ORGANIC CHEMISTRY

Asymmetric multifunctionalization of alkynes via photo-irradiated organocatalysis

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Alkynes represent a family of pivotal and sustainable feedstocks for various industries such as pharmaceuticals, agrochemicals, and materials, and they are widely used as important starting materials for the production of a broad range of chemical entities. Nevertheless, efficient structural elaborations of alkynes in chemical synthesis, especially asymmetric multifunctionalization of alkynes, remain largely unexplored. It is thus imperative to develop new asymmetric synthetic approaches, making use of these richly available chemical feedstocks, and enabling their conversion to value-added chiral molecules. Here, we disclose our findings on highly enantioselective multifunctionalization of alkynes by merging photochemistry and chiral phosphoric acid catalysis. Our reported one-pot synthetic protocol is applicable to all types of alkyne substrates, incorporating all three reactants in a fully atom-economic fashion to produce optically enriched tetrasubstituted triaryl- and diarylmethanes, important structural scaffolds in medicinal chemistry and biological sciences.

INTRODUCTION

Organic synthesis relies fundamentally on the availability of raw materials. The most common chemical feedstocks that can be derived from coal, natural gas, and petrochemical industries are unsaturated hydrocarbons, the employment of which in chemical reactions forms the basis for modern catalysis and synthesis (*1*, *2*). The past decade has witnessed remarkable progress in evolving powerful asymmetric synthetic methods for the transformation of alkenes into various high-valued molecules, enabled by transition metal catalysis, photoredox catalysis, and organocatalysis (*3*–*7*). In stark contrast, asymmetric transformations of simple alkyne substrates lag far behind (Fig. 1A). Hinging on the inherent properties of the alkyne carbon-carbon triple bond, the most prevalent reaction mode of alkynes is the formation of alkenes via metal-mediated π-insertion process to the triple bond (*8*–*12*). When the asymmetric functionalization of alkynes is concerned, there are only a handful of reports, which all used terminal alkyne substrates. Through hydrometalation reactions, chiral *gem*-1,1-disubstitued aminoboryl-, bis-silyl-, or borylsilyl- alkanes were derived via cobalt- or copper-catalyzed difunctionalizations of alkynes (*13*–*16*). Enabled by gold/organo-cooperative catalysis, terminal alkynes were functionalized with nitrones and alcohols for the asymmetric assembly of cyclic/acyclic chiral ketones (*17*, *18*). Alkynes are promising raw materials for further chemical elaborations; their two degrees of unsaturation suggest great synthetic potentials of these simple linear molecules. Therefore, asymmetric synthetic strategies targeting multifunctionalizations of alkynes would be highly desirable. Given the ready availability of alkynyl substrates, we believe that such research endeavors hold great promise for the development of future practical and sustainable synthetic solutions to access chiral molecules.

Visible light photocatalysis has drawn tremendous attention and became an extremely hot research area in recent years (*19*). The popularity of photocatalysis can fundamentally be attributed to photo-driven activations of substrates through the generation of radical species, which are often not possible under thermodynamic conditions. When the asymmetric synthesis of chiral molecules is concerned, cooperative catalysis offers a new paradigm. Specifically, the merger of photocatalysis with transition metal catalysis (*20*–*22*) or with organocatalysis (*23*–*28*) further empowered the art of photo-induced asymmetric catalysis and synthesis to a whole new level. In connection to alkyne activations, photocatalysis can serve as an effective means to activate alkyne substrates, which differs completely from transition metal–catalyzed alkyne π-insertion process. In devising a general strategy for the asymmetric multifunctionalization of alkynes, we bear in mind the following: (i) broad applicability to all different types of alkynes, including both terminal and internal alkynes; (ii) practicality of the method, being convergent, high atom economic, and operationally simple, thus one-pot multiple-component reaction if possible; and (iii) high efficiency in asymmetric induction, ideally under the catalysis of well-established catalyst types. Specifically, we propose that the combination of photochemistry and organocatalysis may offer a viable solution to this challenging task. In our projection, we envisioned that the Paternò-Büchi [2+2] reaction (*29*) between an alkyne and a suitable carbonyl compound may be used for the initial perturbation to the carbon-carbon triple bond, creating the crucial oxetene intermediate. In the presence of chiral phosphoric acid (CPA) and an incoming nucleophile (*30*–*32*), further transformation of oxetene is anticipated to take place, delivering chiral products with a quaternary stereogenic center (Fig. 1B). Note that Sharma and co-workers (*33*) recently reported a photoinduced and zinc-catalyzed nonstereoselective construction of triaryl-substituted quaternary stereocenters from alkynes.

