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Asymmetric β -arylation of cyclopropanols enabled by photoredox and nickel dual catalysis†

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The enantioselective functionalization and transformation of readily available cyclopropyl compounds are synthetically appealing yet challenging topics in organic synthesis. Here we report an asymmetric β -arylation of cyclopropanols with aryl bromides enabled by photoredox and nickel dual catalysis. This dual catalytic transformation features a broad substrate scope and good functional group tolerance at room temperature, providing facile access to a wide array of enantioenriched β -aryl ketones bearing a primary alcohol moiety in good yields with satisfactory enantioselectivities (39 examples, up to 83% yield and 90% ee). The synthetic value of this protocol was illustrated by the concise asymmetric construction of natural product calyxolane B analogues.

Introduction

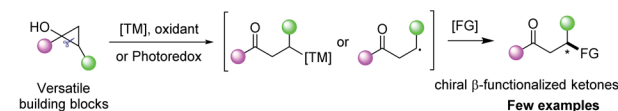
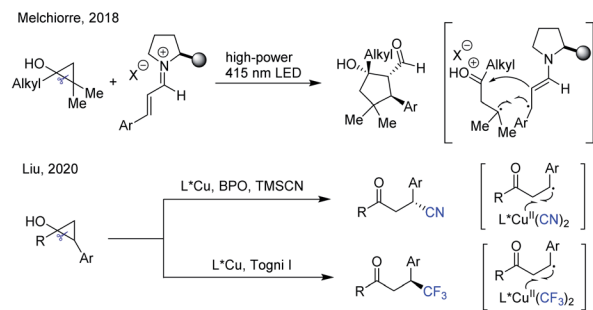
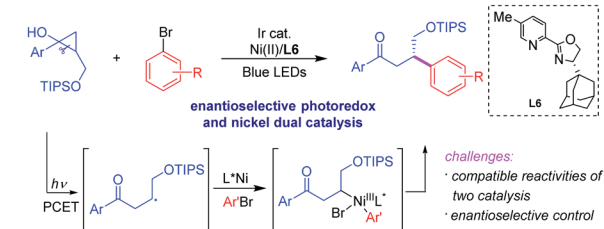
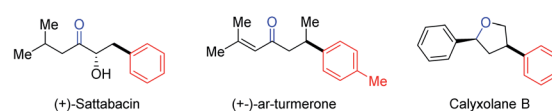
Cyclopropanes are versatile building blocks and participate in a diverse range of fundamental transformations in organic synthesis by taking advantage of their intrinsic high ring strain.¹ Among these cyclopropane derivatives, cyclopropanols, which are usually considered as precursors of ketone homoenolates, have gained emerging interest as three-carbon synthons for new bond formation and natural product synthesis in recent years.² In the presence of transition metal (TM) catalysis or single electron transfer (SET) catalysis, they have been widely applied in the synthesis of β -functionalized ketones by involving intermediates of homoenolates or β -keto radicals generated *via* ring-opening pathways, albeit mostly in racemic forms (Scheme 1A).^{3,4} Despite recent advances,⁵ the development of catalytic asymmetric strategies to access various enantioenriched β -functionalized ketones through ring-opening of cyclopropanols has proven to be quite challenging yet highly desirable.

Over the past decade, photoredox catalysis has become a powerful and reliable tool for developing innovative synthetic methodologies, designing and constructing interesting bioactive molecules and valuable functional materials.⁶ In this context, there has been tremendous progress in the area of photoredox dual catalysis with transition metals,⁷ Lewis acids,⁸ organocatalysts,⁹ and electrocatalysts,¹⁰ providing attractive strategies for the stereoselective and divergent preparation of structurally diverse chiral molecules and pharmacophores.

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Recently, seminal studies have been disclosed toward the asymmetric β -functionalization of cyclopropanols by exploiting

A. General strategies for asymmetric β -functionalization of cyclopropanolsB. Prior art: Asymmetric β -functionalization of cyclopropanolsC. This work: Asymmetric β -arylation of cyclopropanolsRepresentative examples of bioactive compounds with β -aryl moietyScheme 1 Asymmetric β -functionalization of cyclopropanols.

