OL Organic Letters

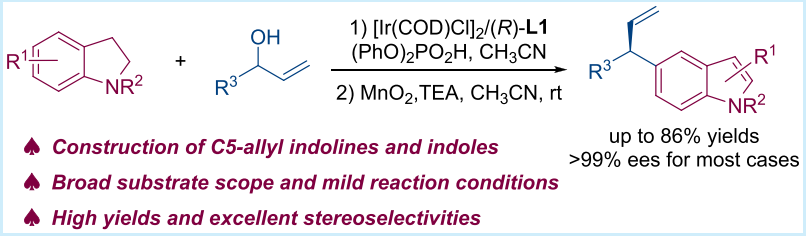
pubs.acs.org/OrgLett Letter

Synthesis of C5-Allylindoles through an Iridium-Catalyzed Asymmetric Allylic Substitution/Oxidation Reaction Sequence of *N*-Alkyl Indolines

Jiamin Lu,[†] Ruigang Xu,[†] Haixia Zeng, Guofu Zhong,* Meifang Wang, Zhigang Ni, and Xiaofei Zeng*

Cite This: *Org. Lett.* 2021, 23, 3426−3431 Read Online

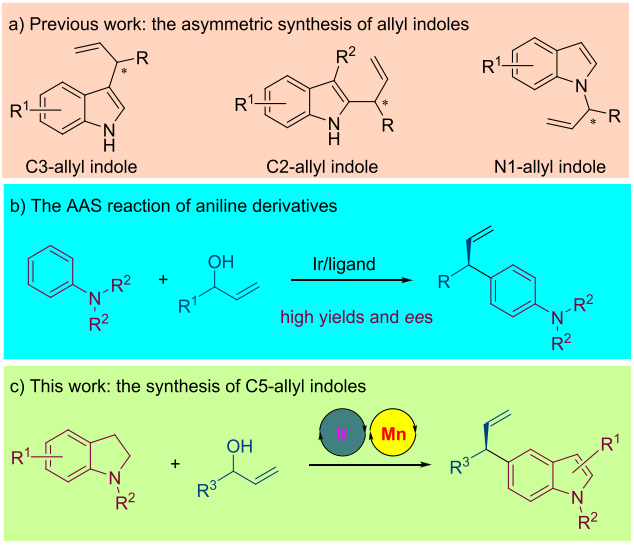
ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Iridium/Brønsted acid cooperative catalyzed asymmetric allylic substitution reactions at the C5 position of indolines have been reported for the first time. The highly efficient protocol allows rapid access to various C5-allylated products in good to high yields (48−97%) and enantioselectivities (82% to >99% ee) with wide functional group tolerance. The transformations allow not only the formation of C5-allylindoline derivatives but also the synthesis of C5-allylindole analogues in good yields and excellent stereoselectivities via an allylation/oxidation reaction sequence.

Optically active indole fragments are ubiquitous features of numerous bioactive natural products and bioactive pharmaceuticals.[1] Thus, the enantioselective functionalization of the indole structure has attracted a great deal of attention,[2] and the transition metal-catalyzed asymmetric allylic substitution (AAS) reaction is particularly useful.[3] There are six C−H bonds and one N−H bond in the indole structure that could be functionalized. It has been proven that the C3 position has priority in the intermolecular AAS reactions, and the first AAS reaction of indoles with allylic acetate was reported by Kocovský and co-workers in 1999.[4a] Since then, several successful examples have been reported by different research groups.[4] In addition, the branched selective N1-allylation reaction of indoles has also been described by Hartwig,[5] You,[6] Krische,[7] and others.[8] Furthermore, asymmetric C2-allylation has also been investigated. To overcome the regioselectivity issues, intramolecular asymmetric indole C2-allylation procedures were disclosed, which allowed the synthesis of annulated chiral C2-allylated indoles stereoselectively.[9] As an exception, Tambar and co-workers developed a chiral phosphoric acid-catalyzed intramolecular asymmetric aza-Claisen rearrangement approach to form chiral C2-allylated 3-amino indoles.[10] Very recently, Zheng, Taylor, Unsworth, and You reported an unprecedented enantioselective intermolecular C2-allylation of 3-substituted indoles, generating the C2-allylated products in excellent enantioselectivities with excellent regiocontrol.[11] However, the methods for the synthesis of 5-allylindoles are still a challenge due to the innate reactivity of the indole skeleton (Scheme 1a).

