Nickel catalysis

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Radical control for enantioselective Csp^3–Csp^3 cross-coupling

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The enantioselective formation of Csp^3–Csp^3 bonds is still a substantial challenge in the synthesis of complex molecules. Now, a photocatalytic system has been developed for the enantioselective alkylation of α-amino Csp^3–H bonds that promotes the generation of two different alkyl radicals, followed by their cross-coupling at a chiral nickel centre.

The development of Csp^3–Csp^3 bond formation reactions has gained much attention, thanks to its potential utility in the synthesis of complex molecules with three-dimensional structural and improved bioactivity[1,2]. For example, the introduction of alkyl groups as small as methyl groups into the alpha position of aliphatic amines has been shown to greatly enhance bioactivity, a phenomenon known as the magic methyl effect[3]. In this context, the enantioselective formation of Csp^3–Csp^3 bonds is still difficult to achieve, and the direct asymmetric Csp^3–H alkylation is an efficient strategy that obviates the use of prefunctionalized substrates. Transition-metal catalysts, namely those utilizing nickel, have achieved notable success in this field; however, most Ni catalysts rely heavily on alkyl halide or pseudohalide substrates[4]. Although strategies for Csp^3–H alkylation have been developed recently to generate racemic products[5,6], a general strategy for direct enantioselective Csp^3–H alkylation remains elusive.

Now, writing in *Nature Catalysis*, Huo and colleagues[7] present a robust synthetic protocol for the enantioselective alkylation of non-acidic Csp^3–H bonds (Fig. 1a). The methodology employs the independent generation of two alkyl radicals via photocatalysis, followed by their enantioselective cross-coupling at a chiral nickel centre. Key to their approach is the generation of a bromine radical by the excited photocatalyst that promotes hydrogen-atom transfer from the α-amino C–H bond and an alkyl radical formation from a redox-active ester (Fig. 1c). Unlike other dual Ni-photocatalyst systems, the chiral Ni catalyst in this protocol is involved only in the cross-coupling reaction, allowing for full control and independent radical formation from the cross-coupling catalyst. The bromine radical was found to be the optimal reagent for hydrogen-atom transfer to activate the α-amino C–H bond over other reagents such as the decatungsten anion or aryl ketones. Moreover, this methodology is, to the best of our knowledge, an early example of the use of hydrogen-atom transfer in enantioselective Csp^3–Csp^3 coupling.

The team successfully applied the developed synthetic protocol to various substrates, including acyclic α-amino substrates and redox-active esters of a wide range of carboxylic acids: they demonstrated incorporation of (trideutero)methyl and ^{13}C methyl groups with good yields and high enantioselectivity, while synthesizing challenging substrates such as chiral aliphatic amines with high enantioselectivity as well (Fig. 1b). Moreover, considering the abundance of cyclic amine-containing compounds among pharmaceuticals, the scope was expanded to include saturated *N*-heterocycles. The cross-coupling reaction also demonstrated tolerance to scale-up and is not too sensitive to air and moisture. Finally, this strategy successfully reduced the number of steps required for the synthesis of a representative bioactive alkaloid, (−)-indolizidine 201, taking an eight-step synthetic sequence down to three steps, as well as pyrrolidine-containing derivatives of dehydrocholic acid and Taxol (paclitaxel), respectively (Fig. 1b). Overall, the developed methodology should allow for rapid and enantioselective access to drug-like aliphatic complex molecules using abundant starting materials.

Thorough mechanistic investigations revealed the presence of both alkyl radicals generated by photocatalysis and the importance of the bromide source (Fig. 1c). In the absence of a chiral Ni catalyst, the cross-coupled product was still obtained but in a racemic mixture, suggesting that radical generation is not dependent on the Ni catalyst. In addition, the presence of bromide ions was essential, either in the form of NaBr or a bromide-containing Ni salt, such as $NiBr_2$•glyme. This was further supported by the lack of activity when nickel sources such as $Ni(COD)_2$, $Ni(acac)_2$ or $NiCl_2$•glyme were employed (COD, 1,5-cyclooctadiene; acac, acetylacetonate). However, when a bromide source was added to these precursors, that catalytic activity was restored. This is distinct from previous studies in which the Ni catalyst usually plays a part in both radical generation and product formation. Mechanistic studies also reveal that a Ni^{I} intermediate is the catalytically active species in the cross-coupling reaction (Fig. 1c). The authors independently synthesized key Ni^{I} and Ni^{II} intermediates and characterized them by electron paramagnetic resonance (EPR) and X-ray diffraction, respectively. These mechanistic studies are essential because they highlight the importance of transient paramagnetic Ni species in controlling single-electron transfer reactions, as proposed recently in other alkyl–alkyl cross-coupling reactions[8]. Furthermore, the authors employed kinetic isotope effect studies that suggest the C–H bond activation to be the rate-determining step.

Although the methodology provided in this study establishes a robust and efficient way to alkylate α-amino Csp^3–H bonds, some limitations remain. For instance, a large excess of amine (4.0 equivalents) relative to the redox-active ester is required for this reaction to maximize product formation. Additionally, using carbamate protecting groups such as *t*-butyloxycarbonyl (Boc) or carboxybenzyl (Cbz), instead of a benzoyl group, greatly reduces product formation. This might be attributed to the inability of the bromine radical to abstract a hydrogen atom from a less hydridic C–H bond, suggesting that careful selection of the protecting group is important.