these novel catalytic protocols. In 2018, the Melchiorre group reported their pioneering work on the enantioselective photochemical organocascade process that converted cyclopropanols and α , β -unsaturated aldehydes into densely functionalized cyclopentanols with excellent stereoselectivities (Scheme 1B).¹¹ Later, Liu and coworkers achieved the asymmetric benzylic trifluoromethylation and cyanation of racemic aryl-substituted cyclopropanols *via* copper-mediated radical ring-opening pathways, which provided robust synthetic methods to access chiral β -CF₃ and β -CN ketones in good yields with high enantioselectivities, respectively (Scheme 1B).¹² In 2020, Huang and Rueping disclosed a general strategy for the remote arylation of ketones from cyclic alcohols *via* photoredox and nickel catalysis, although cyclopropanol was reported as only a single non-enantioselective example.¹³ In spite of these exciting advances, asymmetric β -arylation of cyclopropanols remain unexplored, highlighting the need to develop catalytic enantioselective arylation methods while considering the wide prevalence of β -aryl ketone derivatives in bioactive compounds and pharmaceuticals.¹⁴

In recent years, photoredox/nickel dual catalysis has enabled the non-asymmetric construction of different types of C–C or C–heteroatom bonds under mild reaction conditions, providing attractive alternatives to challenging synthetic metal-catalyzed cross-coupling reactions.¹⁵ Encouraged by recent progress in such enantioselective dual catalysis¹⁶ and our continuous interest in nickel-catalyzed asymmetric radical transformation,¹⁷ we envisioned that engaging a chiral nickel catalyst photocatalytically might serve as a general platform for enantioselective β -functionalization of cyclopropanols to access a series of value-added β -functionalized ketones in a stereoselective fashion (Scheme 1C). To realize this hypothesis, two major challenging issues need to be addressed. First, the reactivity of highly reactive alkyl radicals generated *via* ring-opening of cyclopropanols should be compatible with nickel involved oxidative addition of aryl electrophiles in order to avoid the competing homo-coupling reactions, undesired dimerization of alkyl radicals and other byprocesses. Second, the enantioselective photoredox and nickel dual catalysis remains largely undeveloped.¹⁶ Here we presented our study on asymmetric β -arylation of cyclopropanols enabled by this dual mode catalysis (Scheme 1C).

Results and discussion

We initiated our investigation by using cyclopropanol **1a** bearing a primary alcohol moiety and 4-bromoacetophenone **2a** as model substrates (Table 1). After an extensive survey of different reaction parameters, including photoredox catalysts, nickel complexes, chiral ligands and variation of alcohol protection groups,¹⁸ the best conditions were established when reacting cyclopropanol **1a** (3 equiv.) and 4-bromoacetophenone **2a** (1 equiv.) with photocatalyst [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ [*E*_{1/2}(*P/P[−]) = 1.21 V vs. SCE in MeCN]¹⁹ in the presence of a simple chiral Ni(OAc)₂/Py-(oxazoline) catalyst, collidine as the base and DMF as the solvent under blue-light irradiation, furnishing the desired chiral β -aryl ketone **3a** in 75% yield with a 93 : 7

Table 1 Optimization of reaction conditions^a

Reaction scheme showing the conversion of cyclopropanol **1a** and 4-bromoacetophenone **2a** to β -aryl ketone **3a**. Conditions: [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.5 mmol%), Ni(OAc)₂ (20 mmol%), L₆ (22 mmol%), Collidine (300 mmol%), DMF (0.02 M), 48 hr, 25 °C, Blue LEDs (465 nm).

Chemical structures of ligands L1, L2, L3, L4, L5, and L6 are shown below the reaction scheme.

L1: R₁ = H, R₂ = ^tBu
L2: R₁ = H, R₂ = ^tBu
L3: R₁ = H, R₂ = Ph
L4: R₁ = H, R₂ = ^tBu
L5: R₁ = Me, R₂ = ^tBu
L6: R₁ = Me, R₂ = Ad

