Enantioselective synthesis of N-alkylindoles enabled by nickel-catalyzed C–C coupling

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Enantioenriched N-alkylindole compounds, in which nitrogen is bound to a stereogenic sp3 carbon, are an important entity of target molecules in the fields of biological, medicinal, and organic chemistry. Despite considerable efforts aimed at inventing methods for stereoselective indole functionalization, straightforward access to a diverse range of chiral N-alkylindoles in an intermolecular catalytic fashion from readily available indole substrates remains an ongoing challenge. In sharp contrast to existing C–N bond-forming strategies, here, we describe a modular nickel-catalyzed C–C coupling protocol that couples a broad array of N-indolyl-substituted alkenes with aryl/alkenyl/alkynyl bromides to produce chiral N-alkylindole adducts in single regioisomeric form, in up to 91% yield and 97% ee. The process is amenable to proceed under mild conditions and exhibit broad scope and high functional group compatibility. Utility is highlighted through late-stage functionalization of natural products and drug molecules, preparation of chiral building blocks.

Enantioenriched indole derivatives are of great interest in pharmaceutical science and organic chemistry1–4. Particularly, the indole core is one of the most frequent N-heterocyclic fragment featured in FDA-approved drugs5. Therefore, different methods have been designed for the construction of chiral indole scaffolds5–9. The most typical functionalizations of indoles take place at the C3 positions, due to their innate nucleophilicity5,9. In contrast, the development of techniques involving a stereocenter adjacent to the nitrogen, an essential structural motif imbedded in many biologically active molecules (Fig. 1A)5,9, remains a great challenge, presumably owing to the attenuated nucleophilicity of the nitrogen atom (Fig. 1B). To this end, a few powerful C–N bond-forming approaches have been developed to access chiral N-alkylindoles (Fig. 1B). However, these transformations often rely on the enantioselective intramolecular addition of prefunctionalized indole substrates5,9, or intermolecular N-alkylation (mostly N-allylation) of indoles with C3-blocking substituents8,9 or electron-withdrawing groups8,9–11. Moreover, indirect methods using indole precursors such as indolines or aryl hydrazines were also developed to obtain high regio- and enantioselectivity14–16. Recently, the Vilotijevic and Buchwald groups demonstrated elegant works using N-modified strategy to engage N-silyl indoles and N-(benzoyloxy)indoles in C–N bond-forming reactions, respectively37,38. Despite these remarkable advances, a general, modular and selective synthesis of enantioenriched N-alkylindoles is in crucial demand, particularly if the substrates and catalysts are readily available39,40.

New strategic bond-forming reactions would offer a complementary protocol to existing C–N bond-forming process and an opportunity to explore currently inaccessible chemical space. In this regard, the enantioselective coupling of an α-N-alkyl metal species or an α-N-alkyl radical species represents a straightforward strategy to the synthesis of chiral alkylindoles (Fig. 1C)41,42. However, forgoing a C–C bond asymmetrically at the position α to the indole nitrogen remains elusive43–45. Recently, the Melchiorre43 and Davidson44 groups independently reported impressive works using photoredox chemistry to engage indole-derived α-N-alkyl radical intermediates in N-alkylindole synthesis, despite limited substrate scope and enantioselectivity (Fig. 1C, right). Moreover, in the case, a leaving group (-CO2H or DHP) is necessary for the generation of an α-N-alkyl radical. In contrast,
there have been no reports on generation and coupling of indole-derived α-N-alkyl metal species. The enantioselective Ni-catalyzed reductive coupling of olefins with electrophiles represents an attractive utilization of in-situ generated alkyl-Ni species.56–62. We wondered whether this reductive coupling strategy could be harness to access chiral N-alkylindoles. However, catalytic enantioselective reductive coupling of N-alkenyl indoles faces several challenges. First, current asymmetric reductive coupling is largely limited to the use of linear alkyl-Ni intermediates. Catalytic enantioselective coupling of branched alkyl-Ni intermediates generated from hydronickelation of olefins remains elusive.63,64 Moreover, modulation of the site-selectivity pattern across differently substituted N-alkenyl indoles is unknown. In addition, the propensity of N-alkenyl polymerization and reduction is possible65,66.