Scheme 1. Previous Studies and Approaches for Constructing Chiral C5-Allylindoles



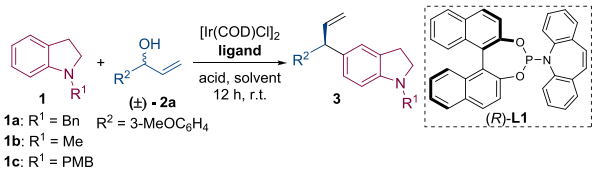
Received: March 15, 2021
Published: April 13, 2021

https://doi.org/10.1021/acs.orglett.1c00810
Org. Lett. 2021, 23, 3426−3431

Chiral C5-substituted indoles are key building blocks in many biologically active compounds, including the antitumor alkaloid drug vinblastine,[12] the haplophytine alkaloid,[13] murrafoline D,[14] the raputindole family,[15] etc., and have attracted a great deal of attention from synthetic chemists. Most indole C5-functionalization reactions involve C−H activation,[2e,16] coupling,[17] and semireduction[18] strategies. However, the dependency on directing groups and the formation of achiral products are obvious drawbacks. Aniline, which is always used as a nucleophile to react with electrophiles due to its high electron density at the *para* position,[19] was successfully applied in the AAS reaction by Fu's research group (Scheme 1b).[20] As a continuation of our research interest in AAS reactions,[21] herein we report the highly stereoselective synthesis of C5-allylindoles through an iridium-catalyzed AAS reaction of *N*-alkyl indolines with allylic alcohols followed by an oxidation reaction in a one-pot reaction (Scheme 1c). This method tolerates a broad range of indolines and 1,2,3,4-tetrahydroquinoline analogues with various functional groups. The transformation could be easily scaled up to gram scale, and the formed products could be applied in the synthesis of bioactive chiral C5-functionalized indoles.

We initially selected the AAS reaction of *N*-benzylindoline (**1a**) with 1-(3-methoxyphenyl)prop-2-en-1-ol (**2a**) as the model substrate (Table 1). The combination of commercially

Table 1. Optimization of Reaction Conditions[a]



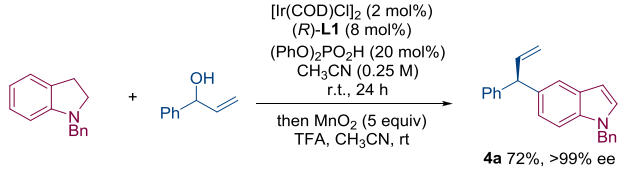
entry	R	acid	solvent	yield (%)[b]	ee (%)[c]
1	Bn	$BF_3{\cdot}Et_2O$	THF	67	96
2	Bn	$BF_3{\cdot}Et_2O$	DCM	74	81
3	Bn	$BF_3{\cdot}Et_2O$	Et_2O	57	95
4	Bn	$BF_3{\cdot}Et_2O$	toluene	60	96
5	Bn	$BF_3{\cdot}Et_2O$	CH_3CN	62	98
6	Bn	$(PhO)_2POOH$	CH_3CN	71	99
7	Bn	$Sc(OTf)_3$	CH_3CN	48	84
8	Bn[d]	$(PhO)_2POOH$[e]	CH_3CN[f]	93	>99
9[g]	Me	$(PhO)_2POOH$	CH_3CN	64	>99
10	PMB	$La(OTf)_3$	CH_3CN	82	>99
11[g]	Ac	$La(OTf)_3$	CH_3CN	–	–

[a]Reaction conditions: 2 mol % $[Ir(COD)Cl]_2$, 8 mol % ligand, 20 mol % $(PhO)_2POOH$, 0.2 mmol of **1a**, and 0.4 mmol of **2a** in solvent at room temperature for 12 h. [b]Isolated yields of **3a**. [c]Determined by HPLC analysis on a chiral stationary phase. [d]With 2.5 equiv of **2a**. [e]With 30 mol % $(PhO)_2POOH$. [f]Reaction concentration of 0.25 M. [g]For 24 h.

available chiral phosphoramidite ligands [e.g., (*R*)-**L2**, (*R*)-**L3**, and (*R*)-**L4**] with an iridium catalyst did not promote the reaction (entries 2−4). In contract, a mixture of $[Ir(COD)Cl]_2$/(*R*)-**L1** and $BF_3{\cdot}Et_2O$ afforded the corresponding AAS product **3a** in 67% yield and 96% ee (entry 1). The reaction could not proceed without acid. The solvent plays an important role in the reaction, and CH_3CN was found to be the best, which gave rise to an ee value of 98% [entries 5−8 (for more details, see Table S2)]. Upon investigation of other acid additives, it was found that the desired product could be afforded in 71% yield and 99% ee in the presence of $(PhO)_2POOH$ [entries 9 and 10 (for more details, see Table S3)]. Further investigation of the equivalents of **2a**, acid additive, catalytic loading, and reaction concentration shows that **3a** could be achieved in 93% yield and >99% ee e by using 2 mol % $[Ir(COD)Cl]_2$, 8 mol % (*R*)-**L2**, and 30 mol % $(PhO)_2POOH$ in CH_3CN (0.25 M) at room temperature for 12 h.

Notably, the methyl- and benzyl-protected indolines were also successful in the reaction, giving the corresponding products in excellent enantioselectivities; however, the yields are lower (entries 12 and 13). Unfortunately, the indolines with electron-withdrawing protecting group, such as acetyl, Boc, alloc, and Ts groups, could not be promoted in the reaction, probably due to the lower nucleophilicity of these substrates (entry 14). Furthermore, the synthesis of C5-allylic indole was tested, and 5 equiv of MnO_2 was added after the completion of the AAS process. Fortunately, desired C5-allylic indole **4a** was obtained in 72% yield without a loss of enantiomeric purity (Scheme 2).