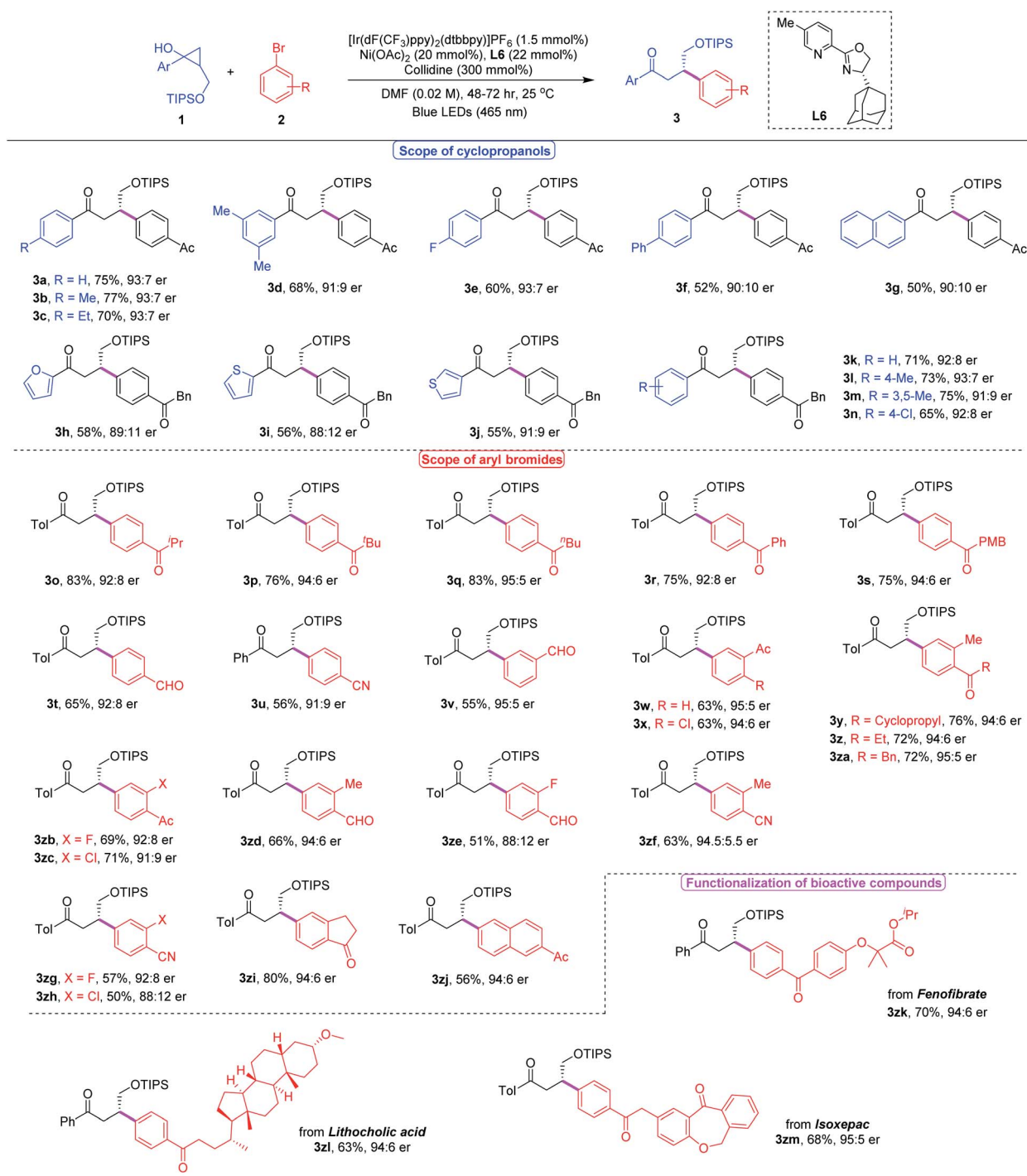
Entry	Variation from standard conditions	Yields ^b	er ^c
1	None	75%	93 : 7
2	L1 instead of L6	0	—
3	L2 instead of L6	20%	60 : 40
4	L3 instead of L6	70%	55 : 45
5	L4 instead of L6	80%	88 : 12
6	L5 instead of L6	77%	90 : 10
7	NiBr ₂ glyme instead of Ni(OAc) ₂	47%	90 : 10
8	P ^{<i>t</i>} Bu ₃ Et ⁺ (EtO) ₂ POO [−] instead of collidine	67%	87 : 13
9	DMA instead of DMF	71%	88 : 12
10	10 °C instead of 25 °C	31%	90 : 10
11	No PC, or no Ni, or no light, or no base	0	—

^a Unless otherwise indicated, all reactions were performed with **1a** (0.30 mmol), **2a** (0.10 mmol), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.5 mmol%), Ni(OAc)₂ (20 mmol%), ligand (22 mmol%), collidine (300 mmol%) in DMF (5 mL), blue LEDs (465 nm), 25 °C, 48 h under a nitrogen atmosphere. ^b Isolated yields. ^c Determined by HPLC analysis. Ad: adamantanyl group.

