CHEMISTRY

Asymmetric redox benzylation of enals enabled by NHC/Ru cooperative catalysis

Shuai Li[1], Yu-Hua Wen[1], Jin Song[2]*, Liu-Zhu Gong[1,3]*

The development of general methods for asymmetric benzylation of prochiral carbon nucleophiles remains a challenge in organic synthesis. The merging of ruthenium catalysis and N-heterocyclic carbene (NHC) catalysis for asymmetric redox benzylation of enals has been achieved, which opens up strategic opportunities for the asymmetric benzylation reactions. A wide range of 3,3′-disubstituted oxindoles with a stereogenic quaternary carbon center widely existing in natural products and biologically interesting molecules is successfully obtained with excellent enantioselectivities [up to 99% enantiomeric excess (ee)]. The generality of this catalytic strategy was further highlighted by its successful application in the late-stage functionalization of oxindole skeletons. Furthermore, the linear correlation between ee values of NHC precatalyst and the product elucidated the independent catalytic cycle of either the NHC catalyst or the ruthenium complex.

INTRODUCTION

Transition metal (TM)–catalyzed alkylation reactions of benzylic derivatives with various nucleophiles are among the most powerful and indispensable tools for the formation of carbon-carbon and carbon-heteroatom bonds in organic synthesis (*1*–*3*). However, only a few examples of asymmetric benzylation reactions have been achieved, and the selection of chiral ligands in conjunction with TMs, including palladium and nickel, has made it possible to produce chiral benzylic derivatives (Fig. 1A) (*4*–*11*). In 2010, Trost and co-workers successfully demonstrated a model approach for the asymmetric benzylation of prochiral carbon nucleophiles via palladium catalysis (*12*–*14*). Very recently, asymmetric benzylic substitutions accomplished through a cooperative combination (*15*–*20*) of isoelectronic π-benzyl palladium/nickel species with chiral organocatalysts (*21*, *22*) or Lewis acids (*23*, *24*) that mediated nucleophiles have greatly progressed. In 2018, Snaddon and co-workers introduced benzotetramisole/Pd cooperatively catalyzed asymmetric benzylation reactions of acetic acid esters (*21*). Most recently, two highly efficient examples of asymmetric benzylation of azomethine ylides enabled by dual metal catalysis have been reported by the Zhang group (*23*) and the Wang group (*24*), respectively. Recently, Guo and co-workers established an α-benzylation reaction of N-unprotected amino acids with excellent stereocontrol (*22*). However, comparing with the well-developed Tsuji-Trost allylation reactions (*25*–*27*), catalytic asymmetric benzylation reactions have been reported much less frequently, probably due to the lack of reliable chirality models and also to the difficulties in the formation of π-benzyl metal species because of the thermodynamically less favorable disruption to aromaticity (*1*–*3*). Nevertheless, the exploration of catalytic systems, in which the π-benzyl metal species are orthogonally reactive toward certain nucleophiles, would be highly desirable for achieving optically active benzylic compounds.

N-heterocyclic carbene (NHC) catalysis, a versatile organocatalytic process, has attracted considerable interest from the synthetic community (*28*–*31*). In recent years, NHC and TM cooperative catalysis (*32*–*34*) has emerged as a versatile tool for accessing asymmetric reactions that were previously difficult to achieve (*35*–*43*), and impressive progress has been made (*44*–*58*) in the knowledge of NHC-TM interplay (*59*), compatible catalyst activation modes, and types of reactions (Fig. 1B). In comparison with the extensively explored Pd, Ir, or Ni-π-allyl species, as well as Cu-allenylidene species, coupling with chiral NHC-adorned nucleophiles, asymmetric reactions mediated by other types of electrophilic TM-activated intermediates, however, is still comprehensively elusive in this area. Recently, our group (*50*, *55*–*58*) demonstrated that the isatin-derived homoenolate equivalent **I** (*60*–*63*) exhibits high facial selectivity and good feasibility with metal-activated electrophiles, providing an important advance to access synthetically valuable oxindole derivatives (Fig. 1C). In light of these pioneering contributions, we were interested in the exploration of a π-benzyl ruthenium system (*64*–*66*) as a class of acceptor electrophile (*38*) in NHC/TM cooperative catalysis. Such a reaction would, in principle, enable umpolung reactivity where an isatin-derived enal functions as a nucleophile in a C—C bond-forming reaction at a benzylic position (Fig. 1D). This redox benzylation of enals, realized through NHC/Ru cooperative catalysis, would not only broaden the domain of NHC/TM cooperative catalytic system but also present pathways for asymmetric benzylation reactions.

RESULTS AND DISCUSSION

Design of the NHC/Ru cooperative catalytic system

Initially, proof-of-concept studies focused upon the asymmetric benzylation reaction of isatin-derived enal **1a** with 2-naphthyl diphenylphosphate **2a** in the presence of NHC/Ru cooperative catalytic system, and the key results are briefly summarized in Table 1 (see tables S1 to S6 for detailed condition optimizations). Several ligands (**L1** to **L3**) (*64*–*66*), together with the ruthenium catalyst, were tested with NHC precatalyst **4a** at room temperature (entries 1 to 3). The use of bipyridine ligand **L2** would furnish the desired product **3aa** in moderate yield and high enantioselectivity. We next

[1]Hefei National Research Center for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China. [2]Institutes of Physical Science and Information Technology, Key Laboratory of Environment-Friendly Polymeric Materials of Anhui Province, Anhui University, Hefei 230601, China. [3]Center for Excellence in Molecular Synthesis of Chinese Academy of Sciences, Hefei 230026, China.
*Corresponding author. Email: gonglz@ustc.edu.cn (L.-Z. G.); jill@ahu.edu.cn (J. S.)

