

A modular approach to catalytic stereoselective synthesis of chiral 1,2-diols and 1,3-diols

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Optically pure 1,2-diols and 1,3-diols are the most privileged structural motifs, widely present in natural products, pharmaceuticals and chiral auxiliaries or ligands. However, their synthesis relies on the use of toxic or expensive metal catalysts or suffer from low regioselectivity. Catalytic asymmetric synthesis of optically pure 1,n-diols from bulk chemicals in a highly stereoselective and atom-economical manner remains a formidable challenge. Here, we disclose a versatile and modular method for the synthesis of enantioenriched 1,2-diols and 1,3-diols from the high-production-volume chemicals ethane-1,2-diol (MEG) and 1,3-propanediol (PDO), respectively. The key to success is to temporarily mask the diol group as an acetonide, which imparts selectivity to the key step of C(sp³)-H functionalization. Additionally, 1,n-diols containing two stereogenic centers are also prepared through diastereoselective C(sp³)-H functionalization. The late-stage functionalization of biological active compounds and the expedient synthesis of chiral ligands and pharmaceutically relevant molecules further highlight the synthetic potential of this protocol.

Optically pure 1,2-diols and 1,3-diols are exceptionally valuable as important and versatile building blocks in the pharmaceutical industry¹. They are key intermediates in the synthesis of various pharmaceuticals, such as dapoxetine, ezetimibe, atomoxetine, etc.^{2–4}. Moreover, optically pure diols are often serving as chiral auxiliaries and ligands for many asymmetric transformations^{5,6}, further highlighting their potential and making them among the most sought-after motifs in asymmetric synthesis (Fig. 1A). To date, the production of optically pure 1,n-diols is mainly through oxidation of alkenes^{7–12}, hydrolysis of epoxides^{13–18}, pinacol coupling^{19,20}, Aldol reaction^{21,22}, reduction of carbonyl compounds^{23–25}, Aldol-Tishchenko reaction²⁶, hydrogen autotransfer^{27–29}, and so on^{30–33} (Fig. 1B). Despite numerous milestones, these approaches often require the use of toxic or expensive metal catalysts or stereochemically pure olefins to achieve high selectivity or suffer from low regioselectivity. In stark contrast, methods capable of obtaining optically pure 1,n-diols from cheap and easily available bulk industrial feedstocks in a highly selective and

atom-economical manner are rarely known and still pose significant challenges.

The direct and enantioselective functionalization of C(sp³)-H bonds represents a transformative synthetic strategy as it allows efficient assembly of high value-added chiral molecules from readily available, inexpensive hydrocarbon feedstocks while minimizing waste generation^{34–39}. In recent years, the expedient combination of photocatalysis and transition-metal catalysis, particularly dual photocatalysis and transition-metal catalysis, has become a powerful means for C(sp³)-H functionalization^{40–50}. The HAT photocatalyst utilizes the energy of photons to trigger homolytic cleavage of the C(sp³)-H bonds^{51–53} without the need for pre-installed directing groups like traditional C-H activation reactions⁵⁴. Taking advantage of nickel's unique ability in alkyl radical coupling, the generated C-centered radicals can participate in a variety of nickel-catalyzed C-C bond-forming reactions^{55,56}. Since the pioneering work of Molander⁵⁷, MacMillan⁵⁸, Doyle⁵⁸ et al.⁵⁹, extensive efforts have been devoted to the

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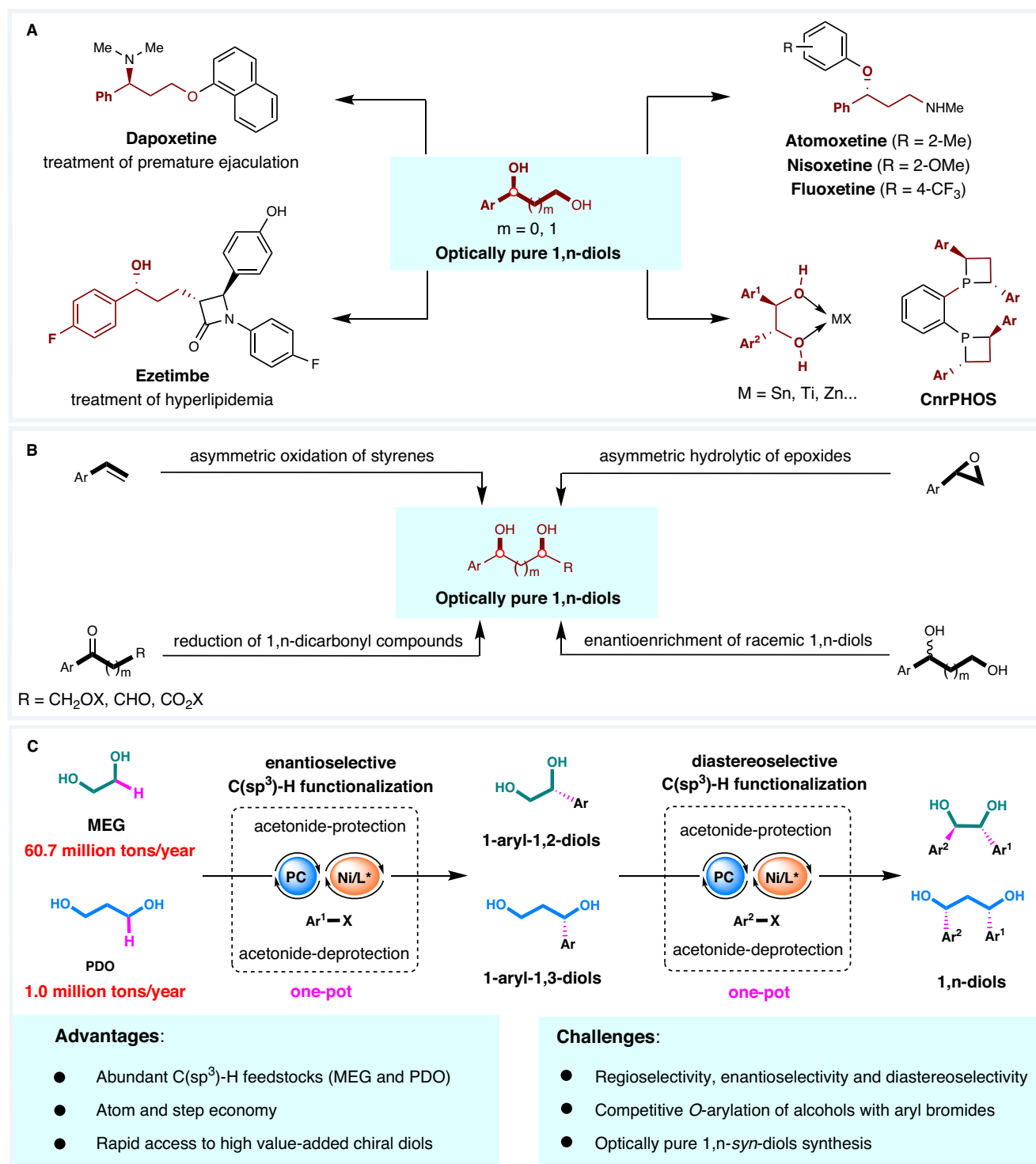


Fig. 1 | The significance of optically pure 1,*n*-diols and the state of the art in their synthesis. **A** Relevant drugs and chiral ligands synthesized from optically pure 1,*n*-diols. **B** Representative methods for the preparation of optically pure 1,*n*-diols. These protocols generally require the use of toxic or expensive metal catalysts. Methods capable of obtaining optically pure 1,*n*-diols from bulk chemicals

with high stereoselectivity and atom economy are rarely known and still face significant challenges. **C** Working hypothesis: one-pot modular construction of chiral 1,*n*-*syn*-diols from high-production-volume chemicals ethylene glycol and 1,3-propanediol via photo-HAT/nickel dual catalysis.

realm of photoredox/nickel dual-catalyzed C(sp³)-H functionalization. However, enantioselective variants remain largely underexplored^{60–67}.