To prove our design conceptually and to test the validity of our proposal, we first chose reaction partners for our intended multicomponent reaction. Quinones are known to go to the triplet state upon photoexcitation (*34*), and they readily undergo Paternò-Büchi [2+2] reaction with alkynes via photoinduction (*35*–*38*). We thus decided to choose benzoquinones as the ketone reaction partner. Given the fact that alkynes are readily available chemical feedstocks (vide supra) and with the intention of making our methodology more general, we hoped to use both internal/terminal alkynes with a wide range of substituents in our reaction. For the selection of nucleophilic moiety, we chose indole derivatives, as indole moieties

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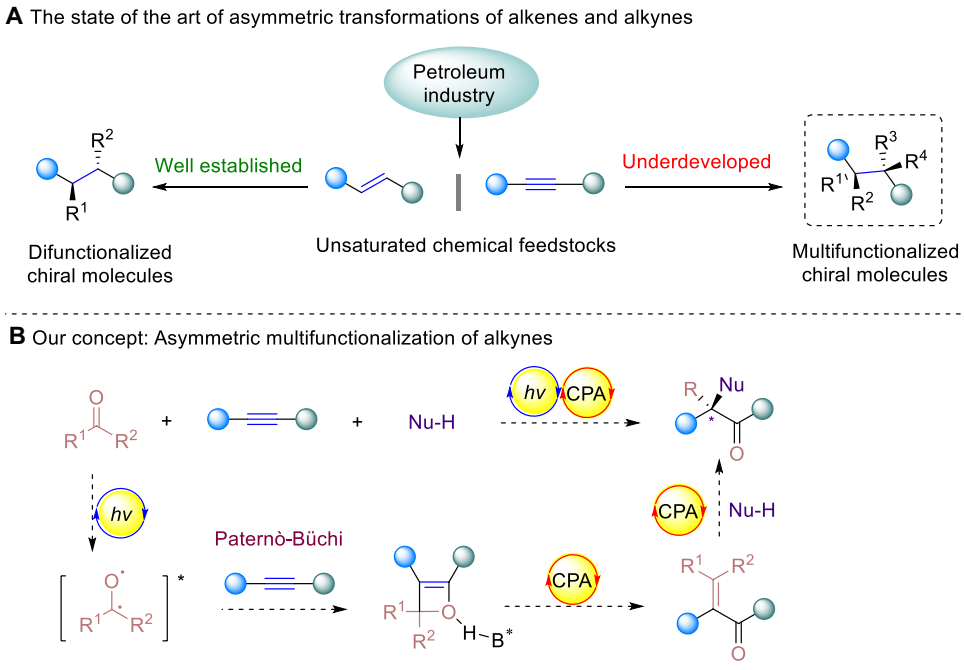

Fig. 1. Background and concept. (**A**) The state of the art of asymmetric conversions of alkenes and alkynes to value-added chiral molecules. (**B**) Concept: Our proposed strategy for the asymmetric multifunctionalization of alkynes via cooperative photo- and organocatalysis. Nu, nucleophile; B*H, chiral Brønsted acid.

are widely present in natural products and bioactive molecules. More specifically, if one end of alkynes is an alkyl or aryl group, then the projected product would contain a diary/triaryl-substituted quaternary stereogenic center, a structural motif that has been found in numerous biologically active molecules, metabolites, and natural products including a range of best-selling pharmaceuticals (e.g., vinblastine, tolterodine, and sertraline; Fig. 2F) (*39*–*42*). Here, we wish to report an efficient asymmetric synthesis of triarylmethanes and diarylmethanes bearing a quaternary stereogenic center, through asymmetric multifunctionalization of simple alkynes via photo-irradiated organocatalysis.

