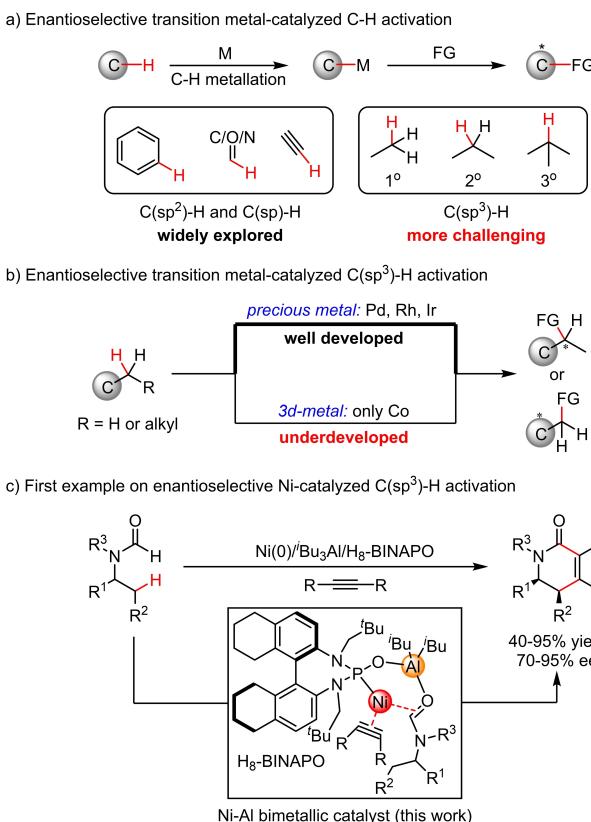


Enantioselective Nickel-Catalyzed C(sp³)–H Activation of Formamides

Yin-Xia Wang[†], Feng-Ping Zhang[†], Hao Chen, Yue Li, Jiang-Fei Li, and Mengchun Ye*^{*}

Abstract: Enantioselective Ni-catalyzed C(sp³)–H bond activation remains an elusive challenge. Herein, we used phosphine oxide-ligated Ni–Al bimetallic catalyst to realize enantioselective Ni-catalyzed aliphatic C(sp³)–H activation of formamides, providing a series of chiral N-containing heterocycles in 40–95 % yield and 70–95 % ee.

Enantioselective transition metal-catalyzed C–H activation via C–H metallation represents one of the most convenient and economical routes to chiral molecules that exist in a large number of natural products and bioactive compounds such as pharmaceuticals and agrochemicals.^[1] Extensively-explored C–H bonds in these reactions are C(sp²)–H or C(sp)–H bonds of arenes, alkenes, aldehydes, imines, formamides or alkynes (Scheme 1a, left). In contrast, unreactive C(sp³)–H bonds such as primary, secondary and tertiary C(sp³)–H bonds are quite resistant to enantioselective activation by chiral metal complexes (Scheme 1a, right), because of steric hindrance around C(sp³)–H bonds and the lack of π-orbitals to interact with metals.^[2] In the last two decades, relying on well-designed chiral ligands or chiral anions, precious metals such as Pd, Rh and Ir have been capable of catalyzing a broad range of enantioselective C(sp³)–H bond activation reactions,^[3] providing good yields and high ee (Scheme 1b, top). However, same strategies are in general ineffective to most 3d-transition metals that are very sensitive to the structure of substrates and ligands.^[4] So far, only one successful example has been reported by Matsunaga, Yoshino and co-workers, who used achiral Co^{III} with an amino acid derivative as a chiral anion to facilitate an enantioselective amidation of primary C(sp³)–H bonds of thioamides (Scheme 1b, bottom).^[5] Given appealing advantages of 3d metals, including high earth abundance, low cost and low bio-toxicity,^[6] the development of 3d metal-catalyzed enantioselective C(sp³)–H bond activation reac-



Scheme 1. Enantioselective transition metal-catalyzed C(sp³)–H activation.

tions are in high demand. Till now, although great progress has been achieved for Ni-catalyzed C–H bond activation and even enantioselective Ni-catalyzed C(sp²)–H bond activation,^[7,8] enantioselective Ni-catalyzed aliphatic C(sp³)–H bond activation still remains an elusive challenge. Herein, we used a new type of H₈-bi(2-naphthylamine)-derived chiral phosphine oxide (H₈-BINAPo) to enable an enantioselective Ni-catalyzed C(sp³)–H activation of formamides for the first time, providing a series of nitrogen-containing heterocycles in 40–95 % yield and 70–95 % ee (Scheme 1c). The H₈-BINAPo-ligated Ni–Al bimetallic catalyst may play a critical role in enabling the formyl C(sp²)–H bond activation, and accelerating subsequent aliphatic C(sp³)–H activation by orienting nickel.

