

## Novel Photoactive Iminium Ion Catalysts for Triplet State-Mediated Asymmetric Cycloadditions

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### Technical Field

The present invention relates to novel photoactive iminium ion catalysts comprising extended  $\pi$ -conjugated aromatic frameworks, specifically indole-based structures, which enable direct access to triplet excited state reactivity without external photosensitizers. The invention further relates to methods for conducting enantioselective [2+2] photocycloaddition reactions utilizing these catalysts, and to the enantioenriched polycyclic products obtained thereby.

### Background of the Invention

Asymmetric organocatalysis mediated by iminium ion intermediates has established itself as a powerful platform for stereocontrolled chemical synthesis. Traditionally, iminium ions have been employed in ground-state reactions or singlet excited state transformations. The excited state reactivity of conventional iminium ions has been limited to singlet state processes due to the forbidden nature of the intersystem crossing transition from the first singlet excited state to the triplet excited state. While triplet state reactivity of iminium ions has been demonstrated using external photosensitizers through energy transfer catalysis, direct excitation of chiral iminium ions to their triplet state via intersystem crossing has remained inaccessible. This limitation arises from the intrinsic photophysical properties of conventional conjugated iminium ions, wherein the singlet-to-triplet intersystem crossing involves a forbidden  $\pi-\pi^*$  to  $\pi-\pi^*$  transition. The inability to directly access triplet state reactivity without external photocatalysts has restricted the development of simplified catalytic systems and limited the scope of achievable transformations in asymmetric synthesis.

### Summary of the Invention

The present invention overcomes the aforementioned limitations by providing structurally modified photoactive iminium ion intermediates that incorporate extended  $\pi$ -conjugated aromatic systems, specifically indole moieties, which enable efficient intersystem crossing to the triplet excited state upon direct light excitation. The invention provides chiral primary amine organocatalysts that condense with indole-3-carboxaldehyde derivatives to form iminium ion intermediates possessing altered photophysical properties compared to conventional iminium ions. These modified iminium ions exhibit the capacity to undergo intersystem crossing from the first singlet excited state to the second triplet excited state, followed by relaxation to the first triplet excited state, thereby accessing previously unavailable triplet reactivity manifolds. The invention further provides methods for conducting organocatalytic enantioselective [2+2] photocycloaddition reactions without the requirement for external photosensitizers, wherein the chiral iminium ion intermediate itself serves as the photoactive species. The catalytic system enables both intramolecular and intermolecular dearomative [2+2] photocycloadditions with high enantioselectivity and yield, providing access to enantioenriched polycyclic compounds containing multiple contiguous stereogenic centers.

The photoactive iminium ion catalysts of the present invention comprise an indole-3-carboxaldehyde derivative condensed with a chiral primary amine organocatalyst in the presence of an acid additive. The indole-3-carboxaldehyde derivative may be substituted at various positions of the indole ring with electron-donating or electron-withdrawing groups including but not limited to halogens, cyano groups, alkyl groups, aryl groups, boronate esters, sulfonates, and trifluoromethyl groups. The chiral primary amine organocatalyst preferably comprises a diphenylprolinol-derived structure or a chiral diamine structure that imparts facial selectivity to the reactive iminium ion intermediate. The acid additive is preferably trifluoroacetic acid, which facilitates the formation and stability of the iminium ion intermediate under the reaction conditions.

The photophysical mechanism of the present invention involves initial photoexcitation of the iminium ion intermediate to its first singlet excited state upon irradiation with visible light in the wavelength range of 360 to 500 nanometers. The relaxed first singlet excited state intermediate undergoes intersystem crossing to the second triplet excited state through a minimum energy crossing point between the singlet and triplet potential energy surfaces. Subsequent relaxation from the second triplet excited state leads to the formation of the first triplet excited state, which serves as the reactive intermediate for the subsequent [2+2] cycloaddition. The incorporation of the iminium moiety into the extended  $\pi$ -system of the indole scaffold modifies the energetics and orbital character of the excited states, thereby enabling the otherwise forbidden intersystem crossing process. The triplet excited state intermediate exhibits a characteristic absorption spectrum with ground state bleaching below 400 nanometers, a sharp absorption centered at 410 nanometers, and a broad absorption in the red portion of the visible spectrum, with a triplet lifetime in the microsecond timescale under inert atmosphere.

The [2+2] photocycloaddition reaction proceeds through a stepwise mechanism initiated by the triplet excited state of the iminium ion intermediate. The triplet

state reacts with the olefinic substrate to form a first carbon-carbon bond, generating a triplet biradical intermediate. This triplet intermediate undergoes intersystem crossing to an open-shell singlet biradical, which subsequently undergoes radical-radical recombination to form the second carbon-carbon bond, yielding the cyclobutane product. The stepwise nature of the mechanism is evidenced by the stereoconvergent outcome of the reaction, wherein substrates containing olefins of different geometries converge to the same major diastereoisomer. The chiral organocatalyst controls the facial selectivity of the cycloaddition through steric interactions that favor approach from one face of the reactive carbon-carbon double bond, thereby determining the absolute configuration of the stereogenic centers formed in the product.

The method of the present invention for conducting enantioselective [2+2] photocycloaddition reactions comprises combining an indole-3-carboxaldehyde derivative with a chiral primary amine organocatalyst in a concentration of 10 to 30 mole percent relative to the substrate, in the presence of trifluoroacetic acid in a ratio of 1.5 to 3.5 equivalents relative to the substrate, in a chlorinated solvent such as chloroform or dichloromethane, under an inert atmosphere of argon or nitrogen. The reaction mixture is irradiated with visible light having a wavelength in the range of 360 to 500 nanometers, preferably at 427 nanometers, at a temperature between -20 degrees Celsius and 40 degrees Celsius, preferably at room temperature or 0 degrees Celsius, for a period of 1 to 24 hours. The intramolecular variant of the reaction employs indole-3-carboxaldehyde derivatives bearing a tethered olefin substituent, typically at the nitrogen atom of the indole ring, wherein the olefin is positioned three to five atoms away from the reactive site. The intermolecular variant employs indole-3-carboxaldehyde derivatives and external olefin coupling partners in a ratio of 1 to 5 equivalents of olefin relative to the indole substrate, wherein suitable olefins include alkyl-substituted olefins, cyclic olefins, electron-deficient olefins, and terpene-derived olefins.

The products obtained by the method of the present invention comprise enantioenriched polycyclic compounds containing fused indoline and cyclobutane rings with up to four contiguous stereogenic centers. The intramolecular photocycloaddition products exhibit diastereomeric ratios greater than 10 to 1 and enantiomeric excesses in the range of 72 to 94 percent. The intermolecular photocycloaddition products exhibit enantiomeric excesses in the range of 74 to 99 percent, with diastereomeric ratios dependent on the structure of the olefin coupling partner. The products may be further derivatized through reduction of carbonyl groups, oxidation of aldehyde groups to carboxylic acids, or homologation to terminal alkynes, providing access to functionalized scaffolds suitable for medicinal chemistry applications and bioconjugation processes.

The present invention provides significant advantages over prior art methods for conducting enantioselective photocycloadditions. The elimination of external photosensitizers simplifies the catalytic system and reduces the potential for undesired side reactions arising from competitive excitation of multiple photoactive species. The direct excitation approach enables selective activation of the iminium ion intermediate without interference from the starting carbonyl compound or product molecules. The high quantum efficiency of iminium ion formation and the microsecond lifetime of the triplet state ensure efficient utilization of absorbed photons for productive chemistry. The modular nature of the catalyst system allows tuning of both the photophysical properties through modification of the indole scaffold and the stereochemical outcome through selection of the chiral amine component.

### Detailed Description of the Invention

The present invention represents a paradigm shift in the field of photoorganocatalysis by enabling direct access to triplet excited state reactivity of iminium ion intermediates without requiring external photosensitizers. The invention is predicated upon the discovery that incorporation of the iminium ion functional group into extended  $\pi$ -conjugated aromatic systems fundamentally alters the photophysical behavior compared to conventional aliphatic or simple  $\alpha,\beta$ -unsaturated iminium ions. Specifically, when the iminium moiety is integrated into the indole heterocyclic framework at the 3-position, the resulting conjugated system exhibits markedly different excited state dynamics that permit efficient intersystem crossing from singlet to triplet manifolds, a process that is typically forbidden in conventional iminium ion photochemistry.