enantiomeric ratio at room temperature (entry 1). Notably, common bis(oxazoline) catalysts **L1** and **L2** were not effective for this reaction (entries 2–3) and other Py-(oxazoline) catalysts **L3** to **L5** gave similar yields (70–80%), albeit in diminished enantioselectivities (entries 4–6). The use of other nickel catalysts, such as NiBr₂, afforded **3a** in lower yield and ee (entry 7). Encouraged by recent progress in the area of proton-coupled electron transfer (PCET),²⁰ we examined various bases which have been frequently applied for the ring-opening transformations of cyclic alcohols through the PCET process.¹⁸ Commercially available base P^{*t*}Bu₃Et⁺(EtO)₂POO[−] generated **3a** in 67% yield with 74% ee (entry 8). Next, the screening of solvents showed that DMF was the optimal solvent for this asymmetric dual reaction (entry 9). Surprisingly, the yield was decreased to 31% when the reaction was conducted at 10 °C due to the very low conversion, albeit with a 90 : 10 enantiomeric ratio (entry 10). Finally, control experiments indicated that the photocatalyst, nickel catalyst, base, and blue-light irradiation were essential for the success of this reaction (entry 11).

With the optimal reaction conditions in hand, we investigated the substrate scope of this asymmetric β -arylation of cyclopropanols (Table 2). In general, the enantioselectivity was sensitive to the 2-substitution groups of cyclopropanols. When the 2-methyl or 2-benzyl substituted cyclopropane-1-ols were used as the substrates, the corresponding products were obtained in 80% yield with 40% ee, and 67% yield with 36% ee, respectively. First, the generality of cyclopropanols bearing the primary alcohol moiety was evaluated. A broad range of

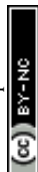


Table 2 Scope of asymmetric β -arylation of cyclopropanols^a

^a Unless otherwise indicated, all reactions were performed under the following conditions: cyclopropanols **1** (0.3 mmol), aryl bromides **2** (0.1 mmol), $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (1.5 mmol%), $\text{Ni}(\text{OAc})_2$ (20 mmol%), **L6** (22 mmol%), collidine (300 mmol%), DMF (5 mL), blue LEDs (465 nm), 48–72 h, 25 °C. Isolated yields. The er values were determined by HPLC analysis.

substituted cyclopropanols bearing an electron-withdrawing (*e.g.* F or Cl) or electron-donating (*e.g.* alkyl substituents) group on the aryl moiety were well tolerated, and delivered the corresponding chiral ketones in 52–77% yields with 80–86% ee (3a–3f, 3k–3n). Cyclopropanol **1g** with the 2-naphthyl group also

proceeded to afford the desired product **3g** in 50% yield with a 90 : 10 er. In addition, reactions with different heteroaryl moieties, such as 2-furyl, 2-thiofuryl and 3-thiofuryl groups, participated well to give the desired ketones in comparable yields and enantioselectivities (3h–3j). Next, the scope of

