Ni-Catalyzed Hydroarylation of Alkynes with Unactivated β -C(sp²)-H Bonds

mengchun ye (✉ mcye@nankai.edu.cn)

Nankai University <https://orcid.org/0000-0002-2019-5365>

Shao-Long Qi

Nankai University

Yu-Peng Liu

Nankai University

Yi Li

Nankai University

Yu-Xin Luan

Nankai University

Article

Keywords:

Posted Date: December 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1114617/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Nature Communications on May 26th, 2022. See the published version at <https://doi.org/10.1038/s41467-022-30367-8>.

Ni-Catalyzed Hydroarylation of Alkynes with Unactivated β -C(sp²)-H Bonds

Shao-Long Qi, Yu-Peng Liu, Yi Li, Yu-Xin Luan, Mengchun Ye*

State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China.

*e-mail: mcye@nankai.edu.cn

Abstract

Hydroarylation of alkynes with unactivated C(sp²)-H bonds via chelated C-H metalation mainly occurs at γ -position to the coordinating atom of directing groups via stable 5-membered metallacycles, while β -C(sp²)-H bond-involved hydroarylation has been a formidable challenge. Herein, we used a phosphine oxide-ligated Ni-Al bimetallic catalyst to enable β -C-H bond-involved hydroarylations of alkynes via a rare 7-membered nickelacycle.

Introduction

Hydroarylation of alkynes with arenes provides a highly atom- and step-economical route to aromatic alkenes that widely exist in natural products, bioactive compounds and material molecules.¹⁻⁸ During the past several decades, a large number of transition metal-catalyzed hydroarylation reactions have been reported. According to electronic nature of arenes, these hydroarylations can be divided into three types (Fig. 1a): electron-rich (hetero)arenes (Type I), electron-deficient (hetero)arenes (Type II) and general arenes with unactivated C(sp²)-H bonds (Type III). Type I reactions mainly proceed via a Friedel-Crafts-type pathway, requiring multiple electron-rich substituents to enhance the electron density of (hetero)arenes.⁹⁻¹¹ This structural requirement results in a limited scope of substrates and difficult site selectivity. Especially in case of less electron-rich arenes, a large excess of substrates is often required for reasonable yields. Instead, most of type II reactions proceed via oxidative addition pathway, because the presence of strong electron-negative heteroatoms or electron-withdrawing groups in substrates leads to uneven

distribution of electron density, and then electron-deficient C–H bonds will easily undergo oxidative addition with metal. However, unique electron demand renders substrates limited to special heterocycles such as pyridines, polyfluoroarenes, imidazoles, and other analogues.^{12–24} To activate arenes with unactivated C(sp²)–H bonds for hydroarylation reactions, chelated C–H metalation has been devised by incorporating proper directing groups in substrates (Type III). With the aid of directing groups, unactivated C(sp²)–H bonds can be metallated, and tuning the size of the formed metallacycles would in principle achieve diverse site selectivities. Owing to these advantages, chelated C–H metalation-involved hydroarylation has been widely explored in the past decades by using various metal catalysts such as Ru,^{25–32} Ir,^{33–36} Rh,^{37–47} Co,^{48–54} Mn,^{55–57} Re^{58,59} and Fe⁶⁰ (Fig 1b, left). However, most examples are limited to C–H bonds at γ -position to the coordinating atoms of directing groups, because the formation of stable 5-membered metallacycles has more favorable entropic effect and ring strain than other larger (6- or 7-membered) or smaller (4-membered) metallacycles. Only two examples are reported for δ -C–H bond-involved hydroarylations via a 6-membered metallacycle (Fig. 1b, middle).^{61,62} In contrast, there are no reports on other C–H bond-involved hydroarylations, especially very challenging β -C–H bond-involved hydroarylations, because a highly-strained 4-membered metallacycle is difficult to form (Fig. 1b, right). To address this elusive challenge to achieve more diverse molecular complexity, herein, we show that a phosphine oxide (PO)-ligated Ni–Al bimetallic catalyst^{63–65} can activate an unactivated β -C–H bond on the phenyl ring of benzimidazole to undergo hydroarylation via a rare 7-membered nickelacycle, bypassing an unstable 4-membered nickelacycle (Fig. 1c). A series of C4-alkenylated 2-phenylbenzimidazoles, including complex bioactive molecules, can be produced in 41–96% yield, providing a distinctive site selectivity beyond traditional selectivity that generally occurs at

C2-phenyl ring via a 5-membered metallacycle.