Ethylene glycol (MEG, annual production of 60.7 million tons) and 1,3-propanediol (PDO, annual production of 1.0 million tons) are both high-production-volume chemicals^{68,69}. The pharmaceutical interest¹² in optically pure 1,2-diols and 1,3-diols prompted us to consider a

different strategy for the preparation of 1,*n*-diols: one that makes use of photo-HAT/nickel dual-catalyzed enantioselective C(sp³)-H functionalization of MEG and PDO (Fig. 1C). To achieve this appealing transformation, a series of challenging issues need to be addressed. First, Ni-catalyzed *O*-arylation of alcohols with aryl bromides has been extensively studied^{70,71}, and this reaction is highly competitive with the

desired C(sp³)-H arylation, leading to chemoselectivity issues. In addition, controlling the enantioselective of C(sp³)-H arylation as well as the diastereoselective of 1, n-diols containing two stereogenic centers are challenges.

We envisioned a strategy to achieve selective C(sp³)-H functionalization of MEG and PDO by temporarily masking diol groups with easily introduced and removed protecting groups, which not only avoids the undesired C-O cross-coupling of alcohol and aryl halides, but also confers selectivity for the critical step of C(sp³)-H functionalization. Herein, we successfully executed this ideal by combining a decatungstate HAT photocatalyst with a chiral nickel catalyst while masking the diol as an acetonide that can be easily introduced and removed. This protocol provides a practical platform for the one-pot construction of enantiomerically enriched 1,2-diols and 1,3-diols from high-production-volume chemicals ethylene glycol and 1,3-propanediol, respectively. In addition, an efficient method to obtain 1, n-diols containing two stereogenic centers through diastereoselective C(sp³)-H arylation was also established. The utility of this method is further demonstrated in the late-stage functionalization of natural products and the synthesis of chiral ligands and many drug-relevant molecules (Fig. 1C).

Results

Reaction development

Initially, we aimed at the direct and enantioselective α -arylation of 1,2-diols. It is textbook knowledge that alcohols generally act as oxygen-centered nucleophiles through their lone electron pairs, whereas there are very few reports using unactivated alkyl alcohols as carbon-centered nucleophiles. MacMillan's group developed direct α -functionalization of alcohols using zinc-mediated deprotonation of alcohol or using tetra-*n*-butylammonium phosphate as a hydrogen-binding catalyst to weaken α -hydroxy C-H bonds^{72,73}. Inspired by these works, we tested these strategies to achieve direct α -arylation of unprotected ethylene glycol (MEG), however, the expected products were not obtained in the presence of chiral ligands.

We envisioned introducing appropriate protecting groups to achieve enantioselective α -arylation of 1,2-diols, but this is not trivial. Because the protecting groups, in addition to serving as a functional handle for enantioselectivity control, should also be easily removed to recover the chiral diols. Using a synergistic catalytic system consisting of a chiral PHOX-nickel catalyst and a triplet excited ketone PC photocatalyst⁶⁷, we examined a series of diol-protecting groups (Table 1). Protection of MEG with benzoyl (**1a**) or silyl (**1b**) did not give the desired product. Considering the ease of introduction and removal of acetonides, we protected MEG into the corresponding cyclic acetal **1c**. However, **3ca** was obtained with a yield of 45%, while the ee value was only 60%. We further screened a variety of cyclic acetals (**1d-1f**) and borate ester (**1g**), but unfortunately no superior results were obtained. These results indicate that protective groups on the oxacycles have a significant impact on enantioselectivity control of this transformation.

To further improve the efficiency and enantioselectivity of this reaction, a series of chiral ligands were then screened (entries 2-6, more details see supplementary Table S1). The bis(oxazoline) ligand **L6** was found to be the most effective in terms of enantioselectivity (80% ee, entry 6). To our delight, higher efficiency and enantioselectivity were obtained using acetone as solvent and inexpensive TBADT (tetra-*n*-butylammonium decatungstate) as photocatalyst (85% ee, entry 7). The acetone/PhCF₃ dual-solvent system was crucial for the success of this transformation, as the enantioselectivity of **3ca** was increased to 90% (entry 8). Finally, we found that increasing the reaction concentration afforded the desired product **3ca** in 71% yield with 90% ee (entry 9). As expected, control experiments confirmed that the nickel catalyst, light, and photocatalyst were indispensable for a successful outcome.

Substrate scope

With the optimal conditions in hand, the generality of this transformation was investigated next (Fig. 2). Aryl bromides bearing a wide range of functional groups, such as ketone (**3ca**), cyano (**3cb**), trifluoromethyl (**3cc**), ester (**3cd** and **3cq**), fluorine (**3ce**), sulfone (**3cg**), trifluoromethoxy (**3ci**), and ether (**3cj**), were perfectly tolerated, providing the corresponding arylated 1,2-diols in good yields with excellent enantioselectivities. Electron-deficient aryl bromides generally exhibited improved efficacy compared to electron-rich aryl bromides. The absolute configuration of **3cg** was determined to be *R* by X-ray single crystal diffraction analysis, and the absolute configurations of all other products were assigned accordingly. Notably, aryl chloride (**3cf** and **3cl**) and aryl boronic ester (**3ch**) were found to be accommodated, opening additional avenues for subsequent synthetic manipulations of the resulting products. The increase in steric hindrance did not significantly affect the reactivity and enantioselectivity, as *meta*- and *ortho*-substituted aryl bromides (**3cl-3cn**) as well as 3,5- and 3,4-disubstituted aryl bromides (**3co-3cp**) were compatible with established methods. 2-Naphthyl bromide is also a competent coupling partner (**3cr**). Heteroaryl bromides containing dibenzofuran (**3cs**), dibenzothiophene (**3ct**), benzothiophene (**3cu**), and pyridines (**3cv** and **3cw**) could be successfully incorporated into the target 1,2-diols. Notably, aryl bromides derived from complex biologically important molecules such as sertraline (**3cy**), cholesterol (**3cz**), (-)-menthol (**3caa**), and estrone (**3cab**) were well tolerated, thus highlighting the potential of this approach for late-stage functionalization of pharmaceutical agents. Moreover, this asymmetric photochemical C(sp³)-H functionalization is not limited to aryl bromides. Alkenyl bromide such as 3-bromocyclohex-2-en-1-one was coupled with **1c** to provide the corresponding optically active 1,2-diol **3cac** with excellent enantioselectivity. Further reduction of the double bond by Pd-C afforded the product **3cad** bearing two stereogenic centers in 88% yield with a diastereoselectivity greater than 95:5. This protocol provides an alternative strategy to address challenging enantioselective and diastereoselective C(sp³)-C(sp³) cross-couplings.

We are pleased to find that our protocol can be further extended for the enantioselective α -arylation of 1,3-diols (Fig. 3). Functional groups such as ketone (**5aa**), trifluoromethyl (**5ac** and **5ao**), ester (**5ad** and **5aq**), chloro (**5af** and **5al**), sulfone (**5ag**), and trifluoromethoxy (**5ai**) were well tolerated, providing the corresponding 1,3-diols in moderate to good yields with excellent enantioselectivities. Heterocycles commonly found in drug molecules, such as furan (**5as**), thiophene (**5at** and **5au**), and pyridine (**5av**), could be successfully embedded into the target 1,3-diols. Furthermore, many complex bioactive molecules such as cholesterol (**5az**), menthol (**5aaa**), and estrone (**5aab**) were successfully converted into the corresponding 1,3-diols, demonstrating the robustness of this asymmetric C(sp³)-H arylation reaction for late-state functionalization of drug molecules and natural products. Enantioselective α -alkenylation of 1,3-diol is also feasible (**5aac**), and further reduction can yield enantiomerically enriched α -alkylated 1,3-diol (**5aad**), which has extremely high synthetic value. Unfortunately, further attempts to extend the enantioselective α -arylation of 1,4-diol (**6a**) were unsuccessful, resulting in the formation of a mixture of regioisomers and reduced enantioselectivity and yields (**7aa**). This result suggests that ring conformation has a greater influence on the reaction outcome, probably because the seven-membered ring has greater strain than the five- and six-membered rings due to transannular crowding.