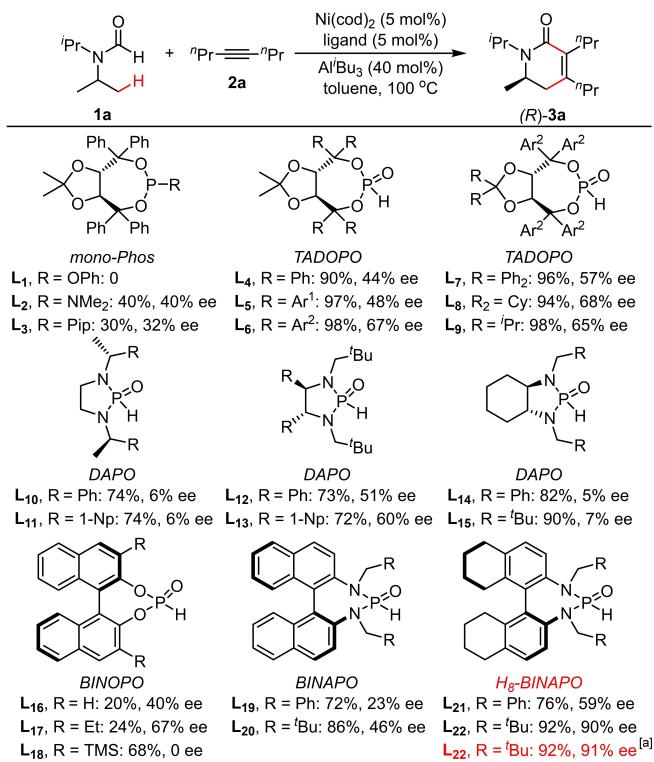
Following Nakao and Hiyama's work on racemic Ni-catalyzed annulation of formamides with alkynes,^[9–11] we selected *N,N*-diisopropyl formamide **1a** and oct-4-yne (**2a**) as model substrates for the investigation of enantioselective

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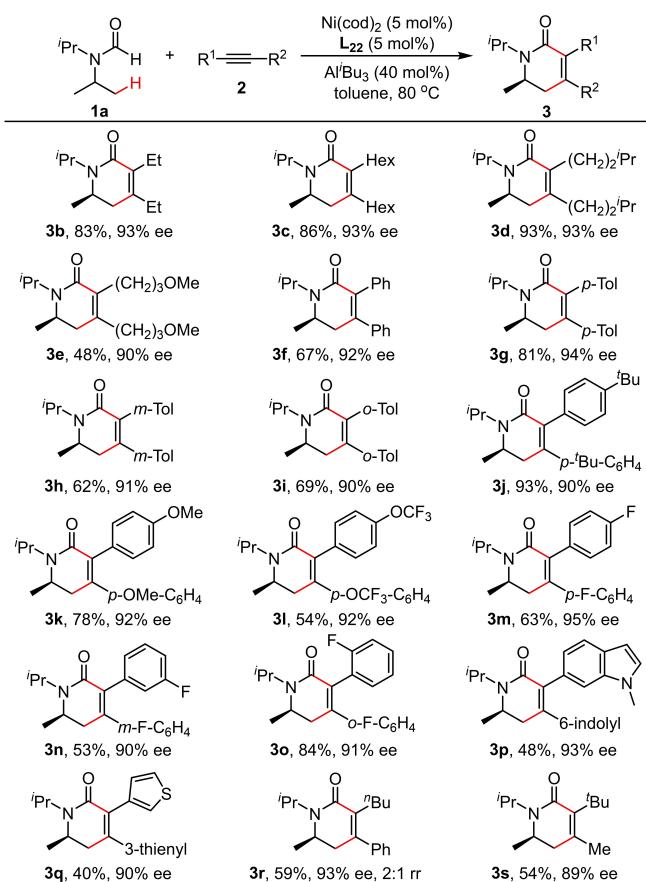
Ni-catalyzed C(sp³)–H bond activation (Scheme 2). We envisioned to use chiral phosphine oxide (PO)-ligated Ni and Al bimetallic catalyst to enhance the reactivity and control the selectivity.^[12,13] This catalyst would activate the formyl C(sp³)–H bond to form a nickelacycle, and the rigidity of this nickelacycle and steric hindrance around metal center would let Ni approach closely to C(sp³)–H bond; meanwhile, chiral PO ligand would facilitate enantioselectivity control. With this consideration in mind, a broad range of chiral ligands were examined. Common phosphines and phosphites proved ineffective (**L**₁), while taddol-based phosphoramidites can promote this reaction, providing 30–40% yield and 32–40% ee (**L**₂ and **L**₃). Pleasingly, the same backbone-based PO ligands greatly improved the reaction, giving up to 90% yield and 44% ee (TADOPO, **L**₄). Extensive modification of substituents on the aromatic rings and protecting groups of diols (**L**₅ to **L**₉) led to only a little improvement of ee (48–68%). To further optimize the conditions, a wider range of chiral backbones such as diamines (DAPO, **L**₁₀ to **L**₁₅), binaphthol (BINAPO, **L**₁₆ to **L**₁₈), and naphthidine (BINAPO, **L**₁₉ and **L**₂₀) were introduced in phosphine oxides, but the resulting ligands delivered either low yield or low ee. Until partially-hydrogenated BINAPO was used as a chiral backbone, a significant improvement was then achieved (H₈-BINAPO, **L**₂₁ and **L**₂₂), providing up to 92% yield and 90% ee. With **L**₂₂ as the optimal ligand, the reaction temperature can be