Fig. 1 TM-catalyzed hydroarylation of alkynes with (hetero)arenes. **a**, Three types of hydroarylations of alkynes and (hetero)arenes: electron-rich arenes (type I), electron-rich arenes (type II) and general arenes with unactivated C(sp²)-H bonds (type III). **b**, Stability of metallacycles and reported various metallacycle-involved hydroarylations: γ -C-H bond-activation-involved hydroarylation (widely explored); δ -C-H bond-activation-involved hydroarylation (rarely explored); β -C-H bond-activation-involved hydroarylation (elusive challenge); **c**, β -C-H bond-involved

hydroarylation via 7-membered metallacycles (this work). D = electron-donating group. W = electron-withdrawing group. DG = directing group.

Results

Reaction optimization. 2-Phenyl benzimidazole (**1a**) bearing both β -C-H bond and γ -C-H bond was selected as a model substrate, because such a structural motif can be found in a large number of bioactive and material molecules.^{66,67} However, due to strong directing ability of imine N atom, transition metal-catalyzed selective C-H activation of 2-phenyl benzimidazoles mainly occurs at γ -C-H bond at *ortho*-position of C2-phenyl ring.⁶⁸⁻⁷⁵ For example, with RhCl(PPh₃)₃ as a catalyst, the reaction of **1a** and oct-4-yne (**2a**) afforded **3a'** as the sole product in 37% yield with a *E:Z* ratio of 6.4:1 (Fig. 2, entry 1). Similarly, the use of [Ru(*p*-cymene)Cl₂]₂ as a catalyst also generated **3a'** in 32% yield (entry 2). Given important bioactivity of C4-alkenylated benzimidazoles and derivatives,^{76,77} reversing traditional γ -C-H bond activation to β -C-H bond activation in the hydroarylation reaction (product **3a**) would be highly desirable. We envisioned to use a ligand-ligated Ni-Al bimetallic catalyst for the investigation: firstly, the coordination of Al-Lewis acid with benzimidazole could direct Ni to activate β -C-H bonds via a 7-membered nickelacycle, bypassing a highly strained 4-membered nickelacycle; secondly, the coordination of Al-Lewis acid would favor inhibiting the activation of γ -C-H bonds on the C2-phenyl ring via a 5-membered nickelacycle. Systematic survey on ligands, Lewis acids, solvents and temperatures revealed the desired C4-alkenylated product **3a** can be indeed obtained. Under the optimal conditions: Ni(cod)₂ (10 mol%), **PO-3** (10 mol%), AlEt₃ (40 mol%) in toluene at 80 °C, **3a** was produced in 84% yield (entry 3). Control experiments showed that the presence of nickel, Al-Lewis acid and phosphine oxide ligand is essential to the reaction efficiency, the removal of any of them would inactivate the reaction (entries 4–6). Ligand examination showed that various phosphines (entries 7–10), N-heterocyclic carbenes (entries 11–13),

and commonly-used phosphine oxides (entries 14–17) were all ineffective, suggesting that the optimal **PO-3** plays a critical role in the reaction. In addition, the selection of Lewis acid proved important. Although AlMe₃ gave a slightly lower yield than that of AlEt₃, all other Lewis acids with either bulkier steric hindrance or weaker Lewis acidity led to a big decrease in yield (entries 18–21).

Fig. 2 Reaction Optimization. Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), toluene (0.4 mL) under N₂ for 12 h. Yield was determined by ¹H NMR. Mes = 2,4,6-trimethylphenyl, Dipp = 2,6-diisopropylphenyl.

Scope of benzimidazoles and alkynes. With the optimized conditions in hand, various C2-aryl benzimidazoles were investigated first (Fig. 3). Results showed that various substituents on C6-position, including alkyl group (**3b** and **3c**), alkenyl group (**3d**), aryl group (**3e**) and heteroaryl group (**3f**, **3g** and **3h**) did not have a strong influence on the reaction efficiency, providing the corresponding products in 76–96% yield. In addition, the investigation on electronic effect proved that either electron-rich group (**3i**) or electron-deficient group (**3j** and **3k**) were also well tolerated, delivering 82–84% yield. Given that C7-substituent would have direct influence on the electronic density of the C4–H bond, two substituents with different electronic property were examined. Methyl group provided 52% yield (**3l**), but electron-deficient fluoro group gave a slightly increasing yield to 67% (**3m**). Different from C6- and C7-positions, C5-position locates closely to the reaction site and substituents on this position would have detrimental effect to the reactivity owing to steric hindrance. For example, C5-methyl afforded trace amount of products and only smaller C5-F group still led to the corresponding product in 48% yield (**3n**). Notably, various N1-substituents are far away from reaction site and can be well compatible with the reaction. For example, methyl group (**3o**) and *tert*-butyl group (**3p**) provided the corresponding products in 75% and 78% yield, respectively. To compare the effect of C2-aryl ring, we also prepared a wide range of C2-arylated benzimidazoles and checked their reactivity. Results showed that either electron-rich groups (**4a** to **4e**) or electron-deficient groups (**4f** to **4i**) at *para* position of C2-phenyl ring can be well tolerated, providing C4-alkenylated products in 58–95% yield without observing C–H activation on the C2-aryl ring. Similar results appeared for substituents at other positions such as ortho- (**4j**), meta (**4k** to **4o**) and even multiple sites (**4p** to **4s**). These results showed that the current method can provide high β -site selectivity for all examined substrates.

