Isolated yield. n.d. = not detected.

cyclization using the photoredox catalysis to furnish **3a** as a single diastereomer *via* an oxidative amination.

With the optimized conditions, the scope of the procedure was examined for the reaction of a series aziridines **2b−o** using **1a** as a standard substrate (Scheme 2). Modulation in the 2-

Scheme 2. Scope of Aziridines[a,b]



[a]Reaction conditions: Amine **1a** (0.30 mmol), aziridines **2b−o** (0.25 mmol), **IQ-D** (3 mol %), DMF (2 mL), white LED 14 W, rt, air. [b]Isolated yield.

aryl ring of **2b−o** with electronically varied substituents was well tolerated. For example, the substrates bearing 2-chloro **2b**, 2-fluoro **2c**, and 2-methyl **2d** groups underwent reaction to produce the heterocycles **3b−d** in 64−86% yields. Similar results were observed with the substrates containing 3-methyl **2e**, 3-methoxy **2f**, and 3-nitro **2g** substituents, producing the heterocycle scaffolds **3e−g** in 56−82% yields, whereas the reaction of the substrates having 4-bromo **2h**, 4-chloro **2i**, 4-fluoro **2j**, 4-methyl **2k**, and 4-phenyl **2l** groups proved to be compatible giving **3h−l** in 68−78% yields. Sterically encumbered substrates, with 2,4-dimethyl **2m** and 2,4,6-trimethyl **2n** substituents, as well as 2-naphthyl aziridine **2o** were tolerated to provide the desired **3m−o** in 66−76% yields. The heterocycles formed as a single diastereomer, and the stereochemistry was confirmed using single crystal X-ray diffraction analysis of **3n**.

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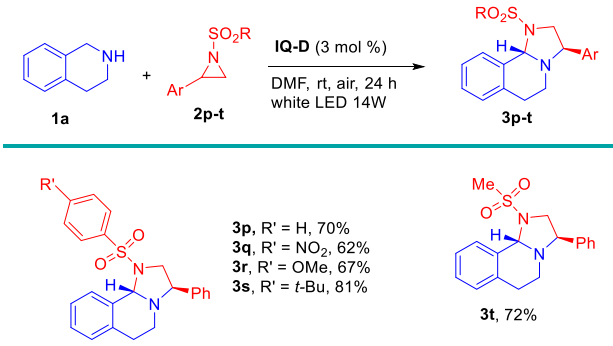
Org. Lett. XXXX, XXX, XXX−XXX

The electronic effect of the *N*-substituents in aziridines was next tested (Scheme 3). *N*-(Phenylsulfonyl)aziridine **2p** underwent reaction to produce **3p** in 70% yield. The reaction of the aziridines bearing 4-nitro **2q**, 4-methoxy **2r**, and 4-*tert*-butyl **2s** functional groups in the *N*-sulfonyl aryl ring furnished **3p**–**3s** in 62–81% yields. In addition, *N*-(methylsulfonyl)-aziridine **2t** reacted to give **3t** in 72% yield. These results suggest that azirdindes having electronically varied *N*-sulfonyl substituents can be successfully coupled.

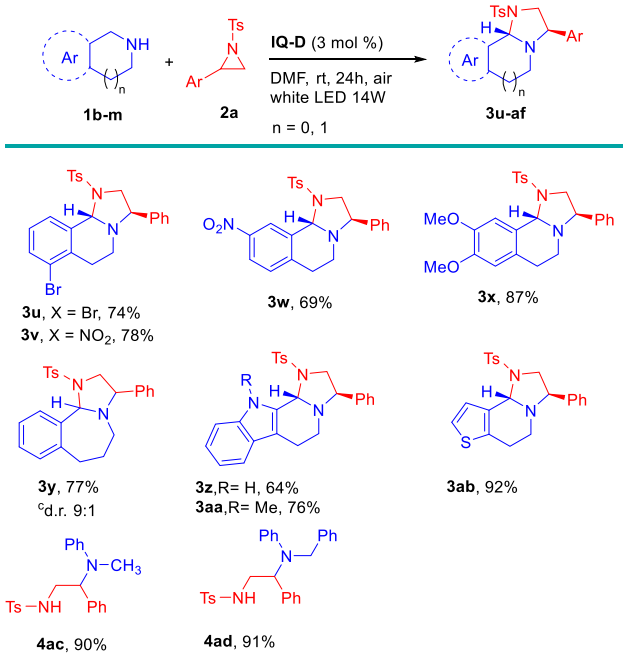
Scheme 3. Scope of *N*-Substituted Aziridines 2p–t[a,b]



[a]Reaction conditions: Amine **1a** (0.30 mmol), aziridines **2p–t** (0.25 mmol), **IQ-D** (3 mol %), DMF (2 mL), white LED 14 W, rt, air. [b]Isolated yield.