Scheme 2. One-Pot Synthesis of C5-Allylindole



To assess the generality of the C5-allylation of indolines, the thus obtained optimal reaction conditions were first applied to diverse substrates. Beyond the parent allylic alcohol, electronically diverse allylic alcohols substituted at the *ortho*, *meta*, or *para* position of the aromatic ring each proceeded smoothly in the AAS reaction, delivering the respective C5-regioselective allylated products with good yields and stereoselectivities (Figure 1). It was found that allylic alcohols bearing electron-donating groups on the phenyl ring (**3a**−**3e**, **3g**, and **3r**−**3u**) gave rise to the products in moderate to good yields (59−98%) with excellent enantioselectivities (92% to >99% ee) in less time than with electron-withdrawing substituents (**3h**−**3q**, 48−87% yields and 97% to >99% ee). In addition, the synthetically important ester group and nitro group were compatible in the reaction, providing the corresponding products in excellent enantioselectivities (97% to >99% ee); however, the yields were relatively lower. Furthermore, heteroaromatic ring-substituted allylic alcohols were also well tolerated, providing the desired products (**3v** and **3w**) with good results. When the naphthyl-substituted allylic alcohol was used, the desired **3x** was afforded in 94% yield and 99% ee.

Next, a broad range of *N*-Bn indolines were examined in the AAS reaction followed by oxidation using MnO_2 as the oxidant (Figure 2). Indolines bearing electron-neutral and electron-donating substituents, including methyl (**4b**−**4e**), phenyl (**4f**), and methoxy (**4g**) groups at positions C2−C6, underwent facile transformations and afforded the corresponding C5-indole allylation products in excellent yields and enantioselectivities. C2 and C3 disubstituted indoles (**1g** and **1h**) also delivered allylation/oxidation products **4g** and **4h**, respectively, with good results.

https://doi.org/10.1021/acs.orglett.1c00810
Org. Lett. 2021, 23, 3426−3431

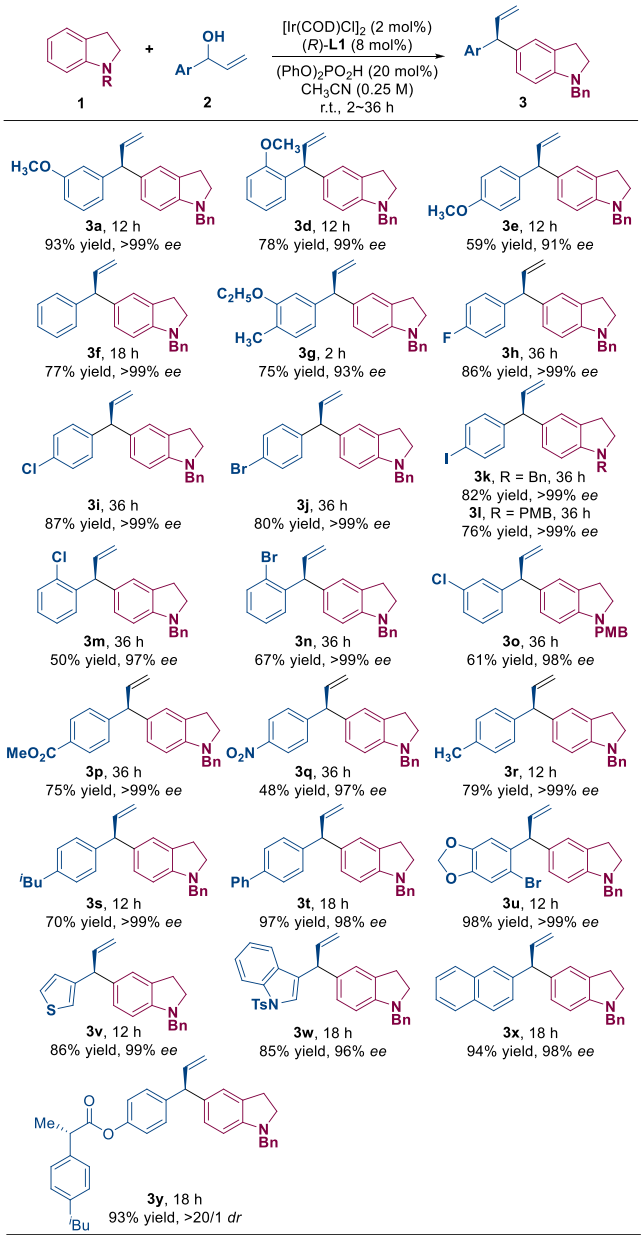


Figure 1. Synthesis of enantioenriched N-allylated indolines with various allylic alcohols.