RESULTS

A general description of our designed reaction and proposed reaction mechanism is illustrated in Fig. 2A. In our projected mechanistic pathways, visible light irradiation on benzoquinone leads to the generation of diradical species, which is captured by the alkyne substrate to form the oxetene intermediate. In the subsequent CPA catalytic cycle, the incoming nucleophile attacks the *para*-quinone methide (*p*-QM) intermediate, leading to the formation of fully functionalized chiral product. We started our investigation by examining a model reaction involving alkyne **1a**, benzoquinone **2a**, and indole **3a**. The ultraviolet-visible (UV-vis) spectra of three compounds were acquired, and only benzoquinone **2a** showed strong absorption band at the visible light region with the maximum absorption at 437 nm (Fig. 2B). Accordingly, the 440-nm Kessil light-emitting diodes (LEDs) were chosen as the source of visible light. Under the irradiation of 440-nm Kessil LEDs, alkyne **1a** smoothly reacted with benzoquinone **2a** to furnish *p*-QM **5a** in 73% yield in 4 hours (see figs. S1 to S2 for details). Notably, in the presence of 5 mole percent (mol %) CPA **4a**, the same reaction was markedly enhanced; **5a** was obtained in 95% yield within 5 min (Fig. 2C). When intermediate **5a** was reacted with **3a** under the catalysis of CPA **4a**, triaryl ketone **6a** was obtained in 96% yield with 97% enantiomeric excess (ee) (Fig. 2D). With all the above studies firmly establishing the feasibility of our proposed multifunctionalization of alkynes via dual photo-/organocatalysis, we then proceeded to established practical one-pot protocol. A systematic reaction screening (see the Supplementary Materials and table S1) established the optimal reaction conditions as follows: In the presence of CPA **4a** and under irradiation of 440-nm Kessil LEDs, the reaction of alkyne **1a** with benzoquinone **2a** and indole **3a** in acetonitrile led to efficient asymmetric alkynyl multifunctionalization, forming triarylmethane **6a** in 95% yield and 95% ee. Without light or CPA, the desired product was not formed, testifying that the visible light activation and phosphoric acid promotion are indispensable for this dual catalytic system (Fig. 2E). Note that side product **6a′** through the direct reaction of indole with benzoquinone was not observed in our reaction.

We examined the scope of this photoinduced organocatalytic method for enantioselective multifunctionalization of alkynes. The reaction was found to be broadly applicable to a range of different indoles (Fig. 3A). Indoles containing various electron-donating groups at the 4-position (**6c** to **6e**) were found to be suitable and so were the indoles bearing an electron-withdrawing substituent at the 4-position (**6f** and **6g**), and excellent chemical yields and ee values were attainable. An aldehyde function in the indole substrate remained intact during the reaction (**6h**). The reaction was also applicable to a diverse array of 5-substituted indole derivatives, regardless of the electronic nature of the substituents, the desired products were obtained in good yields and with very high enantioselectivities (**6i** to **6v**). The absolute configurations of triarylmethane products were assigned on the basis of the x-ray crystallographic analysis of **6u**.