Given that many methods are available for the enantioselective synthesis of monosubstituted 1, n-diols⁷⁻³², it would be highly desirable to directly edit and convert them into 1, n-diols containing two stereogenic centers. We hypothesized that TBADT could further abstract the α -hydrogen atom of 1, n-diols to generate the corresponding α -oxy carbon-centered radical, which could be further engaged in Ni-catalyzed cross-couplings with aryl bromides. Inspired by earlier

Table 1 | Optimization of reaction conditions

masked 1,2-diols

O-arylation: $\text{HO-CH(OAr)-CH}_2\text{-OH} \rightarrow \text{HO-CH(OH)-CH}_2\text{-OH}$

C-H VS O-H activation

$\text{HO-CH(OH)-CH}_2\text{-OH} \xrightarrow{\text{NIBr}_2(\text{DME}) (10 \text{ mol}\%), \text{chiral ligand L}^* (15 \text{ mol}\%), \text{photocatalyst, K}_3\text{PO}_4, \text{solvent, 10 W LEDs, 25 }^\circ\text{C}}$ **3**

Screening masked 1,2-diols^a

(1a) NP, (1b) NP, (1c) **3ca**, 45% y, 60% ee, (1d) **3da**, 44% y, 58% ee, (1e) **3ea**, 25% y, 45% ee, (1f) **3fa**, 36% y, 8% ee, (1g) NP

Photocatalyst

PC, L1, L2, L3, L4, L5, L6, TBADT (2 mol%), TBADT (5 mol%)

Ligand

L1, L2, L3, L4, L5, L6

Solvent

EtOAc, EtOAc, EtOAc, EtOAc, EtOAc, EtOAc, Acetone, Acetone:PhCF₃ = 1:1, Acetone:PhCF₃ = 1:1

Yield of 3ca (%)

30, 24, 10, 42, 11, 43, 47, 71

ee of 3ca (%)

60, 45, 36, 30, 35, 80, 85, 90

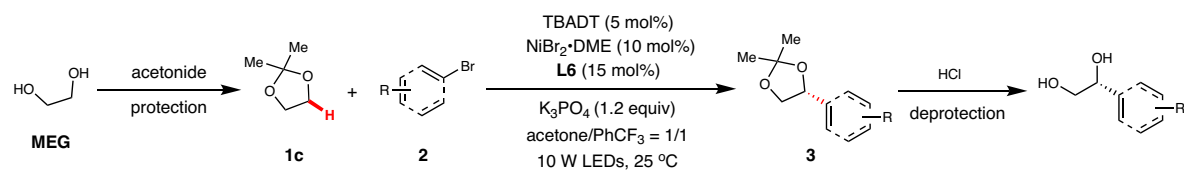
All reactions were carried out on a 0.2 mmol scale with respect to aryl bromide (**2a**). Conditions: NIBr₂·DME (10 mol%), chiral ligand **L** (15 mol%), **2a** (0.2 mmol), photocatalyst, solvent (2.0 mL, 0.1 M) under the irradiation of LEDs (10 W, 390 nm) at 25 °C for 60 h. Yields are for isolated and purified products. The ee values were determined by HPLC using a chiral stationary phase.

^aNP no product.

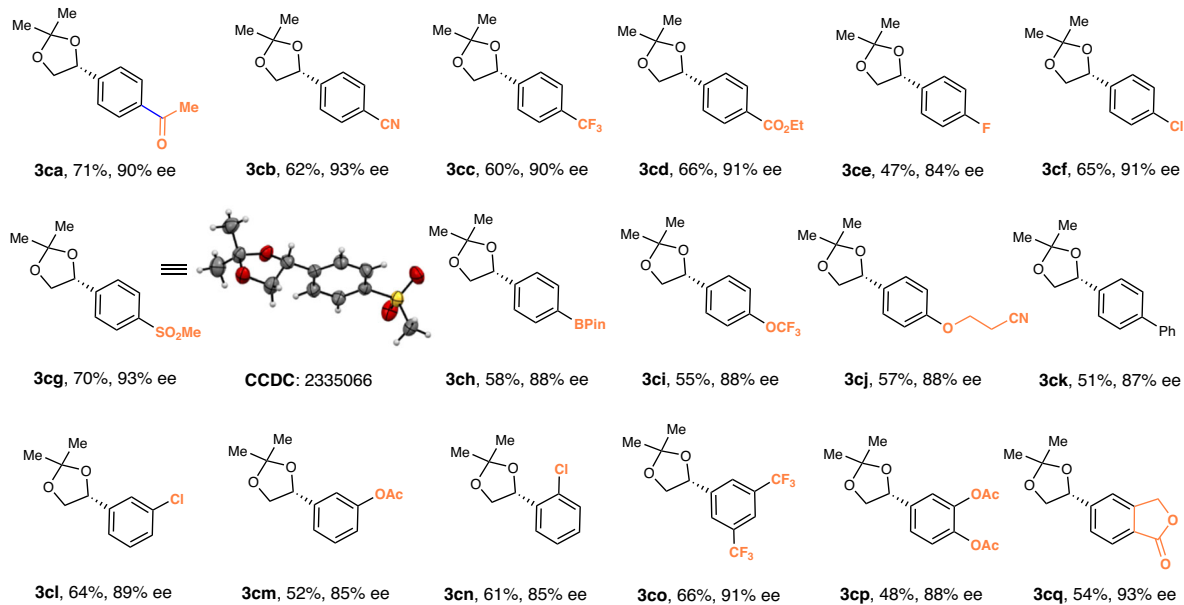
^bThe reaction was performed in EtOAc at 25 °C using **PC** as photocatalyst and **L1** as ligand.

^cThe reaction was performed at -5 °C.

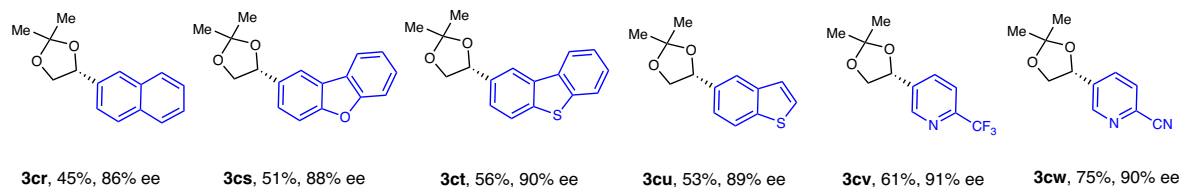
^dAcetone/PhCF₃ (1.0 mL, 0.2 M).