As a part of our interest in chiral alkylamine-bearing molecules,67,68 here, we show a catalytic enantioselective coupling of in-situ generated α-N-alkyl nickel species with aryl/alkenyl/alkynyl bromides, analogous to the C(sp3)–C(sp2)/C(sp) cross-coupling reaction, enabling a unified method toward structurally diverse chiral N-alkylindoles in high yields and ee’s (Fig. 1D). By employing mild conditions, this modular, unified fragment coupling provides practical advantages in reaction efficiency, functional group compatibility, as well as substrate availability and scope, which would be broadly useful yet mechanistically orthogonal to established N-alkylation processes. In particular, application in late-stage diversification of many natural products and drug molecules demonstrates its utility in accelerating access to N-alkylated drug-like complexity.

Fig. 1 | Representative chiral N-alkylindole derivatives and strategies for catalytic enantioselective synthesis of N-alkylindoles. A Representative biologically active chiral N-alkylindole derivatives; B Existing C–N bond-forming methods to access chiral N-alkylindole derivatives; C C–C bond-forming strategy to access chiral N-alkylindole derivatives; D This work: catalytic, modular, unified coupling of α-N-alkyl-Ni species.
indicating the subtle interplay of reagents and solvents in this case. In order to obtain both high yield and high enantioselectivity (entries 5–7), an appropriate solvent and a base (KF) provides the desired product in 36% yield and 79% enantiomeric excess (ee) (entry 8), while NiI2 formed lower reactivity and slightly lower enantioselectivity than their precursor (entries 1–4). Further solvent screening indicated 1,2-dimethoxyethane was superior to other solvents, producing 3a in good yield and ee under room temperature (entry 5). Interestingly, the mixed solvent (DME/DCE) turned out as the best solvent to obtain both high yield and high enantioselectivity (entries 5–7), thus indicating the subtle interplay of reagents and solvents in this case. In addition, use of other nickel salts, NiBr2-DME resulted in higher ee (entry 8), while NiI2-xH2O gave the best result (entry 9).

**Reaction scope**

The generality of this catalytic enantioselective method is broad (Fig. 2). Concerning the aryl bromide, the reaction proceeded smoothly with a wide array of substrates to provide the corresponding products in moderate to high yields with universally high enantioselectivities. Notably, electron-deficient or electron-rich arenes were amenable coupling partners, in which the substituent could be placed at *para* and *meta* position. A variety of functionalities such as a nitrile (2h), trifluoromethyls (2c, 2p, 2r), esters (2d, 2m, 2q), halides (2f, 2g, 2n, 2o), ethers (2i, 2j), and boronic acid pinacol ester (2k) were all readily accommodated. Despite the ability of nickel complex to activated aryl chlorides, our approach could tolerate Ar-Cl groups (2f, 2o). In particular, sensitive functional groups including easily reduced ketone (2a) and aldehyde (2e), and triflate (2k) and boronic acid pinacol ester (2i) commonly used for cross-coupling, all remained intact under the standard reaction conditions. Furthermore, the pharmaceutically important heterocycle–pyridine (2r) was compatible as well.

Next, we sought to survey the influence of the N-vinylindole variants that could be used in the catalytic hydroarylation event. Delightfully, a diverse array of functional groups were suitable at different positions on the benzene ring of the indole, including a 6-methoxy (3s), 6-fluoro (3e), 6-cyano (3u), and 5-methyl (3v) substituent. It is worth noting that alkyl group at the C3-position of the indole scaffold was accommodated, delivering the corresponding product 3w in moderate yield but with excellent enantioselectivity, which is difficult to obtain employing previous CuH catalysis. In addition, carbazole-derived substrate afforded the desired N-alkylated product in moderate yield and enantioselectivity (3x). Gratifyingly, a diverse set of more sterically hindered (Z)-N-alkylindoles were also successfully transformed utilizing this method, and the corresponding N-alkylindoles were readily prepared in useful yields with good levels of enantioselectivity (3y–3dd). However, (E)-N-alkyl indoles performed lower reactivity and slightly lower enantioselectivity than their Z isomers (e.g., 3y: 19%, 84% ee vs. 41%, 87% ee). The isomerization of Z-N-alkenyl substrate to its E isomer was observed during the reaction process, and over 40% of the E/Z mixture could be recovered after the reaction (Supplementary Method). Of note, the C–C bond-forming event occurs regioselectively at the carbon α to the nitrogen of indoles, even in the presence of other directing groups such as amide (3z–3bb), ester (3cc), and aryl (3dd). Especially, this modular reaction could be applied to prepare important serotonin reuptake inhibitor.