The mechanistic basis for this transformation lies in the unique electronic structure of indole-derived iminium ions. In conventional  $\alpha,\beta$ -unsaturated iminium ions formed from simple enals or enones, photoexcitation generates a first singlet excited state with predominantly  $\pi-\pi^*$  character. The transition from this singlet excited state to the triplet manifold requires intersystem crossing from a singlet  $\pi-\pi^*$  state to a triplet  $\pi-\pi^*$  state, which is quantum mechanically forbidden due to the identical orbital occupancy and the requirement for simultaneous spin flip without a change in orbital angular momentum. This restriction arises from the El-Sayed rules, which state that intersystem crossing is most efficient when accompanied by a change in orbital type, such as from  $\pi-\pi^*$  to  $n-\pi^*$  or vice versa. In the indole-derived iminium ions of the present invention, the extended aromatic system provides access to multiple excited states of different orbital character in close energetic proximity, creating opportunities for efficient intersystem crossing through avoided crossings and minimum energy crossing points between states of different multiplicity.

Computational investigations using time-dependent density functional theory at the  $\omega$ B97X-D3/def2-TZVP level of theory reveal that photoexcitation of the indole-derived iminium ion intermediate to the first singlet excited state is followed by relaxation to a geometry wherein the iminium moiety is distorted out of the plane of the indole ring system. This distortion, characterized by a dihedral

angle of approximately 75 degrees between the plane of the iminium nitrogen-carbon fragment and the plane of the indole ring, creates a conformational arrangement wherein the potential energy surfaces of the first singlet excited state and the second triplet excited state approach within approximately 1.66 kilocalories per mole. At a dihedral angle of approximately 37 degrees, a minimum energy crossing point exists between the first singlet excited state and the second triplet excited state, enabling intersystem crossing through spin-orbit coupling interactions. Following this crossing, the molecule relaxes on the second triplet excited state surface until it encounters a second minimum energy crossing point with the first triplet excited state surface. Relaxation to the first triplet excited state then provides the reactive intermediate that undergoes the subsequent [2+2] cycloaddition reaction.

The experimental validation of this triplet state mechanism has been achieved through multiple complementary spectroscopic techniques. Steady-state fluorescence measurements conducted on model iminium ion systems reveal that both the reactive iminium ion bearing a tethered olefin and a non-reactive analogue lacking the olefin exhibit essentially identical fluorescence quantum yields of approximately 0.14 to 0.15 and fluorescence lifetimes of approximately 2.0 nanoseconds. These observations indicate that the singlet excited state is not quenched by the presence of the olefin functional group and therefore cannot be responsible for the observed photochemical reactivity. In contrast, transient absorption spectroscopy measurements conducted using nanosecond laser flash photolysis with excitation at 355 nanometers reveal the formation of a long-lived transient species characterized by ground state bleaching below 400 nanometers, a sharp absorption band centered at 410 nanometers, and a broad absorption extending across the red and near-infrared regions of the spectrum. The kinetic decay of this transient species, monitored at 700 nanometers, exhibits a lifetime of approximately 12 microseconds under nitrogen-purged conditions for the non-reactive model compound, with the decay rate being substantially enhanced in the presence of molecular oxygen, confirming the triplet character of the intermediate. Critically, in the case of the reactive iminium ion bearing the tethered olefin, the triplet state decay is significantly accelerated compared to the model compound, demonstrating that the olefin functional group quenches the triplet state through chemical reaction rather than through energy transfer or electron transfer processes.

The indole-3-carboxaldehyde derivatives employed in the present invention serve as the aldehyde component that condenses with chiral primary amine organocatalysts to form the photoactive iminium ion intermediates. The structural requirements for these substrates are defined by the need to incorporate the aldehyde functional group at the 3-position of the indole ring while providing appropriate substitution patterns at other positions to modulate both the photophysical properties and the reactivity of the resulting iminium ions. The indole nucleus itself provides the extended  $\pi$ -conjugated aromatic system necessary for enabling efficient intersystem crossing, while the 3-position represents the optimal location for aldehyde attachment because it places the iminium ion in direct conjugation with the aromatic system while maintaining the capacity for the 2,3-double bond of the indole to participate in cycloaddition reactions.

For intramolecular photocycloaddition reactions, the indole-3-carboxaldehyde substrates incorporate a tethered olefin substituent attached to the nitrogen atom of the indole ring. The attachment is typically achieved through an amide or carbamate linkage, wherein the nitrogen atom is acylated with a carboxylic acid derivative bearing an alkenyl group at an appropriate distance from the carbonyl carbon. The general structure of these intramolecular substrates can be represented as 1-(alk-n-enoyl)-1H-indole-3-carbaldehyde, where n represents the number of carbon atoms in the chain separating the carbonyl oxygen from the terminal olefin. In preferred embodiments, the value of n is in the range of 3 to 6, with n equal to 4 corresponding to a pentenyl substituent being optimal for forming products with six-membered lactam rings fused to the cyclobutane core. A specific example is 1-(pent-4-enoyl)-1H-indole-3-carbaldehyde, wherein a five-carbon chain bearing a terminal olefin is attached to the indole nitrogen through an amide carbonyl group. This structural arrangement positions the terminal olefin at an optimal distance and trajectory for intramolecular cycloaddition with the 2,3-double bond of the indole ring upon formation and excitation of the iminium ion intermediate.

The substituents at positions 2, 4, 5, 6, and 7 of the indole ring exert significant influence on both the electronic properties of the iminium ion and the stereochemical outcome of the photocycloaddition. Electron-withdrawing substituents such as fluorine, chlorine, bromine, cyano, and trifluoromethyl groups increase the electrophilic character of the iminium ion, facilitating the condensation reaction with the chiral amine and potentially accelerating the rate of the photochemical step. These substituents also induce bathochromic shifts in the absorption spectrum, allowing for excitation with longer wavelength visible light that is less prone to causing undesired side reactions. Conversely, electron-donating substituents such as methyl and methoxy groups reduce the electrophilic character but may enhance the quantum yield of intersystem crossing by raising the energy of  $n-\pi^*$  states associated with the nitrogen lone pair. Specific substitution patterns that have been demonstrated to provide excellent results include 5-fluoroindole, 6-fluoroindole, 7-fluoroindole, 5-bromoindole, 6-bromoindole, 7-bromoindole, 5-cyanoindole, 6-cyanoindole, 4-methylindole, 7-methylindole, 6-(trifluoromethyl)indole, 6-(methoxycarbonyl)indole, 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole, and 6-(4-toluenesulfonyloxy)indole derivatives.

The synthesis of these indole-3-carboxaldehyde substrates is accomplished through standard methods of indole chemistry. The indole nucleus is first N-acylated with the appropriate alkenoic acid or alkenoyl chloride in the presence

of a base such as triethylamine, sodium hydride, or potassium carbonate in a solvent such as tetrahydrofuran, N,N-dimethylformamide, or dichloromethane. The resulting N-acylated indole is then subjected to Vilsmeier-Haack formylation to introduce the aldehyde group at the 3-position. The Vilsmeier-Haack reaction is conducted by treating the N-acylindole with a mixture of phosphorus oxychloride and N,N-dimethylformamide, which generates the Vilsmeier reagent (chloromethyleneiminium chloride) in situ. This electrophilic species attacks the electron-rich 3-position of the indole ring, and subsequent aqueous workup hydrolyzes the intermediate iminium chloride to reveal the aldehyde functional group. Alternatively, for indole substrates bearing sensitive functional groups that might not tolerate the strongly acidic Vilsmeier conditions, the aldehyde can be introduced through other methods such as lithiation at the 3-position followed by quenching with N,N-dimethylformamide, or through palladium-catalyzed carbonylation reactions.

For intermolecular photocycloaddition reactions, simpler indole-3-carboxaldehyde substrates are employed wherein the nitrogen atom bears a protecting group or acyl substituent that does not contain an olefin functional group. Suitable N-substituents for this purpose include benzoyl, acetyl, tert-butoxycarbonyl, benzyloxycarbonyl, and tosyl groups. Among these, the benzoyl group has proven particularly effective because it provides sufficient electron-withdrawing character to activate the aldehyde toward iminium ion formation while remaining stable under the photochemical reaction conditions. The substrate 1-benzoyl-1H-indole-3-carbaldehyde serves as the standard substrate for intermolecular reactions and can be synthesized through sequential N-benzoylation of indole using benzoyl chloride and a base, followed by Vilsmeier-Haack formylation as described above. The presence of the benzoyl group also influences the conformational preferences of the resulting iminium ion, helping to control the facial selectivity of the cycloaddition when external olefins approach from solution.