Aryl Bromides



Heteroaryl Bromides



Aryl Bromides Derived from Complex Molecules

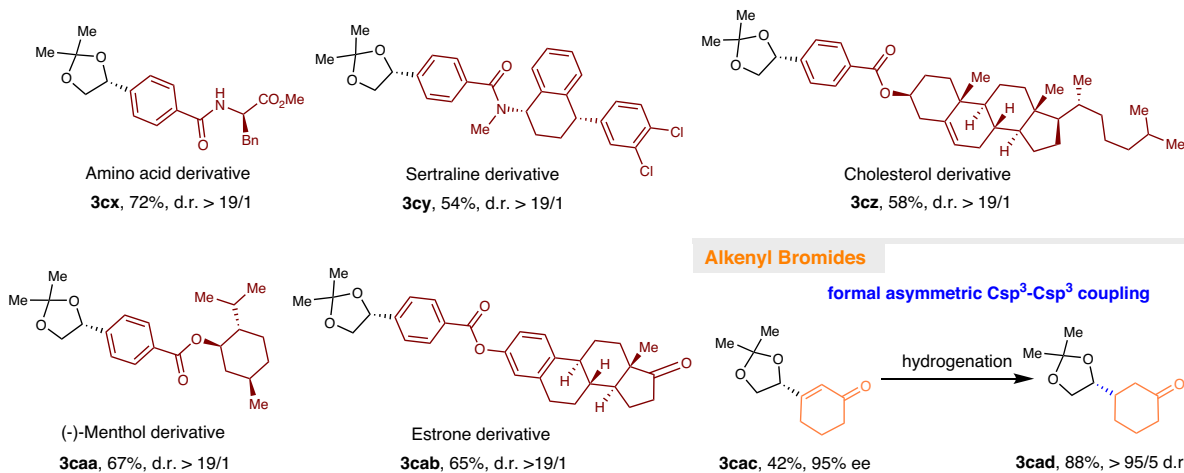
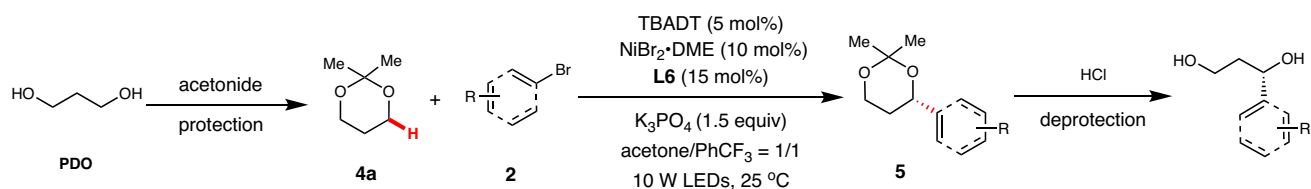
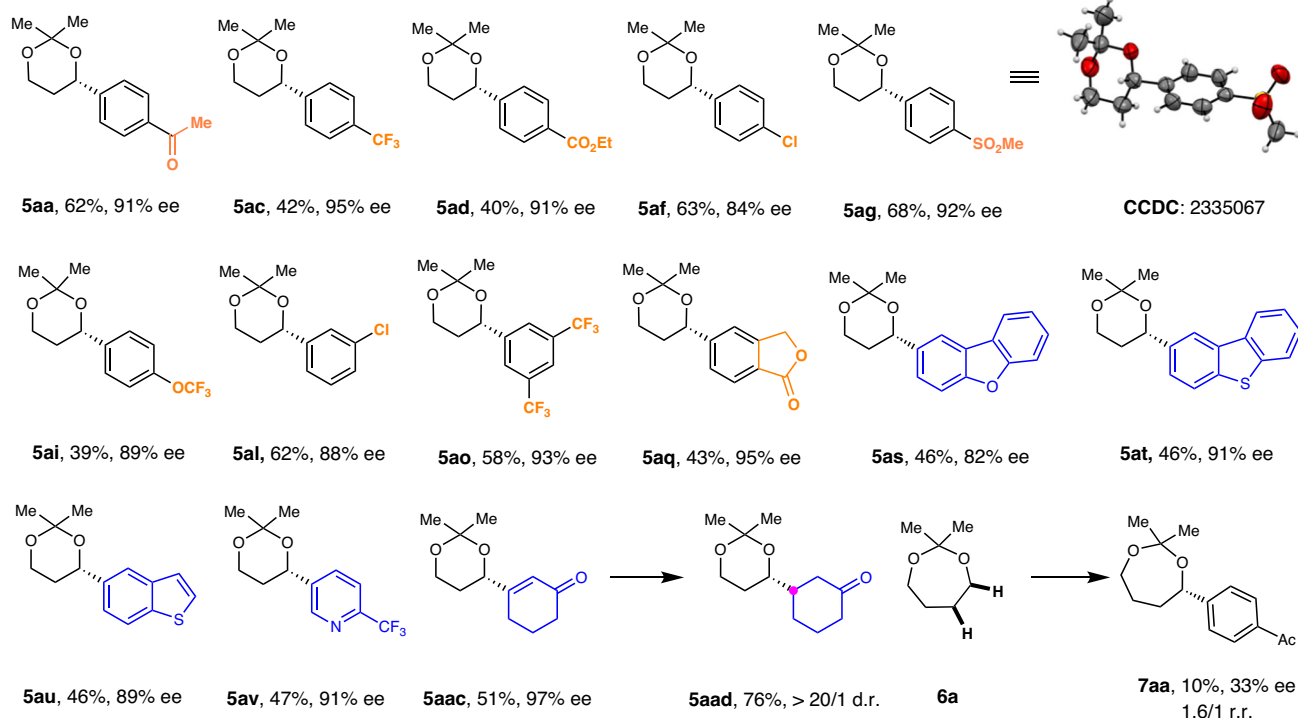


Fig. 2 | Enantioselective synthesis of 1,2-diols. Reaction conditions: **2** (0.2 mmol), **1c** (1.0 mmol), NiBr₂·DME (10 mol%), **L6** (15 mol%), TBADT (5 mol%), K₃PO₄ (0.24 mmol) in acetone (0.5 mL) and PhCF₃ (0.5 mL) under the irradiation of LEDs

(10 W, 390 nm) at 25 °C for 60 h. Yields are for isolated and purified products. The ee values were determined by HPLC using a chiral stationary phase and d.r. ratios were determined by ¹H NMR analysis.



Aryl Bromides



Aryl Bromides Derived from Complex Molecules

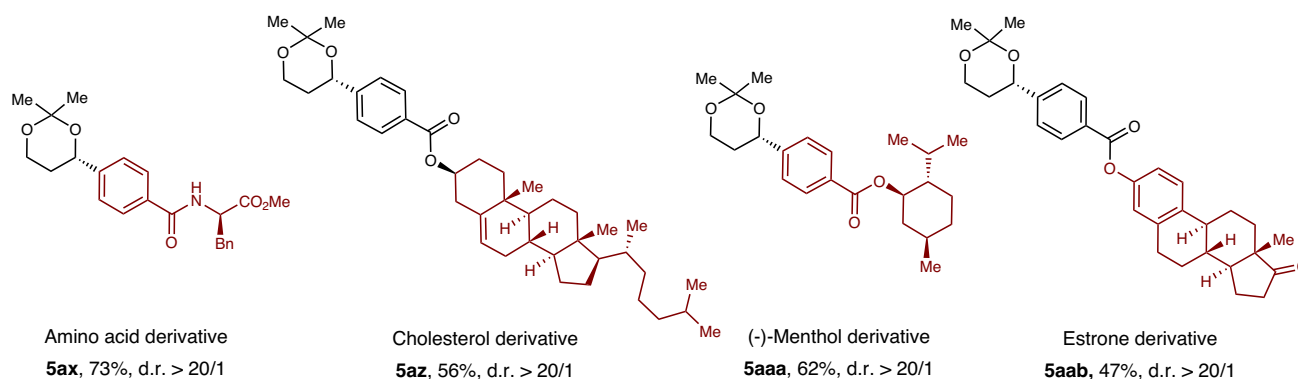


Fig. 3 | Enantioselective synthesis of 1,3-diols. Reaction conditions: **2** (0.2 mmol), **4a** (2.0 mmol), NiBr₂·DME (10 mol%), **L6** (15 mol%), TBADT (5 mol%), K₃PO₄ (0.30 mmol) in acetone (0.5 mL) and PhCF₃ (0.5 mL) under the irradiation of LEDs

(10 W, 390 nm) at 25 °C for 60 h. Yields are for isolated and purified products. The ee values were determined by HPLC using a chiral stationary phase and d.r. ratios were determined by ¹H NMR analysis.

studies that the addition of β-substituted cyclopentyl radicals to alkenes produces predominantly *anti*-addition products^{74–77}, we anticipated that arylation of 1,2-diols should also be highly diastereoselective, since the interaction of SOMO with adjacent oxygen lone pair orbital stabilizes the ring conformation of radical **I**, and the steric hindrance effect of the adjacent substituent (*R*) makes the catalyst complex to approach only from the opposite direction (Fig. 4C). As expected, C(sp³)-H arylation of **3ca** with **2g** in the presence of achiral ligand dtbbpy (**L7**) gave the 1,2-diaryl-1,2-*syn*-diol **9a** with two adjacent

stereocenters in 83% yield with greater than 20/1 diastereoselectivity (Fig. 4A).