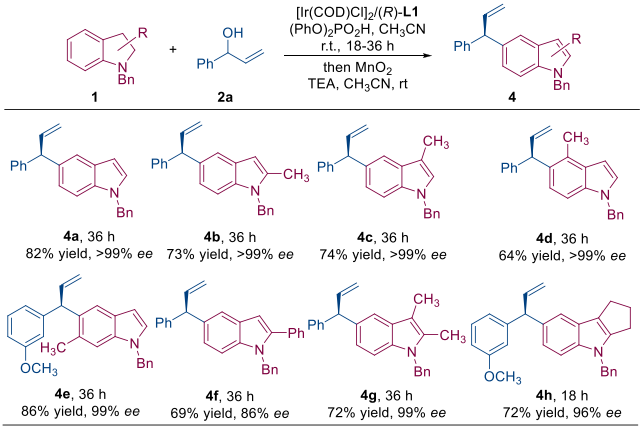


Figure 2. One-pot synthesis of various C5-allylindoles.

Then, the AAS reaction was explored with a series of 1-benzyl-1,2,3,4-tetrahydroquinoline and its analogues (Figure 3). Conveniently, the conditions demonstrated to be optimal

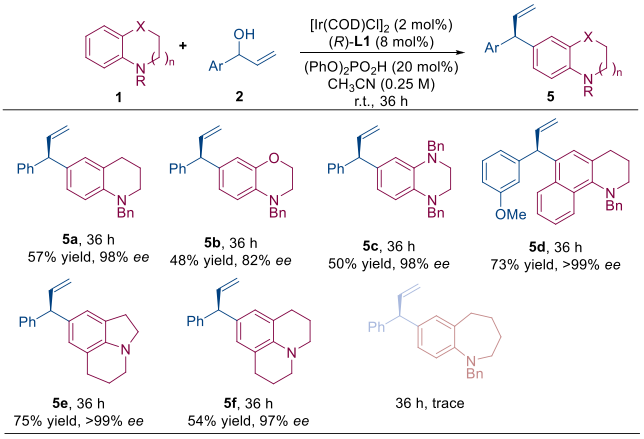
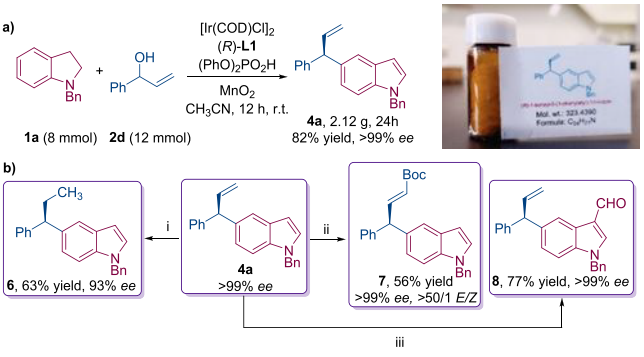


Figure 3. Substrate scope of 1,2,3,4-tetrahydroquinoline analogues.

for *N*-benzyl indoline extended well to these other nucleophiles, which led to a diverse series of allylation products. For example, when 1-benzyl-1,2,3,4-tetrahydroquinoline, 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, 1,4-dibenzyl-1,2,3,4-tetrahydroquinoxaline, and 1-benzyl-1,2,3,4-tetrahydrobenzo[*h*]quinoline were used, products **5a**−**5d**, respectively, were isolated in moderate to good yields.

To further prove the reliability and practicability of our approach, a scaled-up reaction was carried out by using 8.0 mmol of **1a** as the starting material, affording 2.12 g of **4a** in 82% yield and >99% ee (Scheme 3a). The product thus

Scheme 3. (a) Large-Scale Reaction and (b) Versatile Transformations of C5-Allylindole[a]



[a]Conditions: (i) H_2, Pd/C, MeOH, reflux; (ii) $CH_2{=}CHCO_2{}^tBu$, Hoveyda-Grubbs II catalyst, DCM, reflux; (iii) $POCl_3$, DMF, 0 °C to rt.

obtained could be easily elaborated in different ways. The vinyl group of **4a** could be reduced by Pd/C under a hydrogen atmosphere to give corresponding product **6** in 63% yield, with the enantiomeric excess of the product remaining. Compound **4a** could also undergo an olefin metathesis reaction to form **7** in 56% yield with excellent stereoselectivities. Further transformation of **4a** was also successful through a Vilsmeier−Haack formylation, and the respective aldehyde **8** was afforded in 77% yield without erosion of the optical purity (Scheme 3b). Then, the stereodivergent syntheses of

https://doi.org/10.1021/acs.orglett.1c00810
Org. Lett. 2021, 23, 3426−3431

diallylated products were carried out by using **4a** and *ent*-**4a** as the starting materials; all four stereoisomers (**9a**−**9d**) were afforded in 83−85% yields in >20:1 dr, and the ee values were all >99% (see Scheme S5). Finally, the AAS/oxidation strategy could be applied in the enantioselective synthesis of dopamine transporter (DAT) inhibitor 5-indolyl aryl propylamine intermediate through a three-step process, and key intermediate **11** could be obtained in 91% yield and 99% ee (see Scheme S6).

