Nickel-catalyzed enantioselective annulation/alkynylation and Sonogashira reaction to form C(sp$^3$)-C(sp) and C(sp$^2$)-C(sp) bonds, respectively

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Abstract

While traditional Sonogashira reaction requires a palladium catalyst and a copper co-catalyst, some recent variants were reported being promoted by single transition metals. Here we report a single nickel-catalyzed tandem Heck-Sonogashira annulation/alkynylation for enantioselectively constructing C(sp$^3$)-C(sp) bond. In addition, using the same catalytic system, Sonogashira C(sp$^2$)-C(sp) cross-coupling has also been achieved. The alkynylations described in this report are important for the three reasons: 1. C(sp$^3$)/(sp$^2$)-C(sp) bonds exist in many bioactive natural products and drug molecules as well as their key synthetic intermediates; 2. There was no precedent for single nickel-catalyzed Sonogashira reaction owing to the difficulties caused by strong coordination of nickel to the triple bond to inactivate the catalyst; 3. Isolation and characterization of single-crystal structure of a resting state intermediate, di-phosphine chelated σ-alkyl-Ni$^{II}$-I complex, which provided crucial evidence to support the mechanistic postulation and guided DFT calculations.

The carbon-carbon bond is certainly the “foundation” of molecular backbones which give rise to an enormous number of man-made and natural materials. Thus, the development of efficient methods for carbon-carbon bond formation lies at the central theme of organic synthesis$^1$. During the past decades, a wide variety of transition metal-catalyzed carbon-carbon cross-coupling reactions have been developed, including two processes recognized with Nobel Prizes in Chemistry$^1$. Carbon-carbon cross-coupling reactions could be categorized into three types: C-C(sp$^3$), C-C(sp$^2$) and C-C(sp) formations. The first two (for example, the Heck reaction, Suzuki-Miyaura couplings, and Negishi couplings, et al) have been more thoroughly investigated than the last one possible owing to stability and geometric versatility of sp$^3$ and sp$^2$ carbons. Nonetheless, given the fact that the alkynes are functional moieties of numerous natural products and pharmaceutical compounds (Fig. 1a)$^{2,3}$, and feature broad applications in bio-orthogonal labeling (click chemistry) and material science$^{4,5}$, developing C-C(sp) bond formation methods should be one of the chemists’ most pressing tasks. In addition, the sp carbons
brought in by C-C(sp) cross-couplings could be readily transformed into sp³ and sp² carbons under various mild reaction conditions. In this regard, C-C(sp) cross-couplings could be considered as significant complementary approaches to C-C(sp³)/C(sp²) couplings in building up carbon-carbon backbones of natural products, including indole alkaloid derivatives. Among indole alkaloids, 3,3-disubstituted-2-oxoindoles, as either final products⁶ or key intermediates (Fig. 1b)⁷⁻⁸, are of great interest to synthetic chemists and medicinal chemists owing to their biological and pharmaceutical activities. Recently, Ge, Lu and coworkers reported a creation of quaternary centers in 3,3-disubstituted-2-oxoindole alkaloids (Fig. 1c)⁹ via an enantioselective Heck-Sonogashira annulation/alkynylation sequence in a traditional catalytic system where Pd catalyst and Cu co-catalyst were required, plus stoichiometric amount of Ag additive. Here we report our enantioselective Heck/Sonogashira reaction to access the same targets but with using single nickel catalyst (Fig. 1e). In addition, under similar reaction conditions, we forged C(sp²)-C(sp) bonds that are also essential to a number of important natural products and drugs (Fig. 1a).

