OL Organic Letters

pubs.acs.org/OrgLett Letter

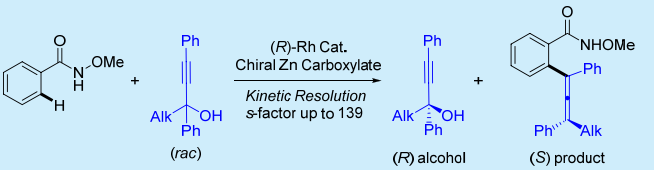
Rhodium-Catalyzed and Chiral Zinc Carboxylate-Assisted Allenylation of Benzamides via Kinetic Resolution

Ruxia Mao, Yanliang Zhao, Xiaohan Zhu, Fen Wang, Wei-Qiao Deng,* and Xingwei Li*

Cite This: https://doi.org/10.1021/acs.orglett.1c02398 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

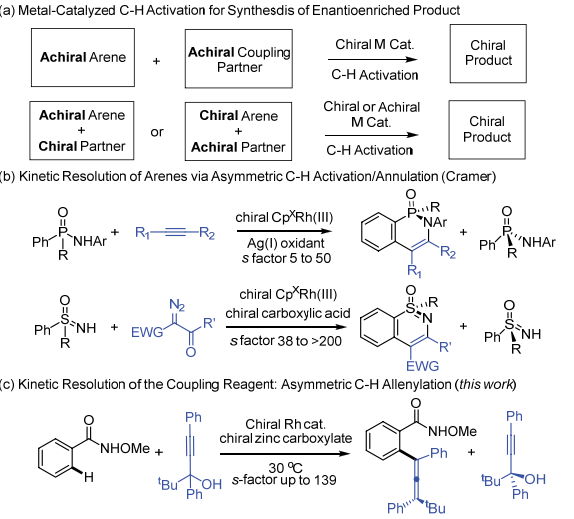
ABSTRACT: Enantioenriched allenes are important building blocks. While they have been accessed by other coupling methodologies, enantioenriched allenes have been rarely obtained via C−H activation. In this work, kinetic resolution of tertiary propargyl alcohols as an allenylating reagent has been realized via rhodium(III)-catalyzed C−H allenylation of benzamides. The reaction proceeded efficiently under mild conditions, and both the allenylated products and the propargyl alcohols were obtained in high enantioselectivities with an *s*-factor of up to 139. The resolution results from bias of the two propargylic substituents and is assisted by a chiral zinc carboxylate additive.



Metal-catalyzed carbon−hydrogen bond activation has provided numerous methodologies toward efficient synthesis of value-added aromatics. This strategy has received increasing attention owing to ready availability of arenes and the high step economy and atom economy of their transformations.[1] In the past decade, Cp*Rh(III) catalysts have proved as a powerful player among the arsenal of metal catalysts, and the generation of organorhodium(III) species bearing a polar Rh(III)-aryl bond has significantly broadened the horizon of C−H functionalization owing to its strong interactions with both polar and nonpolar coupling reagents.[2]

The demand for enantioenriched products has called for development of asymmetric C−H bond activation. Two classes of reactions have been developed depending on chirality of the substrates (Scheme 1a). Coupling of achiral arenes and achiral coupling partners has been heavily explored in enantioselective C−H bond activation catalyzed by a chiral metal catalyst given abundance of achiral substrates (Scheme 1a, top). In this regard, Cramer, Rovis, and You pioneered in enantioselective C−H activation of arenes catalyzed by chiral rhodium cyclopentadienyl complexes,[3] and this area has received increasing attentions. In these reactions, the enantio-determining step (EDS) can be pinpointed to C−H bond cleavage, insertion of π-bonds, or reductive elimination.[4] The EDS of the majority of these reports falls into enantio-determining insertion of olefins,[5] allenes,[5b,6] diazo reagents,[7] and bulky alkynes.[8] Alternatively, enantioenriched products can be obtained using a chiral coupling partner or arene. Achiral catalysts can be used when enantioenriched coupling reagents were employed, leading to enantioenriched products via chirality retention or transfer. The scenario can be complicated when racemic substrates are used. Dynamic kinetic resolution (DKR) may occur in some cases, as has been reported by Cramer in Rh(I)-catalyzed C−H activation using racemic allenes as a coupling partner.[9] The majority of the reaction

Scheme 1. Access to Enantio-Enriched Products via C−H Activation Using a Chiral Substrate



pattern is probably kinetic resolution (KR) in which the two enantiomers reacted with different rates. Two KR systems have been disclosed in Rh(III)-catalyzed C−H activation (Scheme 1b). In 2018, Cramer reported the Rh(III)-catalyzed kinetic resolution of phosphinic amides in [4 + 2] oxidative coupling with internal alkynes,[10] affording the annulated phosphinic