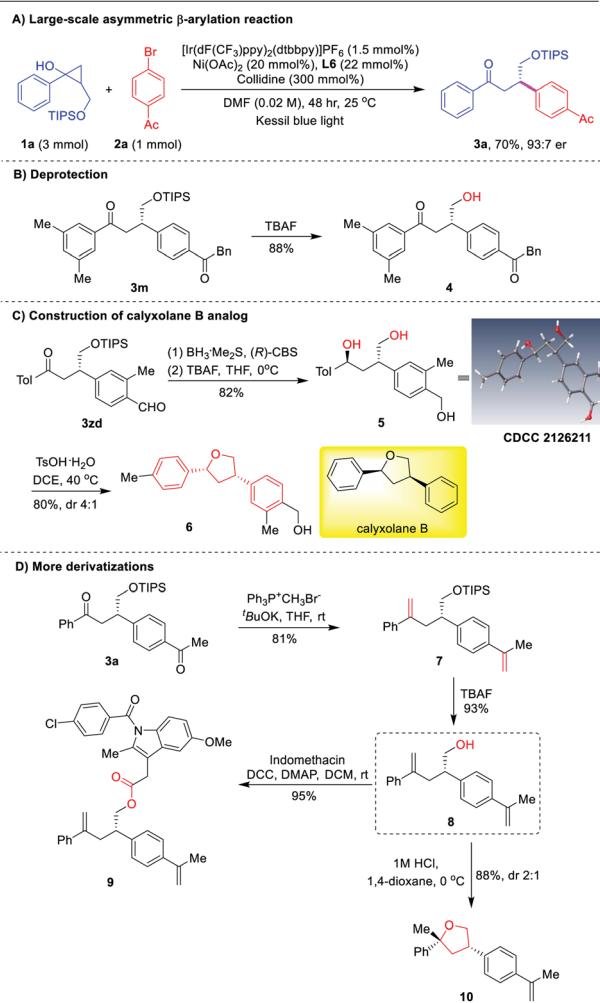


commercially available aryl bromides was examined with cyclopropanol **2a** under the optimized reaction conditions. Typically, electron-deficient aryl bromides were beneficial for this asymmetric photoredox/nickel dual catalytic system. A wide variety of functional groups including ketones, aldehydes, cyanides and halides were well tolerated to provide the desired β -aryl ketones with satisfying results (**3o–3zi**). Moreover, 2-naphthyl substituted aryl bromide **2zj** also successfully yielded the corresponding ketone **3zj** in 56% yield with a 94 : 6 er. However, heteroaryl bromides, including 4-bromo-2-(trifluoromethyl)pyridine, 5-bromo-2-furaldehyde and 5-bromoindole, failed to generate the desired products under current reaction conditions, presumably because of their low reactivities. Encouraged by the mild reaction conditions and broad functional group tolerance, we applied this asymmetric protocol to the late-stage functionalization of complex bioactive molecules. To our delight, a number of complicated compounds, such as fenofibrate, lithocholic acid and isoxepac derived bromides, all proceeded well with cyclopropanol **1a**, delivering the highly functionalized chiral ketones in 63–70% yields with up to 90% ee (**3zk–3zm**).

To demonstrate the synthetic value of this asymmetric β -arylation protocol, a 1.0 mmol scale reaction was carried out, providing the chiral ketone **3a** in 70% yield with 93 : 7 er (Scheme 2A). Then, further derivatization of the products was performed. Direct deprotection of the TIPS group of ketone **3m** afforded the chiral primary alcohol **4** in 88% yield (Scheme 2B). Interestingly, an enantioselective reduction of **3zd** in the presence of the (*R*)-CBS catalyst and borane, followed by deprotection of TIPS would generate chiral tri-hydroxy product **5** in 82% yield with 96% ee (Scheme 2C). The absolute configuration of **5** was determined to be 1*S*, 3*S* by X-ray diffraction.²¹ Subsequently, Brønsted acid catalyzed stereospecific benzylic substitution occurred, furnishing the concise synthesis of a marine natural product *ent*-calyxolane B analog **6** in 80% yield (Scheme 2C).²² Moreover, subjecting **3a** to the Wittig reaction, followed by deprotection of TIPS could generate γ -hydroxy ene **8** in 75% overall yield with 88% ee (Scheme 2D). With product **8** in hand, the indomethacin ester **9** was easily obtained in 95% yield.

Alternatively, treatment of **8** with hydrogen chloride solution (1.0 M in 1,4-dioxane) led to tetrahydrofuran derivative **10** (Scheme 2D), which is a privileged structural unit in natural products and bioactive compounds.²³

To gain more insight into the reaction pathway, a number of control experiments were performed. First, both *trans*-cyclopropanol **1f** and *cis*-cyclopropanol **1f'** were subjected to the standard conditions, producing the corresponding product **3f** in a similar yield with the same enantioselectivity (Scheme 3A). TBS protected cyclopropanol **11** failed to generate product **3b**, indicating that the ring-opening process of cyclopropanols underwent a PECT pathway (Scheme 3B). Furthermore, we conducted the reaction under standard conditions in the presence of TEMPO (2,2,6,6-tetra-methyl-1-piperidinyloxy) as a radical scavenger. As expected, the reaction was completely shut down, and the TEMPO adduct **12** was detected by HRMS (Scheme 3C).¹⁸ In addition, when acrylonitrile **13** was used instead of aryl bromide, the Giese-type product **14** was obtained

