Asymmetric C(sp³)−H functionalization is a persistent challenge in organic synthesis. Here, we report an asymmetric benzylic C−H acylation of alkylarenes employing carboxylic acids as acyl surrogates for the synthesis of α-aryl ketones via nickel and photoredox dual catalysis. This mild yet straightforward protocol transforms a diverse array of feedstock carboxylic acids and simple alkyl benzenes into highly valuable α-aryl ketones with high enantioselectivities. The utility of this method is showcased in the gram-scale synthesis and late-stage modification of medicinally relevant molecules. Mechanistic studies suggest a photocatalytically generated bromine radical can perform benzylic C−H cleavage to activate alkylarenes as nucleophilic coupling partners which can then engage in a nickel-catalyzed asymmetric acyl cross-coupling reaction. This bromine-radical-mediated C−H activation strategy can be also applied to the enantioselective coupling of alkylarenes with chloroformate for the synthesis of chiral α-aryl esters.
Historically, asymmetric catalysis has been largely governed by transition-metal-catalyzed reactions, in which metal−ligand−substrate interactions are tuned to control reaction stereochemistry (Scheme 1a). However, these methods often require high temperatures, harsh reaction conditions, or preformed organometallic feedstock chemicals, which can be challenging to achieve in a process-integrated manner. In contrast, enantioselective approaches remain largely undeveloped for the arylation of C(sp^3)-H bonds with aryl halides, despite their importance in the synthesis of high-value-added molecules from simple feedstock chemicals.

Recently, our laboratory reported a direct enantioselective C(sp^3)-H acylation of N-alkyl benzamides for the synthesis of α-amino ketones; wherein, a chiral nickel catalyst could engage photocatalytically generated α-amino radicals and in situ-activated carboxylic acids in acyl cross-couplings. We reasoned that this strategy could be applied to the asymmetric benzylic C-H acylation of alkylarenes to address the challenges described above for the synthesis of α-aryl ketones via radical C(sp^3)-H functionalization. Despite that initial progress, no examples of enantioselective benzylic C-H acylation have been reported. In addition, there is an increasing demand for the development of benzylic C-H functionalization reactions for the synthesis of high value-added molecules from simple alkylarenes. In this work, we report an enantioselective benzylic C-H acylation of alkylarenes with in situ-activated carboxylic acids enabled by nickel and photoredox dual catalysis.

**Results**

**Reaction design.** The proposed catalytic cycle for this benzylic acylation is shown in the bottom of Fig. 1c. It has been reported that single-electron oxidation of bromide anion by photoexcited photocatalyst can generate bromine radical (E1/2[Br^-/Br] = +1.21 V vs SCE in CH3CN; E1/2[Br^-/Br] = +0.80 V vs SCE in DME)54. According to the literature precedent and our previous mechanistic experiments, we hypothesize that the catalytic reaction is initiated by oxidative addition of Ni(0) catalyst I to an in situ-activated carboxylic acid to afford Ni(II) species II. Subsequent trapping of prochiral benzylic radicals generated from the bromine-radical-mediated HAT process provides Ni(III) complex III, which undergoes reductive elimination to yield the desired product and Ni(I) species IV. A recent computational study of nickel-catalyzed cross-coupling of photoredox-generated benzylic radicals suggested that reductive elimination is the stereochemistry-determining step. Finally, SET between Ni(I) species IV and reduced photocatalyst regenerates the Ni(0) catalyst I and ground-state photocatalyst to close the catalytic cycle.

**Fig. 1** Enantioselective metal-catalyzed approaches for the synthesis of α-aryl ketones. **a** Previous approaches. **b** Dual nickel/photoredox catalyzed C(sp^3)-H functionalization. **c** This work and its mechanistic hypothesis. O.A. oxidative addition, R.E. reductive elimination. Ir(III) = Ir(dF(CF3)ppy)2(dtbppy)PF6.
both catalytic cycles ($E_{1/2}^{\text{red}}$ [Ir(II/III)] = −1.37 V vs SCE in CH$_3$CN).