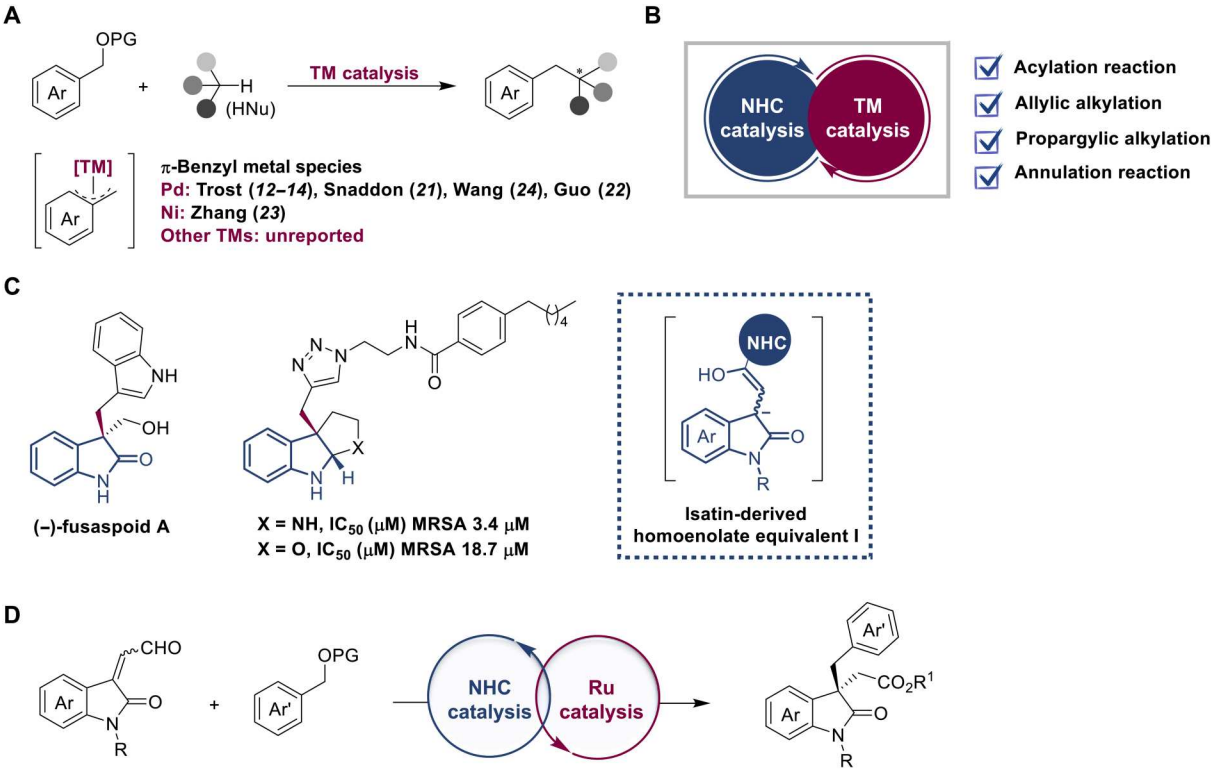


Fig. 1. Asymmetric benzylation reactions via NHC/Ru cooperative catalysis. (**A**) Previous work: TM-catalyzed asymmetric benzylation reactions. (**B**) N-Heterocyclic carbene (NHC)/TM cooperatively catalyzed asymmetric reactions. (**C**) Selected naturally occurring and biologically active oxindoles and pyrroloindolines. (**D**) This work: NHC/Ru cooperatively catalyzed enantioselective benzylation reactions. IC_{50}, median inhibitory concentration. MRSA, methicillin resistant *Staphylococcus aureus*.

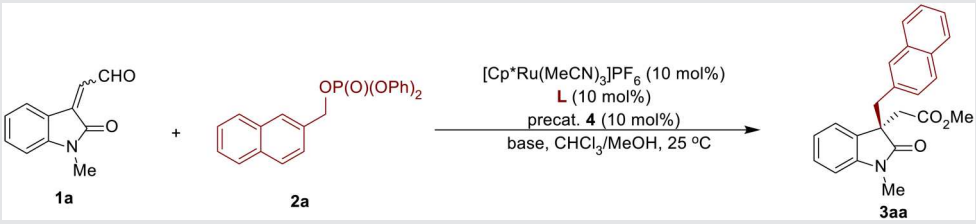
explored different NHC precatalysts **4b** to **4d** (entries 4 to 6) and identified **4b** to be the optimal one (entry 4). Further assessment of base identified Na_2CO_3, which gave the product in an enhanced yield and with 96% enantiomeric excess (ee) (entry 7). When lowering the concentration to 0.05 M, along with the use of 2.0 equiv. of 2-naphthyl diphenylphosphate **2a** in the reaction, the product yield increased to 74% (entries 8 and 9). Eventually, the amount of catalyst loading of **4b** was decreased from 10 to 2.5%, whereas the catalyst activity was retained (entry 10). Control experiments revealed that no desired product was detected in the absence of any of the catalyst components (entries 11 to 13).

Substrate scope

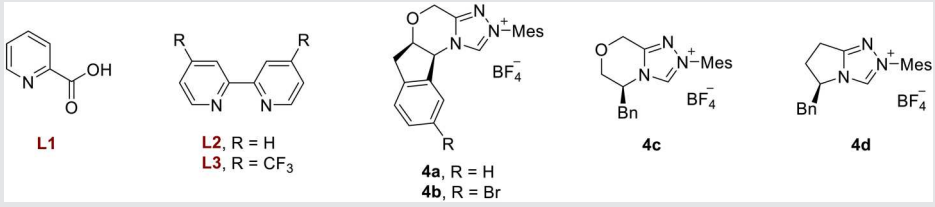
With the optimized reaction conditions in hand, we next investigated the scope of isatin-derived enals **1** (Fig. 2). In general, various isatin-derived enals were allowed to react with 2-naphthyl diphenylphosphate **2a** and gave the corresponding products in satisfactory yields and enantioselectivities. Isatin-derived enals bearing different substituents at the nitrogen atom (R) all proceeded smoothly under the current reaction conditions and gave oxindole derivatives **3aa** to **3ea** in good yields (51 to 72%) with excellent enantioselectivities. Note that the N—H substrate works equally well for this transformation (**3fa**). Various substituted isatin-derived enals including those bearing electron-withdrawing and electron-donating substituents at different positions on the aromatic ring could be tolerated and gave the corresponding compounds **3ga**-**3oa** in high yields and excellent enantioselectivities (95 to 98% ee). The absolute configuration of **3ga** was determined by x-ray crystallography, and the other products were assigned in analogy to **3ga**.

We then sought to expand the reaction to benzylic phosphate electrophiles (Fig. 3). Variation of the electronic properties of the substituents at different positions on the aromatic ring of naphthyl phosphates was tolerated. Different halogen (F, Cl, and Br) atoms substituted at the 6-position of naphthalene ring all afforded benzylation products with excellent enantiocontrol (**3ab** to **3ad**, up to 96% ee). Substrates **2e** to **2j** with functional groups on the aromatic ring, such as vinyl methyl ester and OMe, were successfully transformed into corresponding 3,3′-substituted oxindoles **3ae** to **3aj**. Benzylic electrophiles, such as **2k** to **2n** with phenanthrene, indole, and thiophene substituents, were also compatible with this benzylation process and afforded the corresponding oxindole products **3ak** to **3an** with excellent stereoselectivities (96 to 98% ee). In addition, this protocol was also amenable to the synthesis of 3,3′-substituted oxindoles **3lg** and **3mj**. To further expand the substrate scope, we then applied our NHC/Ru cooperative catalysis to the benzylation reaction of the enal **1a** with simple benzylic electrophiles, which were supposed to have a higher ionization and dearomatization barrier than naphthalene substrates (*13*). The results showed that ortho-substituted benzyl phosphates were good reaction components, although the yield and stereoselectivity were fairly good (**3ao** to **3ar**; see tables S7 and S8 for details). [1,1′-Biphenyl]-2-ylmethanol–derived phosphate **2o** could give product **3ao** in 31% yield and 87% ee. This reaction was well-represented by the benzyl phosphate with two substituents on the benzene ring (**3ap**). Benzyl phosphates with cyclic substituents were also

Table 1. Optimization of the reaction conditions. Unless otherwise specified, all reactions were carried out using **1a** (0.1 mmol), **2a** (0.1 mmol), $[Cp^*Ru(MeCN)_3]PF_6$ (10 mol %), **L** (10 mol %), NHC precatalyst **4** (10 mol %), and base (0.11 mmol) in $CHCl_3$ (0.9 ml) and methanol (MeOH; 0.1 ml) at 25°C for 20 hours under N_2. NMR, nuclear magnetic resonance; HPLC, high-performance liquid chromatography.