Fig. 3 Scope of benzimidazoles. Reaction conditions: **1** (0.4 mmol), **2a** (0.8 mmol), toluene (0.8 mL) under N₂ for 12 h. Yield of isolated products.

Next, the scope of alkynes was investigated (Fig. 4). Aryl alkynes were in general ineffective, which may be attributed to their big steric hindrance and strong coordinative ability with nickel, while various alkyl alkynes such as ethyl (**5a**), *n*-butyl (**5b**), *n*-pentyl (**5c**), *n*-hexyl (**5d**) and *i*-hexyl (**5e**) were compatible very well, providing the corresponding products in 85–89% yield. When functional groups such as phenyl group (**5f**) or hydroxyl group (**5g**) were incorporated into the alkyl

chain, no significant loss of yields were observed. In addition, cyclic alkyne was still compatible with the reaction, providing 51% yield (**5h**). Notably, besides symmetrical alkynes, non-symmetrical alkyne also displayed good reactivity with high regioselectivity (**5i**).

Fig. 4 Scope of alkynes. Reaction conditions: **1a** (0.4 mmol), **2** (0.8 mmol), toluene (0.8 mL) under N_2 for 12 h. Yield of isolated products. TBS = *tert*-butyldimethylsilyl. *n*Pent = *n*-pentyl. *n*Hex = *n*-hexyl.

Synthetic utility. To demonstrate the utility of the reaction, a gram-scale reaction of the model substrates was conducted, providing the desired product **3a** in 81% yield (Fig. 5a). The alkene motif in the product is a versatile synthetic precursor and it can be transformed into alkyl group through hydrogenation (**6**, quantitative yield), epoxide (**7**, 60% yield) and ketone (**8**, 73% yield) through different extent of oxidation. In addition, the selective C–H alkenylation method can be applied to

the late-stage derivation of complex molecules (Fig. 5b). Telmisartan ester, a long-acting antihypertensive drug, can be selectively activated at C4–H of benzimidazole, achieving a new telmisartan derivative **9** in 75% yield. Other bioactive molecules such as tocopherol and estrone-derivatives were also well compatible with the reaction, providing the corresponding products **10** in 52% yield and **11** in 62% yield, respectively. Compared with traditional selectivity that dominantly occurs at *ortho*-C–H bond of C2-phenyl ring of benzimidazoles,^{66–69} the current method provides a different molecular elaboration.

Fig. 5 Synthetic utility. **a**, Gram-scale reaction and product transformations. **b**, Late-stage selective $\beta\text{-C-H}$ bond alkenylation of bioactive molecules such as Telmisartan ester, tocopherol derivative and estrone derivative. $m\text{-CPBA}$ = m -chloro perbenzoic acid.

Mechanistic discussion. To gain insight into this reaction, additional mechanistic experiments were conducted. Deuterium-labeling experiment disclosed that the alkene hydride completely came from the hydride on the C4-position of benzimidazole (Fig. 6a), suggesting a C4–H bond metalation. The determination of kinetic isotopic effect via either intermolecular competitive experiment or

parallel experiments revealed significant isotopic effect (Fig. 6b), suggesting that C4–H bond cleavage may be involved into a rate-determining step. On basis of these results, a plausible mechanism was proposed in Fig. 6c. Al-Lewis acid of phosphine oxide-ligated Ni–Al bimetallic catalyst coordinates to N atom of the imidazole first, and then nickel is directed to selectively activate β -C–H bond to form a 7-membered nickelacycle, bypassing the formation of a more challenging 4-membered nickelacycle and a traditional 5-membered metallacycle. Subsequent alkyne insertion, reductive elimination and catalyst exchange delivered the desired product **3a** and regenerated the bimetallic catalyst.

