



Stereoselective intermolecular radical cascade reactions of tryptophans or γ -alkenyl- α -amino acids with acrylamides via photoredox catalysis

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The radical cascade reaction is considered as one of the most powerful methods to build molecular complexity. However, highly stereoselective intermolecular radical cascade reactions that can produce complex cyclic compounds bearing multiple stereocenters via visible-light-induced photocatalysis have been challenging yet desirable. Herein we report a facile and efficient synthesis of multi-substituted *trans*-fused hexahydrocarbazoles via a stereoselective intermolecular radical cascade reaction of readily available tryptophans and acrylamides enabled by visible-light-induced photoredox catalysis. The *trans*-fused hexahydrocarbazoles with up to five stereocenters including two quaternary ones can be accessed in up to 82% yield, >20/1 diastereoselectivity, and 96% ee. Interestingly, the tetrahydrocarbazoles are favorably formed when the reaction is performed under air. Moreover, by simply switching the starting material from tryptophans to γ -alkenyl substituted α -amino acids, this protocol can be further applied to the stereoselective syntheses of 1,3,5-trisubstituted cyclohexanes which are otherwise challenging to access. Preliminary mechanistic studies suggest that the reaction goes through radical addition cascade and radical-polar crossover processes.

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In the pharmaceutical industry, the growing demand for complex three-dimensional cyclic compounds urges the synthetic chemists to develop novel and efficient strategies to construct these motifs^{1,2}. Radical cascade reactions are considered as one of the most powerful methods to meet this demand^{3–6}. This protocol, which allows the rapid syntheses of valuable complex cyclic molecules, has been widely applied in the total syntheses of natural products^{7–9}. However, many radical transformations involving alkyl radical species usually requires the use of organic halides as substrates, the addition of toxic stannanes as the halogen or hydrogen atom transfer agents, and the use of unstable initiators^{10,11}. In recent years, photocatalysis using visible light has emerged as a promising strategy for the development of novel radical reactions due to its high efficiency and convenience in the generation of various reactive radical species under mild and environmentally friendly conditions^{12–19}. Specifically, the visible-light-induced radical cascade reactions enable the facile construction of diverse cyclic compounds under sustainable conditions^{3,20,21}. Despite these advances, plenty of radical cascade cyclization reactions still rely on either the carefully designed precursors or the intramolecular design, which tempers the appeal of their further synthetic applications. Therefore, it is highly desirable to develop stereoselective intermolecular radical cascade reactions that could produce complex cyclic compounds from readily available starting materials via visible-light-induced photocatalysis.

As a pivotal structure unit, hexahydrocarbazole motif widely occurs in many biologically active polycyclic indoline natural products^{22–26}, such as kopsinine, tubifolidine, aspidospermidine, and vindoline (Fig. 1A). Consequently, great efforts have been devoted to the preparation of functionalized hexahydrocarbazoles^{27–43}. Among those, direct catalytic dearomatization reaction of indole derivatives represents a straightforward and powerful strategy^{44–50}. The *cis*-fused hexahydrocarbazoles are usually obtained through the

dearomatization of substituted or pre-functionalized indole derivatives^{27–33}. In contrast, the syntheses of the *trans*-fused hexahydrocarbazoles are less explored^{36–43}. To date, methods to uncover the highly stereoselective synthesis of this structural motif have been limited to UV-light-induced intramolecular photocyclization of reactive enamine precursors^{36,37} (eq 1, Fig. 1B) as well as Pd-catalyzed intramolecular C–H activation/cyclization reaction (eq 2, Fig. 1B)^{38–43}.

Tryptophan is a commercially available, non-toxic, abundant, and naturally occurring α -amino acid. Accordingly, we questioned whether this readily available material could be directly used to synthesize the *trans*-fused hexahydrocarbazole through a one-step visible-light-induced photocatalytic radical cascade reaction (Fig. 1C). In practice, tryptophan was often used as an α -amino alkyl radical precursor in radical addition reactions via visible-light-induced photocatalysis^{51–58}. In pioneer work, MacMillan and coworkers reported an elegant radical Michael addition reaction of *N*-Boc-tryptophan and diethylethylenemalonate via photocatalysis (Fig. 1D)⁵⁴. In 2016, Zhou and coworkers described an interesting photocatalytic decarboxylative/defluorinative reaction of *N*-Boc-tryptophan and α -trifluoromethyl alkenes (Fig. 1E)⁵⁶. Nevertheless, to the best of our knowledge, there is no general method for the generation of *trans*-fused hexahydrocarbazoles bearing multiple stereocenters through a one-step stereoselective radical cascade reaction of tryptophan via visible-light-induced photocatalysis. Herein, we report a facile and efficient synthesis of multi-substituted *trans*-fused hexahydrocarbazoles via a stereoselective intermolecular radical cascade reaction of readily available tryptophans and acrylamides enabled by visible-light-induced photoredox catalysis (eq 3, Fig. 1F). The *trans*-fused hexahydrocarbazoles with up to five stereocenters including two quaternary ones could be accessed in up to 82% yield, >20/1 diastereoselectivity, and 96% ee. Intriguingly, this protocol could further be applied to the stereoselective syntheses of 1,3,5-