In conclusion, we have developed a highly enantioselective protocol for the synthesis of chiral C5-allylindolines by an iridium-catalyzed AAS reaction of allylic alcohols with various N-protected indolines and their analogues. More importantly, various enantioenriched 5-allylindoles could be achieved through a one-pot strategy involving the Ir-catalyzed asymmetric allylic alkylation and subsequent oxidation of *N*-alkyl indolines. This strategy features mild reaction conditions, readily available starting materials, a wide substrate scope, and excellent stereoselectivities and is easily scaled up. Furthermore, the C5-allylindole products can be used as effective linchpins for the streamlined preparation of various synthetically useful building blocks, which makes this protocol potentially useful in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00810.

Experimental details, analytical data of products, NMR and HPLC spectra, and plausible transition state structure (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Xiaofei Zeng − *College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China;* orcid.org/0000-0003-4222-1365; Email: chemzxf@hznu.edu.cn

Guofu Zhong − *College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China;* orcid.org/0000-0001-9497-9069; Email: zgf@hznu.edu.cn

Authors

Jiamin Lu − *College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China*

Ruigang Xu − *College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China*

Haixia Zeng − *College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China*

Meifang Wang − *College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China*

Zhigang Ni − *College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China;* orcid.org/0000-0002-0109-3275

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00810

Author Contributions

†J.L. and R.X. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the Natural Science Foundation of China (21672048), the Natural Science Foundation of Zhejiang Province (LY18B020015), and Hangzhou Normal University for financial support. X.Z. acknowledges a Xihu Scholar award from Hangzhou City, and G.Z. acknowledges a Qianjiang Scholar from Zhejiang Province in China.

■ REFERENCES

(1) (a) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996. (b) d'Ischia, M.; Napolitano, A.; Pezzella, A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, U.K., 2008; Vol. 3, pp 353−388. (c) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. A Review on Recent Developments of Indole-containing Antiviral Agents. *Eur. J. Med. Chem.* **2015**, *89*, 421−441.

(2) For selected reviews, see: (a) Cacchi, S.; Fabrizi, G. Synthesis and Functionalization of Indoles Through Palladium-catalyzed Reactions. *Chem. Rev.* **2005**, *105*, 2873−2920. (b) Humphrey, G. R.; Kuethe, J. T. Practical Methodologies for the Synthesis of Indoles. *Chem. Rev.* **2006**, *106*, 2875−2911. (c) Bandini, M.; Eichholzer, A. Catalytic Functionalization of Indoles in a New Dimension. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608−9644. (d) Joucla, L.; Djakovitch, L. Transition Metal-Catalyzed, Direct and Site-Selective *N*1-, C2- or C3-Arylation of the Indole Nucleus: 20 Years of Improvements. *Adv. Synth. Catal.* **2009**, *351*, 673−714. (e) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. Beyond C2 and C3: Transition-Metal-Catalyzed C−H Functionalization of Indole. *ACS Catal.* **2017**, *7*, 5618−5627.

(3) (a) Qu, J.-P.; Helmchen, G. Applications of Iridium-Catalyzed Asymmetric Allylic Substitution Reactions in Target-Oriented Synthesis. *Acc. Chem. Res.* **2017**, *50*, 2539−2555. (b) Helmchen, G.; Dahnz, A.; Dubon, P.; Schelwies, M.; Weihofen, R. Iridium-catalyzed asymmetricallylic substitutions. *Chem. Commun.* **2007**, 675−691. (c) Hartwig, J. F.; Stanley, M. Mechanistically Driven Development of Iridium Catalysts for Asymmetric Allylic Substitution. *Acc. Chem. Res.* **2010**, *43*, 1461−1475. (d) Hartwig, J. F.; Pouy, M. J. Iridium-Catalyzed Allylic Substitution. *Top. Organomet. Chem.* **2011**, *34*, 169−208. (e) Kim, S. W.; Zhang, W.; Krische, M. J. Catalytic Enantioselective Carbonyl Allylation and Propargylation via Alcohol-Mediated Hydrogen Transfer: Merging the Chemistry of Grignard and Sabatier. *Acc. Chem. Res.* **2017**, *50*, 2371−2380. (f) Liu, W.-B.; Xia, J.-B.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitutions. *Top. Organomet. Chem.* **2011**, *38*, 155−207. (g) Fu, J.-K.; Huo, X.-H.; Li, B.-W.; Zhang, W.-B. Cooperative Bimetallic Catalysis in Asymmetric Allylic Substitution. *Org. Biomol. Chem.* **2017**, *15*, 9747−9759. (h) Butt, N.; Zhang, W.-B. Transition Metal-catalyzed Allylic Substitution Reactions with Unactivated Allylic Substrates. *Chem. Soc. Rev.* **2015**, *44*, 7929−7967. (i) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855−1969.

(4) (a) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kočovský, P. Molybdenum(II)-Catalyzed Allylation of Electron-Rich Aromatics and Heteroaromatics. *J. Org. Chem.* **1999**, *64*, 2751−2764. (b) Cheung, H. Y.; Yu, W.-Y.; Lam, F. L.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. Enantioselective Pd-Catalyzed Allylic Alkylation of Indoles by a New Class of Chiral Ferrocenyl P/S Ligands. *Org. Lett.* **2007**, *9*, 4295−4298. (c) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. Ir-Catalyzed Regio- and Enantioselective Friedel-Crafts-Type Allylic Alkylation of Indoles. *Org. Lett.* **2008**, *10*, 1815−1818. (d) Cruz, F. A.; Zhu, Y.; Tercenio, Q. D.; Shen, Z.; Dong, V. M.