In a traditional Sonogashira reaction, a palladium catalyst and a copper co-catalyst were typically employed to couple terminal alkynes with electrophiles. Recent years have seen the emerging of Sonogashira type reactions catalyzed by single transition metal, such as Pd¹⁰, Cu¹¹⁻¹³, Ir¹⁴, or Rh¹⁵. Compared with noble metals, nickel catalysis holds high potential for economical and operational benefits owing to its low toxicity, ready commercial availability at much lower cost compared with that of noble metals such as Pd, Ir or Rh. Consequently, there have been reports on some elegant C-C couplings catalyzed by nickel catalysts¹⁹⁻³². Our research group have had the experience of organic transformations promoted by nickel-catalysis ³⁰⁻³³, thus we embarked on using a nickel catalyst rather than palladium in an enantioselective Heck/Sonogashira sequence which forged chiral C(sp³)-C(sp) bond to create sp³ quaternary center. Thus far, there has no precedent for alkynylation with using single nickel catalyst, which could be attributed to the strong coordination of nickel to the triple bond to inactivate the catalyst (Fig. 1d), as observed by Cassar and co-workers³⁴. In this report, we present a single nickel-catalyzed enantioselective Heck-Sonogashira method to establish C(sp²)-C(sp) bonds enantioselectively (Fig. 1e). In addition, we describe our application of this single nickel catalytic system for constructing C(sp²)-C(sp) bonds (Fig. 1e). To the best of our knowledge, this was the first example to employ single nickel to catalyze Sonogashira coupling of terminal alkynes. Of note, in previous reported works, terminal alkynes had to be activated by copper co-catalyst whenever nickel was used as catalyst³⁵⁻³⁷, or only the insertion products, rather than cross-coupling products, were obtained in the absence of copper³⁸⁻⁴⁰. Thus, this method broke the status quo that single nickel catalyst, without copper co-catalyst, could not function for the couplings of terminal alkynes. Most importantly, single-crystal structure of di-phosphine-chelated σ-alkyl-NiII-I complex, which was widely considered as actively catalytic intermediate, was isolated and fully characterized, providing crucial evidence to support the mechanistic postulation and guide DFT calculations.
Fig. 1 | Selected alkyne-containing or alkyne-related natural products and drug molecules and transition metal-catalyzed alkynylations (a–e). a. Alkyne-containing natural products and drug molecules. b. 3,3-Disubstituted-2-oxoindole derivatives as natural products, drug molecules and intermediates to natural products. c. Previous Pd-catalyzed Heck-Sonogashira annulation/alkynylation and Pd-catalyzed cross-coupling. d. Challenges in alkynylation when single Ni catalyst was used. e. Ni-catalyzed enantioselective Heck-Sonogashira annulation/alkynylation and Sonogashira coupling to form C(sp^3)-C(sp) and C(sp^3)-C(sp) bonds, respectively (this work).

Results
Preliminary studies and ligand optimization of annulation/alkynylation. We surmised that the Ni-catalyzed enantioselective Heck/Sonogashira sequence might be possible using terminal alkynes if some special ligands could prevent strong coordination of nickel to the triple bond. Accordingly, our investigation started from screening chiral bidentate ligands by subjecting N-(2-iodophenyl)-N-methylmethacrylamide (1a) with phenylacetylene to a catalyst system which we previous used in decarboxylative alkylation and cyanation reactions (Fig. 2)\textsuperscript{31,32}. In this catalytic system, air-stable and inexpensive nickel chloride (NiCl\textsubscript{2}) was employed as catalyst, 4-cyanopyridine N-oxide as base, Zn as reducing reagent, and LiI and KF as additives. When chiral pyridine-oxazoline-type were employed as ligands (L\textsuperscript{*}1 – L\textsuperscript{*}3), the reaction gave the desired product in good yield but with poor enantiomeric excess (ee). However, reaction using 2-trifluomethylypyridine-oxazoline ligand L\textsuperscript{*}4 only afforded trace amount of the product. A bis-(oxazoline) ligand L\textsuperscript{*}5 resulted in poor yield, and other bis-(oxazoline) ligands (L\textsuperscript{*}6 – L\textsuperscript{*}10) with extended distance between the two nitrogens gave almost no desired product. Trident ligand L\textsuperscript{*}11 and phosphine ligands L\textsuperscript{*}12 and L\textsuperscript{*}13 furnished trace and no product, respectively. Although chiral N, P ligand L\textsuperscript{*}14 did not afford the desired product, phosphine-oxazoline N, P ligand L\textsuperscript{*}15 surprised us with a high yield, albeit a low ee. Encouraged by this result, we then screened quite a few chiral phosphine-oxazoline N, P-ligands with various substituents at 4-position of oxazoline ring, leading to the identification of L\textsuperscript{*}25 which afford the product in 88% yield with 75% ee. We then tried to improve ee by changing solvent, and found that the reaction in 1-methyl-2-pyrroloidinone (NMP) could afford the asymmetric product in a relatively high ee. Switching a phenyl group in the phosphine-oxazoline N, P ligand to naphthalene shut down the reaction (L\textsuperscript{*}26), which implied that the reaction is sensitive to modification on the phenyl rings of L\textsuperscript{*}. Thus, the phosphine-oxazoline N, P ligands with various substituents on their phenyl rings (L\textsuperscript{*}28–L\textsuperscript{*}30) were examined, which lead to identifying L\textsuperscript{*}30 (77% yield/86 % ee). What really delighted us was the identification of L\textsuperscript{*}33 (72% yield/93% ee) via screening of phosferox N, P ligands.