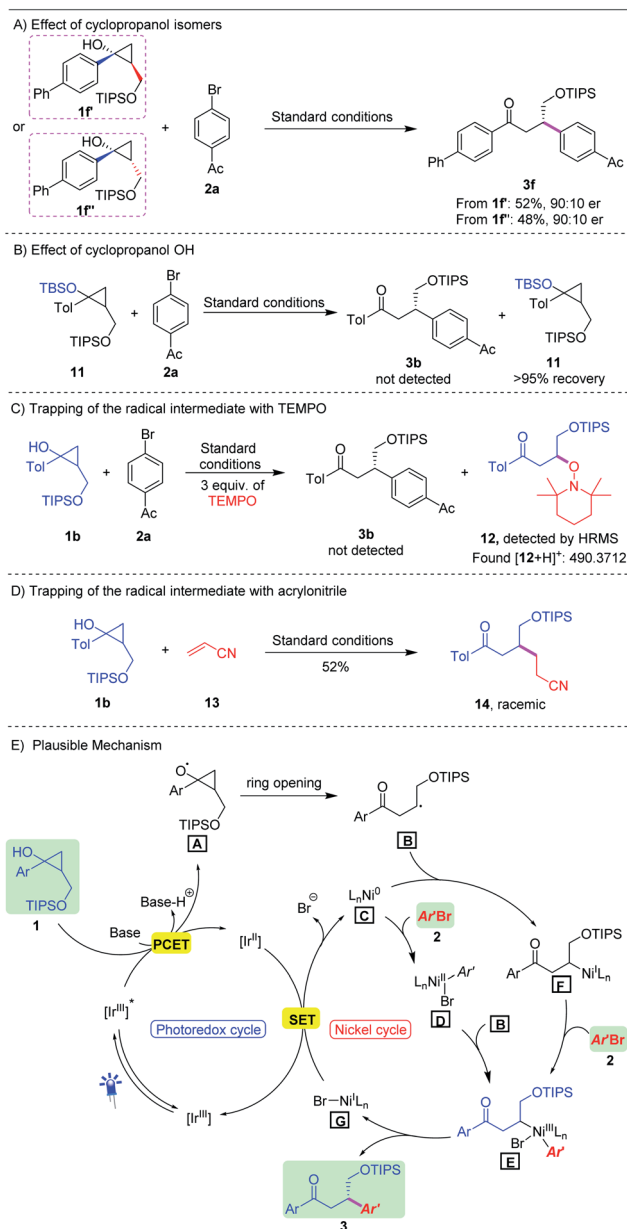


Scheme 2 Large-scale experiment and derivatization of chiral β -aryl ketones.

in 52% yield under the standard conditions, albeit in the racemic form (Scheme 3D). All these results strongly supported that the asymmetric photoredox/nickel dual catalysis process involved a radical pathway.

On the basis of the preliminary mechanistic studies and literature reports,²⁰ we proposed a plausible mechanism for this dual catalytic asymmetric β -arylation reaction as outlined in Scheme 3E. Upon blue-light irradiation, photocatalyst $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]^+$ was promoted to its excited state $^*[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]^+$, which would oxidize the cyclopropanols **1** via a PCET process to generate the key alkoxy radical intermediate **A**. Subsequent ring opening through β -scission of **A** led to secondary alkyl radical **B**. For the nickel catalysis cycle, two possible pathways are involved. Chiral Ni(0) complex **C** underwent oxidative addition with aryl bromides **2** to give intermediate **D**, which then reacted with alkyl radical **B** to form Ni(III) complex **E**. Alternatively, alkyl radical **B** could couple with Ni(0) **C** to yield an alkyl Ni(I) intermediate **F** which was expected to undergo oxidative addition with aryl bromides, generating chiral Ni(III) intermediate **E**. At this stage, we could





Scheme 3 Preliminary mechanistic studies.

not be able to rule out any pathway. Next, reductive elimination from chiral Ni(III) complex E would forge the enantioenriched $C_{sp^3}-C_{sp^2}$ bonds of β -aryl ketones 3 along with expelling the corresponding Ni(I) complex G, and the latter could be reduced by the reduced form of the photocatalyst, thus completing the dual catalytic cycle.

Conclusions

In conclusion, we have developed an enantioselective β -arylation of cyclopropanols enabled by asymmetric photoredox/nickel dual catalysis. This method provides a convenient strategy to assemble a diverse array of highly valuable chiral β -aryl ketones from readily available cyclopropanols and aryl

bromides at room temperature. Moreover, the value of this protocol was demonstrated by the synthesis of calyxolane and tetrahydrofuran analogues. Studies towards expanding the generality of this asymmetric dual catalysis are ongoing.

Data availability

Data for this work, including optimization tables, general experimental procedures, characterization data (NMR and HPLC spectra) for all new compounds and X-ray data are provided in the ESI.†

Author contributions

X. Li designed the project. J. Wang performed the experiments and analyzed the data. X. Li and J. Wang wrote the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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