The chiral primary amine organocatalysts employed in the present invention serve the dual function of condensing with the indole-3-carboxaldehyde substrates to form the iminium ion intermediates and controlling the absolute stereochemistry of the photocycloaddition through asymmetric induction. The catalysts must possess a primary amine functional group for nucleophilic attack on the aldehyde carbonyl, a stereogenic element in close proximity to the reactive site to exert stereocontrol, and sufficient steric bulk to create a differentiated environment for the approach of the olefin to the two faces of the activated double bond. The catalysts should also be sufficiently basic to exist predominantly in the free amine form under the acidic reaction conditions, while being capable of forming stable iminium ions that do not undergo decomposition or side reactions during the photochemical transformation.

The most effective organocatalysts for the present invention are derived from two structural classes: diphenylprolinol derivatives and chiral 1,2-diamines. In the first class, the catalyst structure is based on (S)-diphenyl(pyrrolidin-2-yl)methanol, commonly known as the Jørgensen-Hayashi catalyst after its developers. This molecule possesses a pyrrolidine ring providing the secondary amine that is oxidized to the primary amine in the derivative structures, and a diphenylmethanol substituent at the 2-position of the pyrrolidine that creates a sterically demanding environment. For the present application, the relevant derivative is (S)-2-(bis(3,5-bis(trifluoromethyl)phenyl)phenyl)(trimethylsilyloxy)methylpyrrolidine, wherein the diphenyl groups are replaced with 3,5-bis(trifluoromethyl)phenyl groups to enhance the acidity of the resulting iminium ion, and the hydroxyl group is protected as a trimethylsilyl ether to prevent unwanted side reactions. However, this highly hindered secondary amine catalyst has been found to be insufficiently reactive toward indole-3-carboxaldehydes due to steric congestion around the carbonyl group.

Superior results are obtained with primary amine catalysts derived from chiral 1,2-diamines. The preferred catalyst structure is (1R,2R)-1,2-diphenylethane-1,2-diamine, which possesses two adjacent stereogenic centers each bearing a phenyl substituent and an amino group. This catalyst can condense with aldehydes through either of its two primary amine groups, but steric considerations and electronic effects favor reaction at the less hindered amine. The resulting iminium ion benefits from the presence of the second amino group, which can participate in hydrogen bonding interactions that rigidify the catalyst-substrate complex and enhance stereocontrol. The two phenyl substituents project into space in a manner that creates distinct steric environments on the two faces of the iminium ion  $\pi$ -system, with one face being shielded by the phenyl groups and the other being relatively accessible. This asymmetric shielding pattern translates into preferential approach of the olefin from the less hindered face, determining the absolute configuration of the newly formed stereogenic centers in the product.

Alternative catalyst structures that have shown promise include tert-butyl-substituted derivatives such as (S)-2-(tert-butyltrimethylsilyloxy)-1-phenylethanamine, wherein the stereogenic center bears both a protected hydroxymethyl group and a phenyl substituent. This catalyst combines elements of both the diphenylprolinol and diamine structural classes, providing the primary amine required for efficient condensation with less hindered aldehydes while maintaining significant steric bulk for stereocontrol. Additional catalyst variations include derivatives bearing different aromatic substituents such as naphthyl, biphenyl, or heteroaryl groups in place of the phenyl rings, as well as catalysts incorporating additional functional groups such as ethers, thioethers, or protected amines that can engage in secondary interactions with the substrate or influence the conformational preferences of the iminium ion intermediate.

The mechanism by which these chiral amine catalysts control the stereochemical outcome of the photocycloaddition involves multiple factors. In the ground state

iminium ion, the catalyst-derived stereogenic centers create an asymmetric environment around the reactive carbon-carbon double bond of the indole moiety. The conformational preferences of the iminium ion are governed by steric interactions between the catalyst substituents and the indole ring system, as well as by electronic effects such as  $\pi$ - $\pi$  stacking between aromatic groups. Upon photoexcitation and intersystem crossing to the triplet state, the iminium moiety undergoes out-of-plane distortion as described earlier, and this distortion occurs preferentially toward one face of the indole double bond rather than the other. Computational modeling suggests that the relaxed triplet excited state adopts a geometry wherein the iminium nitrogen-carbon-carbon fragment is rotated approximately 75 degrees out of the indole plane toward the face designated as the Re face in Cahn-Ingold-Prelog nomenclature. This distortion brings the iminium moiety into closer proximity with the tethered olefin or the external olefin approaching from solution, setting up the trajectory for subsequent carbon-carbon bond formation. The chiral catalyst ensures that the distortion occurs consistently toward the same face by creating unfavorable steric clashes when distortion occurs toward the opposite face.

The catalyst loading employed in the present invention is typically in the range of 10 to 30 mole percent relative to the indole-3-carboxaldehyde substrate, with 20 mole percent being optimal for most substrates. This relatively high catalyst loading compared to some other organocatalytic systems is necessitated by several factors. First, the equilibrium for iminium ion formation from indole-3-carboxaldehydes and primary amines is less favorable than for more electrophilic aldehydes due to the electron-donating character of the indole ring, requiring excess catalyst to drive the equilibrium toward the iminium ion. Second, the iminium ion is in dynamic equilibrium with the free aldehyde and amine under the reaction conditions, and a sufficient catalyst concentration must be maintained to ensure that the majority of the substrate exists in the photoactive iminium ion form at any given time. Third, some catalyst may be sequestered through protonation by the trifluoroacetic acid additive or through side reactions with photochemically generated reactive intermediates, reducing the effective catalyst concentration over the course of the reaction. The use of 20 mole percent catalyst loading provides a robust system that maintains high iminium ion concentrations throughout the photochemical transformation while remaining economically feasible for synthetic applications.

The addition of trifluoroacetic acid to the reaction mixture plays multiple critical roles in enabling the successful photocycloaddition reaction. Trifluoroacetic acid, with a pKa of approximately 0.23 in water, is a strong organic acid that readily protonates the carbonyl oxygen of the indole-3-carboxaldehyde substrate, activating it toward nucleophilic attack by the chiral primary amine catalyst. This activation is particularly important for indole-3-carboxaldehydes, which are less electrophilic than aliphatic or aromatic aldehydes due to the electron-donating resonance effect of the indole nitrogen. The protonation of the carbonyl oxygen increases its electrophilicity by withdrawing electron density from the carbonyl carbon, facilitating the initial nucleophilic addition step of iminium ion formation. Following the addition to form the hemiaminal intermediate, the trifluoroacetic acid protonates the hydroxyl group of the hemiaminal, converting it into a better leaving group and promoting the elimination of water to generate the iminium ion. The trifluoroacetate counterion then serves to stabilize the positively charged iminium ion through ionic interactions, preventing premature hydrolysis back to the aldehyde and amine.

Beyond its role in promoting iminium ion formation, trifluoroacetic acid also influences the photophysical behavior of the iminium ion intermediate. The acidic environment suppresses deprotonation of the iminium ion at the  $\alpha$ -position, which would generate an enamine species with completely different photochemical properties. By maintaining the iminium ion in its fully protonated form, the trifluoroacetic acid ensures that the absorption spectrum remains centered in the visible region and that the excited state manifolds accessible upon photoexcitation correspond to those predicted by the computational studies. The acid also prevents adventitious formation of secondary amine species through reduction of the iminium ion or through condensation of the catalyst with photochemically generated intermediates, side reactions that could diminish the catalyst concentration and reduce the overall efficiency of the transformation.

The optimal concentration of trifluoroacetic acid has been determined through systematic variation to be in the range of 1.5 to 3.5 equivalents relative to the indole-3-carboxaldehyde substrate, with 2.5 equivalents providing the best balance of reactivity and selectivity. At lower acid concentrations, the rate of iminium ion formation becomes limiting, and significant amounts of unreacted aldehyde remain even after extended reaction times. This incomplete conversion arises because the equilibrium between the aldehyde, amine, and iminium ion is insufficiently shifted toward the iminium ion product when only substoichiometric amounts of acid are present. At higher acid concentrations exceeding 3.5 equivalents, the excess acid begins to cause competitive protonation of the chiral amine catalyst, converting it into an ammonium salt that is no longer nucleophilic and cannot participate in iminium ion formation. This sequestration of the catalyst effectively reduces the active catalyst concentration and necessitates either longer reaction times or higher catalyst loadings to achieve full conversion. Additionally, very high concentrations of trifluoroacetic acid can promote acid-catalyzed side reactions such as polymerization of the olefin functional groups or decomposition of acid-sensitive products.