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**Table 1 | Summary of the effects of crucial reaction parameters**

| Entry | Variant | Yield (%) | ee (%) |
|-------|---------|-----------|--------|
| 1     | L*1     | 36        | 79     |
| 2     | L*2, L*3, L*4, or L*5 | trace | n.d. |
| 3     | L*6     | 34        | 16     |
| 4     | L*7     | 62        | 58     |
| 5     | L*1, DME as solvent, rt | 80 | 81     |
| 6     | L*1, DCE as solvent, rt | 16 | 88     |
| 7     | L*1, DME/DCE (3:1) as solvent, rt | 82 | 86     |
| 8     | NiBr2-DME as Ni-Cat. vs. entry 7 | 78 | 88     |
| 9     | NiBr2-H2O as Ni-Cat. vs. entry 7 | 81 (77) | 92     |

*See the SI for experimental details, all reactions were carried out in 0.2 mmol scale with respect to 1a. Corrected 1H NMR yields using CH2Br2 as an internal standard were reported. The enantiomeric excesses (ee’s) were determined by HPLC analysis. Isolated yield is shown in the parenthesis. L* chiral ligand; DME 1,2-dimethoxyethane, DCE 1,2-dichloroethane, rt room temperature; h hour; n.d. not detected.
derivatives with good efficiency and enantioselectivities (3z-3bb, 81–92% ee).

In addition to aryl bromides, vinyl bromides were incorporated as well in this reaction, leading to structurally diverse chiral N-allyl indoles 4a-4f in 35–60% yields with 73–95% ee values.

Remarkably, this modular alkenylation complements previously established metal-catalyzed indole N-allylations in that di- and trisubstituted allylic products bearing aryl and alkyl groups are readily accessed27,29,31,70,71.

Besides the C(sp2) bromides, this catalytic C-C bond-forming reaction was also viable for C(sp) bromides –bromoalkynes. While the above standard conditions with ligand L*1 resulted in poor enantiocontrol for the C(sp3)-C(sp) coupling (e.g., 6a: 28% yield, 55% ee), delightfully, the reaction selectivity could be significantly improved by further optimization efforts (see Supplementary Table 7). As shown in Fig. 3, the treatment of bromoalkynes 5 and N-alkenylnolides 1 with 10 mol% NiI2 as the ligand at 0 °C could yield the corresponding chiral N-propargyl indoles 6 in mostly good yields (25–89%) and high levels of enantioselectivity (ee values of 80–97%). A variety of N-alkenyl indoles substituted at the 4-position (6b), 5-position (6c-6g), 6-position (6h-6j), and 7-position (6k, 6l) each underwent efficient hydroalkynylation to provide the corresponding products with uniformly high enantioselectivities. Of note, alkyl group at the C3-position of the indole scaffold was demonstrated being tolerated again (6m).

With regard to medicinal chemistry applications, the generation of product 6g demonstrates tolerance of a pinacol boronate subunit under the conditions of catalytic enantioselective alkynylation. Additionally, more sterically hindered cis-β-substituted N-alkenyl indoles also successfully underwent C(sp3)-C(sp) bond-formation to deliver compounds 6o and 6p, respectively, as single regioisomers with reasonable yields and good enantioselectivities. Similar to the C(sp3)-C(sp3) coupling, the reaction reactivity and stereoselectivity was influenced by the Z and E configuration of N-alkenyl indoles (e.g., 6o).
Beyond the TIPS-substituted ethynyl bromide 5a, TBS- and 3° alkyl-substituted ethynyl bromides 5b-5c proved to be viable coupling partners in this system, affording the desired indole adducts (6q-6r) in 47–74% yields with excellent enantioselectivities. However, ethynyl bromides with less steric hindered alkyl and aryl substitutents delivered inferior results (e.g., R3 = n-Bu: no reaction; R3 = Ph: 26% yield, 50% ee). In addition, it should be noted that the current L*8-ligated nickel catalysis could be expanded to enable the synthesis of chiral N-benzyl and N-allylic indoles in high enantioselectivities (e.g., 3a and 4e).