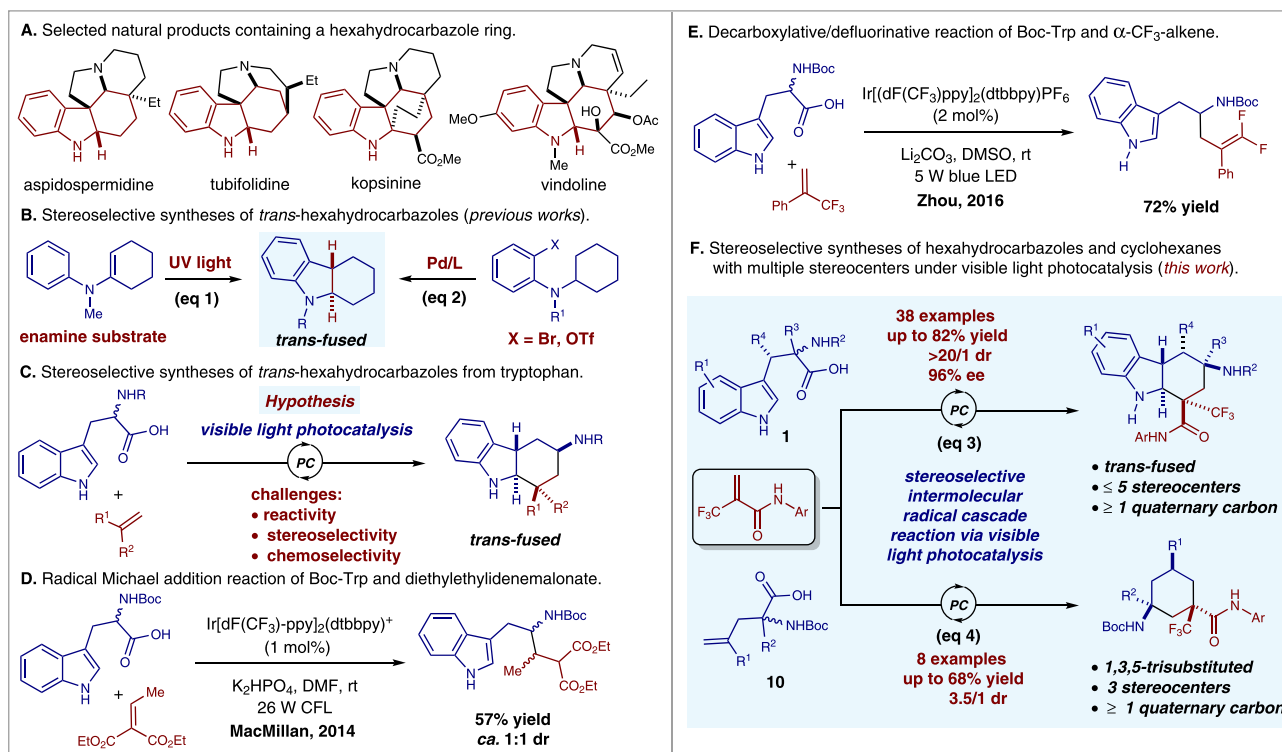
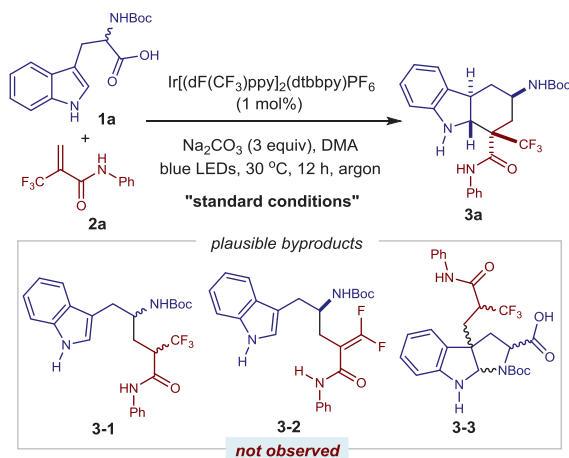


Fig. 1 Syntheses of *trans*-fused hexahydrocarbazoles and 1,3,5-trisubstituted cyclohexanes through stereoselective intermolecular radical cascade reaction under visible light photocatalysis. **A** Natural products containing a hexahydrocarbazole ring. **B** Previous works. **C** Hypothesis. **D** Reaction of Boc-Trp and diethylethylenemalonate. **E** Reaction of Boc-Trp and α -CF₃-alkene. **F** This work. PC photocatalyst, Trp tryptophan.

Table 1 Optimization of the reaction conditions^a.

entry	variation from the standard conditions	yield ^b (%)	dr ^c
1	none	75 ^d	>20:1
2	4-CzIPN instead of Ir-cat.	40	>20:1
3	$\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ instead of Ir-cat.	8	>20:1
4	NaHCO_3 instead of Na_2CO_3	69	>20:1
5	K_2CO_3 instead of Na_2CO_3	60	>20:1
6	no base	18	>20:1
7	no Ir-cat., or no light	NR ^e	NA ^f
8	under air	4 ^g	>20:1

^aReaction conditions: 1 mol% of $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$, 0.3 mmol of Na_2CO_3 , 0.15 mmol of **1a**, 0.1 mmol of **2a** in *N,N*-dimethylacetamide (DMA, 2.0 mL) for 12 h under blue LEDs irradiation at 30 °C.

^bYields of the major diastereomer were determined by ¹H NMR analysis using CH_2Br_2 as internal standard.

^cThe diastereomeric ratio (dr) was determined by crude ¹H NMR analysis.

^dIsolated yield of the major diastereomer.

^eNR = no reaction.

^fNA = not available.

^gYield of **9a** (Fig. 4, dr > 20:1) was 61% as determined by ¹H NMR analysis.

trisubstituted cyclohexanes, which are otherwise challenging to access in a single operation, by simply switching the starting material from tryptophans **1** to γ -alkenyl substituted amino acids **10** (eq 4, Fig. 1F).