In contrast, C(sp³)-H arylation of **5aa** with **2g** under identical conditions led to successful coupling and reversed the diastereoselectivity of the reaction to deliver 1,3-diaryl-1,3-*syn*-diol **10a** as the major product (Fig. 4B). Nevertheless, the diastereoselectivity of the product **10a** bearing 1,3-nonadjacent stereocenters was not ideal (d.r. = 2/1), which reinforces the notion that the 1,3-diastereoselective induction would be far from trivial⁷⁸. We further screened a series of

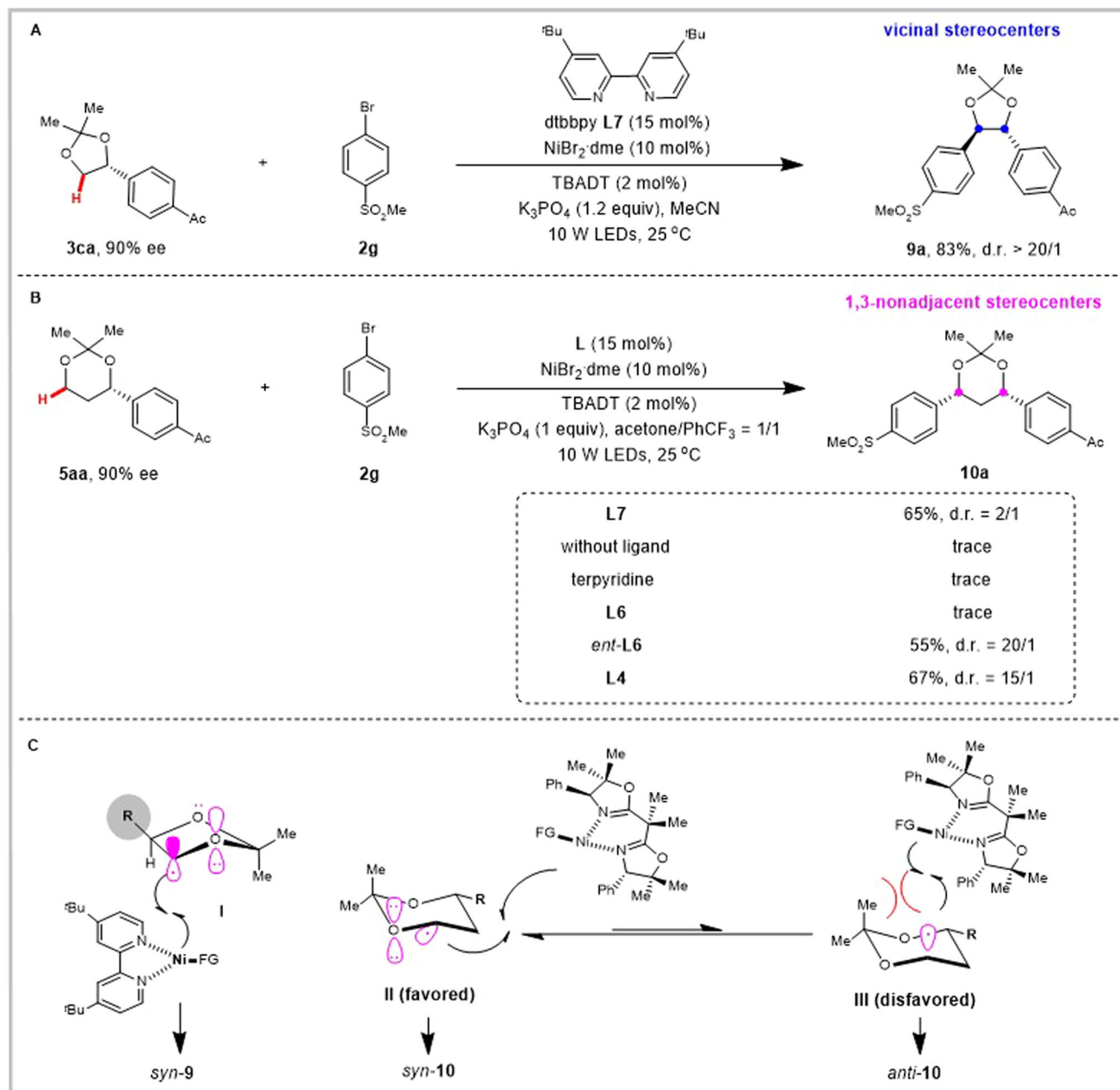
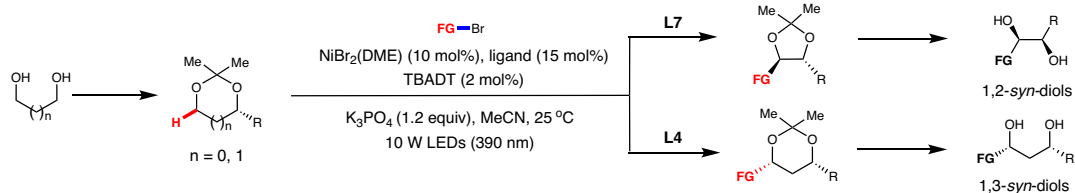


Fig. 4 | Diastereoselective synthesis of 1,2-diaryl-1,2-*syn*-diols and 1,3-diaryl-1,3-*syn*-diols. A Diastereoselective C(sp³)-H arylation of **3ca** for the synthesis of 1,2-diaryl-1,2-*syn*-diol **9a** bearing two adjacent stereogenic centers. **B** Diastereoselective

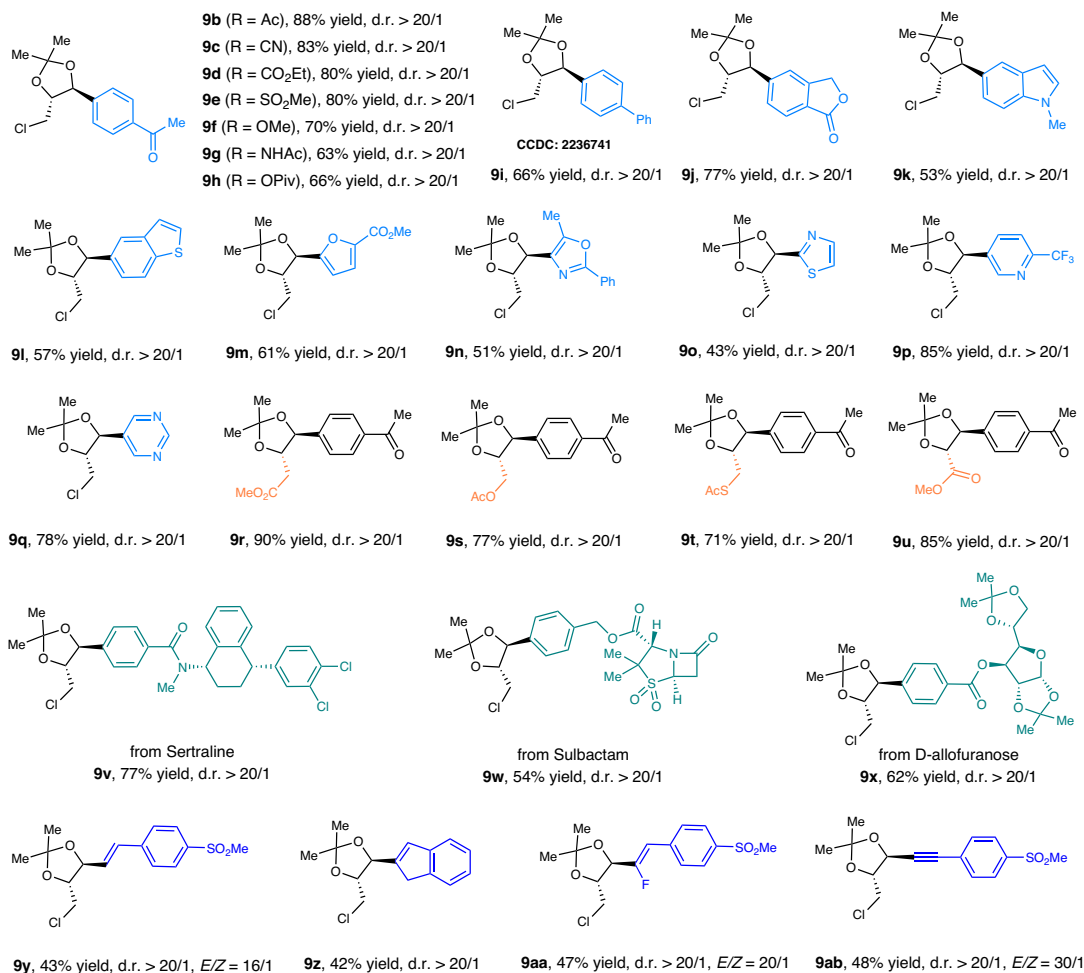
C(sp³)-H arylation of **5aa** for the synthesis of 1,3-diaryl-1,3-*syn*-diol **10a** bearing two nonadjacent stereogenic centers. **C** Proposed stereochemical models for explaining the preferred selectivity.