Fig. 6 Mechanistic experiments. **a**, Deuterium-labeling experiment, showing that C4–D was completely transferred to the alkene of the product. **b**, kinetic isotopic effect determination: a significant KIE for C4–H bond suggests that the activation of C4–H bond could be a rate-determining step. **c**, Proposed mechanism.

In summary, we have developed an unactivated β -C(sp²)-H bond-involved hydroarylation of alkynes, providing a series of C4-alkenylated 2-phenyl benzimidazoles including bioactive complex molecules in 41–94% yield, overriding traditional γ -selectivity via a stable 5-membered metallacycle. The phosphine oxide-ligated Ni–Al bimetallic catalyst effectively directed Ni to generate β -selectivity via a 7-membered metallacycle, bypassing a highly strained 4-membered nickelacycle. The ligand-ligated bimetallic catalyst provides an efficient tool for site selective C–H bond activation and would find wide applications in other types of reactions in future.

Methods

General procedure for β -C(sp²)-H bond-involved hydroarylation. In an argon-filled glove-box, to an oven-dried sealed tube were added Ni(cod)₂ (11.0 mg, 0.04 mmol), **PO-3** (16.0 mg, 0.04 mmol), toluene (0.8 mL), **1** (0.40 mmol), AlEt₃ (1 mol/L in hexane, 160 μ L, 0.16 mmol) and **2** (0.80 mmol) in sequence. The tube was then sealed, removed out of the glove-box and heated at 80 °C with heating mantle as the heat source for 12 h. Then the mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by flash column chromatography using ethyl acetate/hexane as eluent.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information file. For the experimental procedures and data of NMR see Supplementary Methods in Supplementary Information file. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 2101580. These data can be obtained free of

charge from The Cambridge Crystallographic Data Centre via <https://www.ccdc.cam.ac.uk/structures/>.

References

- 1 Nevado, C. & Echavarren, A. M. Transition Metal-Catalyzed Hydroarylation of Alkynes. *Synthesis*. **2**, 167–182 (2005).
- 2 Wang, X. Zhou, L. & Lu, W. Hydroarylation of Alkynes via Aryl C–H Bond Cleavage. *Curr. Org. Chem.* **14**, 289–307 (2010).
- 3 de Haro, T. & Nevado, C. Hydroarylation Reactions. *Comprehensive Organic Synthesis*, 2nd ed. (Ed.: P. Knochel), Elsevier, Amsterdam, **2014**, p. 1621.
- 4 Yamamoto, Y. Synthesis of heterocycles via transition-metal catalyzed hydroarylation of alkynes. *Chem. Soc. Rev.* **43**, 1575–1600 (2014).
- 5 Manikandan, R. & Jeganmohan, M. Recent advances in the ruthenium-catalyzed hydroarylation of alkynes with aromatics: synthesis of trisubstituted alkenes. *Org. Biomol. Chem.* **13**, 10420–10436 (2015).
- 6 Boyarskiy, V. P., Ryabukhin, D. S., Bokach, N. A. & Vasilyev, N. A. Alkenylation of Arenes and Heteroarenes with Alkynes. *Chem. Rev.* **116**, 5894–5986 (2016).
- 7 Biffis, A., Tubaro, C. & Baron, M. Advances in Transition-Metal-Catalysed Alkyne Hydroarylations. *Chem. Rec.* **16**, 1742–1760 (2016).
- 8 Santhoshkumar, R. & Cheng, C.-H. Hydroarylations by cobalt-catalyzed C–H activation. *J. Org. Chem.* **14**, 2266–2288 (2018).
- 9 Kitamura, T. Transition-Metal Catalyzed Hydroarylation Reactions of Alkynes Through Direct Functionalization of C–H Bonds: A Convenient Tool for Organic Synthesis. *Eur. J.*

Org. Chem. 1111–1125 (2009).