The scope of the procedure was further extended to the reaction of a series of cyclic amines **1b–k** employing aziridine **2a** as a standard substrate (Scheme 4). Tetrahydroisoquinoline bearing 5-bromo **1b** and 5-nitro **1c** groups reacted to give **3u** and **3v** in 74% and 78% yields, respectively. The reaction of the substrates with 7-nitro **1d** and 6,7-dimethoxy **1e** substituents furnished **3w** and **3x** in 69% and 87% yields, respectively. Tetrahydro-1*H*-benzo[*b*]azepine **1f** reacted to furnish **3y** as a 9:1 mixture of diastereomers in 77% yield. In addition, tetrahydro-*β*-carbolines **1g–h** and thiophene fused amine **1i** reacted to give the scaffolds **3z** and **3aa–ab** in 64–92% yields, while the reaction of acyclic amines, *N*-methyl **1j** and *N*-benzyl **1k** amines, produced the ring opening **4ac–ad**, which failed to undergo cyclization.

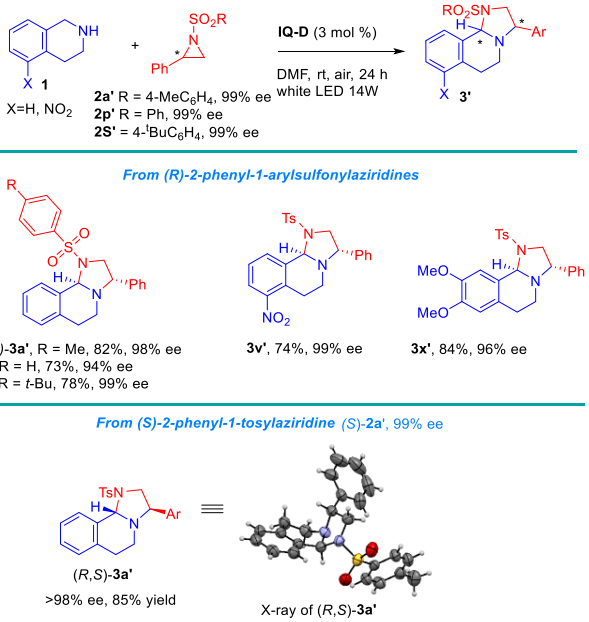
Scheme 4. Scope of Cyclic Amines 1b–m[a,b]



[a]Reaction conditions: Amine **1b–m** (0.30 mmol), aziridines **2a** (0.25 mmol), **IQ-D** (3 mol %), DMF (2 mL), white LED 14 W, rt, air. [b]Isolated yield. [c]Calculated using ^{1}H NMR.

To ascertain the stereospecificity, we inspected the reaction of optically active aziridines (Scheme 5).[9] For instance, (*R*)-2-phenyl-1-tosylaziridine (*R*)-**2a′** underwent reaction with **1a** to give (*S,R*)-**3a′** in 98% ee. Similar results was observed with **1c** and **1x** providing **3v′** and **3x′** in 99% ee and 96% ee, respectively. In addition, the reaction of *N*-phenylsulfonyl (*R*)-**2p′** and 4-(*tert*-butyl)phenyl)-sulfonyl (*R*)-**2s′** aziridines with 1a produced **3p′** and **3s′** in 94 and 99% ee, respectively. Further, (*S*)-2-phenyl-1-arylsulfonylaziridine (*S*)-**2a′** was well-suited, affording (*R,S*)-**3a′** in >98% ee (Scheme 6). The absolute configuration was determined using the single crystal X-ray analysis of (*R,S*)-**3a′**. These results posited the initial ring opening of the aziridine with amine takes place via the stereospecific pathway.[10]

Scheme 5. Enantiospecific Synthesis of Fused Imidazolidines[a,b]



[a]Reaction conditions: amine **1a** (0.30 mmol), **2a′** (0.25 mmol), **IQ-D** (3 mol %), DMF (2 mL), white LED 14W, rt, air. [b]Isolated yield. [c]ee was determined using HPLC.