Entry	L	4	Base	Yield (%)*	ee (%)†
1	**L1**	**4a**	Et_3N	34	62
2	**L2**	**4a**	Et_3N	44	92
3	**L3**	**4a**	Et_3N	33	89
4	**L2**	**4b**	Et_3N	41	95
5	**L2**	**4c**	Et_3N	40	62
6	**L2**	**4d**	Et_3N	28	46
7	**L2**	**4b**	Na_2CO_3	50	96
8‡	**L2**	**4b**	Na_2CO_3	60	96
9‡,§	**L2**	**4b**	Na_2CO_3	74(72)	96
10‡,§,‖	**L2**	**4b**	Na_2CO_3	73(72)	96
11‡,§,‖	**L2**	-	Na_2CO_3	N.D.	
12‡,§,‖	-	**4b**	Na_2CO_3	N.D.	
13‡,§,‖,¶	-	**4b**	Na_2CO_3	N.D.	



*^{1}H NMR yield. The yield of the isolated product **3aa** is given within parentheses. †The enantiomeric excess (ee) was determined by HPLC. N.D., not detected. ‡With $CHCl_3$ (1.8 ml) and MeOH (0.2 ml). §2.0 equiv. of **2a** was used. ‖2.5 mol % of **4b** was used. ¶In the absence of $[Cp^*Ru(MeCN)_3]PF_6$.

suitable coupling partners and afforded the corresponding benzylation products **3aq** (45% yield and 72% ee) and **3ar** (40% yield and 71% ee) in acceptable results.

Synthetic application

The practical synthetic utility of this method was demonstrated by a large-scale reaction, which proceeded smoothly to afford the desired product **3aa** in 68% yield with maintained ee value (Fig. 4A). Last, to explore the synthetic value of benzylation products, **3aa** was transformed into a series of derivatives that retain the chiral integrity of the starting 3,3′-oxindole skeleton (Fig. 4, B to D). For example, the hydrolysis of the ester moiety under basic conditions led to an acid **5** in 98% yield (Fig. 4B). Moreover, the manipulation of the acid unit of **5** delivered the alcohol **6** with maintained ee. Treatment of **3aa** with 9-borabicyclo[3.3.1]nonane at 65°C in tetrahydrofuran (THF) led to the indoline alcohol **7** in 76% yield with 96% ee. The aminolysis of **3aa** with methylamine ethanol solution smoothly afforded amide **8** with no diminution of ee (Fig. 4C). Subsequent reductive cyclization successfully formed the tricyclic product **9** in 60% yield and with 98% ee. The reduction of **3aa** with $LiAlH_4$ in THF led to a furoindoline **10**, and the hexahydropyrrolo[2,3-b]indole and hexahydrofuro[2,3-b]indole motif having a carbon substituent at C-3 are the defining structural features of a diverse collection of natural products and pharmaceutically active molecules (*67*). In addition, starting from the oxindole acid **5** derived from **3aa**, we accomplished an efficient

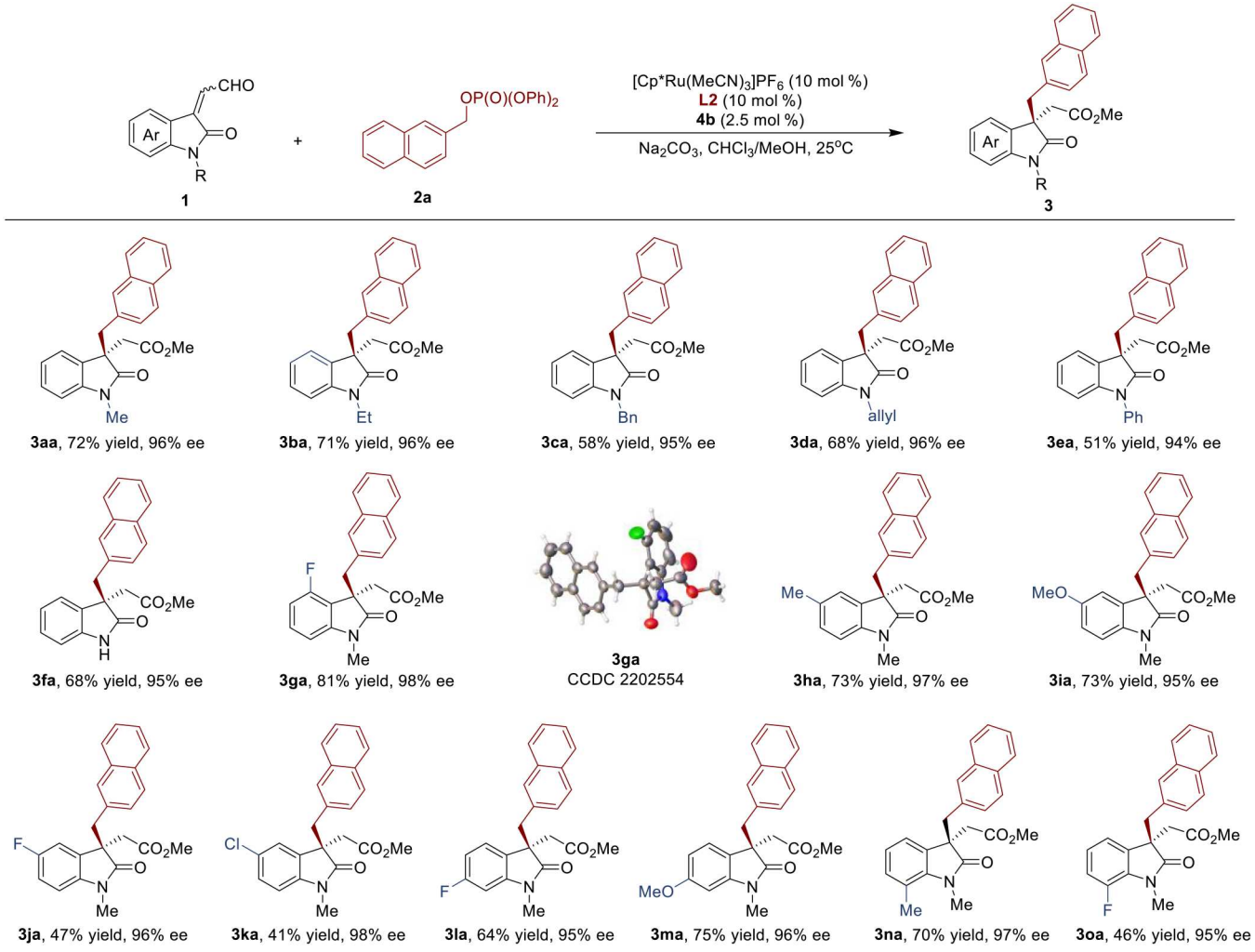


Fig. 2. Substrate scope of enals. Unless otherwise specified, all reactions were carried out using **1** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*Ru(MeCN)_3]PF_6$ (10 mol %), **L2** (10 mol %), NHC precatalyst **4b** (2.5 mol %), and Na_2CO_3 (0.11 mmol) in $CHCl_3$ (1.8 ml) and methanol (MeOH; 0.2 ml) at 25°C for 20 hours under N_2. Yield of isolated product **3**. The ee was determined by high-performance liquid chromatography (HPLC).

access to spirooxindole **11** with structural diversity, and the carbon stereocenter remains intact (Fig. 4D).