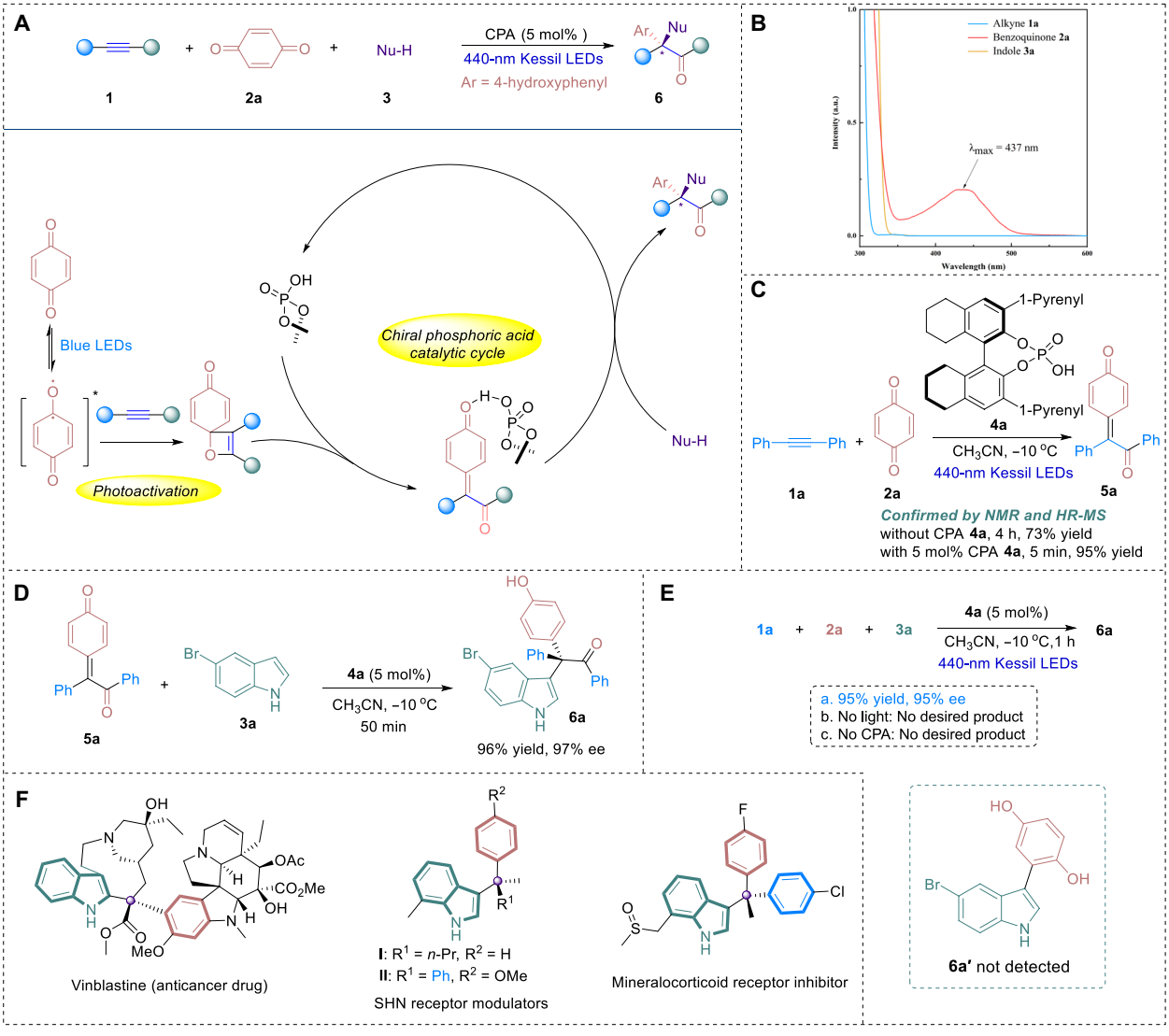

Fig. 2. Reaction design and development. (**A**) Mechanistic pathways of visible light–driven organocatalytic multifunctionalization of alkynes. (**B**) Ultraviolet-visible (UV-vis) spectra of the substrates. (**C**) The reaction of alkyne **1a** with benzoquinone **2a** under visible light irradiation. (**D**) CPA-catalyzed reaction of between **5a** with indole **3a**. (**E**) Standard reaction conditions and control experiments. (**F**) Representative bioactive molecules containing diaryl- and triaryl-methane cores. LED, light-emitting diode; Ar, Aryl; NMR, nuclear magnetic resonance; HR-MS, high-resolution mass spectrum; *n*-Pr, *n*-propyl; SHN, steroid hormone nuclear; a.u., arbitrary units.

The boron group was well-preserved in the product (Bpin in **6v**), which provides a convenient synthetic handle for further transformations. Furthermore, a group of 6-substituted indole substrates were examined, and the reaction proved to be robust, and consistently high yields and ee values were attainable (**6w** to **6ac**). Last, a 7-substituted indole and a diverse array of disubstituted indoles were evaluated, and in all these examples, the desired products were smoothly delivered in excellent yields and enantioselectivities. Notably, the electronic nature of the substituents and the substitution patterns of disubstituted indoles had little influence on the reaction (**6ad** to **6an**).

From the outset, we were aiming at developing a general methodology that is applicable to different alkynes. We then carefully examined the generality of the reaction with respect to alkynes, including all types of internal and terminal alkynes (Fig. 3B). We first examined 1,2-diaryl alkynes bearing different aryl moieties and found that all the reactions proceeded with excellent yields and enantioselectivities (**6ao** to **6au**). Unsymmetrical alkyl aryl alkynes were next evaluated. Alkynes with alkyl groups of different chain length were well tolerated; the reaction proceeded regiospecifically, forming alkyl ketone triarylmethanes in high yields with excellent enantioselectivities (**6av** to **6az**). The excellent regioselectivity of our reaction is likely due to the higher stability of benzyl radical over the alkyl radical, as well as the steric difference between an aryl and an alkyl group (see the Supplementary Materials and figs. S3 to S5 for a more detailed discussion). Notably, alkynes with a long alkyl chain, i.e., *n*-heptyl, and a primary alcohol were both shown to be suitable substrates (**6az** and **6ba**), demonstrating broad applicability of this synthetic protocol. The tolerance of different aryl moieties in the alkyl aryl alkynes was subsequently evaluated, and alkynes bearing a range of