Synthetic applications

More importantly, the present method could be applied in late-stage diversification of complex drug molecules and natural products. As depicted in Fig. 4, aryl bromides derived from complex bioactive molecules canagliflozin derivative, an antidiabetic drug (7a), indomethacin, a nonsteroidal anti-inflammatory drug (7b), and vitamin E, an antioxidant (7c), coupled with N-vinylindole 1a in good yields and stereoselectivities, thus revealing the appeal that our approach might have for lead generation protocols in drug discovery. Furthermore, aryl bromides or N-alkenyl indoles bearing multiple stereocenters originated from vitamin E (7c), D-galactopyranose (7d), and citronellal (7e) were all viable substrates, affording potentially valuable N-alkyl adducts in synthetically useful yields and high diastereoselectivity. To further showcase the robustness and synthetic utility of the method, the catalytic enantioselective synthesis of N-benzyl indole 7a on a gram scale was carried out with similar efficiency (Supplementary Method 1.7).

Notably, the alkynyl group on the chiral N-propargyl indoles provided a useful and versatile handle for derivatizations (Fig. 5). For example, desilylation of 6a provided the enantioenriched terminal alkyn 8, which subsequently underwent the Sonogashira coupling to afford the aryl-substituted alkynyl product. Terminal alkyn 8 underwent a click reaction to give chiral triazole. Reduction of 8 with Lindlar Pd and H2 afforded chiral N-allylic indole, while reduction of 6a with DIBAL-H produced chiral vinylsilyl compound.

Mechanistic studies

To gain insight into the mechanism and origin of selectivity, a series of experiments well conducted. Generally, the reductive coupling...
process consists of π-bond insertion into \( L^* \)Ni–H species, oxidative addition of the resulting \( L^* \)Ni-alkyl intermediate, and reductive elimination to form product and the \( L^* \)Ni-H catalyst \(^{46-63} \). Take the reductive coupling of \( N \)-alkenyl indoles with aryl halides as an example, competition experiments were performed to compare the reactivity between different aryl halides, indicating that (i) electron-deficient aryl bromide is more reactive than an electron-rich one (Fig. 6a–i), and (ii) aryl bromide is more reactive than aryl iodide (Fig. 6a–ii). In fact, a competing reductive hydrodehalogenation event was observed when an aryl iodide was used as the electrophile (Fig. 6a–iii) \(^{73,74} \), suggesting it is disadvantaged for the final product formation that oxidative addition of \( L^* \)Ni complex prior to generation of \( L^* \)Ni-alkyl intermediate. Next, the reductive coupling of \( 1a \) was chosen for kinetic studies, and the reaction progress was monitored by \(^{19} \)Fa n d \(^{1} \)HN M R . Initial experiments disclosed that the reaction was zero-order in \( N \)-alkenyl indole, first-order in catalyst and aryl bromide, and fractional-order in diethoxymethylsilane (Fig. 6b, see also Supplementary Method 1.9.1). Moreover, Hammett studies were also performed to evaluate the influence that electronic variation of the aryl electrophiles had on the rate of hydroarylation (Fig. 6c) \(^{75,76} \). As a result, a variety of para-substituted aryl bromides reacted with \( N \)-vinylindole \( 1a \) at different rates, indicating that electronic variation of the aryl electrophile had a remarkable impact on the rate of \( N \)-vinylindole hydroarylation. A linear relationship was further observed through a Hammett plot. The positive slope (\( \rho = 0.67 \)) suggests negative charge accumulation in the turnover-determining transition state, which is stabilized by electron-withdrawing substituents. Taken together, the above results reveal that oxidative addition is most likely the turnover-limiting step.

Furthermore, a linear correlation was observed by nonlinear effect studies on the enantiomeric composition of chiral ligand \( L^*1 \) and \( N \)-alkylindole product \( 3o \) (Fig. 7a), which is consistent with a ligated nickel catalyst being of a monomeric nature. To identify the enantiodetermining step of the \( N \)-vinylindole hydroarylation reaction, we next investigated linear free energy relationships (LFERs) between the Hammett electronic parameters of various para-substituted aryl bromides and the enantioselectivities of the corresponding products (Fig. 7b) \(^{77,78} \). A linear correlation was observed with para-substituted aryl bromides as enantioselectivity increased with the introduction of electron-withdrawing groups (\( \rho = 1.07 \)): 56% ee and 92% ee were observed for 4-methoxyphenyl bromide (\( \sigma = -0.27 \)) and 4-acetylphenyl bromide (\( \sigma = 0.50 \)), respectively, implying that the enantioselectivity of the process is not solely under catalyst control. In addition, the silane did essentially not affect the enantioselectivity of the reaction. On the basis of these results, oxidative addition is most likely the enantiodetermining step.