Results

Reaction optimization. Our studies were initiated with an exploration of reaction conditions for the intermolecular coupling of commercially available *N*-(*tert*-butoxycarbonyl)tryptophan (**1a**) and *N*-phenyl-2-(trifluoromethyl)acrylamide (**2a**) (Table 1). After an extensive investigation of reaction conditions, it was found that the desired radical cascade cyclization product *trans*-fused hexahydro-1*H*-carbazole **3a** was obtained in 75% yield and >20:1 dr when the reaction was performed with 1 mol% of $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ as the photocatalyst, 3 equiv of Na_2CO_3 as the base and blue LEDs as the light source (entry 1, for the experimental setup, see Supplementary Fig. 1). Notably, the probably competitive radical

addition product **3-1**, radical addition/ β -fluoride elimination product **3-2**, and nucleophilic addition/cyclization product **3-3** were not detected under these photocatalytic conditions, which demonstrated the unique selectivity of the current reaction. The reaction could also proceed when the organic dye 4-CzIPN was used as the photocatalyst (entry 2). However, the use of a ruthenium-based photocatalyst led to low yield of the desired product (entry 3). The reaction also proceeded smoothly when different inorganic bases such as NaHCO_3 and K_2CO_3 were used (entries 4–5). When the reaction was performed in the absence of base, the desired product was obtained with a significantly lower yield (entry 6). Control experiments demonstrated that the photocatalyst and light were indispensable for the product formation (entry 7). Interestingly, when the reaction was performed under air, 4% of the desired product was observed along with 61% of the tetrahydro-1*H*-carbazole **9a** (entry 8, yields were determined by crude ¹H NMR analysis. For details, see Fig. 4).

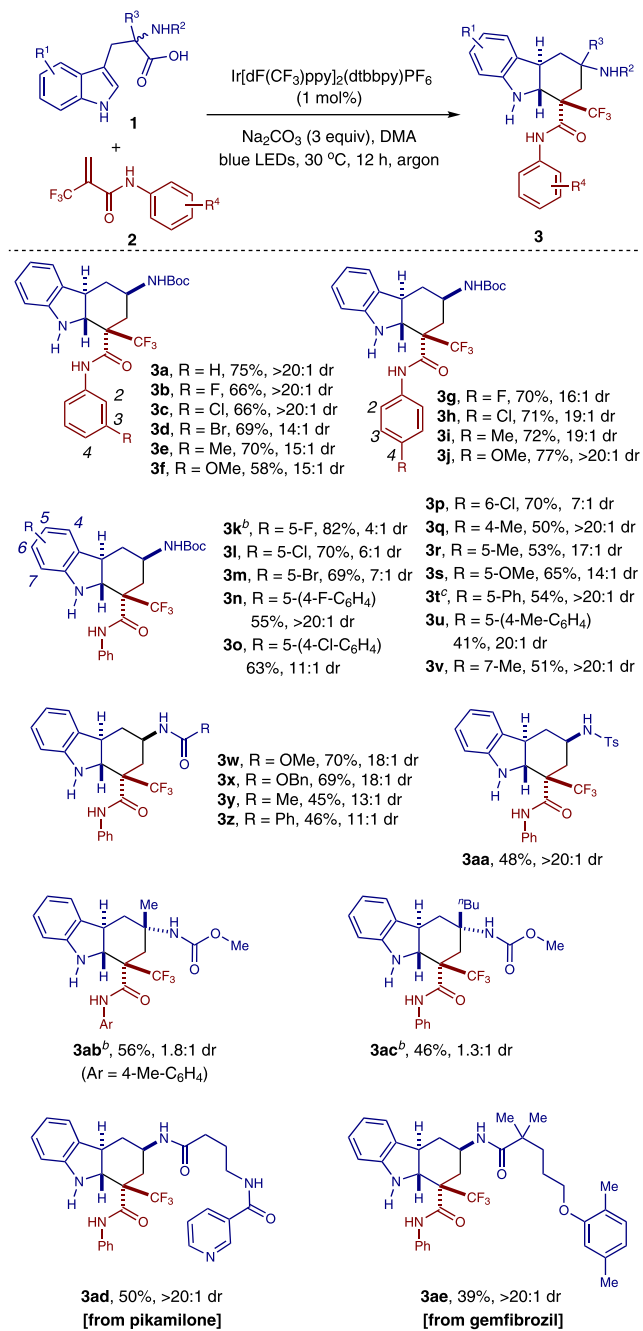


Fig. 2 The substrate scope. ^a Reaction conditions: 1 mol% of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 0.3 mmol of Na₂CO₃, 0.15 mmol of **1**, 0.1 mmol of **2** in DMA (2.0 mL) for 12 h under blue LEDs irradiation at 30 °C. Isolated yields of major diastereomers are reported. The dr was determined by crude ¹H NMR analysis. ^b The combined yield of both diastereomers. ^c The reaction was conducted at 40 °C.