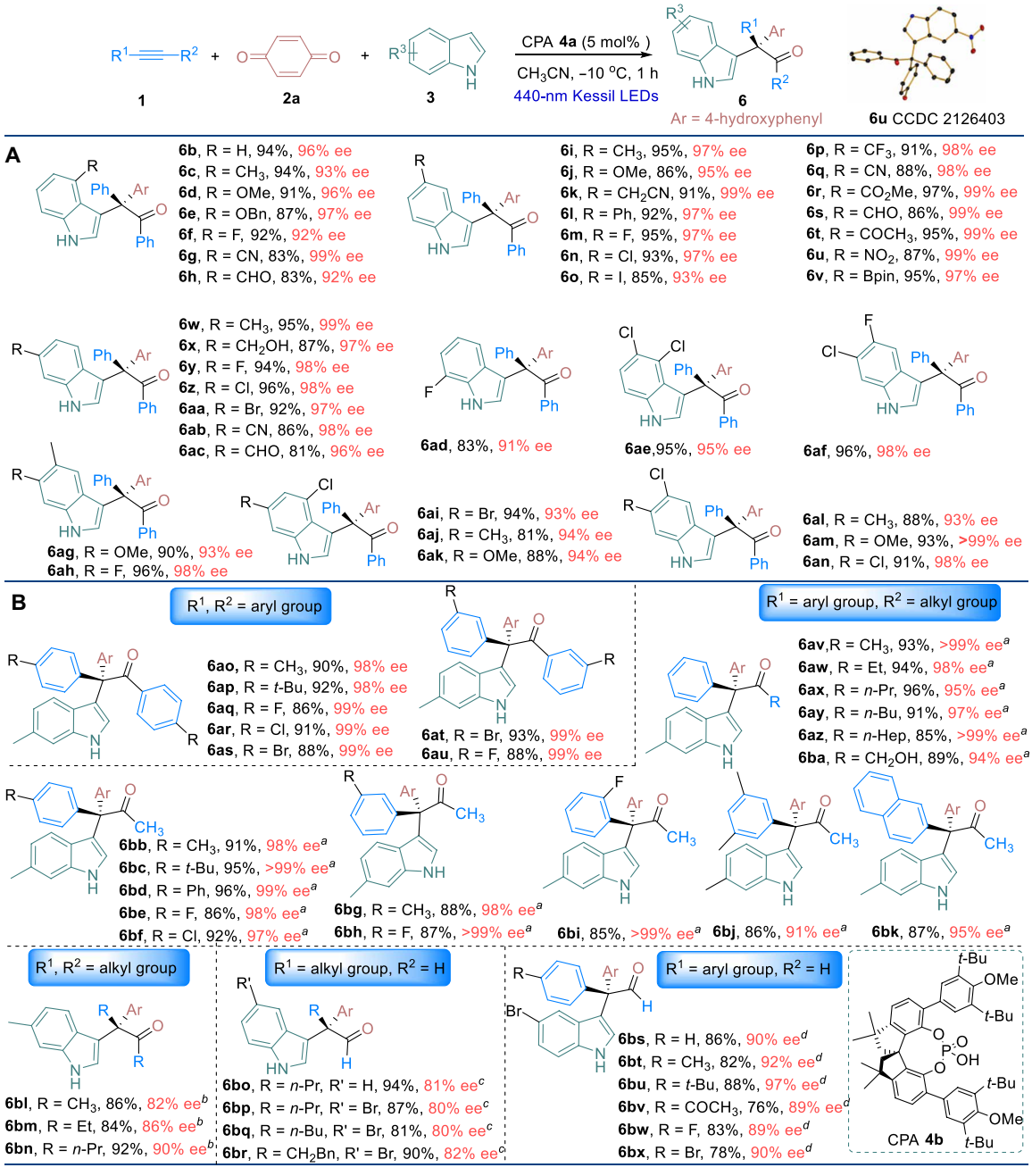

Fig. 3. Reaction scope. Reaction conditions: **1** (0.2 mmol), **2a** (0.1 mmol), **3** (0.1 mmol), **4a** (5 mol %), CH_3CN (3 ml), 440-nm Kessil LEDs, −10°C, and 1 hour; isolated yields reported. (**A**) Scope of indoles. (**B**) Scope of alkynes. *a*, −40°C; *b*, CPA **4b**, butyronitrile, −78°C; *c*, butyronitrile, −78°C; *d*, CPA **4c**, butyronitrile, −78°C; CPA **4c**, (11*aS*)-3,7-bis(1-pyrenyl)-10,11,12,13- tetrahydro-5-hydroxy-diindeno[7,1-*de*:1′,7′-*fg*] [1,3,2]dioxaphosphocin; ee, enantiomeric excess, determined by high-performance liquid chromatography analysis; Pin, pinacolato; *t*-Bu, *tert*-butyl; *n*-Bu, *n*-butyl; *n*-hep, *n*-heptyl.