As shown in Fig. 8, a more complete description of the proposed mechanism is outlined. The syn-hydrometallation of an \( L^* \)Ni-H species into a \( N \)-alkenyl indole would form alkyl-Ni(II) species (B). Subsequently, the selective oxidative addition between a particular isomer of the alkyl-Ni(II) species and the bromide (2, 5) would ultimately generate a single alkyl-Ni(III)-R enantiomer (C), because this step would be both the turnover-determining step and the enantiodetermining step in the
presence of a chiral ligand (L*1, L*8). In particular, the favored enantioselective transition state TS-C would lead to the major enantiomeric product, owing to steric interactions with the ligand phenyl substituents (TS-C'). Then, stereospecific reductive elimination would afford the desired product (3, 4, 6, 7) and regenerate the active nickel hydride species (A). Alternatively, the competitive alkyl-Ni homolysis process was also possible53,55,62,79.

In summary, we have developed a nickel-catalyzed enantioselective, modular coupling of indole-based N-alkyl-Ni fragments with C(sp2)/C(sp) bromides. By the use of easily accessible and stable indole-derived alkenes as nucleophiles, this protocol enables streamlined preparation of enantioenriched N-alkylindole molecules under mild conditions, with previously inaccessible functional group tolerance and chemical space. Application in late-stage diversification of several complex drug molecules and natural products as well as chiral syntheses demonstrates its potential utility in the synthesis of valuable chiral N-alkylated bioactive compounds.

Methods
General procedure for the enantioselective synthesis of N-benzyl and N-alllylic indoles
To an oven-dried 8.0 mL Teflon-screw cap test tube containing a magnetic stir was charged with NiI2·H2O (16.8 mg, 10 mol%) and ligand L*1 (20.2 mg, 15 mol%) under an N2 atmosphere using glove-box techniques. Subsequently, anhydrous DME (1.5 mL) was added, and the mixture was stirred for 15 min at room temperature. Next, KF (35.0 mg, 0.60 mmol, 1.5 equiv.), N-alkenyl indole 1 (0.40 mmol, 1.0 equiv), aryl/alkenyl bromide 2 (0.80 mmol, 2.0 equiv.), DCE (0.5 mL), and (OEt)2MeSiH (78.0 µL, 0.48 mmol, 1.2 equiv.) were sequentially added. Then the tube was sealed with airtight electrical tapes and removed from the glove box and stirred at room temperature for 20–48 h. After that, the reaction mixture was diluted with saturated NH4Cl (aq., 1.0 mL) and EtOAc (5.0 mL). The aqueous phase was extracted with EtOAc (2 × 5.0 mL) and the combined organic phases were concentrated. The crude mixture was purified by flash column chromatography on silica gel using a mixture of PE/EtOAc as eluent to obtain the desired product 3, 4, 7.
tube was sealed with airtight electrical tapes and removed from the glove box and stirred at 0 °C for 36 h. After that, the reaction mixture was diluted with saturated NH4Cl (aq., 1.0 mL) and EtOAc (5.0 mL). The aqueous phase was extracted with EtOAc (2 × 5.0 mL) and the combined organic phases were concentrated. The crude mixture was purified by flash column chromatography on silica gel using a mixture of PE/EtOAc as eluent to obtain the desired product 6.

Data availability
The data relating to the materials and methods, experimental procedures, mechanism research, NMR spectra, and HPLC spectra are available in the Supplementary Information. All other data are available from the authors upon request.