Evaluation of the substrate scope. With the optimized reaction conditions in hand, various substituted tryptophan derivatives **1** and *N*-aryl-2-(trifluoromethyl)acrylamides **2** were tested to establish the generality of the process (Fig. 2). Reactions of *N*-aryl-2-(trifluoromethyl)acrylamides **2** containing either electron-donating or electron-withdrawing groups on the aromatic ring (R⁴) attached to amide moiety all gave the corresponding products in moderate to good yields and good to excellent diastereoselectivities (**3a**–**3j**). In addition, the tryptophan derivatives **1** containing either electron-donating or electron-withdrawing groups on the phenyl ring of the indole moiety (R¹) were probed. The

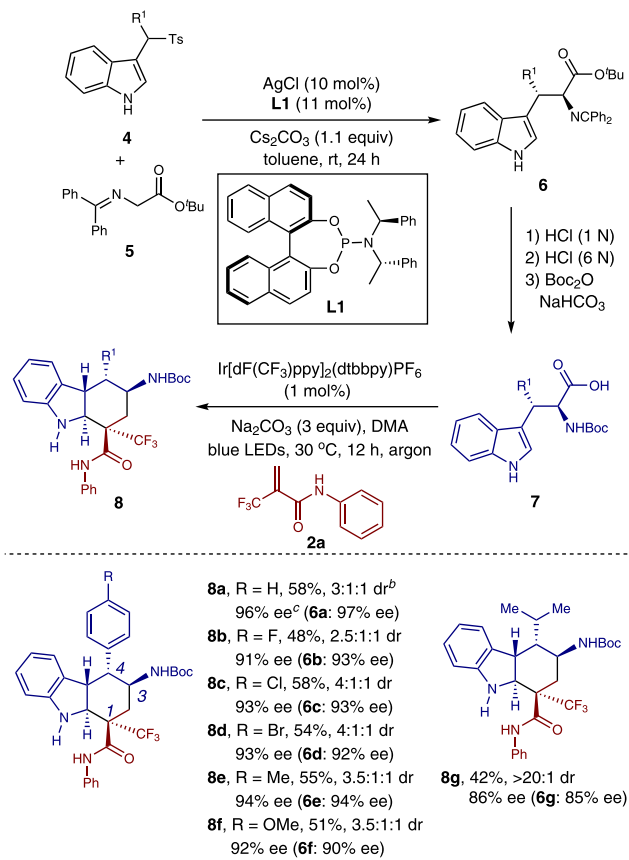


Fig. 3 Diastereoselective syntheses of chiral *trans*-fused hexahydrocarbazoles with five contiguous stereogenic centers. ^a Reaction conditions: 1 mol% of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 0.1 mmol of **2**, 0.15 mmol of **7** and 0.3 mmol of Na₂CO₃ in DMA (2.0 mL) for 12 h under blue LEDs irradiation at 30 °C. Combined isolated yields of the diastereomers are reported. ^b The dr was determined by crude ¹H NMR analysis. ^c Enantiomeric excess (ee) of the major diastereomer was reported. The ee value was determined by HPLC analysis on a chiral stationary phase.

reactions occurred smoothly, affording the corresponding *trans*-fused hexahydrocarbazoles **3** in moderate to good yields and moderate to excellent diastereoselectivities (**3k**–**3v**). Moreover, substrates **1** containing different substituents on the nitrogen atom (R²) of the amino acid moiety were also tested. It was found that the carbamates, simple amides, and sulfonamide were all tolerated under these reaction conditions, affording the corresponding cyclization products in moderate to good yields and good to excellent diastereoselectivities (**3w**–**3aa**). Furthermore, reactions of α , α -disubstituted α -amino acids also occurred, providing the *trans*-fused hexahydrocarbazoles **3ab**–**3ac** with two quaternary carbon centers in moderate yields. Finally, the present method was applied to the late-stage functionalization of the derivatives of drug molecules, providing easy access to two hexahydrocarbazole-containing complex molecules (**3ad**–**3ae**) in moderate yields and excellent diastereoselectivities. The structure and relative configuration of both diastereomers of the hexahydrocarbazole products were assigned by X-ray crystallographic analyses of compounds **3k** and **3ab** (major diastereomers, see Supplementary Figs. 8 and 9), and compounds **3k'** and **3ab'** (minor diastereomers, see Supplementary Figs. 10 and 11) respectively.

Pleasingly, the present method was able to be applied to the diastereoselective syntheses of chiral *trans*-fused hexahydrocarbazoles with five contiguous stereogenic centers (Fig. 3).

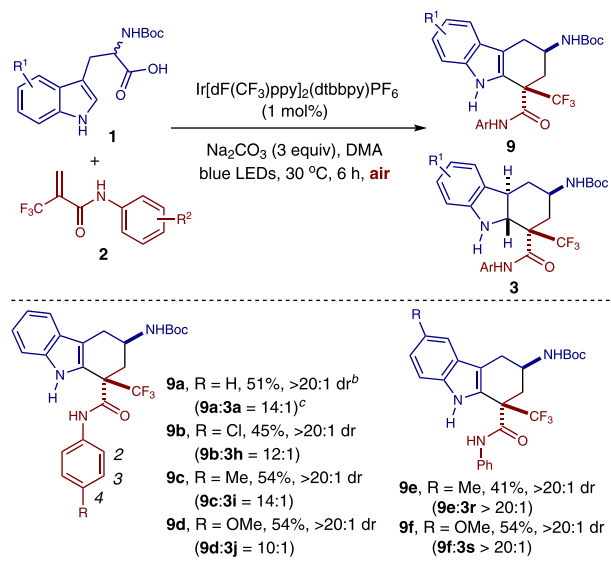


Fig. 4 Syntheses of tetrahydrocarbazoles. ^a Reaction conditions: 1 mol% of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 0.15 mmol of **1**, 0.1 mmol of **2**, and 0.3 mmol of Na₂CO₃ in DMA (2.0 mL) for 6 h under blue LEDs irradiation at 30 °C. Isolated yields of compound **9** are reported. ^b The dr was determined by crude ¹H NMR analysis. ^c The ratio was determined by crude ¹H NMR analysis.