ligands in the hope of improving the diastereoselectivity of the product (Table S2). Using terpyridine as a ligand or in the absence of a ligand failed to obtain the target product **10a**. To our delight, when *ent*-**L6** was used as the ligand, 1,3-diaryl-1,3-*syn*-diol **10a** bearing two nonadjacent stereogenic centers was obtained in 55% yield with greater than 20/1 diastereoselectivity. In addition, when **L4** was used as the ligand, **10a** was obtained in 67% yield with 15:1 diastereoselectivity. The use of ligand **L6** resulted in low yield, suggesting that ligands are the key to regulating the stereoselectivity of the reaction (Fig. 4B). This diastereoselectivity could be explained by the subtle interplay between the steric effect of the nickel catalyst and the stereoelectronic effect of carbon radical. Due to the steric hindrance of nickel complex, we reason that equatorial substitution (radical **II**) is more favorable than axial substitution (radical **III**)⁷⁹, thereby leading to the formation of predominantly 1,3-*syn*-diols (Fig. 4C).

The generality of the diastereoselective C(sp³)-H functionalization protocol for the synthesis of 1,2-diols and 1,3-diols containing two stereogenic centers was evaluated (Fig. 5). Electron-deficient, electron-neutral, and electron-rich aryl bromides were all viable substrates, and various functional groups such as ketone, nitrile, ester, sulfone, ether, and amide were perfectly tolerated (**9a–9j**). Heteroaryl bromides such as indole, benzothiophene, pyridine, and pyrimidine could be successfully incorporated into the target products (**9k–9q**). A variety of synthetically useful functional groups, such as ester, and thioester were found to accommodate, opening additional avenues for derivatization of the resulting products (**9r–9u**). Aryl bromides derived from complex biologically important molecules, such as sertraline (**9v**), sulbactam (**9w**), and *D*-allofuran (**9x**), did not have any adverse effects on efficiency and diastereoselectivity. Remarkably, this method is not limited to aryl bromides, as alkenyl bromides, *gem*-



1,2-diols bearing vicinal stereocenters^a



1,3-diols bearing 1,3-nonadjacent stereocenters^b

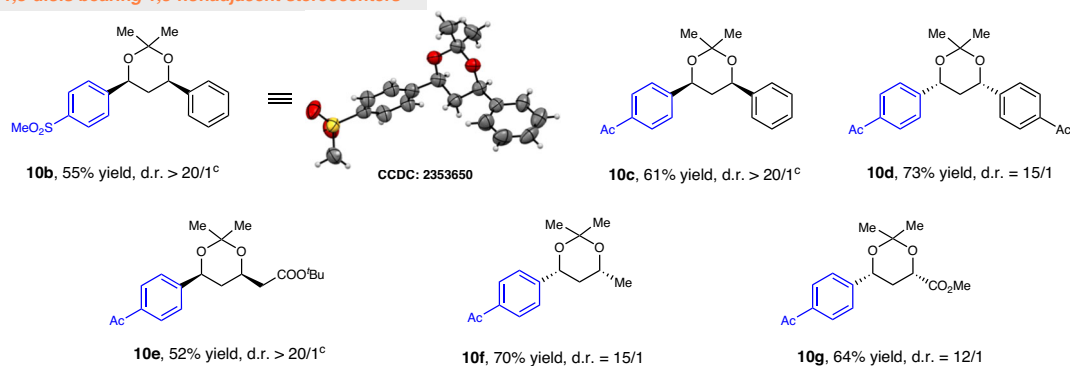


Fig. 5 | Stereoselective synthesis of 1,n-diols bearing two stereogenic centers.

^aNiBr₂DME (10 mol%), dtbbpy **L7** (15 mol%), TBADT (2 mol%), K₃PO₄ (0.24 mmol) in MeCN (1 mL) under the irradiation of LEDs (10 W, 390 nm) at 25 °C. ^bNiBr₂DME (10 mol%), **L4** (15 mol%), TBADT (5 mol%), K₃PO₄ (0.30 mmol) in acetone (0.5 mL)

and PhCF₃ (0.5 mL) under the irradiation of LEDs (10 W, 390 nm) at 25 °C. ^c**L6** was used as the ligand instead of **L4**. The diastereomeric ratios (d.r.) were determined by ¹H NMR analysis.

difluoroalkenes, and alkynyl bromides were also effective coupling partners (**9y–9z** and **9aa–9ab**). In addition, the C(sp³)–H arylation of aryl-substituted 1,3-diols afforded 1,3-diaryl-1,3-*syn*-diols **10b–10d** bearing 1,3-nonadjacent stereocenters in good yields with excellent diastereoselectivity. It is worth noting that alkyl-substituted 1,3-diols could also undergo Csp³–H arylation with high diastereoselectivity to afford the corresponding 1,3-diols **10e–10g**. To summarize, this C(sp³)–H functionalization protocol provides a convenient and practical solution for the stereoselective synthesis of various functionalized 1,2-diols and 1,3-diols.

Mechanistic studies

To gain insight into the reaction mechanism, a series of mechanistic experiments were conducted. The stoichiometric reaction of aryl-Ni(II) complex **11** with **1c** under standard conditions afforded the desired product **3ca** in 33% yield (Fig. 6A). Using 10 mol% of Ar-Ni(II) complex **11** as the catalyst, the reaction of **1c** and **2g** gave the desired product **3cg** in 45% yield (Fig. 6B). These results suggest that aryl-Ni(II) complex may be reactive species in the catalytic cycle. In addition, we synthesized σ -alkyl-Ni(II) complex **12** according to the previously reported procedure⁸⁰ and reacted with **2a** in the presence of Zn⁰ powder. The expected Csp³–Csp² coupling product **13** was isolated in 37% yield (Fig. 6C), suggesting that alkyl-Ni(I) species generated by the reduction of alkyl-Ni(II) by Zn⁰ may participate in the catalytic cycle. Moreover, the reduction potentials of TBADT and L6NiBr₂ were determined using cyclic voltammetry, which supports the feasibility of reducing Ni(II) to Ni(I) and Ni(II) to Ni(I) species by reduced TBADT, respectively. Because the reduction potential of [W₁₀O₃₂]⁵⁻/[W₁₀O₃₂]⁶⁻ ($E = -2.64$ V vs Ag/Ag⁺ in MeCN) is more negative than Ni^I/Ni⁰ ($E = -2.01$ V vs Ag/Ag⁺ in MeCN) (Fig. 6G).

We further prepared the monodeuterated substrate **3ck-D** (99% D) and reacted it with aryl bromide **2a** under standard conditions. The desired 1,2-diaryl-1,2-*syn*-diol **9ck-D** was obtained in 49% yield. Interestingly, no loss of deuterium was observed during the reaction, indicating that the HAT process is stereoselective. This may be due to the large size of TBADT, which can only abstract hydrogen atoms that are in *trans* with the aryl group (Fig. 6D). Intermolecular competitive kinetic isotopic effect (KIE) experiments were performed using **3cae** and **3cae-D2** in mixed mode (Fig. 6E) and parallel mode (Fig. 6F), providing KIE values of 2.2 and 1.1, respectively. These results indicate that the HAT process is not a rate-determining step.

On the basis of our mechanistic investigation and previous studies^{40–50}, a plausible mechanism is proposed in Fig. 6H. Excited tetrabutylammonium decatungstate **A** abstracts an α -hydrogen atom from the acetonide-protected 1,*n*-diols, generating reduced decatungstate **B** and an α -oxygen carbon-centered radical **C**. Nucleophilic addition of radical **C** to Ni(0) species **D** generates alkyl-Ni(I) species **E**, which subsequently undergoes oxidative addition to aryl bromide to form alkyl-Ni(III)-aryl species **F**. Reductive elimination of intermediate **F** delivers the optically pure 1,*n*-diols and Ni(I) species **G**, which undergoes single-electron transfer with decatungstate **H** to regenerate the reduced decatungstate **B** and active Ni(0) catalyst **D** (Fig. 6H, blue). Alternatively, Ni(I) species **E** may be generated by addition of radical **C** to Ni(I) species **G** followed by single-electron reduction of the resulting alkyl-Ni(II) intermediate **J** by decatungstate **H** (Fig. 6H, green).