References
1. Gul, W. & Hamann, M. T. Indole alkaloid marine natural products: an established source of cancer drug leads with considerable promise for the control of parasitic, neurological and other diseases. Life Sci. 78, 442–453 (2005).
2. Kochanowska-Karamyan, A. J. & Hamann, M. T. Marine indole alkaloids: potential new drug leads for the control of depression and anxiety. Chem. Rev. 110, 4489–4497 (2010).
3. Sravanthi, T. V. & Manju, S. L. Indoles: a promising scaffold for drug development. Eur. J. Pharm. Sci. 91, 1–10 (2016).
4. Singh, P. T. & Singh, M. O. Recent progress in biological activities of indole and indole alkaloids: potential new drug leads for the control of depression and anxiety. Eur. J. Biol. Chem. 91, 9–25 (2018).
5. Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J. Med. Chem. 57, 10257–10274 (2014).
6. Bandini, M. & Eichholzer, A. Catalytic functionalization of indoles in a new dimension. Angew. Chem. Int. Ed. 48, 9608–9644 (2009).
7. Dalpozzo, R. Strategies for the asymmetric functionalization of indoles: an update. Chem. Soc. Rev. 44, 742–778 (2015).
8. Trubitsõn, D. & Kanger, T. Enantioselective catalytic synthesis of N-alkylated indoles. Symmetry 12, 1184 (2020).
9. Chen, J.-B. & Jia, Y.-X. Recent progress in transition-metal-catalyzed enantioselective indole functionalizations. Org. Biomol. Chem. 15, 3550–3567 (2017).
10. Lakhdari, S. et al. Nucleophilic reactivities of indoles. J. Org. Chem. 71, 9088–9095 (2006).
11. Otero, N., Mandado, M. & Mosquera, R. A. Nucleophilicity of indole derivatives: activating and deactivating effects based on proton affinities and electron density properties. J. Phys. Chem. A 111, 5557–5562 (2007).
12. D’Ambra, T. E. et al. Conformationally restrained analogs of pravdoline: nanomolar potent, enantioselective, (aminoalkyl)indole agonists of the cannabinoid receptor. J. Med. Chem. 35, 124–135 (1992).
13. Mahaney, P. E. et al. Synthesis and activity of a new class of dual acting norepinephrine and serotonin reuptake inhibitors: 3-(1H-indol-1-yl)-3-arylprop-1-amines. Org. Chem. 74, 8455–8466 (2006).
14. Hernandez, L. S. et al. Flinderoles A–C: antimalarial bis-indole alkaloids from flindersia species. Org. Lett. 11, 329–332 (2009).
15. Gehling, V. S. et al. Discovery, design, and synthesis of indole-based EZH2 inhibitors. Bioorg. Med. Chem. Lett. 25, 3644–3649 (2015).
16. Vaswani, R. G. et al. Identification of (R)-N-[(4-Methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(methyl)-2-methyl-1(1-(2,2,2-trifluoroethyl)piperidin-4-yl)(ethyl)]-1H-indole-3-carboxamide (CPI-1205), a Potent and Selective Inhibitor of Histone Methyltransferase EZH2, Suitable for Phase I Clinical Trials for B-Cell Lymphomas. J. Med. Chem. 59, 9928–9941 (2016).
17. Bandini, M., Eichholzer, A., Tragni, M. & Umani-Ronchi, A. Enantioselective phase-transfer-catalyzed intramolecularaza-michael reaction: effective route to pyrazino-indole compounds. Angew. Chem. Int. Ed. 47, 3238–3241 (2008).
18. Cai, Q., Zheng, C. & You, S.-L. Enantioselective intramolecular Aza-Michael additions of indoles catalyzed by chiral phosphoric acids. Angew. Chem. Int. Ed. 49, 8666–8669 (2010).
19. Ye, K.-Y., Cheng, Q., Zhuo, C.-X., Dai, L.-X. & You, S.-L. An Iridium(l) N-heterocyclic carbene complex catalyzes asymmetric intramolecular allylic amination reactions. Angew. Chem. Int. Ed. 55, 8113–8116 (2016).
20. Kainz, O. M. et al. Asymmetric copper-catalyzed C–N cross-couplings induced by visible light. Science 351, 681–684 (2016).