The reaction medium for the photocycloaddition consists of chlorinated organic solvents, with chloroform being the preferred choice for most substrates. Chloroform provides several advantages for this transformation. Its relatively low polarity compared to polar aprotic solvents such as acetonitrile or dimethylformamide helps to stabilize the charged iminium ion intermediate through solvation while not being so polar as to overly stabilize the ground state

and raise the energy required for photoexcitation. The solvent has excellent transparency in the visible and near-ultraviolet regions of the spectrum, allowing efficient transmission of the incident light to the dissolved substrate and minimizing competitive light absorption by the medium. Chloroform is also chemically inert under the reaction conditions and does not participate in unwanted side reactions with the photochemically generated intermediates. Its moderate boiling point of 61 degrees Celsius allows for easy removal by evaporation during workup while being sufficiently high to prevent excessive evaporation during the photochemical reaction, which could lead to concentration drift and irreproducible results.

Alternative chlorinated solvents that provide comparable results include dichloromethane and 1,2-dichloroethane. Dichloromethane, with a boiling point of 40 degrees Celsius, is somewhat more volatile than chloroform but offers similar polarity and transparency characteristics. It may be preferred for substrates that show sensitivity to the slightly acidic nature of chloroform, which can contain traces of hydrochloric acid and phosgene from decomposition. The solvent 1,2-dichloroethane, with a boiling point of 83 degrees Celsius, is less volatile than chloroform and may be advantageous for reactions requiring elevated temperatures or extended reaction times. For certain substrates, particularly those bearing highly electron-deficient substituents such as cyano groups at the 5-position of the indole ring, mixed solvent systems comprising chloroform and chlorobenzene in a 1:1 ratio provide improved results. The addition of chlorobenzene, which has a higher polarity and better solvating ability for polar substrates, helps to maintain solubility of the starting materials and prevents precipitation of the iminium ion intermediate, which could occur in pure chloroform for some highly polar substrates.

The substrate concentration in the reaction medium is maintained at approximately 0.25 molar, corresponding to a dilution of approximately 4 milliliters of solvent per millimole of substrate. This concentration represents a compromise between several competing factors. Higher concentrations would be desirable from the standpoint of reaction efficiency and throughput, as they would allow more material to be processed in a given volume and would increase the rate of bimolecular steps such as the encounter between the triplet excited iminium ion and the olefin in intermolecular reactions. However, excessively high concentrations lead to inner filter effects wherein the solution becomes optically dense and the incident light is completely absorbed in a thin layer near the surface of the reaction vessel, leaving the bulk of the solution unirradiated. This non-uniform irradiation results in the formation of concentration gradients and local hot spots that can promote side reactions and reduce selectivity. Lower concentrations would provide more uniform irradiation throughout the solution but would reduce the practical throughput and increase solvent consumption. The concentration of 0.25 molar has been found to provide excellent optical clarity while maintaining sufficient concentration for efficient reaction kinetics.

Prior to use in the photochemical reaction, the solvent is subjected to two critical pretreatment steps. First, the solvent is dried over activated 4 Ångström molecular sieves for a period of at least 24 hours to remove traces of water. The presence of water is detrimental to the reaction for several reasons: water competes with the chiral amine catalyst for condensation with the aldehyde, generating achiral iminium ions that dilute the enantiomeric excess of the product; water can hydrolyze the iminium ion back to the aldehyde and amine, reducing the steady-state concentration of the photoactive species; and water can participate in hydrogen bonding interactions that disrupt the secondary structure of the catalyst-substrate complex responsible for stereocontrol. The drying process reduces the water content to less than 50 parts per million, a level that has negligible impact on the reaction outcome. Second, the solvent is degassed by sparging with an inert gas, typically argon or nitrogen, for a period of approximately 10 minutes immediately before use. This degassing step removes dissolved molecular oxygen, which is a highly efficient triplet state quencher due to its paramagnetic ground state configuration. The presence of oxygen dramatically reduces the lifetime of the triplet excited iminium ion intermediate from approximately 12 microseconds under inert atmosphere to less than 1 microsecond in air-saturated solution, greatly diminishing the quantum efficiency of the photochemical transformation.

The photochemical activation of the iminium ion intermediate is accomplished through irradiation with visible light having a wavelength matched to the absorption spectrum of the iminium species. The absorption maximum of typical indole-derived iminium ions lies in the range of 400 to 450 nanometers, corresponding to the violet-blue region of the visible spectrum. For optimal efficiency, the irradiation wavelength should be chosen to coincide with or lie slightly to the blue side of this absorption maximum, ensuring strong light absorption while avoiding excitation wavelengths that might promote undesired photochemical reactions of the starting materials or products. Commercially available light-emitting diode light sources designed for photochemical synthesis have proven highly effective for this purpose. The Kessil PR160L lamp, manufactured by Kessil Lighting of Richmond, California, provides high-intensity illumination at several selectable wavelengths including 390, 400, 427, 456, and 467 nanometers. The 427-nanometer output has been identified as optimal for most substrates, as it provides strong absorption by the iminium ion while being sufficiently removed from the ultraviolet region to minimize side reactions.

The Kessil lamp operates through an array of high-power light-emitting diodes that emit narrow-bandwidth light centered at the specified wavelength with a full width at half maximum of approximately 20 nanometers. The lamp output can be continuously adjusted from 0 to 100 percent of maximum intensity through a built-in potentiometer, allowing fine control over the photon flux delivered to the reaction vessel. For small-scale reactions in the range of 0.1 to 0.5 millimoles,

the lamp is typically operated at 50 percent of maximum intensity, corresponding to a photon flux of approximately 10 to the 17th power photons per second at the position of the reaction vessel. This intensity provides a good balance between rapid reaction rates and minimal heating of the reaction mixture. Higher intensities can be employed for larger-scale reactions or for substrates that exhibit lower quantum yields, while lower intensities may be preferable for thermally sensitive substrates or for reactions where product overexcitation becomes problematic. The lamp is equipped with an integrated cooling fan that maintains the junction temperature of the light-emitting diodes below their maximum rated temperature, ensuring stable light output over extended operating periods.

The spatial arrangement of the light source relative to the reaction vessel is a critical parameter affecting the efficiency and reproducibility of the photochemical transformation. The reaction vessel, typically a 4-milliliter screw-cap vial for reactions in the 0.1 to 0.5 millimole scale, is positioned at a fixed distance from the lamp output window. The optimal distance has been determined to be in the range of 1 to 5 centimeters, with 2 centimeters being standard for most applications. At closer distances, the light intensity becomes very high but the irradiation becomes increasingly non-uniform due to the finite size of the lamp aperture and the resulting angular distribution of the light rays. At greater distances, the irradiation becomes more uniform but the light intensity decreases according to the inverse square law, resulting in longer reaction times. The reaction vessel is typically positioned in a holder or rack that maintains consistent positioning relative to the lamp and may incorporate reflective surfaces to redirect scattered light back toward the reaction vessel, increasing the effective light utilization efficiency.

The reaction vessel itself is constructed from borosilicate glass, which has excellent transmission characteristics in the visible region of the spectrum and provides good chemical resistance to the reaction medium. The vial is equipped with a polytetrafluoroethylene-lined screw cap that provides an effective seal against gas exchange while being chemically inert and temperature resistant. The cap incorporates a septum that allows for the introduction of reagents via syringe and for the insertion of a needle to serve as a vent during the initial sparging with inert gas. The vial is charged with a magnetic stir bar, typically a cylindrical bar with dimensions of 6 millimeters in length and 2 millimeters in diameter, which provides continuous agitation of the reaction mixture during irradiation. The stirring serves multiple purposes: it promotes uniform distribution of heat generated by light absorption, prevents concentration gradients from developing, and continuously refreshes the solution at the illuminated surface to ensure that all molecules have equal opportunity for photoexcitation.