- 10 Jia, C. et al. Efficient Activation of Aromatic C–H Bonds for Addition to C–C Multiple Bonds. *Science* **2000**, **287**, 1992–1995 (2000).
- 11 Tsukada, N., Mitsuboshi, T., Setoguchi, H. & Inoue, Y. Stereoselective cis-Addition of Aromatic C-H Bonds to Alkynes Catalyzed by Dinuclear Palladium Complexes. *J. Am. Chem. Soc.* **125**, 12102–12103 (2003).
- 12 Nakao, Y. Hydroarylation of Alkynes Catalyzed by Nickel. *Chem. Rec.* **11**, 242–251 (2011).
- 13 Gao, K. & Yoshikai, N. Low-Valent Cobalt Catalysis: New Opportunities for C–H Functionalization. *Acc. Chem. Res.* **47**, 1208–1219 (2014).
- 14 Wang, Y.-X. & Ye, M. Recent advances in Ni–Al bimetallic catalysis for unreactive bond transformation. *Sci. China Chem.* **61**, 1004–1013 (2018).
- 15 Nakao, Y., Kanyiva, K. S., Oda, S. & Hiyama, T. Hydroheteroarylation of Alkynes under Mild Nickel Catalysis. *J. Am. Chem. Soc.* **128**, 8146–8147 (2006).
- 16 Kanyiva, K. S., Nakao, Y. & Hiyama, T. Nickel-Catalyzed Addition of Pyridine-N-oxides across Alkynes. *Angew. Chem. Int. Ed.* **46**, 8872–8874 (2007).
- 17 Nakao, Y., Kashiwara, N., Kanyiva, K. S. & Hiyama, T. Nickel-Catalyzed Alkenylation and Alkylation of Fluoroarenes via Activation of C-H Bond over C-F Bond. *J. Am. Chem. Soc.* **130**, 16170–16171 (2008).
- 18 Nakao, Y., Kanyiva, K. S. & Hiyama, T. A Strategy for C-H Activation of Pyridines: Direct C-2 Selective Alkenylation of Pyridines by Nickel/Lewis Acid Catalysis. *J. Am. Chem. Soc.* **130**, 2448–2449 (2008).
- 19 Nakao, Y., Idei, H., Kanyiva, K. S. & Hiyama, T. Direct Alkenylation and Alkylation of

- Pyridone Derivatives by Ni/AlMe₃ Catalysis. *J. Am. Chem. Soc.* **131**, 15996–15997 (2009).
- 20 Liu, S., Sawicki, J. & Driver, T. G. Ni-Catalyzed Alkenylation of Triazolopyridines: Synthesis of 2,6-Disubstituted Pyridines. *Org. Lett.* **14**, 3744–3747 (2012).
- 21 Yu, M.-S., Lee, W.-C., Chen, C.-H., Tsai, F.-Y. & Ong, T.-G. Controlled Regiodivergent C–H Bond Activation of Imidazo[1,5-a]pyridine via Synergistic Cooperation between Aluminum and Nickel. *Org. Lett.* **16**, 4826–4829 (2014).
- 22 Li, Z. & Duan, W.-L. Palladium-Catalyzed C–H Alkenylation of Arenes with Alkynes: Stereoselective Synthesis of Vinyl Chlorides via a 1,4-Chlorine Migration. *Angew. Chem. Int. Ed.* **57**, 16041–16045 (2018).
- 23 Yin, G. et al. Ligand-Controlled Ni(0)–Al(III) Bimetal-Catalyzed C3–H Alkenylation of 2-Pyridones by Reversing Conventional Selectivity. *ACS Catal.* **11**, 4606–4612 (2021).
- 24 Zhang, T. et al. A directive Ni catalyst overrides conventional site selectivity in pyridine C–H alkenylation. *Nat. Chem.* **2021**, 10.1038/s41557-021-00792-1.
- 25 Kakiuchi, F., Yamamoto, Y., Chatani, N. & Murai, S. Catalytic Addition of Aromatic C–H Bonds to Acetylenes. *Chem. Lett.* 681–682 (1995).
- 26 Cheng, K., Yao, B., Zhao, J. & Zhang, Y. RuCl₃-Catalyzed Alkenylation of Aromatic C–H Bonds with Terminal Alkynes. *Org. Lett.* **10**, 5309–5312 (2008).
- 27 Hashimoto, Y., Hirano, K., Satoh, T., Kakiuchi, F. & Miura, M. Ruthenium(II)-Catalyzed Regio- and Stereoselective Hydroarylation of Alkynes via Directed C–H Functionalization. *Org. Lett.* **14**, 2058–2061 (2012).
- 28 Reddy, M. C. & Jeganmohan, M. Ruthenium-catalyzed highly regio- and stereoselective hydroarylation of aryl carbamates with alkynes via C–H bond activation. *Chem. Commun.* **49**,

481–483 (2013).