Scheme 2. Reaction optimization. Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), toluene (0.5 mL) under N₂ for 12 h; yield of isolated products; ee was determined by chiral HPLC.^[a] 80 °C, 2 h. Pip = piperidinyl. Ar¹ = 3,5-Me₂C₆H₃, Ar² = 2-MeC₆H₄. Np = naphthyl. TMS = trimethylsilyl.

further decreased to 80 °C without loss of yield (92%) and even with a little higher ee (91%). We reasoned that the partial hydrogenation of naphthyl rings led to bigger steric hindrance and a larger dihedral angle of P center,^[14] thus providing a well-matched interaction between the substrate and the catalyst. Major enantiomer of the product was assigned by single crystal X-ray diffraction analysis as the (*R*)-configuration.^[15]

With the optimal ligand in hand, we first investigated the scope of alkynes. As shown in Scheme 3, various alkyl groups including linear alkyl group (**3b** and **3c**), branched alkyl group (**3d**) and methoxy-substituted alkyl group (**3e**) were all well compatible, providing the corresponding product in 48–90% yield and 90–93% ee. Beyond alkyl groups, various aryl groups (**3f** to **3o**) bearing either electron-donating groups such as Me group on different positions of the aromatic rings (**3g** to **3i**), 'Bu group (**3j**) and MeO group (**3k**) or electron-withdrawing groups such as CF₃O group (**3l**) and F (**3m**, **3n** and **3o**) all underwent the reaction smoothly, providing the corresponding products in 53–93% yield and 90–95% ee. In addition, heteroaryl groups were also found to be suitable alkyne substituents, and both 6-indolyl group (**3p**) and 3-thienyl group (**3q**) delivered the desired products in 40–48% yield and 90–93% ee. Non-symmetrical alkynes were also suitable substrates,



Scheme 3. Scope of alkynes. Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), toluene (0.5 mL) under N₂ for 2 h; yield of isolated products; ee was determined by chiral HPLC. Hex = *n*-hexyl. Tol = tolyl.

providing 54–59 % yield and 89–93 % ee (**3r** and **3s**). Regioisomer ratio was in general dependent on steric discrimination between two substituents of alkynes. For example, aryl alkyl alkyne gave an isomer ratio of 2:1 (**3r**), whereas *tert*-butyl methyl alkyne significantly enhanced the regioselectivity, providing **3s** as a sole isomer.