monosubstituted phenyls were found to be suitable, regardless of the position or electronic nature of the substituent (**6bb** to **6bi**). Moreover, methyl aryl alkynes bearing a disubstituted aromatic moiety or a 2-naphthalenyl group were proven to be good substrates (**6bj** and **6bk**). The 1,2-dialkyl alkynes represent a class of challenging substrates, and their applications in asymmetric synthesis are rare. Through further reaction optimizations (see the Supplementary Materials and table S2), we were able to extend our reaction protocol to include such alkynes as suitable reaction partners (**6bl** to **6bn**). Last, this multifunctionalization strategy was applicable to terminal alkynes, including both aryl and alkyl substituents at one alkyne terminal. Synthetically, being able to include terminal alkynes in our current strategy is truly valuable, which makes it possible to prepare highly hindered quaternary aldehydes, which are difficult to synthesize yet highly important synthetic building blocks. In all the examples examined, optically enriched aldehydes with an adjacent

quaternary stereogenic center were obtained in good yields and with high enantioselectivities (**6bo** to **6bx**). When dialkyl alkynes or alkyl terminal alkynes were used in the reaction, diarylmethanes containing a quaternary carbon center and a ketone/aldehyde function were derivatized. Notably, diarylmethanes are useful structural motifs and a common pharmacophore present in a range of drugs, their synthesis therefore has attracted good attention from synthetic chemists (*43*–*46*). Our strategy herein offers a straightforward efficient synthetic route to access these important scaffolds.

Conceptually, our methodology should be applicable to other nucleophilic partners, we therefore carried out preliminary studies to evaluate suitability of a number of nucleophiles in our reaction (Fig. 4). Naphthol, pyrrole, phenol, and aniline were all found to be suitable, and the desired products were formed in good yields. For an asymmetric variant of the above reactions, extensive screening of different catalytic systems/catalysts is required. Through quick investigation (see tables S4 to S6), we were able to obtain alkyne-functionalized products through reactions with 1-naphthol, 2-methylpyrrole, and 3-methoxyphenol in good to excellent enantioselectivities, although the employment of 4-bromoaniline as a nucleophile only led to the formation of a product with low ee value under the current CPA catalytic system (see the Supplementary Materials and table S7). However, when 2-phenylethan-1-ol or diphenylphosphine oxide was used as a nucleophile, no desired product was observed. Whereas the above investigation of suitable nucleophiles is not comprehensive, these preliminary proof-of-concept studies suggest great synthetic potentials of the methodology documented herein.

To demonstrate the practicability of our method, a scale-up experiment was performed in the presence of 1 mol % CPA catalyst, and triaryl aldehyde (**6bs**) was obtained in gram quantity (83% yield) with 92% ee (Fig. 5A). Furthermore, our one-pot protocol was applied to the late-stage functionalization of complex natural products and drugs, including (+)-borneol, (−)-menthol, sulbactam (antibiotic drug), and (+)-δ-tocopherol, and all the reactions proceeded in good yields, with perfect regio- and diastereoselectivities (Fig. 5B). These modified complex molecules may potentially have enhanced biological activities over the original molecules. This reported one-pot asymmetric multifunctionalization of alkynes furnishes triaryl chiral scaffolds containing a quaternary stereogenic center, which are important structural motifs. Aldehydes **6bo** and **6bs** were elaborated synthetically to complete the synthesis of both diarylmethane- and triarylmethane-type steroid hormone nuclear (SHN) receptor modulators I and II, which serve as key candidates in the development of the drugs for physiological disorders, especially for congestive heart diseases (*42*). Our synthetic manipulations featured similar strategies of using modified Caglioti reaction for deoxygenation of aldehyde (*47*) and rhodium-catalyzed C-H activation (*48*) as crucial steps (Fig. 5C).