- 29 Villuendas, P. & Urriolabeitia, E. P. Ru-Catalyzed Regioselective C–H-Hydroarylation of Alkynes with Benzylthioethers Using Sulfur as Directing Group. *Org. Lett.* **17**, 3178–3181 (2015).
- 30 Zhang, W. et al. Highly Stereoselective Ruthenium(II)-Catalyzed Direct C2-*syn*-Alkenylation of Indoles with Alkynes. *Org. Lett.* **17**, 1349–1352 (2015).
- 31 Zhang, J., Shrestha, R., Hartwig, J. F. & Zhao, P. A decarboxylative approach for regioselective hydroarylation of alkynes. *Nat. Chem.* **8**, 1144–1151 (2016).
- 32 Biafora, A., Khan, B. A., Bahri, J., Hower, J. M. & Goossen, L. J. Doubly Regioselective C–H Hydroarylation of Unsymmetrical Alkynes Using Carboxylates as Deciduous Directing Groups. *Org. Lett.* **19**, 1232–1235 (2017).
- 33 Satoh, T., Nishinaka, Y., Miura, M. & Nomura, M. Iridium-Catalyzed Regioselective Reaction of 1-Naphthols with Alkynes at the *peri*-Position. *Chem. Lett.* 615–616 (1999).
- 34 Tsuchikama, K., Kasagawa, M., Hashimoto, Y.-K., Endo, K. & Shibata, T. Cationic iridium–BINAP complex-catalyzed addition of aryl ketones to alkynes and alkenes via directed C–H bond cleavage. *J. Organomet. Chem.* **693**, 3939–3942 (2008).
- 35 Takebayashi, S. & Shibata, T. [Ir(cod)₂]BARF-Catalyzed C–H Bond Alkenylation and Alkylation of Ferrocenes. *Organometallics* **31**, 4114–4117 (2012).
- 36 Nagamoto, M., Fukuda, J.-i., Hatano, M., Yorimitsu, H. & Nishimura, T. Hydroxo-iridium-Catalyzed Hydroarylation of Alkynes and Bicycloalkenes with *N*-Sulfonylbenzamides. *Org. Lett.* **19**, 5952–5955 (2017).
- 37 Aulwurm, U. R., Melchinger, J. U. & Kisch, H. Transition Metal Complexes of Diazenes. 35.

Synthesis of 1-(Arylamino)indoles by Rhodium-Catalyzed Addition of Alkynes to 1,2-Diaryldiazenes. *Organometallics* **14**, 3385–3395 (1995).

- 38 Lim, Y.-G., Lee, K.-H., Koo, B. T. & Kang, J.- B. Rhodium(I)-catalyzed *ortho*-alkenylation of 2-phenylpyridines with alkynes. *Tetrahedron Lett.* **42**, 7609–7612 (2001).
- 39 Lim, S.-G., Lee, J. H., Moon, C. W., Hong, J. B. & Jun, C.-H. Rh(I)-Catalyzed Direct *ortho*-Alkenylation of Aromatic Ketimines with Alkynes and Its Application to the Synthesis of Isoquinoline Derivatives. *Org. Lett.* **5**, 2759–2761 (2003).
- 40 Shibata, Y., Otake, Y., Hirano, M. & Tanaka, K. Amide-Directed Alkenylation of sp^2 C–H Bonds Catalyzed by a Cationic Rh(I)/ BIPHEP Complex Under Mild Conditions: Dramatic Rate Acceleration by a 1-Pyrrolidinecarbonyl Group. *Org. Lett.* **11**, 689–692 (2009).
- 41 Schipper, D. J., Hutchinson, M. & Fagnou, K. Rhodium(III)-Catalyzed Intermolecular Hydroarylation of Alkynes. *J. Am. Chem. Soc.* **132**, 6910–6911 (2010).
- 42 Zhao, P., Niu, R., Wang, F., Han, K. & Li, X. Rhodium(III)- and Ruthenium(II)-Catalyzed Olefination of Isoquinolones. *Org. Lett.* **14**, 4166–4169 (2012).
- 43 Min, M., Kim, D. & Hong, S. $AgSbF_6$ -controlled diastereodivergence in alkyne hydroarylation: facile access to *Z*- and *E*-alkenyl arenes. *Chem Commun.* **50**, 8028–8031 (2014).
- 44 Nobushige, K., Hirano, K., Satoh, T. & Miura, M. Rhodium(III)-Catalyzed *ortho*-Alkenylation through C–H Bond Cleavage Directed by Sulfoxide Groups. *Org. Lett.* **16**, 1188–1191 (2014).
- 45 Martínez, Á. M. Rh^I/Rh^{III} catalyst-controlled divergent aryl/heteroaryl C–H bond functionalization of picolinamides with alkynes. *Chem. Sci.* **6**, 5802–5814 (2015).