Substrate scope of the annulation/alkynylation. With the optimized conditions in hand, a great array of substrates was examined (Fig. 3). Various substituted arylacetylenes were first tested (3a-3m), furnishing products in mild to good yields with good enantioselectivities (> 90% ee). Functional groups, including fluorine (3f, 3g), chlorine (3h), methoxy (3j), nitrile (3k), and ester (3l), were all well tolerated. Thienylacetylene and ferrocenylacetylene could be coupled to form the products in excellent ee (3m and 3n). Substituents on arenes of the substrate 1a varying from electron-rich to electron-deficient groups were all compatible (3o-3u), affording the products in satisfactory yields with good ee values. The reaction with the β-substituted acrylamides, such as phenyl or benzyl-substituted ones, could perform to create quaternary carbon centers enantioselectively (3v–3y). Ethyl substituent on the N in the substrate affected the enantioselectivity moderately (3z and 3aa), but benzyl group seemed to bring the enantioselectivity back (3ab) albeit in lower yield. We have also prepared 3,3-disubstituted-2-oxoindole derivatives with protected alkynes (3ac–3af), which could be readily transformed in terminal alkyne-containing derivatives after removing protecting groups. Protected propargylamine-containing product 3ag’s enantiomeric structure was unambiguously unveiled by its single-crystal x-ray diffraction data. When the enantiomer of L\textsuperscript{*}33 was used as the ligand, we obtained S-configuration product (3ah) which could be used as a key intermediate in the synthesis of natural products
esermethole, physostigmine, flustramide A and flustramide B$^{7,8}$.

Fig. 2 | Ligand screening for single nickel-catalyzed asymmetric Heck-Sonogashira annulation/alkynylation.

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$^a$ NMP as solvent, and 4Å MS was added. $^b$ DMF as solvent. $^c$ DMF as solvent, $^d$ reactions run at 80℃.
Fig. 3 | Substrate scope of Ni-catalyzed enantioselective tandem Heck-Sonogashira annulation/alkynylation.
Reactions were run at 0.2 mmol scale with L*33 as the ligand. a The enantiomer of L*33 was used as ligand.
Fig. 4 | Substrate scope of the Ni-catalyzed Sonogashira coupling. Reactions were run at 0.5 mmol scale with L as 1,10-phenanthroline (phen). * Reaction temperature 70 °C.

Ni-catalyzed Sonogashira coupling. Encouraged by the success in the above-described tandem
Heck-Sonogashira reaction to establish $C(sp^3)$-$C(sp)$ bonds, we were then wondering some variants of the catalytic system could be used to realize the constructions of $C(sp^3)$-$C(sp)$ bonds. Buter, Feringa and co-workers recently reported complementary approach to the Sonogashira reaction to forge $C(sp^3)$-$C(sp)$ bond\(^1\). However, the method requires preparation of air- and moisture-sensitive lithium acetylides from terminal alkynes. Therefore, we were intrigued to explore nickel catalyzed Sonogashira cross-coupling using alkynes directly. By switching the chiral ligand to commonly used achiral ligand 1,10-phenanthroline (phen), we quickly located the optimized reaction conditions under which a number of substituted aryl iodide substrates were subjected to single nickel-catalyzed Sonogashira couplings (Fig. 4). It was found that the reactions with aryl iodides containing electron-neutral, -donating and -withdrawing groups were all proceeded smoothly to furnish their corresponding products in mild to good yields (5b–5l). Various functional groups, such as chloro (5d, 5k, 5o–5t, 5v), ether (5g, 5j), ester (5f), trifluoromethyl (5h), hydroxy (5i) and cyano (5e) were all compatible to the established conditions. X-ray diffraction analysis of single crystal of 5h clearly revealed the formation of $C(sp^2)$-$C(sp)$ bond. Notably, heteroaryl iodides could afford coupling products in reasonable yields (5m and 5n). We also explored the scope of acetylenes (5o–5x) including protected alkynes (5u–5x), and found that functional groups on phenyl rings in aryl acetylenes were well tolerated too (5o–5t). Under the established conditions with a slight increase of the reaction temperature (from 60 °C to 70 °C), aryl bromide substrates performed as effective as the iodo ones in terms of yield and scope (5a–5f and 5y–5al). Single crystal X-ray analysis of 5ak and 5al clearly showed the $C(sp^3)$-$C(sp)$ bond formation.