DISCUSSION

Whereas alkynes are a class of the most important feedstocks in chemical industry, their utilizations as starting materials in asymmetric catalysis and synthesis remained largely unexplored. In particular, asymmetric multifunctionalization of alkynes is an area that needs to be attended urgently, as it holds great promise in synthetic chemistry. We have established highly enantioselective multifunctionalization of alkynes in this report, by merging photochemistry and organocatalysis, to achieve activations of carbon-carbon triple bonds and excellent stereochemical controls via cooperative catalytic strategy. The reported protocol features a one-pot, three-component, and fully atom-economical enantioselective construction of challenging triarylmethane and diarylmethane structural motifs bearing a quaternary stereogenic center. The combination of photoinduced [2+2] cycloaddition between benzoquinone-derived biradical and alkynes and remote asymmetric 1,6-addition via CPA catalysis are the key steps in the whole reaction sequence. In a broader context, we hope that our findings disclosed herein will lead to subsequent intensive efforts toward asymmetric multifunctionalization of alkynes, offering more practical synthetic solutions to convert these simple, abundant, and readily available feedstocks to a good range of value-added chiral molecular architectures.

MATERIALS AND METHODS

All starting materials were obtained from commercial suppliers (Sigma-Aldrich and Tokyo Chemical Industry) and directly used without further purification unless otherwise stated. All reactions

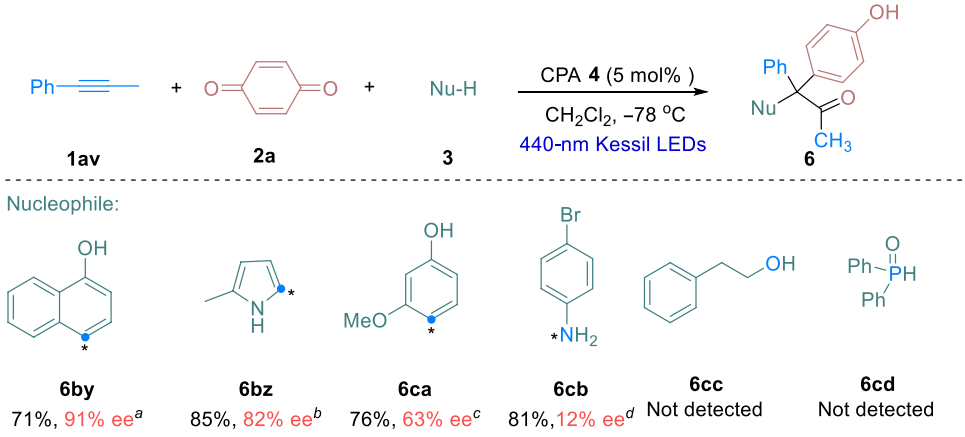

Fig. 4. Evaluation of other nucleophiles. Reaction conditions: **1av** (0.2 mmol), **2a** (0.1 mmol), **3** (0.1 mmol), **4** (5 mol %), CH_2Cl_2 (3 ml), 440 nm Kessil LEDs, and −78°C. *a*, CPA **4b** was used; *b*, CPA **4d** was used; *c*, CPA **4c** was used; *d*, CPA **4d** was used. *This atom on the nucleophile bonds to the reactant with exclusive regioselectivity.