Plausible mechanism

We performed a set of experiments with ee-varied chiral NHC precatalyst **4b**, ruthenium-bipyridine complex, isatin-derived enal **1a**, and 2-naphthyl diphenylphosphate **2a** under the standard conditions (Table 1, entry 10). As depicted in Fig. 5A (see table S9 for details), a linear relationship between the ee values of the NHC precatalyst and benzylation product **3aa** was observed, which suggests that one molecule of NHC gets involved in the enantio-determining step to work as an organocatalyst and that the ruthenium-bipyridine complex is the reactive metal species in the catalytic system. The coordination event between NHC and the ruthenium center had little effect on the stereochemical control. On the basis of these experimental results and previous findings (*28*–*34*, *64*–*66*), a plausible reaction pathway is proposed and summarized in Fig. 5B. The Breslow intermediate **I** (or azolium homoenolate species **II**) is generated from the reaction of the enal **1a** and NHC catalyst. Meanwhile, the ruthenium complex coordinates with 2-naphthyl diphenylphosphate **2a** and then undergoes oxidative addition to generate a π-benzyl ruthenium species **III** (*64*–*66*). Afterward, the homoenolate species **II** (or **I**) attacks the π-benzyl ruthenium intermediate **III** preferentially from the unblocked bottom face by the substituents on NHC and affords a benzylation intermediate **IV**. Last, the intermediate **IV** delivers the final benzylation product **3aa** by regenerating the ruthenium catalyst and releasing the NHC catalyst via methanolysis.

In conclusion, we have developed an NHC/Ru cooperatively catalyzed asymmetric redox benzylation reaction of enals with benzylic phosphates. By integrating NHC catalysis and ruthenium catalysis, the direct enantioselective coupling of NHC-bound homoenolate with a π-benzyl ruthenium species proceeds well to provide a rapid and stereoselective method to access 3,3′-oxindole skeletons with great tolerance of functional groups in high yields (up to 91%) and with excellent enantioselectivity (up to 99% ee). Mechanistic studies confirm that the free carbene catalyst and the Ru catalyst work well independently to accomplish their own catalytic

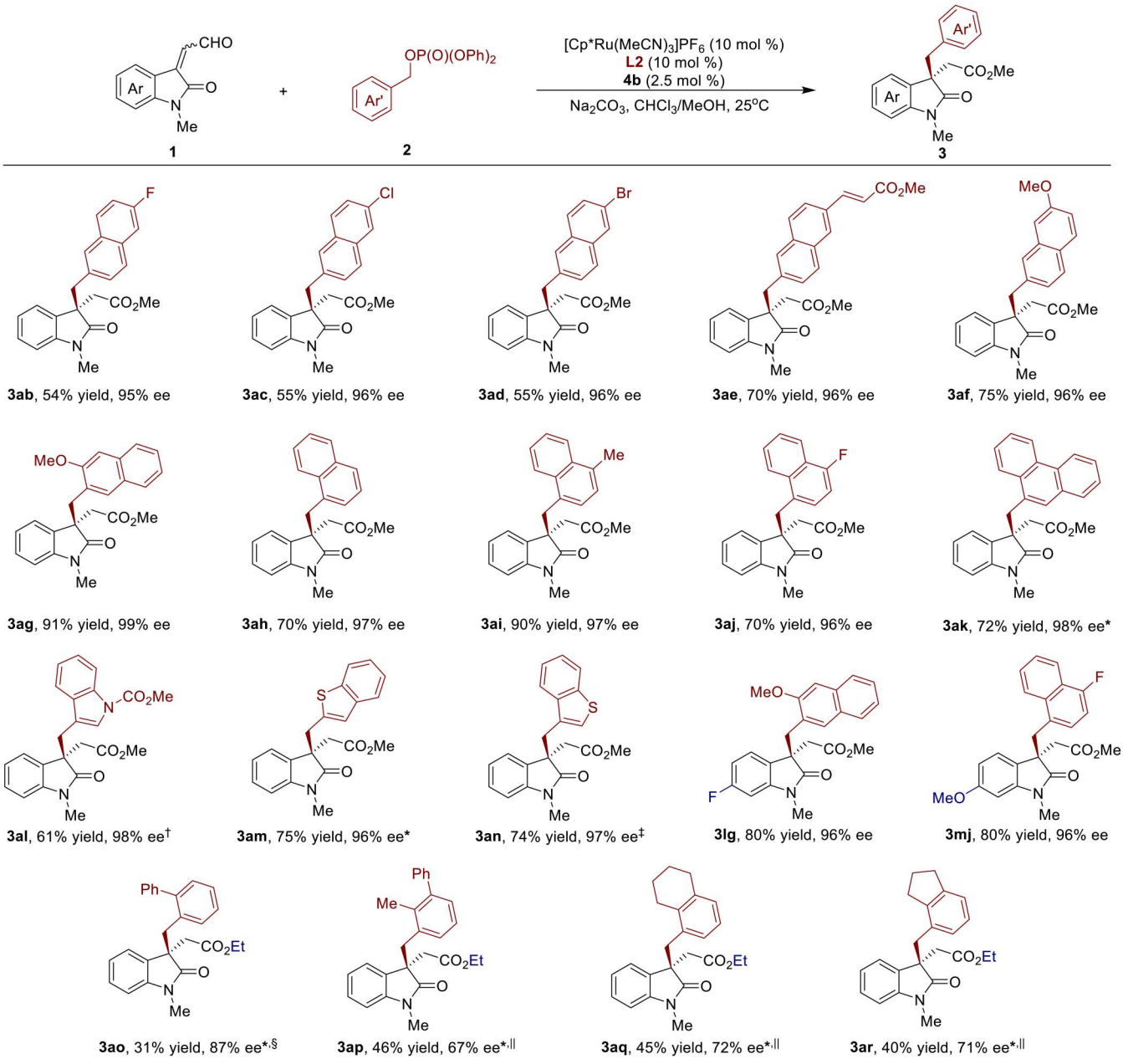


Fig. 3. Substrate scope of benzylic phosphate electrophiles. Unless otherwise specified, all reactions were carried out using **1** (0.1 mmol), **2** (0.2 mmol), $[Cp^*Ru(MeCN)_3]PF_6$ (10 mol %), **L2** (10 mol %), NHC precatalyst **4b** (2.5 mol %), and Na_2CO_3 (0.11 mmol) in $CHCl_3$ (1.8 ml) and MeOH (0.2 ml) at 25°C for 20 hours under N_2. Yield of isolated product **3**. The ee was determined by HPLC. *With 10 mol % of NHC precatalyst **4b**. †CO_2Me-protected 2-naphthalene methanol was used. ‡With 20 mol % of NHC precatalyst **4b** at 0°C. §With $[Cp^*Ru(MeCN)_3]PF_6$ (20 mol %), **L2** (20 mol %), **1a** (0.3 mmol), **2** (0.1 mmol), and Et_3N (0.11 mmol) in ethanol (EtOH; 0.5 ml) at 60°C. ||With $[Cp^*Ru(MeCN)_3]PF_6$ (20 mol %), **L2** (20 mol %), **1a** (0.2 mmol), **2** (0.1 mmol), and Et_3N (0.11 mmol) in EtOH (1.0 ml) at 40°C.

roles without quenching each other. Further studies on the exploration of NHC/TM cooperative catalytic systems are the topics of the ongoing investigation.