The reaction temperature is maintained in the range of -20 degrees Celsius to 40 degrees Celsius, depending on the specific substrate and the desired outcome. For most intramolecular photocycloadditions, ambient temperature in the range of 20 to 25 degrees Celsius provides excellent results. Room temperature operation simplifies the experimental setup and avoids the need for specialized temperature control equipment while providing sufficient thermal energy for the triplet state intermediate to surmount the small barriers associated with conformational reorganization and bond formation steps. For intermolecular reactions involving sterically hindered olefins or for substrates that can form multiple diastereomeric products, conducting the reaction at reduced temperature such as 0 degrees Celsius can enhance diastereoselectivity by increasing the energy difference between competing transition states and allowing the stereocontrol exerted by the chiral catalyst to more effectively discriminate between different reaction pathways. Temperature control at 0 degrees Celsius is readily achieved by immersing the reaction vessel in an ice-water bath, while lower temperatures down to -20 degrees Celsius can be accessed using dry ice-acetone or other cryogenic baths. Elevated temperatures in the range of 30 to 40 degrees Celsius may be beneficial for sluggish reactions or for substrates where the quantum yield of intersystem crossing is low and thermal population of higher-lying states is advantageous.

The duration of irradiation required to achieve complete conversion of the starting material to product varies depending on the substrate structure, the catalyst employed, the light intensity, and the reaction scale. For optimized intramolecular photocycloadditions of simple indole-3-carboxaldehyde derivatives at 0.1-millimole scale with 50 percent lamp intensity, typical reaction times are in the range of 3 to 18 hours. Substrates bearing electron-withdrawing substituents that enhance the rate of iminium ion formation and increase the quantum yield of triplet formation tend to react more rapidly, with complete conversion achievable in 3 to 6 hours. Substrates bearing electron-donating substituents or bulky substituents that hinder approach of the olefin may require extended reaction times of 12 to 18 hours. The progress of the reaction can be monitored by thin-layer chromatography, with samples withdrawn periodically and analyzed for disappearance of the aldehyde starting material and appearance of the product. Upon completion, as judged by thin-layer chromatography showing no remaining starting material, the irradiation is ceased and the reaction mixture is processed for isolation of the product.

The detailed experimental protocol for conducting the intramolecular enantioselective [2+2] photocycloaddition begins with the preparation of the reaction vessel and reagents. A 4-milliliter screw-cap vial equipped with a polytetrafluoroethylene-lined cap is flame-dried under vacuum and allowed to cool under a stream of argon gas to ensure complete exclusion of moisture. A magnetic stir bar is placed in the vial, and the indole-3-carboxaldehyde substrate is added as a solid in an amount corresponding to 0.1 millimoles, or 26 milligrams for the case of 1-(pent-4-en-1-yn-1-yl)-1H-indole-3-carbaldehyde (molecular weight 255.3 grams per mole). The chiral primary amine organocatalyst (1R,2R)-1,2-diphenylethane-1,2-diamine is then added as a solid in an amount of

20 mole percent, corresponding to 0.02 millimoles or 4.2 milligrams (molecular weight 212.3 grams per mole). The vial is sealed with the cap and then purged with argon gas by inserting a needle through the septum and flowing argon through the headspace for approximately 2 minutes while venting through a second needle.

Chloroform solvent that has been previously dried over 4 Ångström molecular sieves is measured in a volume of 0.4 milliliters (corresponding to a final substrate concentration of 0.25 molar) and transferred to a separate vial where it is degassed by sparging with argon gas for 10 minutes. A long needle is inserted deep into the solvent and argon gas is bubbled through at a moderate flow rate of approximately 50 milliliters per minute while the vial remains open to atmosphere through a short needle serving as a vent. This vigorous sparging ensures removal of dissolved oxygen to a concentration well below the level that would significantly quench the triplet excited state. After degassing is complete, the chloroform is transferred via syringe to the reaction vial containing the substrate and catalyst. Trifluoroacetic acid is then added via micropipette in an amount of 2.5 equivalents relative to the substrate, corresponding to 0.25 millimoles or 19 microliters (density 1.489 grams per milliliter, molecular weight 114.0 grams per mole). The addition of trifluoroacetic acid immediately results in the formation of the iminium ion, evidenced by the development of a yellow-orange coloration in the reaction mixture.

The reaction vial is then placed in a holder positioned at a distance of 2 centimeters from the output window of the Kessil PR160L lamp, which has been prewarmed for 10 minutes to ensure stable light output. The lamp is set to 427 nanometers wavelength and 50 percent intensity. The magnetic stirring is initiated at a rate of approximately 600 revolutions per minute, sufficient to create a visible vortex in the solution without causing excessive splashing. The lamp is switched on to begin the irradiation, and the reaction is allowed to proceed for a period of 6 hours. During this time, the temperature of the reaction mixture is monitored periodically using an infrared thermometer to ensure that it does not rise above 30 degrees Celsius, which could occur due to absorption of light energy. If excessive heating is observed, the lamp intensity may be reduced or a small fan may be directed toward the reaction vial to provide additional cooling through convective heat transfer. After 6 hours of irradiation, a small aliquot is removed via syringe and analyzed by thin-layer chromatography on silica gel using a mobile phase of 30 percent ethyl acetate in hexanes. If starting material remains detectable, irradiation is continued for additional 2-hour periods until complete consumption is achieved.

Upon completion of the photochemical step, the lamp is switched off and the reaction vial is removed from the irradiation setup. The vial is opened and the solvent is removed by rotary evaporation under reduced pressure at a bath temperature not exceeding 30 degrees Celsius to prevent thermal decomposition of the product. The resulting crude material is a yellow oil that contains the desired cycloadduct along with residual organocatalyst and trifluoroacetic acid salts. This crude material is subjected to nuclear magnetic resonance spectroscopy analysis to determine the conversion and diastereomeric ratio. A known amount of dibromomethane is added as an internal standard, and the sample is dissolved in deuterated chloroform and analyzed by proton nuclear magnetic resonance spectroscopy. The integrations of diagnostic resonances corresponding to the product and any remaining starting material are compared to the integration of the dibromomethane standard to calculate the nuclear magnetic resonance yield. The diastereomeric ratio is determined by integration of well-resolved resonances corresponding to the different diastereoisomers, although for most intramolecular substrates only a single diastereoisomer is observed, corresponding to a diastereomeric ratio exceeding 20:1.

The crude product is then subjected to derivatization to facilitate purification and determination of enantiomeric excess. The crude material is dissolved in dichloromethane in a concentration of 0.25 molar, and (carbethoxymethylene)triphenylphosphorane (ethyl 2-(triphenylphosphoranylidene)acetate) is added in an amount of 2.5 equivalents relative to the initial substrate loading. This ylide reagent undergoes a Wittig reaction with the aldehyde functional group present in the cycloadduct, converting it to an  $\alpha,\beta$ -unsaturated ester. The reaction is allowed to proceed at room temperature with stirring for a period of 16 hours, after which the crude mixture is directly subjected to column chromatography on silica gel. The column is packed with silica gel (particle size 40 to 63 micrometers, 230 to 400 mesh) in a ratio of approximately 50 grams of silica gel per gram of crude material, and elution is performed using a gradient beginning with pure hexanes and gradually increasing the proportion of ethyl acetate to 30 percent over the course of the column. The product-containing fractions are identified by thin-layer chromatography and ultraviolet visualization at 254 nanometers, and these fractions are combined and concentrated by rotary evaporation to provide the purified product as a colorless to pale yellow solid or oil.

The enantiomeric excess of the purified product is determined by ultra-performance convergence chromatography on a chiral stationary phase. The analysis is performed using a Waters Acuity UPC2 system equipped with a photodiode array detector operating at 254 nanometers. The separation is achieved using a Chiralpak IC column (250 millimeters length, 4.6 millimeters internal diameter, 5 micrometer particle size) manufactured by Daicel Corporation of Osaka, Japan. The mobile phase consists of supercritical carbon dioxide modified with methanol in a ratio that is optimized for each specific substrate, typically in the range of 5 to 20 percent methanol. The flow rate is maintained at 2.0 milliliters per minute, the column temperature is held at 40 degrees Celsius, and the backpressure regulator is set to maintain a system pressure of 150 bar. Under these conditions, the two enantiomers of the derivatized product elute as baseline-resolved peaks with retention times

typically differing by 0.5 to 2 minutes. The enantiomeric excess is calculated from the integrated peak areas according to the formula enantiomeric excess equals the absolute value of the quantity peak area of major enantiomer minus peak area of minor enantiomer, divided by the quantity peak area of major enantiomer plus peak area of minor enantiomer, multiplied by 100 percent. For most intramolecular substrates, enantiomeric excesses in the range of 88 to 92 percent are routinely obtained, corresponding to an enantiomeric ratio of approximately 25:1 to 49:1.