**Fig. 5. Synthetic applications of Ni-catalyzed asymmetric annulation/alkynylation.** Conditions: a) n-Bu$_4$NF, THF, 30 °C, 3 h; b) TsN$_3$, CuTc, toluene, 30 °C, 24 h; (c) NiCl$_2$, 4-cyanopyridine N-oxide, KF, Zn, Trifluoroacetic anhydride, H$_2$O, DMAc, 30 °C, 24 h; (d) Pd/C, H$_2$, MeOH, 30 °C, 12 h; e) N-Tosyl-2-iodoaniline, Pd(PPh$_3$)$_2$Cl, Cul, 1,1,3,3-Tetramethylguanidine, DMF, 50 °C, 24 h.

**Synthetic utility of the annulation/alkynylation method.** To showcase the synthetic utility of Ni-catalyzed asymmetric annulation/alkynylation, we explored further chemical manipulations of the annulation/alkynylation products (Fig. 5). For example, oxindole 6, obtained from deprotection of 3ae which was prepared in gram scale via the annulation/alkynylation (Fig. 3), was subjected to click
chemistry to afford triazole 7a, or to our previously developed cyanation to furnish exclusively Markovnikov vinyl nitrile 7b. From intermediate 6, we also prepared asymmetric 3,3-disubstituted oxindole 7c which is difficult to be accessed enantioselectively otherwise. Oxindole 7d, an important intermediate for natural product synthesis, was readily harvested from chemical transformation of 6.

Fig. 6 | DFT calculation of Ni-catalyzed asymmetric annulation/alkynylation and Sonogashira coupling, a-b. a. DFT-calculated free-energy profiles of the resting states and transition states (TS) (including the optimized geometries of TS1-4) in Ni-catalyzed asymmetric annulation/alkynylation. b. Single-crystal structure of a resting state intermediate, di-phosphine-chelated σ-alkyl-Ni(II)-I complex 15.

**Mechanistic studies of annulation/alkynylation.** To gain additional insights into the mechanism, we carried out density-functional theory (DFT)-calculations to study the free energy profiles of a proposed pathway (Fig. 6a). Oxidative addition of 1a onto Ni0 forms complex B, which was 59.3 kcal/mol exothermic (A→B). The energy of B was set to zero for simplicity. Cyclization of B yielded resting state C to which a migratory insertion of alkyne afforded D with disrupting the Ni-O coordination. It should be noted that the amide oxygen assisted the abstraction of the alkyne terminal proton in the transition state TS3. The rate limiting step was the coupling step with a reasonable energy
barrier of 26.1 kcal/mol, which is consistent with previous DFT studies on the coupling reactions catalyzed by Ni and Cu. The mechanistic postulation (Fig. 6a) was crucially based on the existence of resting state complex C whose isolation and characterization would provide key evidence to support the proposed mechanistic pathway. Given the difficulties in harvesting the resting state C, we shifted our focus to getting a complex analogous to C with using a structurally less sophisticated di-phosphorous ligand (14). After tremendous effort, we were eventually able to obtain an instantaneous intermediate state di-phosphine chelated σ-alkyl-NiI-I complex (15) whose structure was assigned unambiguously by X-ray crystallography (Fig. 6b). Complex 15 provided strong supporting evidence that the nickel-ligand-substrate complex C was formed before addition of terminal alkyne. Isolation and characterization of complex 15 is extremely meaningful as these kinds of resting states have previously been considered as an unisolatable active species in catalytical cycles.

Fig. 7 | Elucidation of reaction mechanism of Ni-catalyzed Sonogashira coupling. a. Preparation of metal-ligand-substrate complex 16 and Sonogashira coupling catalyzed by complex 16. b. DFT-calculated free-energy profiles of Ni-catalyzed Sonogashira coupling and the optimized geometries of transition states.