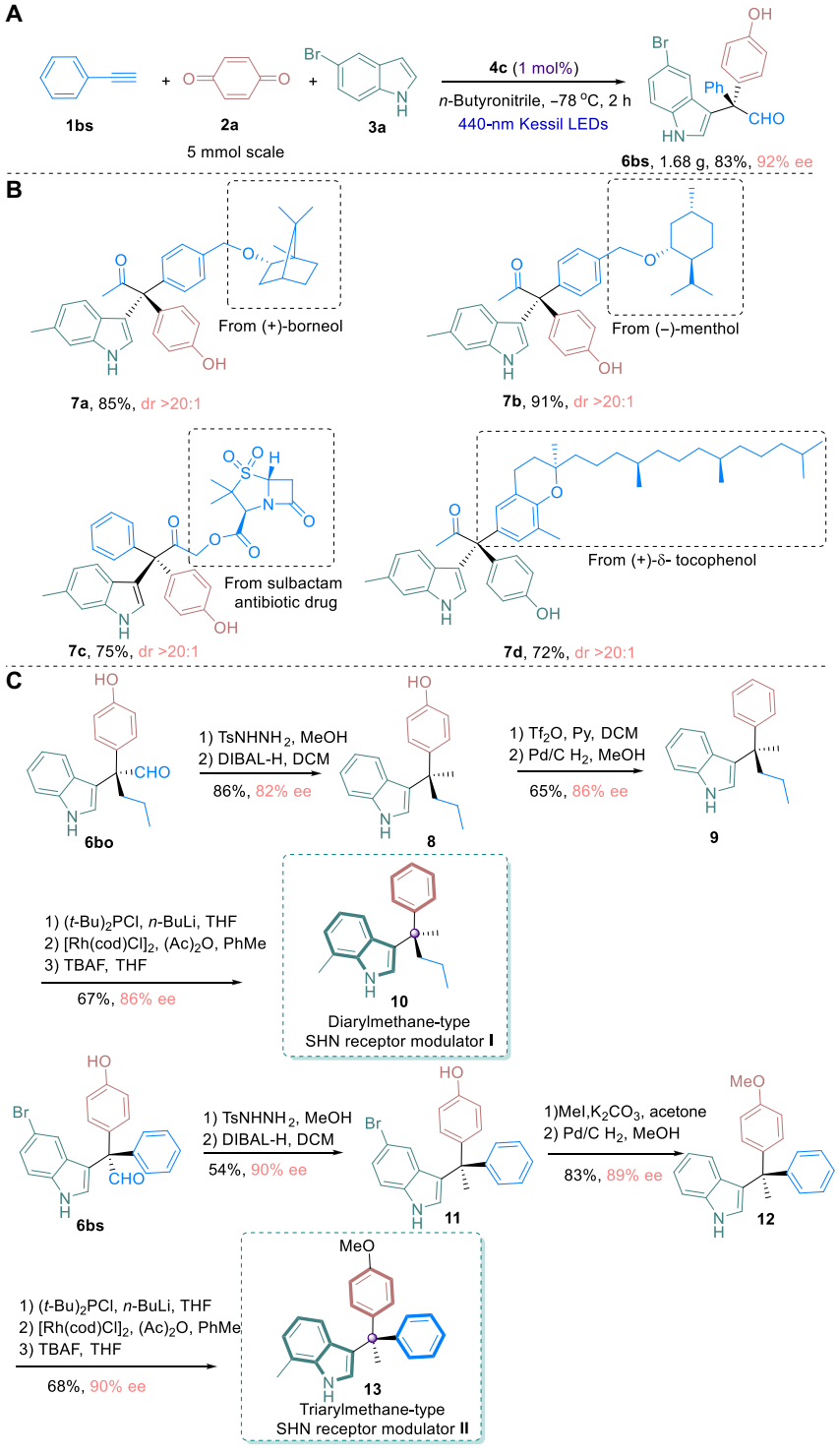

Fig. 5. Synthetic applications. (**A**) Scale-up experiment. (**B**) Late-stage functionalization of complex natural products and drugs. (**C**) Synthetic routes of steroid hormone nuclear receptor modulators. Ts, tosyl; DIBAL-H, diisobutylaluminium hydride; Tf, triflate; cod, cyclooctadiene; Ac, acetyl.

were carried out under argon atmosphere with magnetic stirring. Alkynes were synthesized according to literature procedures (*49*–*51*). All CPAs were purchased from Daicel Chiral Technologies.

Column chromatographic purification was performed on silica gel 200 to 300 mesh. The 440-nm Kessil LEDs were purchased from kessil.com. ^{1}H nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra were recorded on a Bruker AV-III400 (400 MHZ) or AMX500 (500 MHz) spectrometer. Chemical shifts were calibrated using residual solvent as an internal reference [$CDCl_3$: 7.28 parts per million (ppm) ^{1}H NMR and 77.10 ppm ^{13}C NMR]. ^{1}H NMR spectroscopy

splitting patterns were designated as singlet, doublet, triplet, and quartet. Splitting patterns that could not be interpreted or easily visualized were designated as multiplet or broad. All high-resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer; the calculated values are based on the most abundant isotope. Absorption spectra were recorded in 1-cm path quartz cuvettes using an Edinburgh FS-5 spectrofluorometer. Chiral high-performance liquid chromatography analyses were performed on an Agilent 1100 Series using a Daicel CHIRALPAK column (IA, IC, IF, IG, and AD to AH) with hexanes/*i*-PrOH as the eluent (*52*).

General procedure for the asymmetric multifunctionalization of alkynes

Alkyne **1** (0.2 mmol), benzoquinone **2a** (0.1 mmol; 10.8 mg), indole (0.1 mmol); CPA **4a**, **4b**, **4c**, or **4d** (5 mol %); and CH_3CN, CH_2Cl_2, or *n*-butyronitrile (3.0 ml) were added to a dried and argon-filled 5-ml screw-cap vial equipped with a magnetic stir bar. The mixture was then irradiated by 440-nm Kessil LEDs at −10°, −40°, or −78°C. The reaction mixture was concentrated under reduced pressure after 1 hour, and the residue was purified by column chromatography on silica gel to furnish the product.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at https://science.org/doi/10.1126/sciadv.add2574

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