The intermolecular variant of the enantioselective [2+2] photocycloaddition follows a similar protocol with modifications to accommodate the presence of an external olefin coupling partner. A 4-milliliter screw-cap vial equipped with a polytetrafluoroethylene-lined cap and magnetic stir bar is flame-dried and cooled under argon. The indole-3-carboxaldehyde substrate, typically 1-benzoyl-1H-indole-3-carbaldehyde, is added in an amount of 0.1 millimoles (25 milligrams for molecular weight 249.3 grams per mole). The chiral diamine organocatalyst (1R,2R)-1,2-diphenylethane-1,2-diamine is added in 20 mole percent loading (0.02 millimoles, 4.2 milligrams). The external olefin coupling partner is then added as a liquid if it is sufficiently non-volatile, or as a solution in degassed chloroform if it is volatile. The amount of olefin added is 3.0 equivalents relative to the indole substrate, corresponding to 0.3 millimoles. For example, in the case of methylenecyclohexane (molecular weight 96.2 grams per mole, density 0.799 grams per milliliter), a volume of 37 microliters is added.

The vial is sealed and purged with argon, and then degassed chloroform is added via syringe to bring the total volume to 0.4 milliliters. Since the olefin itself occupies some volume, the volume of chloroform added must be adjusted to account for this displacement and maintain the overall substrate concentration at 0.25 molar. Trifluoroacetic acid is then added in an amount of 2.5 equivalents (0.25 millimoles, 19 microliters), and the reaction vial is placed in the irradiation setup. The reaction is irradiated with the Kessil lamp at 427 nanometers and 50 percent intensity for a period of 18 hours, which is longer than typically required for intramolecular reactions due to the entropic penalty associated with bringing together two separate molecules in the cycloaddition step. The longer reaction time ensures that the equilibrium between forward cycloaddition and retro-cycloaddition is driven toward the product, and that the system has sufficient time to sample the conformational space required for optimal stereocontrol.

After 18 hours of irradiation, the reaction is worked up by removing the solvent under reduced pressure. Unlike the intramolecular products, which bear an aldehyde functional group requiring derivatization, the intermolecular products can often be directly purified and analyzed. The crude material is subjected to proton nuclear magnetic resonance analysis to determine conversion and diastereomeric ratio as described above. The crude product is then purified by column chromatography on silica gel using an appropriate eluent system, typically a gradient of 10 to 40 percent ethyl acetate in hexanes. The purified products are obtained as colorless solids or viscous oils and are characterized by nuclear magnetic resonance spectroscopy, infrared spectroscopy, and high-resolution mass spectrometry. The enantiomeric excess is determined by ultra-performance convergence chromatography on chiral stationary phase using conditions optimized for each specific product structure. Intermolecular photocycloadditions with methylenecyclohexane provide products in 70 percent yield and 94 percent enantiomeric excess as single diastereoisomers, while reactions with more complex olefins such as (R)-(-)-carvone provide products in 45 percent yield as mixtures of diastereoisomers, each diastereoisomer exhibiting greater than 99 percent enantiomeric excess.

The scope of the intramolecular enantioselective [2+2] photocycloaddition reaction encompasses a wide range of indole-3-carboxaldehyde derivatives bearing different substituents at various positions of the indole ring. Halogen substituents at the 5-position, including 5-fluoroindole, 5-chloroindole, and 5-bromoindole derivatives, provide cycloadducts in yields ranging from 72 to 82 percent with enantiomeric excesses of 88 to 92 percent. The reaction with 5-fluoro-1-(pent-4-enyl)-1H-indole-3-carbaldehyde furnishes the corresponding cycloadduct in 82 percent yield and 90 percent enantiomeric excess after 6 hours of irradiation. The 5-bromo analogue provides 72 percent yield and 88 percent enantiomeric excess. These results demonstrate that the electronic perturbation introduced by the halogen substituent does not significantly disrupt the photophysical properties or the stereochemical control mechanism, and that the size variation from fluorine (van der Waals radius 1.47 Ångströms) to bromine (van der Waals radius 1.85 Ångströms) is well accommodated by the catalyst pocket.

Substituents at the 6-position of the indole ring also provide excellent results. The 6-fluoroindole derivative furnishes product in 66 percent yield and 82 percent enantiomeric excess, while the 6-bromoindole analogue provides 73 percent yield and 90 percent enantiomeric excess. The 6-cyanoindole substrate, bearing a strongly electron-withdrawing substituent, reacts to give product in 50 percent yield and 89 percent enantiomeric excess. This substrate requires modified reaction conditions, specifically irradiation at 400 nanometers rather than 427 nanometers due to the blue-shifted absorption spectrum induced by the cyano group, and an extended reaction time of 18 hours. A mixture of chloroform and chlorobenzene in 1:1 ratio is employed as the solvent to maintain solubility of the polar cyano-substituted iminium ion. The 6-trifluoromethylindole derivative provides 71 percent yield and 90 percent enantiomeric excess, demonstrating tolerance of this strongly electron-withdrawing and sterically demanding substituent. Functional groups that enable further synthetic elaboration, such as the 6-boronate ester substituent in 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(pent-4-enyl)-1H-indole-3-carbaldehyde, are also compatible, providing product in 81 percent yield and 91 percent enantiomeric excess. This boronate ester functional group can

subsequently undergo Suzuki-Miyaura cross-coupling reactions to install aryl or alkenyl substituents, greatly expanding the structural diversity accessible from the cycloadduct products.

Substituents at the 7-position are equally well tolerated. The 7-fluoroindole derivative provides cycloadduct in 82 percent yield and 90 percent enantiomeric excess, while the 7-bromoindole analogue furnishes 67 percent yield and 91 percent enantiomeric excess. Electron-donating substituents such as methyl groups can be introduced at the 4-position or 7-position. The 4-methylindole substrate provides product in 70 percent yield and 90 percent enantiomeric excess after 12 hours of irradiation, while the 7-methylindole analogue furnishes 46 percent yield and 72 percent enantiomeric excess after 18 hours. The reduced yields and enantioselectivities observed for some methyl-substituted substrates may arise from increased steric congestion in the catalyst-substrate complex or from perturbation of the excited state energetics by the electron-donating methyl groups. Disubstituted indole substrates can also be employed. The 5-fluoro-6-cyanoindole derivative, bearing two electron-withdrawing groups, reacts at 400 nanometers wavelength for 18 hours to provide product in 50 percent yield and 89 percent enantiomeric excess, demonstrating the cumulative electronic effects of multiple substituents.

Variations in the structure of the tethered chain connecting the nitrogen atom to the olefin are also well accommodated. While the standard substrate employs a pent-4-enyl tether creating a six-membered lactam ring in the product, alternative tether lengths can be used. A but-3-enyl tether, one carbon shorter, provides a product with a five-membered lactam ring in 40 percent yield and 94 percent enantiomeric excess. The reduced yield may arise from the increased ring strain in the five-membered lactam or from suboptimal positioning of the olefin for cycloaddition. A hex-5-enyl tether, one carbon longer, furnishes a product with a seven-membered lactam ring in 80 percent yield and 84 percent enantiomeric excess. Substituents on the tethering chain itself can also be introduced. A substrate bearing a methyl group at the carbon atom adjacent to the nitrogen atom reacts to provide product with four contiguous stereogenic centers in 84 percent yield, 75 percent enantiomeric excess, and 9:1 diastereomeric ratio. The reduced enantiomeric excess compared to the unsubstituted substrate reflects the increased complexity of the stereocontrol problem when additional stereogenic centers are present, but the high diastereoselectivity demonstrates that the chiral catalyst effectively controls the relative configuration of all four stereocenters.

The polycyclic products obtained from the enantioselective [2+2] photocycloaddition reactions possess an aldehyde functional group that serves as a versatile handle for subsequent synthetic transformations. This aldehyde can be selectively manipulated without affecting the other functional groups present in the molecule, allowing for the preparation of structurally diverse derivatives while maintaining the stereochemical integrity established during the photochemical step. Three representative transformations have been developed to showcase the synthetic utility of these cycloadducts: oxidation to the carboxylic acid, homologation to the terminal alkyne, and reduction to the primary alcohol.