An alternative mechanism involves the oxidative addition of Ni(0) species **D** to aryl bromide to afford aryl-Ni(II) intermediate **I**, which intercepts radical **C** to form alkyl-Ni(III)-aryl species **F** (Fig. 6H, red). Previous studies via DFT calculations found that aryl-Ni(II) is thermodynamically easier to reduce than Ni(I) to Ni(0), suggesting that the reaction process may not involve aryl-Ni(II) species⁸¹. Nevertheless, given that the stoichiometric reaction supports the intermediacy of aryl-Ni(II), we cannot rule out this possibility.

Synthetic applications

To demonstrate the utility of our developed catalytic regime, we developed a one-pot enantioselective approach to directly convert ethylene glycol and 1,3-propanediol to the corresponding optically pure 1,2-diols and 1,3-diols via acetonide-protection, C(sp³)–H arylation, and subsequent deprotection (Fig. 7A). Furthermore, a one-pot diastereoselective protocol was also established to transform diols into 1,2-diols with two adjacent stereocenters (Fig. 7B). Photo reactors cannot be scaled up by the conventional strategy of enlarging the dimensions due to the light attenuation effect. However, this C(sp³)–H arylation reaction can be scaled up and achieve the gram-scale preparation of optically pure 1,2-diol **3co** and 1,3-diol **5aa** without reducing yield and enantioselectivity (Fig. 7C).

The product, **3cp**, was easily converted into Epinephrine in three steps with a yield of 64%, which can be used to treat a variety of conditions including anaphylaxis, cardiac arrest, and asthma (Fig. 7D). The product **3cn** was readily transferred into the anticonvulsant drug (*R*)-Carisbamate in three steps via hydrolysis and carbamation (Fig. 7E). Additionally, the lead prodrug (Pradefovir) for the treatment of hepatitis B could be synthesized from **5al** by a known procedure (Fig. 7F)⁸². Solabegron, a drug which acts as a selective agonist for the β_3 adrenergic receptor⁸³, could be synthesized from **3cl** (Fig. 7G). Hydrolysis of product **3co** followed by selective activation of the primary alcohol as a mesylate and displacement with ethanolamine afforded the amine **20**. Following a reported procedure⁸⁴, amine **20** can be used to synthesize aprepitant, a drug used to prevent chemotherapy-induced nausea and vomiting (Fig. 7H).

Threo-3-chloro-1-(4-hydroxy-3-methoxyphenyl)propane-1,2-diol **22**, a nature phenylpropanoid with antioxidant activity, was synthesized via one-pot C(sp³)–H arylation of (*R*)- α -chlorohydrin followed by hydrolysis to remove the protecting groups, which is much more concise than the known process⁸⁵ (Fig. 7I). PydiPhos ligand **24** exhibits excellent regioselectivity in olefin hydroformylation, but its synthesis requires ten steps starting from *L*-tartaric acid⁸⁶. Strikingly, using our protocol, PydiPhos **24** was synthesized from commercially available and inexpensive (*R*)- α -chlorohydrin in only two steps (Fig. 7I). The phthalimide-protecting group of **25** was removed with hydrazine to obtain aminodiol **26**, which is an advanced intermediate for the synthesis of (*S,S*)-(+)-Reboxetine, a marketed drug for the treatment of major depressive disorder (Fig. 7J)⁸⁷. Moreover, the product **28** obtained by the stereoselective arylation of amino acid derivative **27** was easily converted into **29**, which is a common intermediate for the synthesis of natural products bursatellin and preoxazin (Fig. 7K)⁸⁸. To summarize, the C(sp³)–H functionalization protocol provides a convenient avenue to access chiral ligands and biologically active natural products.

Methods

General procedure for the synthesis of 1-aryl-1,2-diols

An oven-dried 10-mL vial equipped with a PTFE-coated stir bar was charged with NiBr₂(dme) (6.1 mg, 0.02 mmol, 10 mol%), **L6** (11.7 mg, 0.03 mmol, 15 mol%) and anhydrous acetone (0.5 mL). This reaction mixture was stirred at room temperature for 1 h in an argon-filled glovebox. TBADT (33.5 mg, 0.02 mmol, 5 mol%), aryl or alkenyl bromide **2** (0.2 mmol, 1 equiv), 2,2-dimethyl-1,3-dioxolane **1c** (102.1 mg, 1.0 mmol, 5 equiv), K₃PO₄ (50.9 mg, 0.24 mmol, 1.2 equiv) and PhCF₃ (0.5 mL) was then added. The reaction mixture was stirred and irradiated with a 10 W 390 nm LED lamp at 25 °C for 60 h. The resulting mixture was removed from light, diluted with ethyl acetate, and passed through a pad of celite. The celite plug was further washed with ethyl acetate. The combined solvent was then evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the corresponding products.