Mechanistic studies of Ni-catalyzed Sonogashira coupling. In order to elucidate the reaction mechanism of the formation of C(sp²)-C(sp) bond, we synthesized the organo-nickel complex 16 (Fig. 7a) which was then used to catalyze the Sonogashira coupling reaction of 4ab and 2a to afford product
5ab in 62% yield. The stoichiometric reaction of the organonickel complex 16 with terminal alkyne 2a could also form 5ab, albeit in lower yield (see SI). These results indicated the complex 16 could be a crucial intermediate in the catalytic cycle. DFT calculations were performed on a proposed pathway involving activation of terminal alkynes by nickel (Fig. 7b). The alkyne terminal proton was likely attracted by the weak base 4-cyanopyridine N-oxide, and the transformation from F to G was almost barrierless. The rate-limiting step was the coupling step from G to H, which seemed to encounter a reasonable barrier of 16.0 kcal/mol (TS6).

Conclusions

In summary, we have developed a single nickel-catalyzed enantioselective Heck/Sonogashira annulation/alkynylation and a single nickel-catalyzed Sonogashira reaction to forge C(sp^3)-C(sp) and C(sp^2)-C(sp) bonds, respectively. The reactions, with broad substrate scopes and mild conditions, are the first single nickel-catalyzed Sonogashira-type couplings without using co-catalyst. The usefulness of our methods was demonstrated by not only a broad scope across a range of both terminal alkyne and coupling partners, but also the gram-scale further transformations of the coupling products. Based on the single-crystal structure of a model resting state intermediate and the DFT calculations, a convincing mechanism was proposed to illustrate a reaction pathway where nickel activates terminal alkynes. The C(sp^2/sp^2)-C(sp) bond formations described in this report provide inexpensive and environmentally friendly complimentary approaches to the existing noble metal-catalyzed coupling methods.

Methods

General Procedure for Ni-Catalyzed Annulation/Alkynylation Reaction. To a solution of a chiral ligand (0.04 mmol) in NMP (1.0 mL) was added nickel chloride (0.03 mmol) to result in a mixture which was stirred under N₂ at room temperature for 1 h. Then, N-(2-iodoaryl)acrylamide 1 (0.20 mmol), terminal alkyne 2 (0.40 mmol), 4-cyanopyridine N-oxide (0.4 mmol), KF (0.30 mmol), NaI (0.3 mmol), and zinc powder (0.2 mmol), and NMP (3.0 mL) were added to the mixture successively. The reaction mixture was heated under N₂ at 80 °C for 48 h, poured into water (80 mL), and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with brine (8 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual crude was subjected to flash column chromatography (hexanes: EtOAc) to afford the product.

General Procedure for Ni-Catalyzed Sonogashira Coupling of Aryl Iodide (or Bromide) and Terminal Alkyne. To a solution of 1,10-phenanthroline (0.075 mmol) in DMAc (2.00 mL) was added nickel chloride (0.05 mmol) to result in mixture which was stirred under N₂ at room temperature for 30 min. Then, aryl halide ArX (4) (X = I or Br) (0.50 mmol), terminal alkyne 2 (0.75 mmol), 4-cyanopyridine N-oxide (0.75 mmol), KF (0.75 mmol), zinc powder (0.60 mmol) and DMAc (3.00 mL) were added to the mixture successively. The reaction mixture was heated under N₂ (at 60 °C when X = I or 70 °C when X = Br) for 48 h, poured into water (100 mL), and extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual crude was subjected to flash column
chromatography (hexanes: EtOAc) to afford the product.

**Data availability**

All of the characterization data and experimental protocols are provided in this article and its Supplementary Information. Data are also available from the corresponding author on request.

**References**


**Acknowledgements**
We are grateful for financial support from the National Natural Science Foundation of China (NSFC) (No. 21877067), and Tsinghua-Peking Centre for Life Science. We thank professor Yanxing Jia at Peking University (PKU) for solving the structure of complex 15.

**Author contributions**
H.C. designed the experiments and prepared the manuscript. Y. A. L. revised the manuscript. H. C. conducted the nickel-catalyzed asymmetric reactions and analyzed the data. L. Y. and H. C. conducted the nickel-catalyzed Sonogashira coupling reactions and analyzed the data. B. G. conducted DFT calculations and H. C. draw the figure of the potential energy status. B. T. guided the DFT calculations. X. L. supervised the whole project.

**Competing interests**
The authors declare no competing interests.