The oxidation of the aldehyde to the carboxylic acid is accomplished using the Pinnick oxidation protocol, which employs sodium chlorite as the oxidant in combination with hydrogen peroxide and a pH buffer. The crude product from the photochemical reaction, without prior purification or removal of the organocatalyst, is dissolved in a mixture of acetonitrile and water in a 4:1 volume ratio to a concentration of approximately 0.1 molar. Sodium chlorite (technical grade, 80 percent, available from Sigma-Aldrich) is added in an amount of 5 equivalents relative to the cycloadduct, and potassium dihydrogen phosphate is added in an amount of 5 equivalents to maintain the pH at approximately 4.5. Hydrogen peroxide (30 percent aqueous solution) is added dropwise in an amount of 1 equivalent, serving to convert any chlorine dioxide byproduct back to chlorite and prevent its escape as a toxic gas. The reaction mixture is stirred at room temperature for 3 hours, during which time the aldehyde is oxidized to the carboxylic acid through the intermediacy of the gem-diol and the chlorite ester. After 3 hours, the reaction is quenched by addition of saturated aqueous sodium thiosulfate solution to reduce any remaining oxidant, and the mixture is extracted with ethyl acetate. The organic phase is washed with brine, dried over sodium sulfate, and concentrated to provide the crude carboxylic acid. This material is purified by column chromatography on silica gel using a mobile phase containing 1 percent acetic acid to suppress ionization of the carboxylic acid and improve peak shape. The purified carboxylic acid is obtained in 68 percent yield over the two steps from the indole-3-carboxaldehyde starting material, and exhibits 92 percent enantiomeric excess, identical to the value observed for the aldehyde precursor, confirming that no racemization occurs during the oxidation.

The homologation of the aldehyde to the terminal alkyne is achieved through a two-step Corey-Fuchs procedure. In the first step, the crude aldehyde from the photochemical reaction is dissolved in dichloromethane to a concentration of 0.25 molar, and triphenylphosphine is added in an amount of 2.2 equivalents. The solution is cooled to 0 degrees Celsius in an ice-water bath, and carbon tetrabromide is added in an amount of 2.2 equivalents. This combination generates (dibromomethylene)triphenylphosphorane in situ, which reacts with the aldehyde through a Wittig-type mechanism to form a 1,1-dibromoalkene. The reaction is allowed to warm to room temperature and stirred for 18 hours to ensure complete conversion. The mixture is then concentrated and purified by column chromatography on silica gel to provide the 1,1-dibromoalkene intermediate. In the second step, this intermediate is dissolved in dimethyl sulfoxide to a concentration of 0.1 molar, and cesium carbonate is added in an amount of 3 equivalents. The mixture is heated to 120 degrees Celsius for 18 hours, during which time the base promotes elimination of both bromine atoms to generate the terminal alkyne. The reaction mixture is cooled, diluted with water,

and extracted with ethyl acetate. The organic phase is washed with brine, dried over sodium sulfate, and concentrated. Purification by column chromatography on silica gel provides the terminal alkyne product in 55 percent yield over the three steps from the starting indole-3-carboxaldehyde, with 92 percent enantiomeric excess retained.

The concomitant reduction of both the aldehyde and the lactam carbonyl groups is accomplished using lithium aluminum hydride, a powerful reducing agent capable of reducing both functional groups in a single operation. The crude aldehyde from the photochemical reaction is dissolved in anhydrous tetrahydrofuran that has been freshly distilled from sodium benzophenone ketyl to ensure rigorously dry conditions. The solution is cooled to 0 degrees Celsius, and a suspension of lithium aluminum hydride in tetrahydrofuran (1 molar concentration, available from Sigma-Aldrich) is added dropwise in an amount of 4 equivalents relative to the cycloadduct. This stoichiometry accounts for the requirement of 2 equivalents of hydride for reduction of the aldehyde (which is reduced to the alcohol via transfer of two hydride equivalents) and 2 equivalents for reduction of the lactam (which is reduced to the amine via cleavage of the carbon-nitrogen bond and transfer of hydride). The reaction is allowed to warm to room temperature and stirred for 18 hours. After this time, the excess lithium aluminum hydride is carefully quenched by sequential addition of water, 15 percent aqueous sodium hydroxide, and additional water in a 1:1:3 ratio by volume. This Fieser workup procedure converts the aluminum salts to a granular precipitate that can be removed by filtration. The filtered solution is concentrated and purified by column chromatography on silica gel, providing the fully reduced product in 64 percent yield over the two steps from the starting material, with 91 percent enantiomeric excess. This product possesses a primary alcohol functional group in place of the aldehyde and a secondary amine in place of the lactam, greatly expanding the possibilities for further functionalization and coupling reactions.

### Theoretical Basis of the Present Invention

#### Photophysical Equations

Absorption and Excitation Process:

$$I_{abs} = I_0(1 - 10^{-\epsilon c l})$$

where  $I_{abs}$  represents the intensity of light absorbed by the iminium ion solution in units of einstein per liter per second,  $I_0$  denotes the incident photon flux in einstein per liter per second,  $\epsilon$  is the molar extinction coefficient of the iminium ion intermediate at the irradiation wavelength in units of liter per mole per centimeter,  $c$  represents the molar concentration of the iminium ion in moles per liter, and  $l$  is the optical path length through the reaction vessel in centimeters.

Quantum Yield of Intersystem Crossing:

$$\Phi_{ISC} = \frac{k_{ISC}}{k_{ISC} + k_f + k_{IC}}$$

where  $\Phi_{ISC}$  represents the quantum yield of intersystem crossing from the first singlet excited state to the triplet manifold (dimensionless),  $k_{ISC}$  denotes the rate constant for intersystem crossing in reciprocal seconds,  $k_f$  is the rate constant for fluorescence emission from the first singlet excited state in reciprocal seconds, and  $k_{IC}$  represents the rate constant for internal conversion from the first singlet excited state to the ground state in reciprocal seconds.

Triplet State Lifetime:

$$\tau_{T1} = \frac{1}{k_{reaction} + k_{T,decay} + k_q[O_2]}$$

where  $\tau_{T1}$  represents the observed lifetime of the first triplet excited state in seconds,  $k_{reaction}$  denotes the first-order or pseudo-first-order rate constant for the photochemical reaction (cycloaddition) in reciprocal seconds,  $k_{T,decay}$  is the intrinsic decay rate constant of the triplet state in the absence of quenchers and reaction partners in reciprocal seconds,  $k_q$  represents the bimolecular quenching rate constant for triplet quenching by molecular oxygen in liters per mole per second, and  $[O_2]$  is the concentration of dissolved oxygen in moles per liter.

Energy of Excited States:

$$E_{S1} = \frac{hc}{\lambda_{abs,max}}$$

where  $E_{S1}$  represents the energy of the first singlet excited state in joules per molecule,  $h$  denotes Planck's constant ( $6.626 \times 10^{-34}$  joule seconds),  $c$  is the speed of light in vacuum ( $2.998 \times 10^8$  meters per second), and  $\lambda_{abs,max}$  represents the wavelength of maximum absorption in meters.

#### Stereochemical Selectivity Equations

Enantiomeric Excess:

$$ee = \frac{|[R] - [S]|}{[R] + [S]} \times 100 \%$$

where  $ee$  represents the enantiomeric excess expressed as a percentage,  $[R]$  denotes the concentration or amount of the R enantiomer, and  $[S]$  represents the concentration or amount of the S enantiomer.

Relationship Between Enantiomeric Excess and Energy Difference:

$$ee = \frac{e^{-\Delta\Delta G^\ddagger/RT} - 1}{e^{-\Delta\Delta G^\ddagger/RT} + 1} \times 100 \%$$

where  $\Delta\Delta G^\ddagger$  represents the difference in activation free energy between the transition states leading to the two enantiomeric products in joules per mole,  $R$  denotes the universal gas constant (8.314 joules per mole per kelvin), and  $T$  represents the absolute temperature in kelvin.

Diastereomeric Ratio:

$$dr = \frac{[major]}{[minor]}$$

where  $dr$  represents the diastereomeric ratio (dimensionless),  $[major]$  denotes the concentration or amount of the major diastereoisomer, and  $[minor]$  represents the concentration or amount of the minor diastereoisomer.

#### Kinetic Equations

Rate of Iminium Ion Formation:

$$r_{formation} = k_{cond}[aldehyde][amine][H^+] - k_{hyd}[iminium][H_2O]$$

where  $r_{formation}$  represents the net rate of iminium ion formation in moles per liter per second,  $k_{cond}$  denotes the second-order rate constant for the acid-catalyzed condensation reaction in liter squared per mole squared per second,  $[aldehyde]$  is the concentration of the indole-3-carboxaldehyde substrate in moles per liter,  $[amine]$  represents the concentration of the free base form of the chiral primary amine catalyst in moles per liter,  $[H^+]$  denotes the concentration of protons (from trifluoroacetic acid) in moles per liter,  $k_{hyd}$  is the rate constant for hydrolysis of the iminium ion back to aldehyde and amine in liter per mole per second,  $[iminium]$  represents the concentration of the iminium ion intermediate in moles per liter, and  $[H_2O]$  is the concentration of water in moles per liter.