MATERIALS AND METHODS

General information

All solvents were purified according to the solvents handbook. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. All reactions were performed under a dinitrogen atmosphere using Schlenk line techniques or inside a dinitrogen-filled glove box. Flash column chromatography was carried out using 300- to 400-mesh silica gel at medium pressure. ^{1}H NMR (nuclear magnetic resonance) and ^{13}C NMR spectra were recorded at 25°C on Bruker Advance 500-MHz NMR spectrometers. High-resolution mass spectral analysis was performed on a Thermo LTQ Orbitrap XL (ESI+) or a P-SIMS-Gly of Bruker Daltonics Inc. (EI+). Optical rotations were

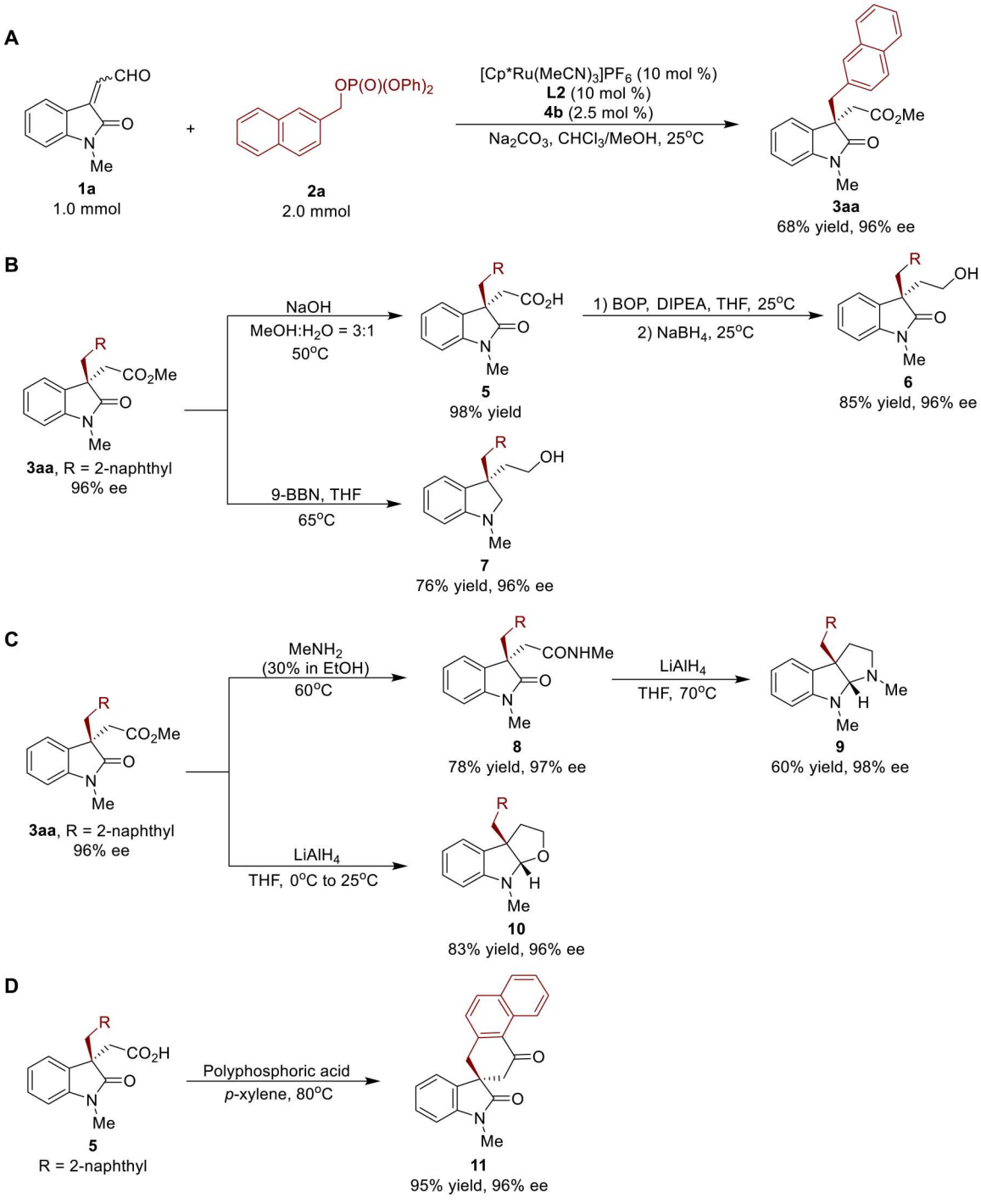


Fig. 4. Product derivatization. (**A**) Large scale reaction. (**B**) to (**D**) Synthetic transformations. BOP, benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium; 9-BBN, 9-borabicyclo[3.3.1]nonane; DIPEA, N,N-diisopropylethylamine; THF, tetrahydrofuran.

determined at 589 nm (sodium D line) by using a PerkinElmer 343 polarimeter. The measurement of ees was performed on Waters-Alliance (2998, Photodiode Array Detector).

General procedure for the synthesis of chiral products 3

A flame-dried Schlenk tube equipped with a magnetic stirring bar was taken into the glove box and charged with $[Cp^*Ru(MeCN)_3]PF_6$ [0.01 mmol, 10 mole percent (mol %)] and 2,2′-bipyridine (**L2**) (0.01 mmol, 10 mol %). Outside the glove box, $CHCl_3$ (0.9 ml) and methanol (MeOH) (0.1 ml) were added to the Schlenk tube under a positive pressure of nitrogen and the solution was stirred at 25°C for 30 min. Then, the NHC precatalyst **4b** (0.0025 mmol, 2.5 mol %), isatin-derived enal **1** (0.1 mmol, 1.0 equiv.), benzylic derivative **2** (0.2 mmol, 2.0 equiv.), Na_2CO_3 (0.11