Alkyne Hydroheteroarylation: Enantioselective Coupling of Indoles and Alkynes via Rh-Hydride Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 10641−10644. For selected examples of dearomative intermolecular asymmetric indole C3-allylation, see: (e) Trost, B. M.; Quancard, J. Palladium-Catalyzed Enantioselective C-3 Allylation of 3-Substituted-1H-Indoles Using Trialkylboranes. *J. Am. Chem. Soc.* **2006**, *128*, 6314−6315. (f) Liu, Y.; Du, H. Pd-Catalyzed Asymmetric Allylic Alkylations of 3-Substituted Indoles Using Chiral P/Olefin Ligands. *Org. Lett.* **2013**, *15*, 740−743. (g) Zhang, X.; Han, L.; You, S.-L. Ir-catalyzed Intermolecular Asymmetric Allylic Dearomatization Reaction of Indoles. *Chem. Sci.* **2014**, *5*, 1059−1063. (h) Zhang, X.; Liu, W.-B.; Tu, H.-F.; You, S.-L. Ligand-enabled Ir-catalyzed Intermolecular Diastereoselective and Enantioselective Allylic Alkylation of 3-Substituted Indoles. *Chem. Sci.* **2015**, *6*, 4525−4529. (i) Jia, M.; Monari, M.; Yang, Q.-Q.; Bandini, M. Enantioselective Gold Catalyzed Dearomative [2 + 2]-Cycloaddition between Indoles and Allenamides. *Chem. Commun.* **2015**, *51*, 2320−2323. (j) Müller, J. M.; Stark, C. W. Diastereodivergent Reverse Prenylation of Indole and Tryptophan Derivatives: Total Synthesis of Amauromine, Novoamauromine, and epi-Amauromine. *Angew. Chem., Int. Ed.* **2016**, *55*, 4798−4802. (k) Gao, R.-D.; Xu, Q.-L.; Zhang, B.; Gu, Y.; Dai, L.-X.; You, S.-L. Palladium(0)-Catalyzed Intermolecular Allylic Dearomatization of Indoles by a Formal [4 + 2] Cycloaddition Reaction. *Chem. - Eur. J.* **2016**, *22*, 11601−11604. (l) Panda, S.; Ready, J. M. Palladium Catalyzed Asymmetric Three-Component Coupling of Boronic Esters, Indoles, and Allylic Acetate. *J. Am. Chem. Soc.* **2017**, *139*, 6038−6041. (m) Gao, R.-D.; Ding, L.; Zheng, C.; Dai, L.-X.; You, S.-L. Palladium(0)-Catalyzed Intermolecular Asymmetric Allylic Dearomatization of Polycyclic Indoles. *Org. Lett.* **2018**, *20*, 748−751. (n) Ding, L.; Gao, R.-D.; You, S.-L. Palladium(0)-Catalyzed Intermolecular Asymmetric Cascade Dearomatization Reaction of Indoles with Propargyl Carbonate. *Chem. - Eur. J.* **2019**, *25*, 4330−4334.

(5) Stanley, L. M.; Hartwig, J. F. Iridium-Catalyzed Regio- and Enantioselective N-Allylation of Indoles. *Angew. Chem., Int. Ed.* **2009**, *48*, 7841−7844.

(6) Liu, W.-B.; Zhang, X.; Dai, L.-X.; You, S.-L. Asymmetric N-Allylation of Indoles Through the Iridium-Catalyzed Allylic Alkylation/Oxidation of Indolines. *Angew. Chem., Int. Ed.* **2012**, *51*, 5183−5187.

(7) Kim, S. W.; Schempp, T. T.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Regio- and Enantioselective Iridium-Catalyzed N-Allylation of Indoles and Related Azoles with Racemic Branched Alkyl-Substituted Allylic Acetates. *Angew. Chem., Int. Ed.* **2019**, *58*, 7762−7766.

(8) (a) Chen, L.-Y.; Yu, X.-Y.; Chen, J.-R.; Feng, B.; Zhang, H.; Qi, Y.-H.; Xiao, W.-J. Enantioselective Direct Functionalization of Indoles by Pd/Sulfoxide-Phosphine-Catalyzed N-Allylic Alkylation. *Org. Lett.* **2015**, *17*, 1381−1384. (b) Chen, Q.-A.; Chen, Z.; Dong, V. M. Rhodium-Catalyzed Enantioselective Hydroamination of Alkynes with Indolines. *J. Am. Chem. Soc.* **2015**, *137*, 8392−8395.