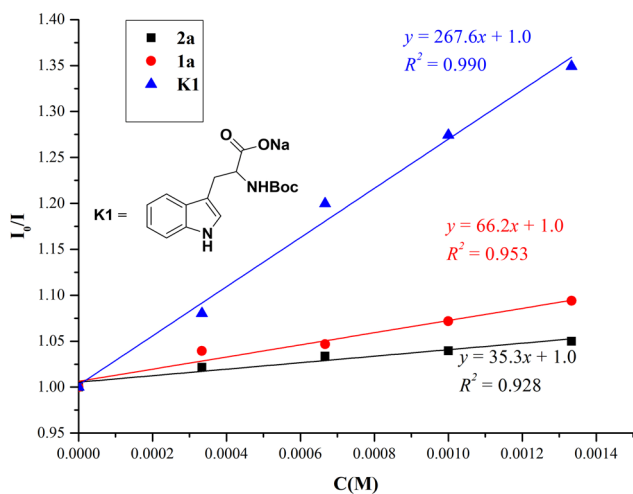


Fig. 5 Stern-Volmer quenching experiments of ^{*}Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ with compounds **1a, **2a**, and **K1**.** A solution of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ in *N,N*-dimethylacetamide was excited at 380 nm and the emission intensity at 481 nm was observed.

Reactions of chiral β -aryl-substituted tryptophan derivatives **7** containing either electron-withdrawing or electron-donating groups on the aromatic ring (R^1) attached to β -carbon of the α -amino acid moiety all gave the corresponding chiral *trans*-fused hexahydrocarbazoles bearing five contiguous stereocenters (**8a–8f**). In addition, reaction of the β -alkyl-substituted α -amino acid also occurred smoothly, affording the desired product **8g** in moderate yield and excellent diastereoselectivity. Notably, the enantiomeric purity of the starting material **6**, which could be easily prepared via a simple Ag-catalyzed enantioselective reaction of glycine derivatives **5** with sulfonylindoles **4**⁵⁹, was well-preserved under these photocatalytic conditions (**8a–8g**). The structure and absolute configuration of the major

diastereomers of the hexahydrocarbazole products were assigned by an X-ray crystallographic analysis of compound **8a** (Supplementary Fig. 12). The absolute configuration was determined as (1*S*, 3*S*, 4*R*, 5*S*, 6*S*).

Interestingly, the reaction also proceeded when it was performed under air, affording tetrahydro-1*H*-carbazole **9a** favorably (**9a:3a** = 14:1) with moderate yield and excellent diastereoselectivity (Fig. 4, for the experimental setup, see Supplementary Fig. 2). Several substituted tryptophan derivatives **1** and *N*-aryl-2-(trifluoromethyl)acrylamides **2** were tested to establish the generality of the process. Reactions of tryptophan derivatives **1** and *N*-aryl-2-(trifluoromethyl)acrylamides **2** containing either electron-donating or electron-withdrawing groups on the aromatic ring (R^1 or R^2) attached to the indole or amide moiety all led to the tetrahydro-1*H*-carbazoles **9** favorably in moderate yields and excellent diastereoselectivities (**9b–9f**). The structure and relative configuration of the tetrahydrocarbazole products were assigned by an X-ray crystallographic analysis of compound **9a** (see Supplementary Fig. 13).

Mechanistic studies. To probe the reaction pathway, preliminary mechanistic studies were carried out (Figs. 5 and 6). It was found that the excited photocatalyst ^{*}Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ could be quenched by acrylamide **2a**, *N*-Boc-tryptophan **1a**, and its sodium salt **K1** respectively according to the Stern–Volmer luminescence quenching studies (Fig. 5, for experimental details, see Supplementary Fig. 7). However, the reductive quenching of ^{*}Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ by either *N*-Boc-tryptophan **1a** or its sodium salt **K1** was more efficient than the oxidative quenching of the excited photocatalyst by substrate **2a**, which indicates the former process is possibly the initiation step of the photoredox catalytic cycle (for the cyclic voltammetry measurement experiments of compounds **1a**, **2a**, and **K1**, see the Supplementary Figs. 3–6). In addition, when the enantiopure (*R*)-*N*-Boc-tryptophan (*R*)-**1a** was utilized under the reaction conditions, the racemic product **3a** was obtained (Fig. 6A). These results suggest that the α -aminoalkyl radical is formed via photoinduced decarboxylation. Furthermore, 93% of deuterium incorporation at the C3-position of the hexahydrocarbazole product was observed when D₂O was added to the reaction mixture (Fig. 6B). These results suggest that the carbon anion in the benzylic position of indoline moiety is plausibly generated via radical-polar crossover^{60,61}. Interestingly, when the *N*-methyl substituted acrylamide **2'** was used as a substrate for the reaction, the competitive radical addition/ β -fluoride elimination product **3'** was obtained instead of the hexahydrocarbazole⁵⁶, which indicates that the N–H bond of the amide moiety is very crucial for this unique radical cascade cyclization reaction (Fig. 6C). The plausible hydrogen bonding effect between the amide N–H bond and the CF₃ moiety might benefit the intramolecular cyclization. Moreover, in order to figure out whether the tetrahydrocarbazole **9a** was formed via oxidation of *trans*-hexahydrocarbazole **3a**, two control experiments were performed. Either low conversion or no reaction was observed when this transformation was carried out using the same conditions as shown in Fig. 4 or the conditions without photocatalyst (Fig. 6D). These results suggest that benzylic radical species **I-3** might be involved as an intermediate during the oxidation process (for details, see Fig. 7)^{62,63}.