- 46 Shibata, K., Natsui, S. & Chatani, N. Rhodium-Catalyzed Alkenylation of C–H Bonds in Aromatic Amides with Alkynes. *Org. Lett.* **19**, 2234–2237 (2017).
- 47 Xu, H.-J. et al. Rh(III)-Catalyzed meta-C–H Alkenylation with Alkynes. *J. Am. Chem. Soc.* **141**, 76–79 (2019).
- 48 Halbritter, G., Knoch, F., Wolski, A. & Kisch, H. Functionalization of Aromatic Azo Compounds by the Cobalt-Catalyzed, Regioselective Double Addition of Toluene: 2,6-Distilbenzylazobenzenes and 2,3-Dihydrocinnolines. *Angew. Chem. Int. Ed.* **33**, 1603–1605 (1994).
- 49 Gao, K., Lee, P.-S., Fujita, T. & Yoshikai, N. Cobalt-Catalyzed Hydroarylation of Alkynes through Chelation-Assisted C–H Bond Activation. *J. Am. Chem. Soc.* **132**, 12249–12251 (2010).
- 50 Lee, P.-S., Fujita, T. & Yoshikai, N. Cobalt-Catalyzed, Room-Temperature Addition of Aromatic Imines to Alkynes via Directed C–H Bond Activation. *J. Am. Chem. Soc.* **133**, 17283–17295 (2011).
- 51 Ding, Z. & Yoshikai, N. Mild and Efficient C2-Alkenylation of Indoles with Alkynes Catalyzed by a Cobalt Complex. *Angew. Chem. Int. Ed.* **51**, 4698–4701 (2012).
- 52 Fallon, B. J. et al. C–H Activation/Functionalization Catalyzed by Simple, Well-Defined Low-Valent Cobalt Complexes. *J. Am. Chem. Soc.* **137**, 2448–2451 (2015).
- 53 Wang, S. et al. Cobalt(III)-catalyzed alkenylation of arenes and 6-arylpurines with terminal alkynes: efficient access to functional dyes. *Chem. Commun.* **52**, 2709–2712 (2016).
- 54 Zhou, X. et al. Cp*Co^{III}-Catalyzed Branch-Selective Hydroarylation of Alkynes via C–H Activation: Efficient Access to α -gem-Vinylindoles. *ACS Catal.* **7**, 7296–7304 (2017).

- 55 Zhou, B., Chen, H. & Wang, C. Mn-Catalyzed Aromatic C–H Alkenylation with Terminal Alkynes. *J. Am. Chem. Soc.* **135**, 1264–1267 (2013).
- 56 Shi, L., Zhong, X., She, H., Lei, Z. & Li, F. Manganese catalyzed C–H functionalization of indoles with alkynes to synthesize bis/trisubstituted indolylalkenes and carbazoles: the acid is the key to control selectivity. *Chem. Commun.* **51**, 7136–7139 (2015).
- 57 Wang, H., Pesciaioli, F., Oliveira, J. C. A., Warratz, S. & Ackermann, L. Synergistic Manganese(I) C–H Activation Catalysis in Continuous Flow: Chemoselective Hydroarylation. *Angew. Chem. Int. Ed.* **56**, 15063–15067 (2017).
- 58 Kuninobu, Y., Kikuchi, K., Tokunaga, Y., Nishina, Y. & Takai, K. Hydroarylation of acetylenes, acrylates, and isocyanates with heteroaromatic compounds under rhenium catalysis. *Tetrahedron.* **64**, 5974–5981 (2008).
- 59 Chang, Y.-C., Prakash, S. & Cheng, C.-H. Re^I-Catalyzed highly regio- and stereoselective C–H addition to terminal and internal alkynes. *Org. Chem. Front.* **6**, 432–436 (2019).
- 60 Wong, M. Y., Yamakawa, T. & Yoshikai, N. Iron-Catalyzed Directed C2-Alkylation and Alkenylation of Indole with Vinylarenes and Alkynes. *Org. Lett.* **17**, 442–445 (2015).
- 61 Wang, D. et al. Rhodium-catalysed direct hydroarylation of alkenes and alkynes with phosphines through phosphorous-assisted C–H activation. *Nat. Comm.* **10**, 3539 (2019).
- 62 Zhang, Z., Cordier, M., Dixneuf, P. H. & Soulé, J.-F. Late-Stage Diversification of Biarylphosphines through Rhodium(I)-Catalyzed C–H Bond Alkenylation with Internal Alkynes. *Org. Lett.* **22**, 5936–5940 (2020).
- 63 Donets, P. A. & Cramer, N. Diaminophosphine Oxide Ligand Enabled Asymmetric Nickel-Catalyzed Hydrocarbamylation of Alkenes. *J. Am. Chem. Soc.* **135**, 11772–11775

(2013).