To gain insight in the mechanism, a series of control experiments and theoretical studies were performed. Amine **1a** underwent reaction with **2a** to give **4a** in quantitative yield, which showed no cyclization in the absence of the photoredox catalyst. In addition, the compound **4a** underwent C–H amination to give **3a** in 91% yield using **IQ-D***, which suggests that the reaction involves a tandem ring opening and oxidative amination using photoredox catalysis (see SI). The Stern–Volmer quenching studies posited that the electron transfer occurs at **4a** to **IQ-D*** (see SI). An alternative pathway, proceeding via the electron transfer from **1a** to **IQ-D***, leads to the formation of 3,4-dihydroisoquinoline and light-mediated

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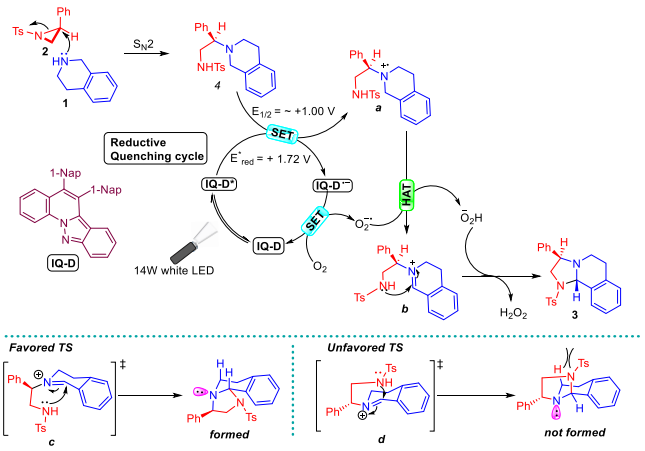
Org. Lett. XXXX, XXX, XXX–XXX

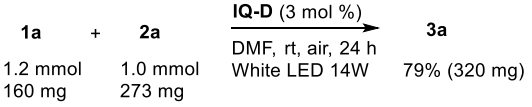
Scheme 6. Proposed Mechanism and Stereochemical Model



ring opening of aziridine, which is unlikely because no quenching was observed at **IQ-D*** by **1a** or **2a**. Next, we measured the oxidation potential, E_{ox}^{exp} = 0.92 to 1.05 V and E_{ox}^{DFT} = +1.14 to +1.26 V, for a series of electronically varied intermediates **4a**, **4j–k**, and **4p–q** as the representative examples, which suggest that they can be oxidized by the excited **IQ-D*** $E^{*}_{red}{}^{exp}$ = +1.72 V and $E^{*}_{red}{}^{DFT}$ = +1.52 V (see SI). In addition, the reaction generates H_2O_2, which was confirmed using the iodide test (KI in acetic acid) which suggests that O_2 plays an important role in the catalysis (see SI). Further, the one-pot ($[P_H/P_D]$ = 3.3) and parallel (k_H/k_D = 4.3) kinetic isotope experiments suggest that the hydrogen atom transfer (HAT) can be the rate-determining step (see SI). These experimental results and literature reports[1,2] suggest that the stereospecific ring opening of aziridine **2** with **1** can produce **4** with an inverted stereochemistry (Scheme 5). The visible light irradiation of **IQ-D** can produce the excited **IQ-D***, which can undergo single electron transfer (SET) with **4** to afford the radical cation **a** and radical anion **IQ-D**$^{\bullet-}$. The latter can react with oxygen (air) to generate **IQ-D** and $O_2^{\bullet-}$ via the SET. Hydrogen atom transfer (HAT) from the radical cation **a** to $O_2^{\bullet-}$ can yield HO^{2-} and imine **b**. HO^{2-} mediated cyclization of **c** can lead to the formation of the target compound **3**. Formation of the single diastereomer suggests that the cyclization can take place via the transition state TS **c** compared to that of TS **d**, which can be attributed to the 1,3-diaxial interaction. The proposed reaction pathway was further examined by computational studies using M06/6-31+G(d,p) (see SI). The reaction of **1a** with **2a** can produce **4** through the TS-1 with an activation barrier of 37.30 kcal/mol (Figure 2). Formation of **4** is favored, as the stabilization is much more than the activation barrier. When the relative stability of **4** was compared with **4′**, **4′** is around 2 kcal/mol less stable than **4**, and thus the formation of **4′** is ruled out. SET from the catalyst to **4** can give **a**, which is 2.80 kcal/mol more stable than **4**. Interaction of $O^{2\bullet-}$ with a through TS-2 can form **b**, and this step is the rate-determining step as the barrier for the formation is highest (38.55 kcal/mol). This finding is in accordance with the observed experimental results. The abstraction of a proton from **b** can form **c** through TS-3, which is a quick reaction with the barrier of 1.55 kcal/mol and the stabilization of more than 12 kcal/mol. Cyclization of **c** can lead to the target **3**, which is very fast, as the activation barrier TS-4 is less than 1 kcal/mol. The relative stability of **3** and **3′** were compared to prove that the formation of **3** is favored over **3′**.