Based on the above experimental observations, a plausible reaction pathway was proposed, as shown in Fig. 7. Firstly, the α -aminoalkyl radical **I-1** generated by photoinduced decarboxylation adds to α,β -unsaturated amide **2a** to form radical intermediate **I-2**. This tertiary alkyl radical intermediate would subsequently undergo a radical cyclization onto the indole ring to generate the tertiary benzylic radical intermediate **I-3**. Finally, the

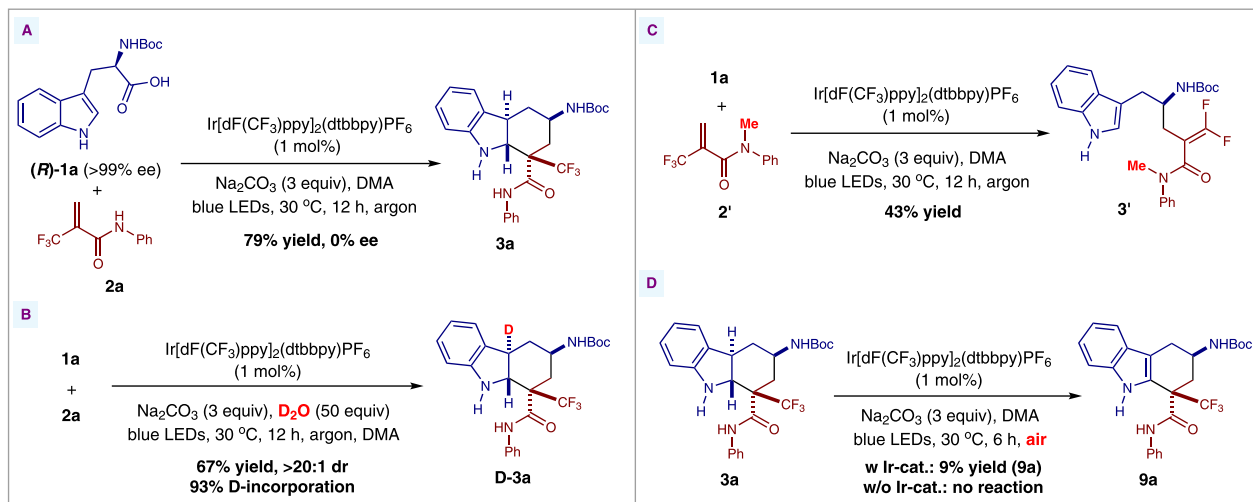


Fig. 6 Mechanistic experiments. **A** Reaction of enantiopure (*R*)-*N*-Boc-tryptophan (*R*)-**1a** with substrate **2a**. **B** Deuterium experiment. **C** Reaction of *N*-methyl substituted acrylamide **2'** with substrate **1a**. **D** Control experiments.

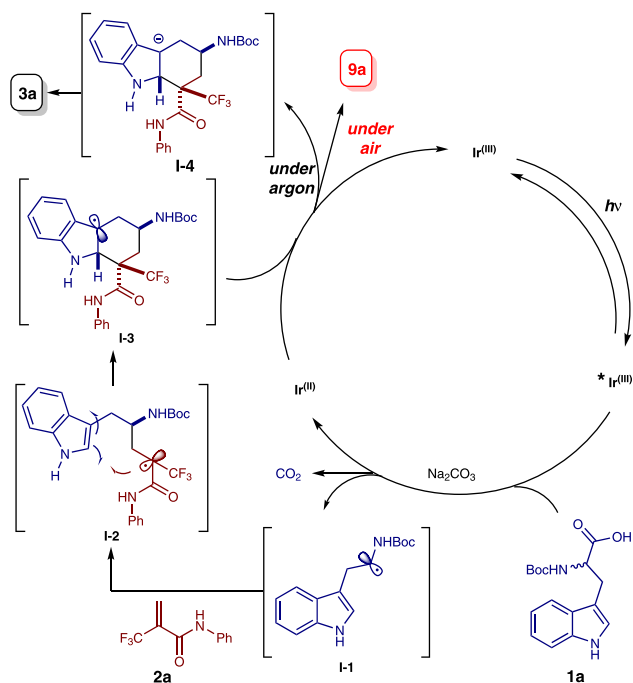


Fig. 7 A plausible reaction pathway. A plausible reaction pathway for the formation of products **3a** and **9a** was proposed.

hexahydrocarbazole **3a** is obtained via reduction of the benzylic radical intermediate **I-3** by Ir(II) and subsequent protonation under inert atmosphere. Interestingly, when this benzylic radical intermediate **I-3** is exposed to air under the reaction conditions, the tetrahydro-1*H*-carbazole **9a** is formed favorably.

Rational expansion of the method. To further test the generality of the current method, this radical cascade cyclization strategy was applied to the synthesis of 1,3,5-trisubstituted cyclohexanes (Fig. 8). To our delight, by simply switching the starting material from tryptophans **1** to the alkenyl substituted amino acids **10**, several 1,3,5-trisubstituted cyclohexanes bearing at least one quaternary carbon stereocenter were obtained in moderate yield and up to 3.5:1 dr under the photocatalytic conditions (**11a–11h**). Notably, the 1,3,5-trisubstituted cyclohexane with two quaternary carbon stereogenic centers (**11h**) could also be accessed via this

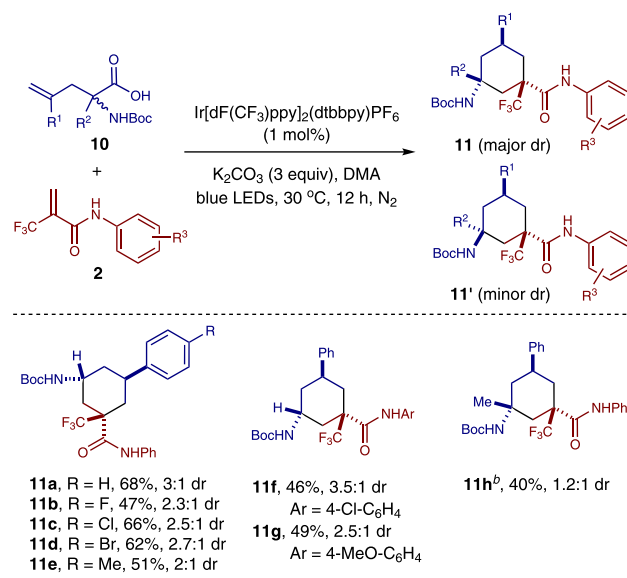


Fig. 8 Application to the syntheses of 1,3,5-trisubstituted cyclohexanes.