**Reaction optimization.** Our investigation began with an exploration of reaction conditions for the coupling of 4-ethylbiphenyl and 3-phenylpropanoic acid (Table 1). Based on previously reported elegant strategies and our recent conditions for carboxylic acid activation in ketone synthesis, dimethyl dicarbonate (DMDC) was chosen as the activating agent to generate mixed anhydride in situ from carboxylic acids. After an extensive study of reaction parameters (also see Supplementary Table 1), we were delighted to find that a simple chiral nickel/bis(oxazoline) catalyst and a known Ir-photocatalyst could provide the acylation product in 85% yield and 94% ee (entry 1). An attractive feature of this transformation is that only commodity chemicals are involved in this reaction. From the standpoint of commercial availability, carboxylic acids are perhaps the most ubiquitous functional group. The reaction could be also performed at room temperature with similar efficiency (entry 2).

| Entry | Variation from standard conditions | Yield (%) | ee (%) |
|-------|-----------------------------------|-----------|--------|
| 1     | None                              | 85        | 94     |
| 2     | 25°C, instead of 10°C              | 83        | 90     |
| 3     | Ni(acac)$_2$ instead of NiBr$_2$glyme | 6         | -      |
| 4     | as entry 3, but plus 1.5 equiv NaBr | 62        | 88     |
| 5     | Boc$_2$O, instead of DMDC          | 14        | 93     |
| 6     | DMBP, instead of PC                | 0         | -      |
| 7     | No NH$_4$Cl                         | 54        | 93     |
| 8     | No Ni, or no PC, or no light       | 0         | -      |
| 9     | C1–C4, instead of (acid+DMDC + NH$_4$Cl) as shown below | 49       | 93     |
| 10    | L1–L5, instead of (S)-L as shown below | 69       | 93     |

Reactions were conducted on a 0.1 mmol scale. The yields were determined through GC analysis using n-dodecane as an internal standard. DMDC dimethyl carbonate. PC Ir[dl(CF$_3$)$_2$ppy$_2$(dtbbpy)PF$_6$, instead of (acid), instead of DMDC, and NH$_4$Cl did not provide improvements (entry 9). Other chiral ligands such as L1 and L2 also demonstrated low catalytic activity (entry 10).

**Late-stage functionalization.** Given the particularly broad functional group tolerance of our method, we sought to demonstrate the utility of this operationally convenient method in the late-stage functionalization of medicinally relevant molecules (Fig. 3). Specifically, acylation of benzyl C−H bonds of drugs such as ibuprofen, fenoprofen, ketoprofen, and naproxen, provided corresponding drug analogs in good yields and enantioselectivities (47–51). Employing menthol and amino acid derivatives as alkylation coupling partners led to good diastereoselectivities (52–55). With oxaprozin, stearic acid, oleic acid, 2,4-D, and lithocholic acid derivatives as acyl donors, the acylation proceeded with good stereoselectivity (56–61).

**Evaluation of substrate scope.** We next investigated the scope for cross-coupling of alkylarenes with carboxylic acids employing the optimized reaction conditions (Fig. 2). This transformation was compatible with many functional groups, such as chloride (7, 44), bromide (8, 43, 32, and 33), fluoride (9, 19, 24, and 31), ether (10, 14, and 42), nitrile (11), carbamate (12), ester (13, 40, and 41), olefin (15, 16), boronate ester (34), pyrazole (35), and heteroaromatic moieties (17, 36, and 46). Remarkably, the alkyl halide, aryl halide, aryl boronate ester, and terminal olefin can serve as versatile synthetic handles for further structural elaborations. Pyrazole- and thiophene-based heterocycles are commonly found in pharmaceutically relevant compounds. The coupling of 4-ethylbiphenyl with carboxylic acids bearing different steric properties resulted in good yields and enantioselectivities (18, 19). The corresponding methyl carboxylate was a significant side product for the cross-coupling of aromatic carboxylic acids. For the alkylarene component, acylation of para-substituted alkylarene bearing diverse electronic properties resulted in good yields and enantioselectivities (20–27). When the alkylarene featuring more than one benzyl C−H site was used, monoaoylation products could be obtained in good yields and ee’s (28–30). The homobenzyl bulky substrate was a competent coupling partner (39). Acylation of indane provided 45 in good yield and slightly reduced enantioselectivity. Under the current reaction conditions, the sterically hindered coupling partners such as the β-branched carboxylic acids and ortho-substituted alkylarene (33) led to low efficiency or no product formation (also see Supplementary Table 1).