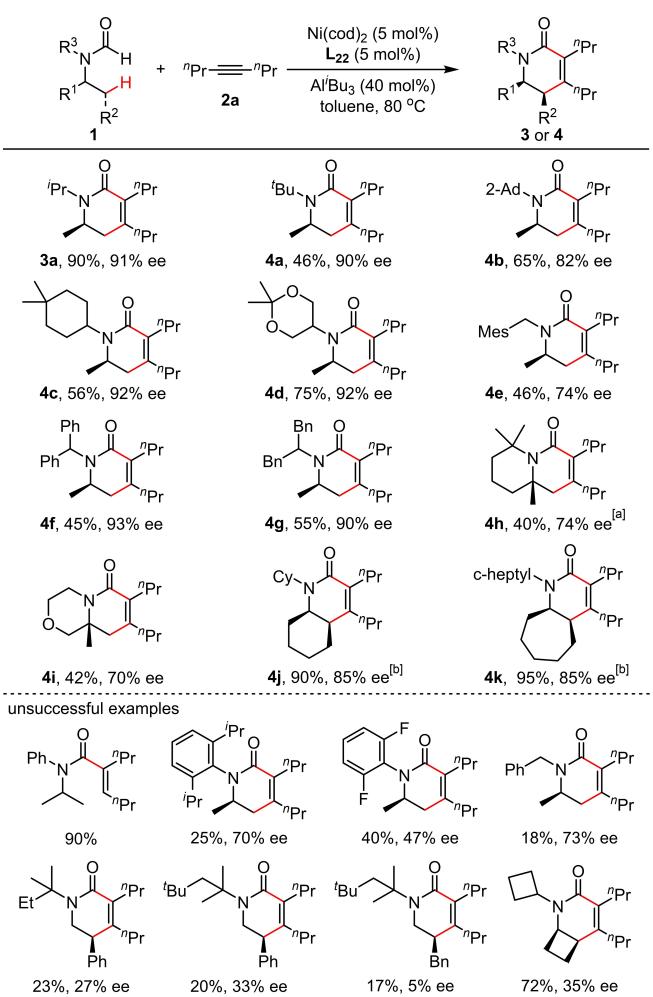
Next, a series of formamides bearing various substituents were investigated (Scheme 4). When *tert*-butyl group was installed as a N-substituent, the desired product **4a** was smoothly obtained in 46 % yield and 90 % ee, yet accompanied by a side product that was generated via the activation of primary C–H bonds of *tert*-butyl group in 42 % yield. When steric hindrance of the N-substituent was increased, this undesired reaction can be inhibited. For example, 2-adamantyl group (**4b**), cyclohexyl group with two methyl groups at the 4'-position (**4c**) and 1,3-dioxan-5-yl group with two methyl groups at the 2'-position (**4d**) delivered the corresponding products in 56–75 % yield and

82–92 % ee, without observing the activation of 2-adamantyl or cyclohexyl group.

In addition, arene-containing N-substituents were also compatible with the reaction. For example, mesityl group (**4e**), diphenylmethyl group (**4f**) and dibenzylmethyl group (**4g**) afforded the corresponding products in 45–55 % yield and 74–93 % ee. Besides isopropyl groups, other methyl groups in cyclic amides (**4h** and **4i**) were also tolerated in the reaction, providing the corresponding products in 40–42 % yield and 70–74 % ee. Moreover, methylene C(sp³)–H bonds, which were not easily activated by transition metal catalysts because of big steric hindrance,^[16] can be smoothly activated, providing 90–95 % yield and the same 85 % ee (**4j** and **4k**). However, in these cases, more flexible ligands such as **L**₅ or **L**₆ was needed to replace the optimal ligand **L**₂₂ for achieving better enantioselectivity. These secondary C(sp³)–H activation reactions have rarely been reported to proceed via 3d metal catalysts before, demonstrating that the current reaction provides a robust method for 3d metal-catalyzed C–H activation. Notably, some unsuccessful examples have also been listed at the bottom of Scheme 4 and the Supporting Information (Page S28). For example, N-aryl and benzyl formamides gave no annulation or lower yield (18%–40%) with lower ee (47%–73%). Non-cyclic methylene C–H bonds still can be activated, yet affording lower yield (17%–23%) and lower ee (5%–33%).