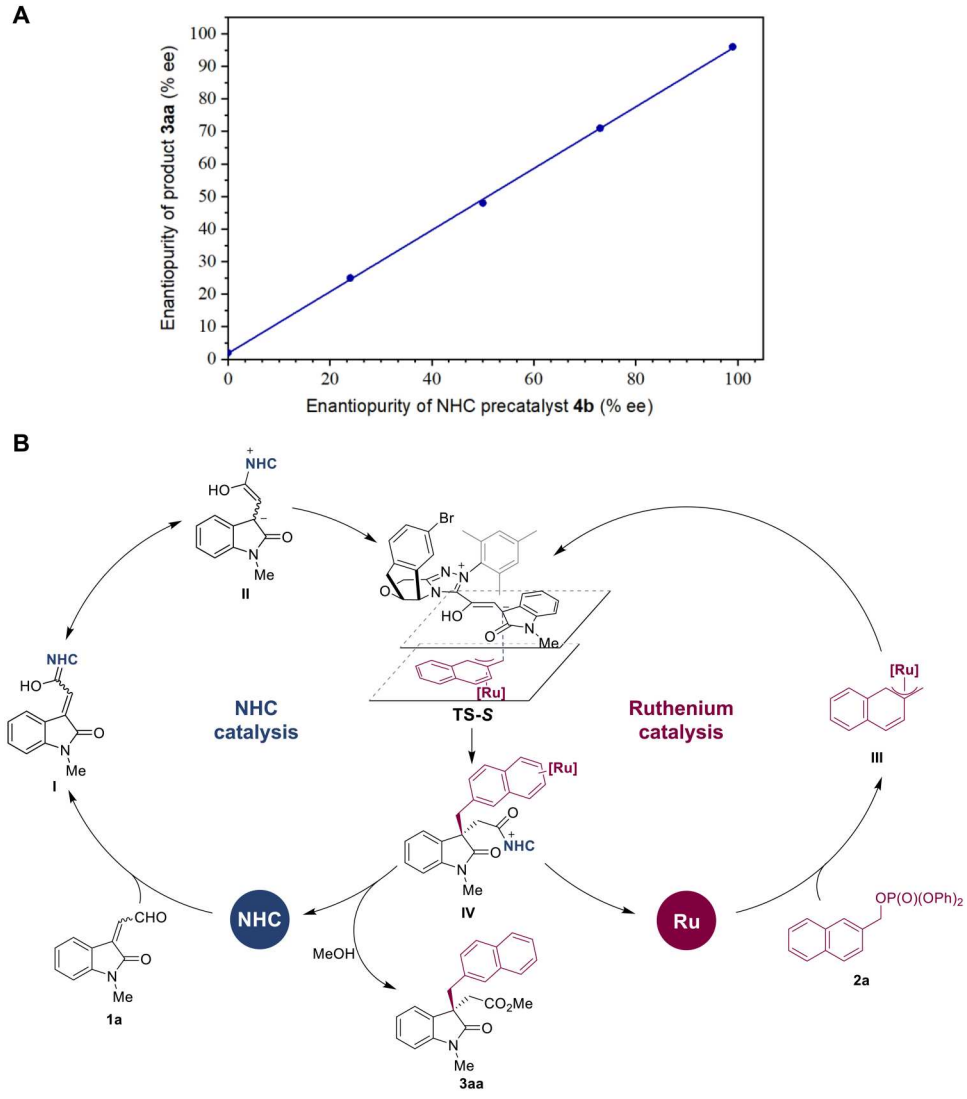


Fig. 5. Mechanistic proposal for NHC/Ru cooperative catalysis. (**A**) Correlation of ee values of NHC precatalyst and product **3aa**. (**B**) Proposed catalytic cycle.

mmol, 1.1 equiv.), $CHCl_3$ (0.9 ml), and MeOH (0.1 ml) were added under a positive pressure of nitrogen, and then, the solution was stirred at 25°C for 16 to 24 hours. After the reaction was complete, the reaction mixture was filtered through a short pad of silica gel and the solvent was evaporated under vacuum. The residue was purified by silica gel chromatography to afford the desired product **3**.

Supplementary Materials

This PDF file includes:

Supplementary Text
Tables S1 to S9
Fig. S1

REFERENCES AND NOTES

1. B. Liégault, J.-L. Renaud, C. Bruneau, Activation and functionalization of benzylic derivatives by palladium catalysts. *Chem. Soc. Rev.* **37**, 290–299 (2008).
2. B. M. Trost, L. C. Czabaniuk, Structure and reactivity of late transition metal η^3-benzyl complexes. *Angew. Chem. Int. Ed.* **53**, 2826–2851 (2014).
3. J. L. Bras, J. Muzart, Production of Csp^3–Csp^3 bonds through palladium-catalyzed Tsuji–-Trost-type reactions of (hetero)benzylic substrates. *Eur. J. Org. Chem.* **15**, 2565–2593 (2016).
4. J.-Y. Legros, M. Toffano, J.-C. Fiaud, Asymmetric palladium-catalyzed nucleophilic substitution of racemic 1-naphthylethyl esters. *Tetrahedron: Asymmetry* **6**, 1899–1902 (1995).
5. M. Assié, A. Meddour, J.-C. Fiaud, J.-Y. Legros, Enantiodivergence in alkylation of 1-(6-methoxynaphth-2-yl)ethyl acetate by potassium dimethyl malonate catalyzed by chiral palladium-DUPHOS complex. *Tetrahedron: Asymmetry* **21**, 1701–1708 (2010).
6. S. Tabuchi, K. Hirano, M. Miura, Palladium-catalyzed asymmetric benzylic alkylation of active methylene compounds with α-naphthylbenzyl carbonates and pivalates. *Angew. Chem. Int. Ed.* **55**, 6973–6977 (2016).
7. X. Shen, L. Qian, S. Yu, Photoredox/palladium-cocatalyzed enantioselective alkylation of secondary benzyl carbonates with 4-alkyl-1,4-dihydropyridines. *Sci. China Chem.* **63**, 687–691 (2020).
8. A. Najib, K. Hirano, M. Miura, Palladium-catalyzed asymmetric benzylic substitution of secondary benzyl carbonates with nitrogen and oxygen nucleophiles. *Org. Lett.* **19**, 2438–2441 (2017).
9. A. Matsude, K. Hirano, M. Miura, Palladium-catalyzed benzylic phosphorylation of diarylmethyl carbonates. *Org. Lett.* **20**, 3553–3556 (2018).
10. Q. Dai, L. Liu, J. Zhang, Palladium/xiao-phos-catalyzed kinetic resolution of *sec*-phosphine oxides by *P*-benzylation. *Angew. Chem. Int. Ed.* **60**, 27247–27252 (2021).