- 64 Liu, Q.-S. et al. Ni–Al Bimetallic Catalyzed Enantioselective Cycloaddition of Cyclopropyl Carboxamide with Alkyne. *J. Am. Chem. Soc.* **139**, 18150–18153 (2017).
- 65 Li, J.-F., Luan, Y.-X. & Ye, M. Bimetallic anchoring catalysis for C–H and C–C activation. *Sci. China Chem.* **2021**, 64, 1923–1937.
- 66 Xing, Y. et al Chemically stable anion exchange membranes based on C2-Protected imidazolium cations for vanadium flow battery. *J. Membr. Sci.* **618**, 118696 (2021).
- 67 L'abbate, F. P. et al. Hemozoin inhibiting 2-phenylbenzimidazoles active against malaria parasites. *Eur. J. Med. Chem.* **159**, 243–254 (2018).
- 68 Bellina, F. & Rossi, R. Regioselective Functionalization of the Imidazole Ring via Transition Metal-Catalyzed C-N and C-C Bond Forming Reactions. *Adv. Synth. Catal.* **352**, 1223–1276 (2010).
- 69 Tang, Z., Mai, S., Zhou, Y. & Song, Q. Divergent synthesis of α -aryl ketones/esters via rhodium-catalyzed selective deesterification and decarbonylation of diazo compounds. *Org. Chem. Front.* **5**, 2583–2587 (2018).
- 70 Lim, Y.-G., Lee, K.-H., Koo, B. T. & Kang, J.-B. Rhodium(I)-catalyzed *ortho*-alkenylation of 2-phenylpyridines with alkynes. *Tetrahedron Lett.* **42**, 7609–7612 (2001).
- 71 Dhole, S. & Sun, C.-M. Direct Access to Dihydrobenzoimidazo[2,1-*a*]isoquinolines through Ruthenium-catalyzed Formal [4+2] Annulation. *Adv. Synth. Catal.* **361**, 535–541 (2019).
- 72 Gui, J. et al. C–H Methylation of Heteroarenes Inspired by Radical SAM Methyl Transferase. *J. Am. Chem. Soc.* **136**, 4853–4856 (2014).
- 73 Gao, G.-L., Yang, C. & Xia, W. Selective C–H trifluoromethylation of benzimidazoles

through photoredox catalysis. *Chem. Commun.* **53**, 1041–1044 (2017).

- 74 Chatani, N., Fukuyama, T., Kakiuchi, F. & Murai, S. Ru₃(CO)₁₂-Catalyzed Coupling of Heteroaromatic C-H/CO/Olefins. Regioselective Acylation of the Imidazole Ring. *J. Am. Chem. Soc.* **118**, 493–494 (1996).
- 75 Fukuyama, T., Chatani, N., Tatsumi, J., Kakiuchi, F. & Murai, S. Ru₃(CO)₁₂-Catalyzed Site-Selective Carbonylation Reactions at a C–H Bond in Aza-Heterocycles. *J. Am. Chem. Soc.* **120**, 11522–11523 (1998).
- 76 Morningstar, M. L. et al Synthesis, Biological Activity, and Crystal Structure of Potent Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase That Retain Activity against Mutant Forms of the Enzyme. *J. Med. Chem.* **50**, 4003–4015 (2007).
- 77 White, A. W. et al Resistance-Modifying Agents. 9. 1 Synthesis and Biological Properties of Benzimidazole Inhibitors of the DNA Repair Enzyme Poly(ADP-ribose) Polymerase. *J. Med. Chem.* **43**, 4084–4097 (2000).

Acknowledgments

This work was supported by the National Natural Science Foundation of China (21871145, 91856104), the Natural Science Foundation of Tianjin of China (19JCZDJC37900) and Frontiers Science Center for New Organic Matter, Nankai University (63181206).

Author contributions

S.-L.Q. discovered and developed the reactions. Y.-P.L., Y.L. and Y.-X.L. performed part of synthetic experiments. M.Y. conceived, designed the investigations and wrote the manuscript. S.-L.Q. wrote the Supplementary Information.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at <http://doi.org/10.1038/>.

Correspondence and requests for materials should be addressed to M.Y.

Reprints and permission information is available at <http://npg.nature.com/reprints>

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SIhydroarylation11252021.pdf](#)