(9) (a) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. Highly Enantioselective Synthesis of Tetrahydro-*β*-Carbolines and Tetrahydro-*γ*-Carbolines Via Pd-Catalyzed Intramolecular Allylic Alkylation. *J. Am. Chem. Soc.* **2006**, *128*, 1424−1425. (b) Bandini, M.; Eichholzer, A. Enantioselective Gold-Catalyzed Allylic Alkylation of Indoles with Alcohols: An Efficient Route to Functionalized Tetrahydrocarbazoles. *Angew. Chem., Int. Ed.* **2009**, *48*, 9533−9537. (c) Wu, Q.-F.; Zheng, C.; You, S.-L. Enantioselective Synthesis of Spiro Cyclopentane-1,3′-indoles and 2,3,4,9-Tetrahydro-1H-carbazoles by Iridium-Catalyzed Allylic Dearomatization and Stereospecific Migration. *Angew. Chem., Int. Ed.* **2012**, *51*, 1680−1683. (d) Bandini, M.; Bottoni, A.; Chiarucci, M.; Cera, G.; Miscione, G. P. Mechanistic Insights into Enantioselective Gold-Catalyzed Allylation of Indoles with Alcohols: The Counterion Effect. *J. Am. Chem. Soc.* **2012**, *134*, 20690−20700. (e) Schafroth, M. A.; Rummelt, S. M.; Sarlah, D.; Carreira, E. M. Enantioselective Iridium-Catalyzed Allylic Cyclizations. *Org. Lett.* **2017**, *19*, 3235−3238. (f) Wang, Y.; Zhang, P.; Di, X.; Dai, Q.; Zhang, Z.-M.; Zhang, J. Gold-Catalyzed Asymmetric Intramolecular Cyclization of N-Allenamides for the Synthesis of Chiral Tetrahydrocarbolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 15905−15909. (g) Grugel, C. P.; Breit, B. Rhodium-Catalyzed Enantioselective Cyclization of 3-Allenyl-indoles: Access to Functionalized Tetrahydrocarbazoles. *Org. Lett.* **2019**, *21*, 5798−5802.

(10) Maity, P.; Pemberton, R. P.; Tantillo, D. J.; Tambar, U. K. Brønsted Acid Catalyzed Enantioselective Indole Aza-Claisen Rearrangement Mediated by an Arene CH-O Interaction. *J. Am. Chem. Soc.* **2013**, *135*, 16380−16383.

(11) Rossi-Ashton, J. A.; Clarke, A. K.; Donald, J. R.; Zheng, C.; Taylor, R. J. K.; Unsworth, W. P.; You, S.-L. Iridium-Catalyzed Enantioselective Intermolecular Indole C2-Allylation. *Angew. Chem., Int. Ed.* **2020**, *59*, 7598−7604.

(12) For selected examples, see: (a) Lenz, J. A.; Robat, C. S.; Stein, T. J. Vinblastine as a Second Rescue for the Treatment of Canine Multicentric Lymphoma in 39 Cases (2005 to 2014). *J. Small Anim. Pract.* **2016**, *57*, 429−434. (b) Tazi, A.; Lorillon, G.; Haroche, J.; Neel, A.; Dominique, S.; Aouba, A.; Bouaziz, J.-D.; de Margerie-Melon, C.; Bugnet, E.; Cottin, V.; Comont, T.; Lavigne, C.; Kahn, J.-E.; Donadieu, J.; Chevret, S. Vinblastine Chemotherapy in Adult Patients with Langerhans Cell Histiocytosis: A Multicenter Retrospective Study. *Orphanet Journal of Rare Diseases* **2017**, *12*, 95. (c) Nobre, L.; Pauck, D.; Golbourn, B.; Maue, M.; Bouffet, E.; Remke, M.; Ramaswamy, V. Effective and Safe Tumor Inhibition Using Vinblastine in Medulloblastoma. *Pediatr. Blood Cancer* **2019**, *66*, No. e27694.

(13) For selected examples, see: (a) Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. Total Synthesis of (+)-Haplophytine. *Angew. Chem., Int. Ed.* **2009**, *48*, 7600−7603. (b) Nicolaou, K. C.; Dalby, S. M.; Li, S.-L.; Suzuki, T.; Chen, D. Y.-K. Total Synthesis of (+)-Haplophytine. *Angew. Chem., Int. Ed.* **2009**, *48*, 7616−7620.

(14) Kumar, V. P.; Gruner, K. K.; Kataeva, O.; Knölker, H.-J. Total Synthesis of the Biscarbazole Alkaloids Murrafoline A-D by a Domino Sonogashira Coupling/Claisen Rearrangement/Electrocyclization Reaction. *Angew. Chem., Int. Ed.* **2013**, *52*, 11073−11077.

(15) Vougogiannopoulou, K.; Fokialakis, N.; Aligiannis, N.; Cantrell, C.; Skaltsounis, A.-L. The Raputindoles: Novel Cyclopentyl Bisindole Alkaloids from Raputia Simulans. *Org. Lett.* **2010**, *12*, 1908−1911.