Overall Reaction Rate:

$$r_{overall} = \Phi_{reaction} \cdot I_{abs}$$

where  $r_{overall}$  represents the overall rate of product formation in moles per liter per second,  $\Phi_{reaction}$  denotes the overall quantum yield for the photochemical transformation (dimensionless, defined as moles of product formed per einstein of photons absorbed), and  $I_{abs}$  represents the rate of light absorption as defined above in einstein per liter per second.

Stern-Volmer Equation for Triplet Quenching:

$$\frac{\tau_0}{\tau} = 1 + k_q\tau_0[Q]$$

where  $\tau_0$  represents the triplet lifetime in the absence of quencher in seconds,  $\tau$  denotes the observed triplet lifetime in the presence of quencher in seconds,  $k_q$  is the bimolecular quenching rate constant in liters per mole per second, and  $[Q]$  represents the concentration of quencher (such as oxygen or 2,5-dimethylhexa-2,4-diene) in moles per liter.

#### Thermodynamic Equations

Equilibrium Constant for Iminium Ion Formation:

$$K_{eq} = \frac{[iminium][H_2O]}{[aldehyde][amine][H^+]}$$

where  $K_{eq}$  represents the equilibrium constant for iminium ion formation (units of liter squared per mole squared), and the bracketed terms represent the equilibrium concentrations of the respective species in moles per liter.

Free Energy Relationship:

$$\Delta G^\ddagger = -RT \ln \left( \frac{k_B T}{h} \cdot \frac{k}{T} \right)$$

where  $\Delta G^\ddagger$  represents the activation free energy for a given reaction step in joules per mole,  $R$  denotes the universal gas constant (8.314 joules per mole per kelvin),  $T$  is the absolute temperature in kelvin,  $k_B$  represents Boltzmann's constant ( $1.381 \times 10^{-23}$  joules per kelvin),  $h$  denotes Planck's constant ( $6.626 \times 10^{-34}$  joule seconds), and  $k$  is the observed rate constant for the reaction step in reciprocal seconds for a unimolecular process or in appropriate units for higher-order processes.

Gibbs Free Energy of Excited States:

$$\Delta G_{excited} = E_{excited} - T\Delta S_{excited}$$

where  $\Delta G_{\text{excited}}$  represents the free energy of the excited state relative to the ground state in joules per mole,  $E_{\text{excited}}$  denotes the electronic energy of the excited state in joules per mole (calculated from the absorption or emission wavelength),  $T$  is the absolute temperature in kelvin, and  $\Delta S_{\text{excited}}$  represents the entropy change associated with excitation in joules per mole per kelvin (typically negative due to the more ordered nature of excited states).

### Computational Chemistry Equations

Time-Dependent Density Functional Theory Excitation Energy:

$$\omega_I = E_{S_I} - E_{S_0} = \sqrt{(\epsilon_a - \epsilon_i)^2 + 4|K_{ia}|^2}$$

where  $\omega_I$  represents the excitation energy to the  $I$ th excited state in hartrees or electronvolts,  $E_{S_I}$  denotes the energy of the  $I$ th singlet excited state,  $E_{S_0}$  represents the ground state energy,  $\epsilon_a$  is the orbital energy of the virtual (unoccupied) molecular orbital  $a$  in hartrees,  $\epsilon_i$  denotes the orbital energy of the occupied molecular orbital  $i$  in hartrees, and  $K_{ia}$  represents the coupling matrix element between the occupied and virtual orbitals in hartrees.

Spin-Orbit Coupling Matrix Element:

$$\langle S_1 | \hat{H}_{SO} | T_n \rangle = \sum_{\mu} \langle S_1 | \hat{L}_{\mu} | T_n \rangle \langle T_n | \hat{S}_{\mu} | S_1 \rangle$$

where the left side represents the spin-orbit coupling matrix element between the first singlet excited state  $S_1$  and the  $n$ th triplet excited state  $T_n$  in reciprocal centimeters,  $\hat{H}_{SO}$  denotes the spin-orbit coupling Hamiltonian operator, the summation runs over the three spatial components  $\mu$  ( $x, y, z$ ),  $\hat{L}_{\mu}$  represents the orbital angular momentum operator for component  $\mu$ , and  $\hat{S}_{\mu}$  denotes the spin angular momentum operator for component  $\mu$ .

Minimum Energy Crossing Point Optimization:

$$f = \alpha (E_{S_1} - E_{T_n})^2 + (1 - \alpha) |\nabla E_{S_1} - \nabla E_{T_n}|^2$$

where  $f$  represents the objective function to be minimized during location of the minimum energy crossing point between singlet state  $S_1$  and triplet state  $T_n$  in atomic units,  $\alpha$  is a weighting factor (typically 0.02) that balances energy and gradient matching (dimensionless),  $E_{S_1}$  and  $E_{T_n}$  represent the energies of the respective states in hartrees, and  $\nabla E_{S_1}$  and  $\nabla E_{T_n}$  denote the energy gradients (forces) on the respective surfaces in hartrees per bohr.

Density Functional Theory Energy Expression:

$$E_{\text{DFT}}[\rho] = T_s[\rho] + V_{ne}[\rho] + J[\rho] + E_{XC}[\rho]$$

where  $E_{\text{DFT}}[\rho]$  represents the total electronic energy as a functional of the electron density  $\rho$  in hartrees,  $T_s[\rho]$  denotes the kinetic energy of non-interacting electrons in hartrees,  $V_{ne}[\rho]$  represents the nuclear-electron attraction energy in hartrees,  $J[\rho]$  is the classical Coulomb repulsion energy between electrons in hartrees, and  $E_{XC}[\rho]$  denotes the exchange-correlation energy that accounts for all quantum mechanical effects beyond classical electrostatics in hartrees.

### Photochemical Reaction Coordinate Equations

Marcus Theory for Electron Transfer (Adapted for Bond Formation):

$$k_{ET} = \frac{2\pi}{\hbar} |V|^2 \frac{1}{\sqrt{4\pi\lambda k_B T}} \exp\left(-\frac{(\Delta G^0 + \lambda)^2}{4\lambda k_B T}\right)$$

where  $k_{ET}$  represents the rate constant for the electron transfer or bond formation step in reciprocal seconds,  $\hbar$  denotes the reduced Planck constant ( $1.055 \times 10^{-34}$  joule seconds),  $V$  represents the electronic coupling matrix element between reactant and product states in joules,  $\lambda$  is the reorganization energy in joules,  $k_B$  denotes Boltzmann's constant ( $1.381 \times 10^{-23}$  joules per kelvin),  $T$  represents the absolute temperature in kelvin, and  $\Delta G^0$  is the standard free energy change for the reaction step in joules.

Arrhenius Equation for Temperature Dependence:

$$k_{ET} = \frac{2\pi}{\hbar} |V|^2 \frac{1}{\sqrt{4\pi\lambda k_B T}} \exp\left(-\frac{(\Delta G^0 + \lambda)^2}{4\lambda k_B T}\right)$$

where  $k$  represents the rate constant for a thermally activated process in reciprocal seconds or appropriate units,  $A$  denotes the pre-exponential factor (same units as  $k$ ),  $E_a$  represents the activation energy in joules per mole,  $R$  is the universal gas constant (8.314 joules per mole per kelvin), and  $T$  denotes the absolute temperature in kelvin.

Radical Recombination Rate:

$$k_{\text{recomb}} = \frac{8RT}{3\eta} \exp\left(-\frac{\Delta G_{\text{recomb}}^\ddagger}{RT}\right)$$

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where  $k_{\text{recomb}}$  represents the rate constant for radical-radical recombination in liters per mole per second,  $R$  denotes the universal gas constant (8.314 joules per mole per kelvin),  $T$  is the absolute temperature in kelvin,  $\eta$  represents the viscosity of the solvent in pascal seconds, and  $\Delta G_{\text{recomb}}^\ddagger$  denotes the activation free energy for the recombination step in joules per mole (typically very small or zero for diffusion-controlled processes).

### Prior Art Reference

Corti, V., Simionato, G., Rizzo, L. *et al.* Triplet state reactivity of iminium ions in organocatalytic asymmetric [2 + 2] photocycloadditions. *Nat. Chem.* (2025). <https://doi.org/10.1038/s41557-025-01960-3>