**Gram-scale synthesis and parallel synthesis.** To demonstrate the scalability of the present method, two 20.0 mmol scale reactions were performed in a common flask to produce 5.35 g of chiral ketone product 8, and 9.13 g of lithocholic acid derivative 60 with excellent stereoselectivity and good yield (Fig. 4a). To further demonstrate the synthetic utility, two types of drug analagols derived from (S)-flurbiprofen and artesunate were prepared in parallel with high yields and excellent stereoselectivities (Fig. 4b). More than 100 mg of product was obtained in all cases. It is noteworthy that the labile peroxide subunit in artesunate was tolerated particularly well under mild conditions. This powerful
**Fig. 2 Substrate scope of enantioselective acylation of benzylic C(sp³)−H bonds with carboxylic acids.** All data represent the average of two experiments. Unless otherwise stated, reactions were conducted on a 0.5 mmol scale under standard conditions. aIn place of the standard conditions, chiral ligand L3, 3.0 equiv DMDC, and 3.0 equiv K2HPO4 were used.
method enables the streamlined synthesis of drug analogs, providing
attractive opportunities for the rapid exploration of structure-activity
relationships in drug discovery62, as well as complementing the existing
methods for the synthesis chiral α-aryl ketones7–13.

Mechanistic observations. We next performed preliminary
mechanistic studies for this newly developed method (Fig. 5). The
primary kinetic isotope effect was observed in intermolecular
parallel and competition experiments, which suggested that C−H
cleavage significantly contributed to the rate-determining step
(Fig. 5a). When the reaction was performed in the presence of an
electron-deficient alkene, the benzylic acylation was completely
inhibited, and a racemic adduct 71 was obtained in 58% yield
(Fig. 5b, top). This observation supported the benzylic radical
might be involved in the catalytic cycle. Moreover, in the absence
of nickel catalyst and in situ-generated acyl electrophile (Fig. 5b,
bottom), the addition of 1.5 equiv of NaBr to the coupling of 4-
ethylbiphenyl with electron-deficient alkene led to the adduct
71 in 16% yield, which suggested photochemical oxidatively
generated bromine radical was likely involved in the acylation reaction.

Rational expansion. Finally, we questioned whether this
benzyl radical–mediated C−H cleavage strategy could be
applied to the synthesis of α-aryl esters rather than α-aryl
ketones63–65. Indeed, replacing the in situ-generated mixed
anhydride with commercially available phenyl chloroformate led
to a number of α-aryl esters in good yields and selectivities under
similar conditions (Fig. 6). Chiral ligand L2 proved to be optimal
for this transformation.

Discussion
In summary, a direct enantioselective benzyllic C(sp3)−H acylation
for the synthesis of α-aryl ketones has been developed.
Several attractive features are noteworthy. First, both coupling
partners, carboxylic acids and alkylbenzenes, have broad commercial availability. Second, this operationally simple and scalable method has a broad substrate scope and excellent functional group tolerance. Third, this mild protocol can be applied to the late-stage modification of pharmaceutically relevant molecules. Finally, the asymmetric synthesis of α-aryl esters is also accessible based on a simply rational expansion. The development of enantioselective $\text{C}(\text{sp}^3) - \text{H}$ alkylation for the construction of $\text{C}(\text{sp}^3) - \text{C}(\text{sp}^3)$ bonds is underway in our laboratory.

**Methods**

Representative procedure for the synthesis of α-aryl ketone 1. In a nitrogen-filled glovebox, Ir(η$^2$-C$_2$H$_4$)$_2$Cl$_2$ (0.10 mmol), H$_2$OAc (1.5 mmol), NH$_4$Cl (25.3 mg, 0.50 mmol), NaH (60.5 mg, 1.50 mmol), i-PrOAc (11.3 mL) were added sequentially to a 15 mL vial. The reaction mixture was stirred at room temperature for 30 min, after which it turned to a purple suspension. Next, 3-phenylpropanoic acid (75.0 mg, 0.50 mmol) was added as a solid, followed by addition of 4-ethylbenzene (0.75 mL, 2.0 M in i-PrOAc, 1.50 mmol) via a 1.0 mL syringe. The vial was then capped with a polytetrafluoroethylene septum cap, and DMDC (80.0 µL, 0.75 mmol) was added via a 100 µL syringe. The vial was next transferred out of the glovebox, and vacuum grease was applied to cover the entire top of the septum cap. Then, the reaction mixture was stirred at 10 °C in an ETOH bath for 5 min, followed by irradiation with a 40 W blue LED lamp (Kessil PR160L, 427 nm). The reaction was stirred at 10 °C under irradiation for 25 h. The reaction mixture was then passed through a short pad of silica gel, with Et$_2$O as the eluent (~35 mL). The resulting mixture was concentrated, and the residue was purified by flash chromatography on silica gel, which provided the desired acylation product 1 in 82% yield and 94% ee as a white solid. All new compounds were fully characterized (See the Supplementary Methods).

**Data availability**

The data that support the findings of this study are available within the article and its Supplementary Information files. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 2058381 (59). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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