11. W.-Q. Cai, Q. Wei, Q.-W. Zhang, Ni-catalyzed enantioselective benzylation of secondary phosphine oxide. *Org. Lett.* **24**, 1258–1262 (2022).
12. B. M. Trost, L. C. Czabaniuk, Palladium-catalyzed asymmetric benzylation of 3-aryl oxindoles. *J. Am. Chem. Soc.* **132**, 15534–15536 (2010).
13. B. M. Trost, L. C. Czabaniuk, Benzylic phosphates as electrophiles in the palladium-catalyzed asymmetric benzylation of azlactones. *J. Am. Chem. Soc.* **134**, 5778–5781 (2012).
14. B. M. Trost, L. C. Czabaniuk, Palladium-catalyzed asymmetric benzylation of azlactones. *Chem. A Eur. J.* **19**, 15210–15218 (2013).
15. A. E. Allen, D. W. C. MacMillan, Synergistic catalysis: A powerful synthetic strategy for new reaction development. *Chem. Sci.* **3**, 633–658 (2012).
16. Z. Du, Z. Shao, Combining transition metal catalysis and organocatalysis—An update. *Chem. Soc. Rev.* **42**, 1337–1378 (2013).
17. D.-F. Chen, Z.-Y. Han, X.-L. Zhou, L.-Z. Gong, Asymmetric organocatalysis combined with metal catalysis: Concept, proof of concept, and beyond. *Acc. Chem. Res.* **47**, 2365–2377 (2014).
18. B. A. Arndtsen, L.-Z. Gong, *Asymmetric Organocatalysis Combined with Metal Catalysis* (Springer, 2020).
19. L.-Z. Gong, *Asymmetric Organo-Metal Catalysis: Concepts, Principles, and Applications* (Wiley-VCH, 2022).
20. D.-F. Chen, L.-Z. Gong, Organo/transition-metal combined catalysis rejuvenates both in asymmetric synthesis. *J. Am. Chem. Soc.* **144**, 2415–2437 (2022).
21. K. J. Schwarz, C. Yang, J. W. B. Fyfe, T. N. Snaddon, Enantioselective α-benzylation of acyclic esters using π-extended electrophiles. *Angew. Chem. Int. Ed.* **57**, 12102–12105 (2018).
22. J.-H. Liu, W. Wen, J. Liao, Q.-W. Shen, Y. Lin, Z.-L. Wu, T. Cai, Q.-X. Guo, Catalytic asymmetric Tsuji–Trost α—benzylation reaction of N-unprotected amino acids and benzyl alcohol derivatives. *Nat. Commun.* **13**, 2509 (2022).
23. Y. Peng, C. Han, Y. Luo, G. Li, X. Huo, W. Zhang, Nickel/copper-cocatalyzed asymmetric benzylation of aldimine esters for the enantioselective synthesis of α-quaternary amino acids. *Angew. Chem. Int. Ed.* **61**, e202203448 (2022).
24. X. Chang, J.-D. Ran, X.-T. Liu, C.-J. Wang, Catalytic asymmetric benzylation of azomethine ylides enabled by synergistic lewis acid/palladium catalysis. *Org. Lett.* **24**, 2573–2578 (2022).
25. B. M. Trost, D. L. Van Vranken, Asymmetric transition metal-catalyzed allylic alkylations. *Chem. Rev.* **96**, 395–422 (1996).
26. J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, Transition metal-catalyzed decarboxylative allylation and benzylation reactions. *Chem. Rev.* **111**, 1846–1913 (2011).
27. O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J.-E. Bäckvall, A. Pfaltz, M. A. Pericàs, M. Diéguez, Recent advances in enantioselective Pd-catalyzed allylic substitution: From design to applications. *Chem. Rev.* **121**, 4373–4505 (2021).
28. J. Mahatthananchai, J. W. Bode, On the mechanism of N-heterocyclic carbene-catalyzed reactions involving acyl azoliums. *Acc. Chem. Res.* **47**, 696–707 (2014).
29. D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, Organocatalytic reactions enabled by *N*-heterocyclic carbenes. *Chem. Rev.* **115**, 9307–9387 (2015).
30. R. S. Menon, A. T. Biju, V. Nair, Recent advances in employing homoenolates generated by N-heterocyclic carbene (NHC) catalysis in carbon–carbon bond-forming reactions. *Chem. Soc. Rev.* **44**, 5040–5052 (2015).
31. H. Ohmiya, N-Heterocyclic carbene-based catalysis enabling cross-coupling reactions. *ACS Catal.* **10**, 6862–6869 (2020).
32. D. T. Cohen, K. A. Scheidt, Cooperative lewis acid/N-heterocyclic carbene catalysis. *Chem. Sci.* **3**, 53–57 (2012).
33. M. H. Wang, K. A. Scheidt, Cooperative catalysis and activation with N-heterocyclic carbenes. *Angew. Chem. Int. Ed.* **55**, 14912–14922 (2016).
34. K. Nagao, H. Ohmiya, N-Heterocyclic carbene (NHC)/metal cooperative catalysis. *Top. Curr. Chem. (Cham)* **377**, 35 (2019).
35. Y. Bai, S. Xiang, M. L. Leow, X.-W. Liu, Dual-function Pd/NHC catalysis: Tandem allylation–isomerization–conjugate addition that allows access to pyrroles, thiophenes and furans. *Chem. Commun.* **50**, 6168–6170 (2014).
36. K. Liu, M. T. Hovey, K. A. Scheidt, A cooperative *N*-heterocyclic carbene/palladium catalysis system. *Chem. Sci.* **5**, 4026–4031 (2014).
37. Y. Bai, W. L. Leng, Y. Li, X.-W. Liu, A highly efficient dual catalysis approach for *C*-glycosylation: Addition of (*o*-Azaaryl)carboxaldehyde to glycals. *Chem. Commun.* **50**, 13391–13393 (2014).
38. S. Yasuda, T. Ishii, S. Takemoto, H. Haruki, H. Ohmiya, Synergistic N-heterocyclic carbene/palladium-catalyzed reactions of aldehyde acyl anions with either diarylmethyl or allylic carbonates. *Angew. Chem. Int. Ed.* **57**, 2938–2942 (2018).
39. H. Haruki, S. Yasuda, K. Nagao, H. Ohmiya, Dehydrative allylation between aldehydes and allylic alcohols through synergistic N-heterocyclic carbene/palladium catalysis. *Chem. A Eur. J.* **25**, 724–727 (2019).
40. W. Yang, B. Ling, B. Hu, H. Yin, J. Mao, P. J. Walsh, Synergistic N-heterocyclic carbene/palladium-catalyzed umpolung 1,4-addition of aryl iodides to enals. *Angew. Chem. Int. Ed.* **59**, 161–166 (2020).
41. Y.-F. Han, Z.-H. Gao, C.-L. Zhang, S. Ye, NHC/copper-cocatalyzed [4 + 3] annulations of salicylaldehydes with aziridines for the synthesis of 1,4-benzoxazepinones. *Org. Lett.* **22**, 8396–8400 (2020).
42. W. Bi, Y. Yang, S. Ye, C. Wang, Umpolung coupling of pyridine-2-carboxaldehydes and propargylic carbonates *via N*-heterocyclic carbene/palladium synergetic catalysis. *Chem. Commun.* **57**, 4452–4455 (2021).
43. H. Liu, Y.-F. Han, Z.-H. Gao, C.-L. Zhang, C. Wang, S. Ye, Cooperative N-heterocyclic carbene/nickel-catalyzed hydroacylation of 1,3-dienes with aldehydes in water. *ACS Catal.* **12**, 1657–1663 (2022).
44. D. A. DiRocco, T. Rovis, Catalytic asymmetric α-acylation of tertiary amines mediated by a dual catalysis mode: N-heterocyclic carbene and photoredox catalysis. *J. Am. Chem. Soc.* **134**, 8094–8097 (2012).
45. C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius, Cooperative N-heterocyclic carbene/palladium-catalyzed enantioselective umpolung annulations. *J. Am. Chem. Soc.* **138**, 7840–7843 (2016).
46. C. Guo, D. Janssen-Müller, M. Fleige, A. Lerchen, C. G. Daniliuc, F. Glorius, Mechanistic studies on a cooperative NHC organocatalysis/palladium catalysis system: Uncovering significant lessons for mixed chiral Pd(NHC)(PR_3) catalyst design. *J. Am. Chem. Soc.* **139**, 4443–4451 (2017).
47. S. Singha, T. Patra, C. G. Daniliuc, F. Glorius, Highly enantioselective [5 + 2] annulations through cooperative N-heterocyclic carbene (NHC) organocatalysis and palladium catalysis. *J. Am. Chem. Soc.* **140**, 3551–3554 (2018).
48. S. Singha, E. Serrano, S. Mondal, C. G. Daniliuc, F. Glorius, Diastereodivergent synthesis of enantioenriched α,β-disubstituted γ-butyrolactones via cooperative N-heterocyclic carbene and Ir catalysis. *Nat. Catal.* **3**, 48–54 (2020).
49. J. Zhang, Y.-S. Gao, B.-M. Gu, W.-L. Yang, B.-X. Tian, W.-P. Deng, Cooperative N-heterocyclic carbene and iridium catalysis enables stereoselective and regiodivergent [3 + 2] and [3 + 3] annulation reactions. *ACS Catal.* **11**, 3810–3821 (2021).
50. Y.-Y. Li, S. Li, T. Fan, Z.-J. Zhang, J. Song, L.-Z. Gong, Enantioselective formal [4 + 3] annulations to access benzodiazepinones and benzoxazepinones via NHC/Ir/urea catalysis. *ACS Catal.* **11**, 14388–14394 (2021).
51. L. Zhou, X. Wu, X. Yang, C. Mou, R. Song, S. Yu, H. Chai, L. Pan, Z. Jin, Y. R. Chi, Gold and carbene relay catalytic enantioselective cycloisomerization/cyclization reactions of ynamides and enals. *Angew. Chem. Int. Ed.* **59**, 1557–1561 (2020).
52. J. Jiang, X. Wang, S. Liu, S. Zhang, B. Yang, Y. Zhao, S. Lu, Enantioselective cascade annulation of α-amino-ynones and enals enabled by gold and oxidative NHC relay catalysis. *Angew. Chem. Int. Ed.* **61**, e202115464 (2022).
53. K. Namitharan, T. Zhu, J. Cheng, P. Zheng, X. Li, S. Yang, B.-A. Song, Y. R. Chi, Metal and carbene organocatalytic relay activation of alkynes for stereoselective reactions. *Nat. Commun.* **5**, 3982 (2014).
54. J. Chen, P. Yuan, L. Wang, Y. Huang, Enantioselective β-protonation of enals via a shuttling strategy. *J. Am. Chem. Soc.* **139**, 7045–7051 (2017).
55. Z.-J. Zhang, L. Zhang, R.-L. Geng, J. Song, X.-H. Chen, L.-Z. Gong, N-heterocyclic carbene/copper cooperative catalysis for the asymmetric synthesis of spirooxindoles. *Angew. Chem. Int. Ed.* **58**, 12190–12194 (2019).
56. Z.-J. Zhang, Y.-H. Wen, J. Song, L.-Z. Gong, Kinetic resolution of aziridines enabled by N-heterocyclic carbene/copper cooperative catalysis: Carbene dose-controlled chemoswitchability. *Angew. Chem. Int. Ed. Engl.* **60**, 3268–3276 (2021).
57. Y.-H. Wen, Z.-J. Zhang, S. Li, J. Song, L.-Z. Gong, Stereodivergent propargylic alkylation of enals via cooperative NHC and copper catalysis. *Nat. Commun.* **13**, 1344 (2022).
58. T. Fan, J. Song, L.-Z. Gong, Asymmetric redox allylic alkylation to access 3,3′-disubstituted oxindoles enabled by Ni/NHC cooperative catalysis. *Angew. Chem. Int. Ed.* **61**, e202201678 (2022).
59. D. Janssen-Müller, C. Schlepphorst, F. Glorius, Privileged chiral N-heterocyclic carbene ligands for asymmetric transition-metal catalysis. *Chem. Soc. Rev.* **46**, 4845–4854 (2017).
60. L. Wang, S. Li, M. Blümel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen, D. Enders, Asymmetric synthesis of spirobenzazepinones with atroposelectivity and spiro-1,2-diazepinones by NHC-catalyzed [3+4] annulation reactions. *Angew. Chem. Int. Ed.* **55**, 11110–11114 (2016).
61. L. Wang, S. Li, M. Blümel, R. Puttreddy, A. Peuronen, K. Rissanen, D. Enders, Switchable access to different spirocyclopentane oxindoles by N-heterocyclic carbene catalyzed reactions of isatin-derived enals and N-sulfonyl ketimines. *Angew. Chem. Int. Ed.* **56**, 8516–8521 (2017).
62. Q. Liu, S. Li, X.-Y. Chen, K. Rissanen, D. Enders, Asymmetric synthesis of spiro-oxindole-ε-lactones through N-heterocyclic carbene catalysis. *Org. Lett.* **20**, 3622–3626 (2018).