21. Arredondo, V., Hiew, S. C., Gutman, E. S., Premachandra, I. D. U. A. & Van Vranken, D. L. Enantioselective palladium-catalyzed carbene insertion into the N–H bonds of aromatic heterocycles. Angew. Chem. Int. Ed. 56, 4156–4159 (2017).
22. Chen, M. & Sun, J. Catalytic Asymmetric N-Alkylation of Indoles and Carbazoles through 1,6-Conjugate Addition of Aza-para-quinone Methides. Angew. Chem. Int. Ed. 56, 4583–4587 (2017).
23. Cai, Y., Gu, Q. & You, S.-L. Chemoselective N–H functionalization of indole derivatives via the Reissert-type reaction catalyzed by a chiral phosphoric acid. Org. Biomol. Chem. 16, 6146–6154 (2018).
24. Allen, J. R., Bahamonde, A., Furukawa, Y. & Sigman, M. S. Enantioselective N-alkylation of indoles via an intermolecular Aza-Wacker-type reaction. J. Am. Chem. Soc. 141, 8670–8674 (2019).
25. Wang, Y., Wang, S., Shan, W. & Shao, Z. Direct asymmetric N-propargylation of indoles and carbazoles catalyzed by lithium SPINOL phosphate. Nat. Commun. 11, 226 (2020).
26. Enders, D., Wang, C. & Raabe, G. Enantioselective synthesis of 3H-Pyrrolo[1,2-a]Indole-2-carbaldehydes via an organocatalytic domino Aza-Michael/Aldol condensation reaction. Synthesis 2009, 4119–4124 (2009).
27. Stanley, L. M. & Hartwig, J. F. Iridium-Catalyzed Regio- and Enantioselective N-Alkylation of Indoles. Angew. Chem. Int. Ed. 48, 7841–7844 (2009).
28. Hong, L., Sun, W., Liu, C., Wang, L. & Wang, R. Asymmetric Organo-nocatalytic N-Alkylation of Indole-2-carbaldehydes with α,β-Unsaturated Aldehydes: One-Pot Synthesis of Chiral Pyrrole[1,2-a]Indole-2-carbaldehydes. Chem. Eur. J. 16, 440–444 (2010).
29. Trost, B. M., Osipov, M. & Dong, G. Palladium-catalyzed dynamic kinetic asymmetric transformations of vinyl aziridines with nitrogen heterocycles: rapid access to biologically active pyrroles and indoles. J. Am. Chem. Soc. 132, 15800–15807 (2010).
30. Huang, L., Wei, Y. & Shi, M. Asymmetric substitutions of O-Boc-protected Morita–Baylis–Hillman adducts with pyrrole and indole derivatives. Org. Biomol. Chem. 10, 1396–1405 (2012).
31. Chen, L.-Y. et al. Enantioselective direct functionalization of indoles by Pd/sulfoxide-phosphate-catalyzed N-allylic alkylation. Org. Lett. 17, 1381–1384 (2015).
32. Mukherjee, S., Shee, S., Poisson, T., Besset, T. & Biju, A. T. Enantioselective N-heterocyclic carbene-catalyzed cascade reaction for the synthesis of pyrroloquinolines via N–H functionalization of indoles. Org. Lett. 20, 6998–7002 (2018).
33. Yang, X. et al. Enantioselective indole N–H functionalization enabled by addition of carbene catalyst to indole aldehyde at remote site. ACS Catal. 9, 10971–10976 (2019).
34. Liu, W.-B., Zhang, X., Dai, L.-X. & You, S.-L. Asymmetric N-alkylation of indoles through the iridium-catalyzed allylic alkylation/oxidation of indolines. Angew. Chem. Int. Ed. 51, 5183–5187 (2012).
35. Chen, Q.-A., Chen, Z. & Dong, V. M. Rhodium-catalyzed enantioselective hydroamination of alkenes with indolines. J. Am. Chem. Soc. 137, 8392–8395 (2015).
36. Xu, K., Gilles, T. & Breit, B. Asymmetric synthesis of N-allylic indoles via regio- and enantioselective alkylation of aryl hydrazines. Nat. Commun. 6, 7616 (2015).
37. Zi, Y., Lange, M., Schultz, C. & Vlottihejv, I. Latent nucleophiles in Lewis base catalyzed enantioselective N-alkylations of N-heterocycles. Angew. Chem. Int. Ed. 58, 10727–10731 (2019).
hydrometallation of olefins; F.L. directed the asymmetric metal-catalyzed cross-couplings. Nature Commun. 12, 638 (2021).