^a Reaction conditions: 1 mol% of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 0.1 mmol of **2**, 0.15 mmol of **10** and 0.3 mmol of K₂CO₃ in DMA (2.0 mL) for 12 h under blue LEDs irradiation at 30 °C. Combined isolated yields of both diastereomers are reported. The dr was determined by crude ¹H NMR analysis. ^b The reaction was performed with 2 mol% of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, and 2.0 equiv of **10** for 18 h.

one-step radical cascade cyclization reaction. This strategy provides a straightforward and efficient pathway for the construction of 1,3,5-trisubstituted cyclohexanes which are challenging to be synthesized in one step. The structure and relative configuration of both diastereomers of the 1,3,5-trisubstituted cyclohexane products were assigned by X-ray crystallographic analyses of the derivative of compound **11a** (major diastereomer, see Supplementary Fig. 14) and compound **11d'** (minor diastereomer, see Supplementary Fig. 15) respectively.

Synthetic applications. Finally, in order to demonstrate the synthetic utility of the present method, a 1.0 mmol-scale reaction and several transformations of the multi-substituted *trans*-fused

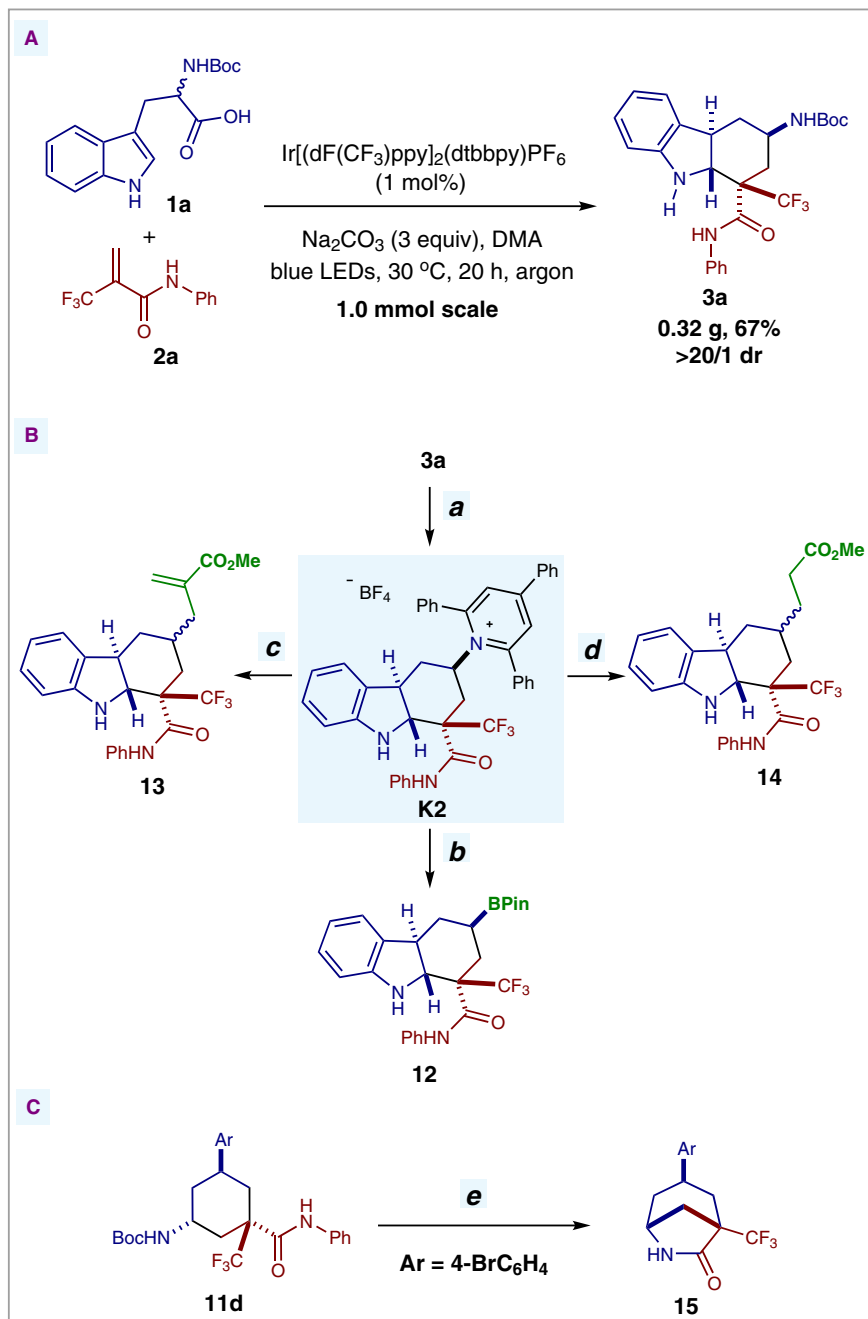


Fig. 9 Synthetic application. **A** 1.0 mmol-scale reaction. **B** Synthetic transformations of **3a**. **C** Transformation of **11d**. Reaction conditions: [a] (i) CF_3COOH , CH_2Cl_2 , $0\text{ }^\circ\text{C} \rightarrow \text{rt}$; (ii) 2,4,6-triphenylpyrylium tetrafluoroborate, EtOH , $140\text{ }^\circ\text{C}$, 68% yield over 2 steps, >20:1 dr. [b] (i) Bis(catecholato)diboron, DMA , blue LEDs, $30\text{ }^\circ\text{C}$; (ii) Et_3N , pinacol, DMA , $30\text{ }^\circ\text{C}$, 57% yield over 2 steps, >20:1 dr. [c] Methyl 2-[(phenylsulfonyl)methyl]acrylate, diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, DMA , blue LEDs, $40\text{ }^\circ\text{C}$, 74% yield, 1.8:1 dr. [d] Methyl acrylate, diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, DMA , blue LEDs, $40\text{ }^\circ\text{C}$, 50% yield, 3:1 dr. [e] (i) CF_3COOH , CH_2Cl_2 , $0\text{ }^\circ\text{C} \rightarrow \text{rt}$; (ii) NaOH , $\text{MeOH}/\text{H}_2\text{O}$, $100\text{ }^\circ\text{C}$, 69% yield over 2 steps, >20:1 dr.

hexahydrocarbazoles and cyclohexanes were carried out. Under the photocatalytic conditions, 1.0 mmol-scale reaction of substrates **1a** and **2a** occurred smoothly, providing product **3a** in excellent diastereoselectivity and moderate yield (Fig. 9A). In addition, these radical cascade cyclization products are readily transformed to other valuable building blocks. Treatment of the *trans*-fused hexahydrocarbazole **3a** with 2,2,2-trifluoroacetic acid and then 2,4,6-triphenylpyrylium tetrafluoroborate furnished Katritzky pyridinium salt **K2** in excellent diastereoselectivity and moderate yield (path **a**, Fig. 9B)^{64–66}. This pyridinium salt

could be further transformed to other structural motifs bearing a *trans*-fused hexahydrocarbazole core through the mild, catalyst-free visible-light-induced deaminative functionalization reactions (paths **b–d**, Fig. 9B)^{67,68}. Notably, the *trans*-fused hexahydrocarbazole product **12**, bearing a Bpin group that could be readily applied in the following functionalization, could be easily accessed through this mild photoinduced deaminative borylation in excellent diastereoselectivity and moderate yield (path **b**, Fig. 9B)⁶⁷. Interestingly, the bridged lactam-containing product **15** could be prepared in excellent diastereoselectivity and