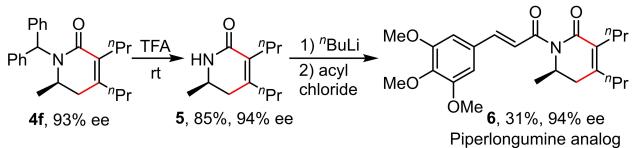
To demonstrate the utility of the current reaction, product transformation was conducted. Compound **4f** can be easily deprotected in the presence of trifluoroacetic acid to generate free amide **5** in 85 % yield (Scheme 5a), which was then treated with acyl chloride to afford bioactive piperlongumine analog **6** in 31 % yield.^[17] To gain more insights into the mechanism, we conducted deuterium-labeling experiments to determine kinetic isotope effect of the activation of two C–H bonds of substrate **1b**. A low *k*_H/*k*_D (1.14) was observed for formyl C(sp²)–H bond (Scheme 5b), while a relatively higher *k*_H/*k*_D (2.13) was obtained for aliphatic isopropyl C(sp³)–H bond (Scheme 5c), suggesting that the activation of C(sp³)–H bond could be a rate-determining step. On the basis of the racemic reaction and relevant DFT-calculations,^[9] together with our previous experience in PO–Ni–Al catalysis,^[13c] a plausible mechanism was proposed in Scheme 5d: PO-ligated Ni–Al catalyst coordinates to formamide **1a** and alkyne **2a** first. Then formyl C–H bond cleavage occurs to form intermediate **A** via oxidative addition or concerted ligand-to-ligand H transfer.^[18] Subsequently, C(sp³)–H bond cleavage takes place to generate intermediate **B**. Finally, alkyne insertion and reductive elimination provided the desired product and regenerated the catalyst. Given that the second C(sp³)–H cleavage was a rate-determining step, a possible stereochemical model was proposed in the Supporting Information.

In summary, we have developed the first example on enantioselective Ni-catalyzed aliphatic C(sp³)–H bond activation of formamides, providing a series of chiral N-containing heterocycles in 40–95 % yield and 70–95 % ee. Various dialkyl, diaryl and alkylarylmethyl alkynes, together with primary and secondary C(sp³)–H bonds were well compat-

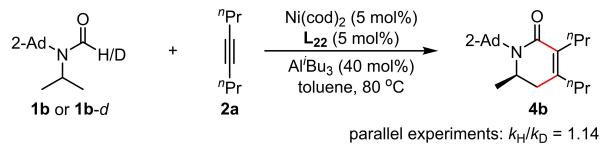


Scheme 4. Scope of formamides. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), toluene (0.5 mL) under N₂ for 2–8 h; yield of isolated products; ee was determined by chiral HPLC:^[a] **L**₅ (5 mol %) instead of **L**₂₂,^[b] **L**₆ (5 mol %) instead of **L**₂₂. Ad = adamantyl. Mes = mesityl. Cy = cyclohexyl.

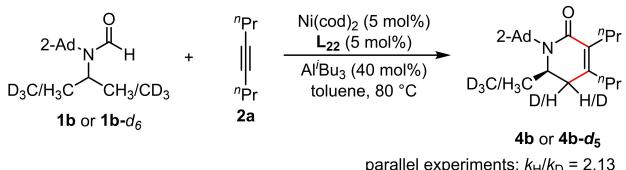
a) synthetic utility



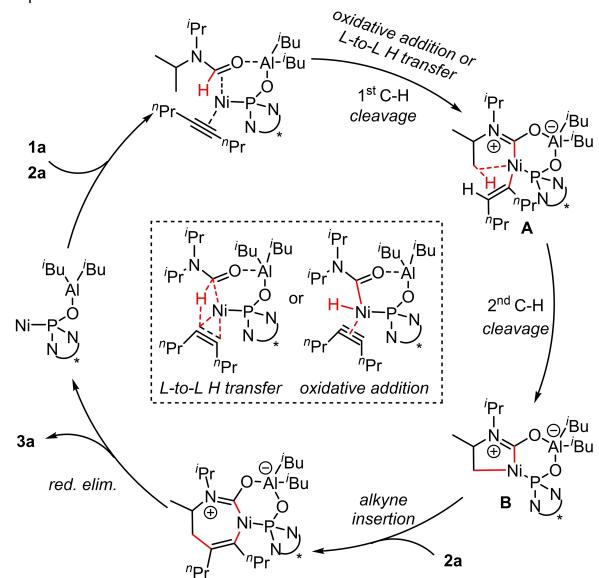
b) Kinetic isotope effect of formyl H



c) Kinetic isotope effect of methyl H



d) Proposed mechanism

**Scheme 5.** Synthetic utility and mechanistic experiments.

ible. The newly-developed H₈-BINAPo ligand could be applied in a wider range of enantioselective C–H activation reactions in future.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Bimetal · C–H Functionalization · Cyclization · Formamides · Nickel

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