63. Wang, S. et al. Enantioselective access to chiral aliphatic amines and alcohols via Ni-catalyzed hydroalkylations. Nat. Commun. 12, 2771 (2021).

64. Maki, Y., Mori, H. & Endo, T. Xanthate-mediated controlled radical polymerization of N-vinylindole derivatives. Macromolecules 40, 6109–6130 (2007).

65. Nakabayashi, K. & Mori, H. Recent progress in controlled radical polymerization of N-vinyl monomers. Eur. Polym. J. 49, 2808–2838 (2013).

66. Rainka, M. P., Aye, Y. & Buchwald, S. L. Copper-catalyzed asymmetric conjugate reduction as a route to novel β-azaheterocyclic acid derivatives. Proc. Natl Acad. Sci. USA 101, 5821–5823 (2004).

67. Sorensen, C. C. & Leibrish, F. A. Stereoselective helix-sense-selective cationic polymerization of N-vinylcarbazole using chiral Lewis acid catalysis. J. Am. Chem. Soc. 144, 8487–8492 (2022).

68. Wu, X., Ren, J., Shao, Z., Yang, X. & Qian, D. Transition-metal-catalyzed asymmetric couplings of α-aminoalkyl fragments to access chiral alkylamines. ACS Catal. 11, 6560–6577 (2021).

69. Rattanangkool, E., Vilaivan, T., Sukwattanasinitt, M. & Wacharasin, C. Nickel-catalyzed asymmetric hydroamination of olefins; X.Y. directed some experiments on the enantioselective synthesis of N-benzyl indoles; L.L. and J.R. optimized the reaction conditions, conducted the control experiments, evaluated the scope of the reaction and applied this reaction to the diversification of the natural products and drugs; J.Z. and X.W. helped to evaluate the scope of the reaction; D.Q. wrote the manuscript.

Competing interests
The authors declare no competing interest.

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Author contributions
D.Q. directed the enantioselective synthesis of N-benzyl and N-allyl indoles; Z.S. directed the enantioselective synthesis of N-propargyl indoles; X.Y. directed some experiments on the enantioselective synthesis of N-benzyl indoles; L.L. and J.R. optimized the reaction conditions, conducted the control experiments, evaluated the scope of the reaction and applied this reaction to the diversification of the natural products and drugs; J.Z. and X.W. helped to evaluate the scope of the reaction; D.Q. wrote the manuscript.

70. Kim, S. W., Schempp, T. T., Zbieg, J. R., Stivala, C. E. & Krische, M. J. Regio- and enantioselective iridium-catalyzed N-allylation of indoles and related azoles with racemic branched alky-substituted allylic acetates. Angew. Chem. Int. Ed. 58, 7762–7766 (2019).

71. Sun, M., Liu, M. & Li, C. Rhodium-catalyzed chemo-divergent regio- and enantioselective allylic alkylation of indoles. Chem. Eur. J. 27, 3457–3462 (2021).

72. Cernek, T., Dykstra, K. D., Tyagarajan, S., Vachal, P. & Kriska, S. W. The medicinal chemist’s toolbox for late stage functionalization of drug-like molecules. Chem. Soc. Rev. 45, 546–576 (2016).

73. Lipshutz, B. H., Tomooka, T. & Pfeiffer, S. S. Mild and selective reductions of aryl halides catalyzed by low-valent nickel complexes. Tetrahedron Lett. 42, 7737–7740 (2001).

74. Alonso, F., Beletskaya, I. P. & Yus, M. Metal-mediated reductive hydrodehalogenation of organic halides. Chem. Rev. 102, 4009–4092 (2002).

75. Hammett, L. P. The effect of structure upon the reactions of organic compounds. Benzen derivatives. J. Am. Chem. Soc. 59, 96–103 (1937).

76. Hansch, C., Leo, A. & Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. Chem. Rev. 91, 165–195 (1991).

77. Jensen, K. H. & Sigman, M. S. Evaluation of catalyst acidity and substrate electronic effects in a hydrogen bond-catalyzed enantioselective reaction. J. Org. Chem. 75, 7194–7201 (2010).

78. Bandar, J. S., Pirnot, M. T. & Buchwald, S. L. Mechanistic studies lead to dramatically improved reaction conditions for the Cu-catalyzed asymmetric hydroamination of olefins. J. Am. Chem. Soc. 137, 14812–14818 (2015).

79. Gutierrez, O., Tellis, J. C., Primer, D. N., Molander, G. A. & Kozlowski, M. C. Nickel-catalyzed cross-coupling of photoredox-generated radicals: uncovering a general manifold for stereocoreversion in nickel-catalyzed cross-couplings. J. Am. Chem. Soc. 137, 4896–4899 (2015).