Finally, the scale-up (1 mmol) of the procedure was studied using **1a** with **2a** as the representative substrates (Scheme 7). The reaction occurred to give the target heterocycle **3a** in 79% yield.

Scheme 7. Scale-up Reaction



In conclusion, the stereospecific assembly of fused imidazolines is developed from *N*-sulfonyl aziridines and secondary cyclic amines via a tandem ring opening/C–H amination using

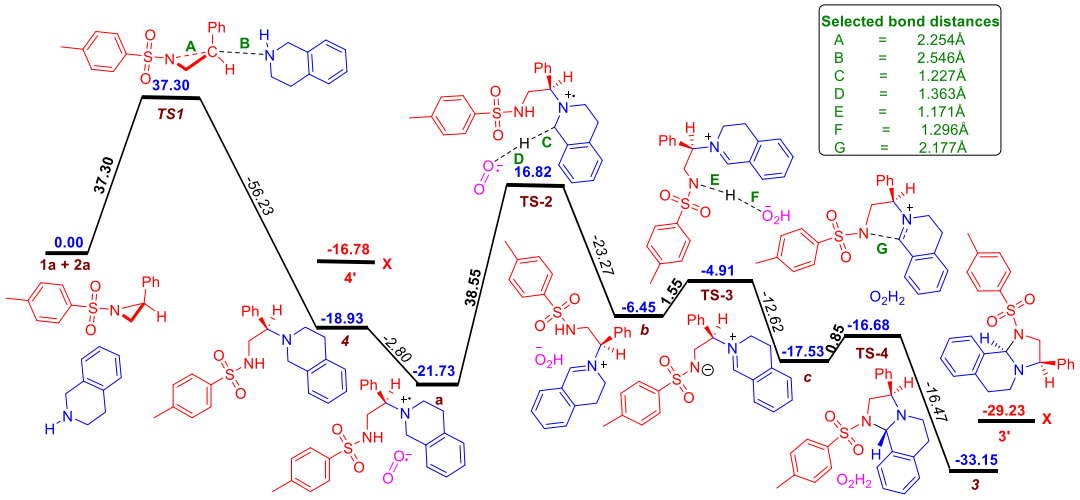


Figure 2. Calculated energy profile of tandem ring opening/C–H amination reaction at M06/6-31+G(d,p) level of theory. "Numbers in blue colors" depict the relative energies (kcal/mol), "numbers in bold" show the activation barrier, and "numbers in italics" show the stabilization. All energy values are given in kcal/mol. Important interatomic distances in transition state structures are given in green color in Å unit. Red color numbers and cross sign (X) show the unfavored intermediate or product.

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visible IQ photoredox catalysis. The redox properties of the IQs have been demonstrated using DFT and TD-DFT studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02957.

Experimental procedure, crystal data, characterization data, and NMR spectra (^{1}H, ^{13}C, and ^{19}F) of the products (PDF)

Accession Codes

CCDC 1937814 and 1937816 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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