63. Z.-H. Gao, K.-Q. Chen, Y. Zhang, L.-M. Kong, Y. Li, S. Ye, Enantioselective N-heterocyclic carbene-catalyzed synthesis of spirocyclic oxindole-benzofuroazepinones. *J. Org. Chem.* **83**, 15225–15235 (2018).
64. K. Suzuki, H. Tsuji, M. Kawatsura, Ruthenium-catalyzed benzylic substitution of benzyl esters with stabilized carbon nucleophiles. *Chem. Commun.* **56**, 3273–3276 (2020).
65. H. Tsuji, K. Suzuki, M. Kawatsura, Ruthenium-catalyzed stereospecific benzylic alkylation of optically active benzyl esters with malonate nucleophiles. *Tetrahedron Lett.* **69**, 152947 (2021).
66. M. D. Mbaye, B. Demerseman, J. Renaud, L. Toupet, C. Bruneau, $[Cp^*(\eta^2\text{-bipy})(MeCN)Ru^{II}][PF_6]$ catalysts for regioselective allylic substitution and characterization of dicationic $[Cp^*(\eta^2\text{-bipy})(\eta^3\text{-allyl})Ru^{IV}][PF_6]_2$ intermediates. *Angew. Chem. Int. Ed.* **42**, 5066–5068 (2003).
67. P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Álvarez, Structure, bioactivity and synthesis of natural products with hexahydropyrrolo[2,3-b]indole. *Chem. A Eur. J.* **17**, 1388–1408 (2011).

Acknowledgments
Funding: We acknowledge financial support from the National Natural Science Foundation of China (grant nos. 21831007 and 22071229). **Author contributions:** L.-Z.G. and J.S. conceived the study. S.L. performed the experiments and analyzed the data. Y.-H.W. synthesized some of the substrates and analyzed the data. All authors discussed the results and prepared the manuscript. **Competing interests:** The authors declare that they have no competing interests. **Data and materials availability:** All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials.

Submitted 30 October 2022
Accepted 16 March 2023
Published 19 April 2023
10.1126/sciadv.adf5606