(16) (a) Xu, Q.-L.; Dai, L.-X.; You, S.-L. Diversity Oriented Synthesis of Indole-based Peri-annulated Compounds via Allylic Alkylation Reactions. *Chem. Sci.* **2013**, *4*, 97−102. (b) Yang, Y.; Gao, P.; Zhao, Y.; Shi, Z. Regiocontrolled Direct C−H Arylation of Indoles at the C4 and C5 Positions. *Angew. Chem., Int. Ed.* **2017**, *56*, 3966−3971. (c) Zhang, W.-Z.; Xu, G.-Y.; Qiu, L.; Sun, J.-T. Gold-catalyzed C5-alkylation of Indolines and Sequential Oxidative Aromatization: Access to C5-functionalized Indoles. *Org. Biomol. Chem.* **2018**, *16*, 3889−3892. (d) Hussain, N.; Frensch, G.; Zhang, J.-D.; Walsh, P. J. Chemo- and Regioselective C(sp3)-H Arylation of Unactivated Allylarenes by Deprotonative Cross-coupling. *Angew. Chem., Int. Ed.* **2014**, *53*, 3693−3697.

(17) (a) Denmark, S. E.; Werner, N. S. *γ*-Selective Cross-Coupling of Allylic Silanolate Salts with Aromatic Bromides Using Trialkylphosphonium Tetrafluoroborate Salts Prepared Directly from Phosphine•Borane Adducts. *Org. Lett.* **2011**, *13*, 4596−4599. (b) Denmark, S. E.; Werner, N. S. Cross-Coupling of Aromatic Bromides with Allylic Silanolate Salts. *J. Am. Chem. Soc.* **2008**, *130*, 16382−16393.

(18) Chen, Z.-W.; Dong, V. M. Enantioselective Semireduction of Allenes. *Nat. Commun.* **2017**, *8*, 784.

(19) For selected examples, see: (a) Jia, W.-L.; Westerveld, N.; Wong, K. M.; Morsch, T.; Hakkennes, M.; Naksomboon, K.; Ángeles Fernández-Ibáñez, M. Selective C−H Olefination of Indolines (C5) and Tetrahydroquinolines (C6) by Pd/S,O-Ligand Catalysis. *Org. Lett.* **2019**, *21*, 9339−9342. (b) Ertugrul, B.; Kilic, H.; Lafzi, F.; Saracoglu, N. Access to C5-Alkylated Indolines/Indoles via Michael-Type Friedel−Crafts Alkylation Using Aryl-Nitroolefins. *J. Org. Chem.* **2018**, *83* (16), 9018−9038. (c) Jørgensen, K. A. Asymmetric Friedel-Crafts Reactions: Catalytic Enantioselective Addition of Aromatic and

https://doi.org/10.1021/acs.orglett.1c00810
Org. Lett. 2021, 23, 3426−3431

Heteroaromatic C-H Bonds to Activated Alkenes, Carbonyl Compounds, and Imines. *Synthesis* **2003**, *7*, 1117−1125.
(20) Tian, H.; Zhang, P.-X.; Peng, F.; Yang, H.-J.; Fu, H. Chiral Cyclic Ligand-Enabled Iridium-Catalyzed Asymmetric Arylation of Unactivated Racemic Allylic Alcohols with Anilines. *Org. Lett.* **2017**, *19*, 3775−3778.
(21) (a) Shen, D.; Chen, Q.-L.; Yan, P.-P.; Zeng, X.-F.; Zhong, G.-F. EnantioselectiveDearomatization of Naphthol Derivatives with Allylic Alcohols by Cooperative Iridium and Brønsted Acid Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 3242−3246. (b) Pan, S.-L.; Wu, B.-Q.; Hu, J.-J.; Xu, R.-G.; Jiang, M.; Zeng, X.-F.; Zhong, G.-F. Palladium-Catalyzed Allylic Substitution Reaction of Benzothiazolylacetamide with Allylic Alcohols in Water. *J. Org. Chem.* **2019**, *84*, 10111−10119. (c) Yan, P.-P.; Pan, S.-L.; Hu, J.-J.; Lu, L.-M.; Zeng, X.-F.; Zhong, G.-F. Palladium Catalyzed Controllable Mono- or Di-Allylic Substitution Reaction of Benzothiazolylacetate with Allylic Alcohols. *Adv. Synth. Catal.* **2019**, *361*, 1322−1334. (d) Xu, R.-G.; Li, K.; Wang, J.-Q.; Lu, J.-M.; Pan, L.-N.; Zeng, X.-F.; Zhong, G.-F. Direct Enantioselective Allylic Substitution of 4-Hydroxycoumarin Derivatives with Branched Allylic Alcohols via Iridium Catalysis. *Chem. Commun.* **2020**, *56*, 8404−8407. (e) Hu, J.-J.; Pan, S.-L.; Zhu, S.; Yu, P.-Y.; Xu, R.-G.; Zhong, G.-F.; Zeng, X.-F. Pd-Catalyzed Dearomative Asymmetric Allylic Alkylation of Naphthols with Alkoxyallenes. *J. Org. Chem.* **2020**, *85*, 7896−7904.

https://doi.org/10.1021/acs.orglett.1c00810
Org. Lett. 2021, 23, 3426−3431