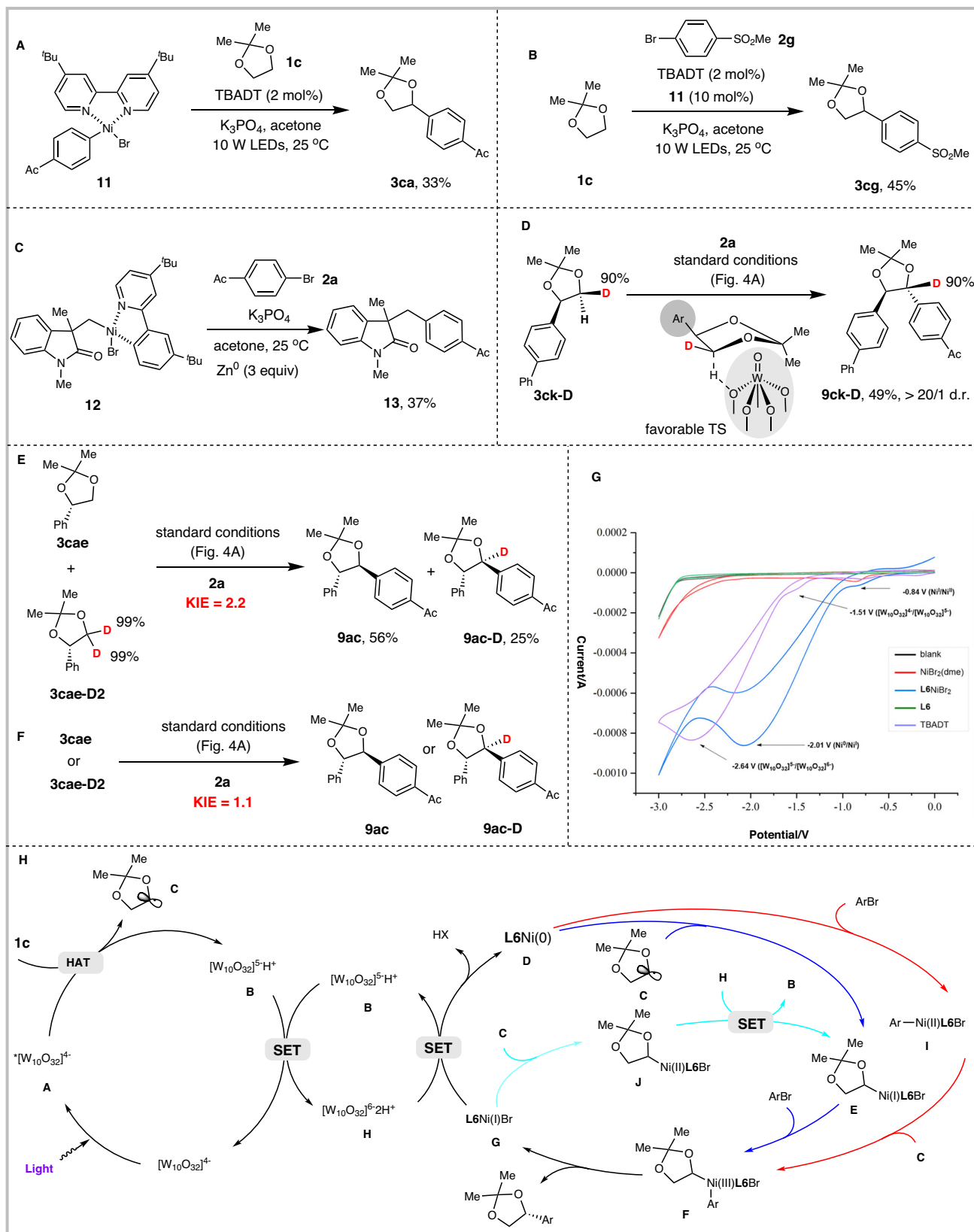


Fig. 6 | Mechanistic studies and proposed mechanism. **A** Stoichiometric reaction with Ar-Ni(II)Br complex. **B** Catalytic reaction with Ar-Ni(II)Br complex. **C** Stoichiometric reaction with alkyl-Ni(II)Br complex. **D** Intramolecular competition experiment of **3ck-D**. **E** Intermolecular competition KIE experiment. **F** Side-by-side KIE experiments. **G** Determining the reduction potentials of TBADT and L6NiBr₂ by cyclic voltammetry. **H** Proposed mechanism.

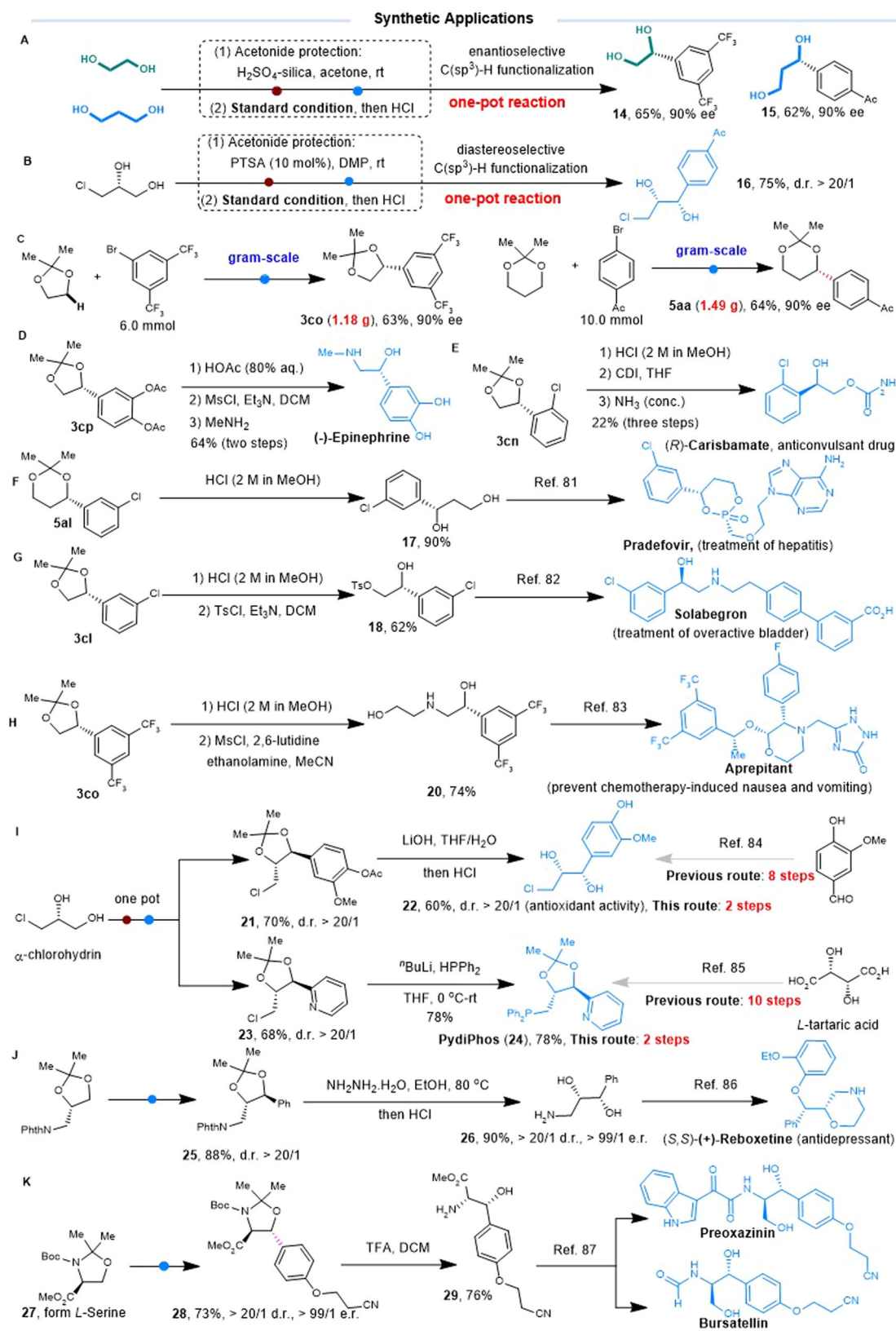


Fig. 7 | Applications in the synthesis of chiral ligands and natural products.

A One-pot enantioselective synthesis of optically pure 1,2-diol from ethylene glycol and 1,3-propanediol. **B** One-pot diastereoselective synthesis of 1,2-diol bearing two stereogenic centers. **C** Gram-scale preparation of optically pure 1,2-diol **3co** and 1,3-diol **5aa**. **D** Asymmetric synthesis of (-)-Epinephrine. **E** Asymmetric synthesis of (*R*)-Carisbamate. **F** Formal synthesis of Pradefovir.

G Formal synthesis of Solabegron. **H** Formal synthesis of Aprepitant. **I** Concise and asymmetric synthesis of natural phenylpropanoid and chiral ligand PydiPhos. **J** Formal synthesis of (*S,S*)-(+)-Reboxetine. **K** Formal synthesis of (-)-Bursatellin and Preoxazin. *n*-BuLi butyl lithium, PTSA *p*-toluene sulfonic acid, DMP 2,2-dimethoxypropane, Phth phthalimide, CDI 1,1'-carbonyldiimidazole, TsCl 4-toluenesulfonyl chloride, TFA trifluoroacetic acid.

General procedure for the synthesis of 1-aryl-1,3-diols

An oven-dried 10-mL vial equipped with a PTFE-coated stir bar was charged with NiBr₂(dme) (6.1 mg, 0.02 mmol, 10 mol%), **L6** (11.7 mg, 0.03 mmol, 15 mol%) and anhydrous acetone (0.5 mL). This reaction mixture was stirred at room temperature for 1 h in an argon-filled glovebox. TBADT (33.5 mg, 0.02 mmol, 5 mol%), aryl or alkenyl bromide **2** (0.2 mmol, 1 equiv), 2,2-dimethyl-1,3-dioxane **4a** (232.0 mg, 2.0 mmol, 10 equiv), K₃PO₄ (63.6 mg, 0.3 mmol, 1.5 equiv) and PhCF₃ (0.5 mL) was then added. The reaction mixture was stirred and irradiated with a 10 W 390 nm LED lamp at 25 °C for 60 h. The resulting mixture was removed from light, diluted with ethyl acetate and passed through a pad of celite. The celite plug was further washed with ethyl acetate. The combined solvent was then evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the corresponding products.

Data availability

All data are available from the corresponding author upon request. The authors declare that all the data supporting the findings of this work are available within the article and its Supplementary Information files. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 2335066 (**3cg**), 2335067 (**5ag**), 2236741 (**9g**), and 2353650 (**10b**). Copies of the data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/>.

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Author contributions

W.K. conceived and directed this project. S.X., Y.P., Y.S., H.G. and A.L. conducted the experimental investigations. S.X., Y.S. and Y.P. analyzed and interpreted the experimental data. W.K. wrote the manuscript with feedback from other authors. All authors contributed to discussions. S.X., Y.P. and Y.S. contributed equally.

Competing interests

The authors declare no competing interests.

Additional information

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