moderate yield through a simple two-step transformation of 1,3,5-trisubstituted cyclohexane **11d** (path **e**, Fig. 9C).

Discussion

In this work, we have achieved the stereoselective intermolecular radical cascade reactions of readily available tryptophans and acrylamides via visible-light-induced photoredox catalysis, thus providing easy access to an array of *trans*-fused hexahydrocarbazoles with up to five stereogenic centers including two quaternary ones in up to 82% yield, >20/1 diastereoselectivity, and 96% ee. The reaction is distinguished by its broad substrate scope, its power in the rapid generation of molecular complexity from simple starting materials, environmentally friendly reaction conditions, and application to the late-stage functionalization. In addition, the reaction can be diverted to the syntheses of tetrahydrocarbazoles when it is performed under air. Moreover, this radical cascade protocol can further be applied to the stereoselective syntheses of 1,3,5-trisubstituted cyclohexanes by simply switching the starting material from tryptophans to α -alkenyl substituted α -amino acids. This strategy allows the rapid preparation of *trans*-fused hexahydrocarbazoles and cyclohexanes with multiple stereocenters from simple amino acids and acrylamides. Further studies on the reaction mechanism and the development of other stereoselective intermolecular radical cascade reactions via visible-light-induced photoredox catalysis are ongoing in our laboratory.

Methods

Representative procedure for the synthesis of *trans*-fused hexahydrocarbazole **3a**.

To a Young Schlenk tube (10 mL) were added Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (1.1 mg, 0.001 mmol, 1 mol%), **1a** (45.7 mg, 0.15 mmol, 1.5 equiv), **2a** (21.5 mg, 0.1 mmol, 1.0 equiv), Na₂CO₃ (31.8 mg, 0.3 mmol, 3.0 equiv), and N,N-dimethylacetamide (DMA, 2.0 mL). Subsequently, the reaction mixture was degassed through several freeze-pump-thaw cycles until no bubbles were released. The reaction mixture was stirred under argon at 30 °C, and irradiated by a 5 W blue LED lamp ($\lambda = 450\text{--}460$ nm, the tube was placed at ~2 cm away from the light source). After 12 h, the reaction mixture was passed through a short pad of celite and washed with ethyl acetate. The solvents were evaporated under reduced pressure to give the crude mixture, which was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 40:1 to 15:1, silica gel was soaked with a solution of petroleum ether and triethylamine (1000/1, v/v) before use) to afford the title compound **3a** as a white solid (35.7 mg, 75% yield).

Data availability

The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 2108643 (**3k**), 2108649 (**3ab**), 2108644 (**3k'**), 2108650 (**3ab'**), 2108651 (**8a**), 2108652 (**9a**), 2108653 (the derivative of compound **11a**), and 2108655 (**11d'**). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. Complete experimental procedures and compound characterization data are available in the Supplementary Information or from the corresponding author upon request.

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Author contributions

J.-T. L., J.-N. L., J.-L. W., D.-K. W., and Y.-Z. Y. performed the experiments and analyzed the data. C.-X. Z. directed the project and wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information


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