In conclusion, Huo and colleagues have demonstrated a robust methodology that allows for the enantioselective (trideutero)methylation and alkylation of α-amino Csp^3–H bonds. The use of a bromine

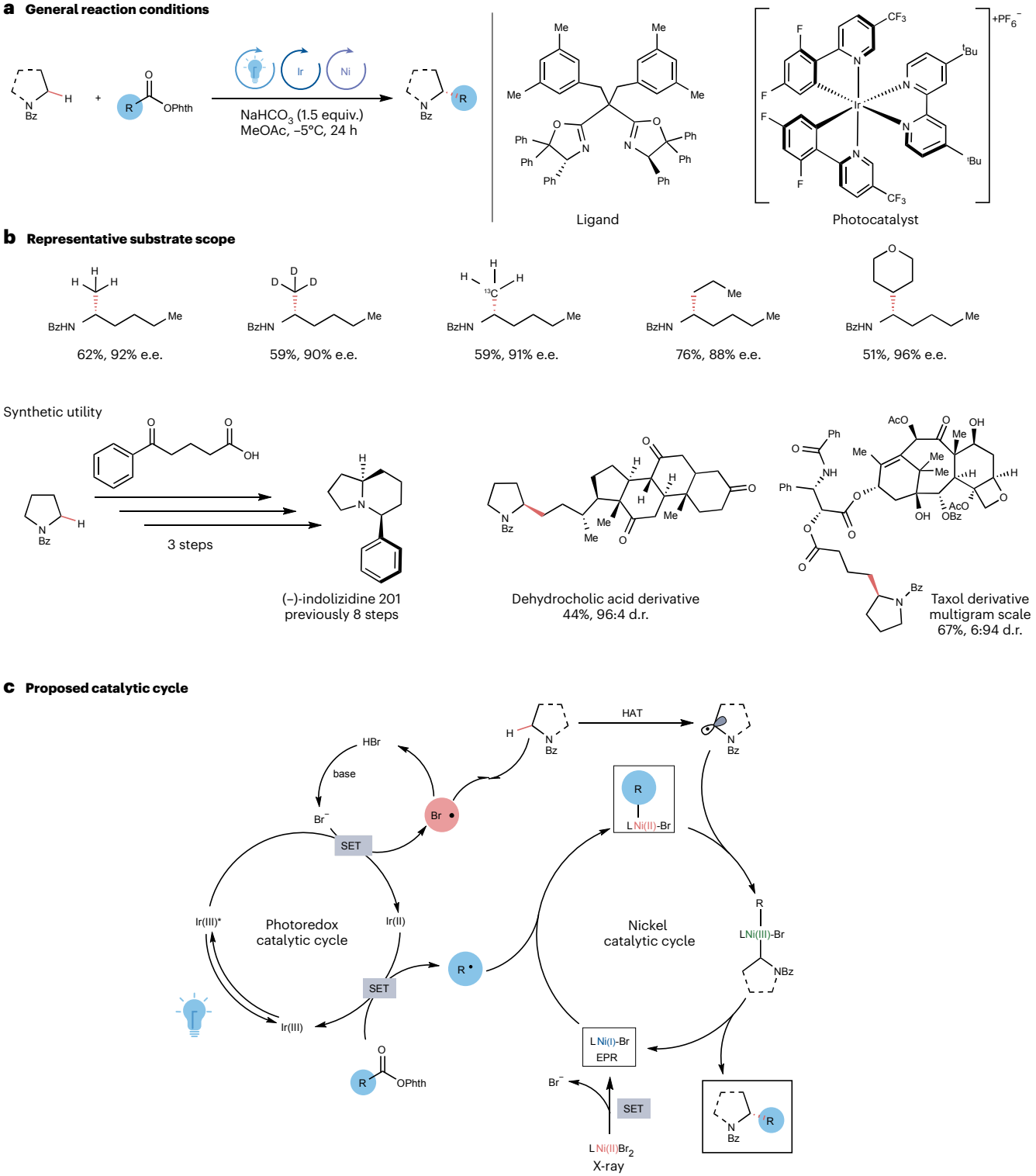

Fig. 1 | Photochemical enantioselective alkylation of α-amino Csp^3–H bonds with redox-active esters. a, General reaction conditions for the enantioselective Csp^3–Csp^3 cross-coupling reaction (where $NiBr_2$•glyme is used as both catalyst and bromide source). **b**, Representative substrate scope of the developed methodology. **c**, Proposed catalytic cycle based on extensive mechanistic studies (the isolated key catalytic Ni intermediate species are highlighted in rectangles). R, ligand; ee, enantiomeric excess; dr, diastereomeric ratio; equiv., equivalents; SET, single-electron transfer; HAT, hydrogen-atom transfer; EPR, electron paramagnetic resonance; Bz, benzyl; Phth, phthalimide; Bu, butyl; Me, methyl.

radical as an internal reagent for hydrogen-atom transfer combined with the radical generation through reductive decarboxylation enables a redox-neutral process for radical generation. The two different alkyl radicals are captured by a chiral nickel catalyst, resulting in an enantioselective Csp^3–Csp^3 cross-coupling. This protocol features a broad substrate scope, including acyclic and saturated *N*-heterocycle amines, and has various applications in the synthesis of drug candidates and natural product derivatives. In addition, the authors simplify the synthetic routes to several complex bioactive aliphatic amines. The findings of this study will offer valuable insights for improving the synthesis of complex bioactive molecules, marking an important step forward in the field of organic synthesis.

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Competing interests

The authors declare no competing interests.