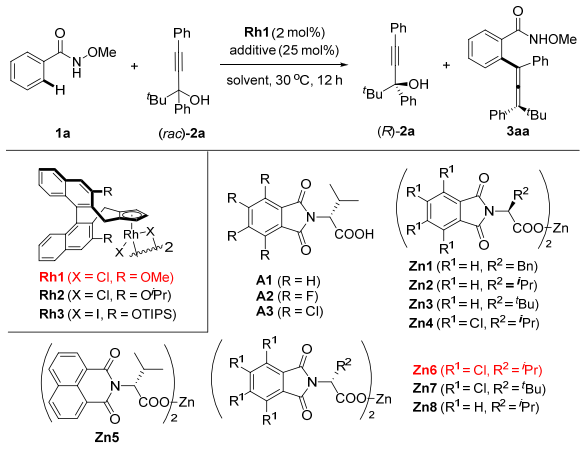
Received: July 19, 2021

amide with an *s*-factor of 5−50. Recently, the same group extended the kinetic resolution methodology to the [4 + 2] annulation of aryl alkyl sulfoximines with ketone-activated diazo reagents,[11] affording an *s*-factor of up to >200. Despite the impressive methodology, these reactions are limited to the resolution of chiral arenes.[10−12]

In 2014, Ma pioneered in Rh(III)-catalyzed C−H activation of arenes with propargyl alcohols/esters as allenylating reagents.[13] The catalysts have been subsequently extended to other transition metals such as Co(III), Ru(II), and Mn(I).[14] Besides terminal C−H alkenylation products, catalytic C−H allenylation also provided various key intermediates en route to synthesis of complex structural platforms.[15] While chiral allenes have been accessed via asymmetric Heck coupling or insertion of alkynes into carbenes,[16] asymmetric C−H allenylation has been rarely explored.[17] Previous C−H activation-based access to enantioenriched allenes relied on employment of enantio-enriched propargyl alcohols/esters with central-to-axial chirality transfer.[13,18] Given the abundance of racemic propargyl alcohols, KR seems a superior but underexplored process. We now report kinetic resolution of propargyl alcohols via asymmetric C−H allenylation of benzamides (Scheme 1c).

We initiated our investigation with the optimization studies of the coupling of *N*-methoxybenzamide (**1a**) and an unprotected propargyl alcohol (**2a**, Scheme 2). The reaction

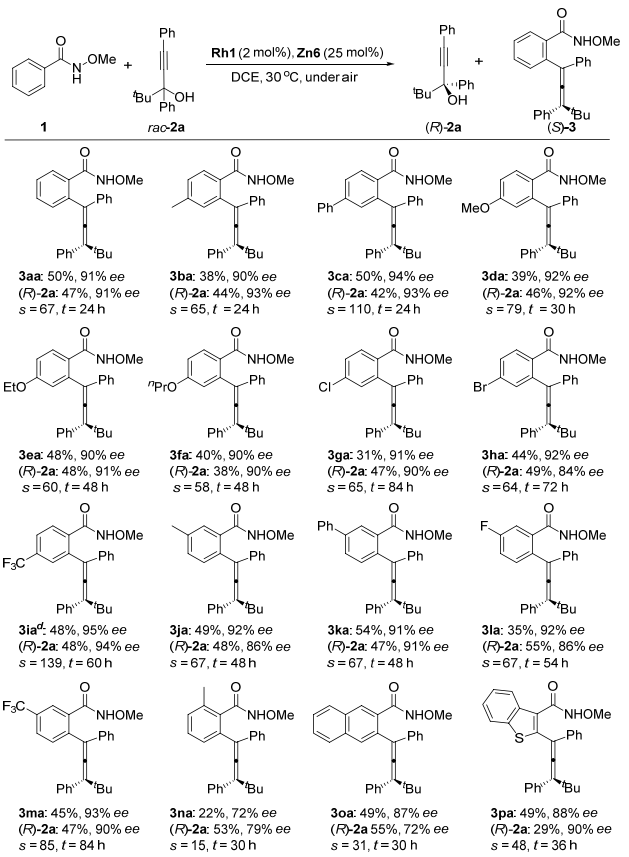
Scheme 2. Catalysts and Additives Used for Optimization



proceeded with poor selectivity when catalyzed by the chiral catalyst (*R*)-**Rh1** (2 mol %) in the presence of PivOH and AgOAc additives (entry 1, Table S1). While a combination of a chiral rhodium catalyst and chiral carboxylic acid (CCA) generally led to improved enantioselectivity,[7c,19] it was found that the coupling still suffered from low *s*-value when a commonly used CCA was introduced (entries 2−5). Zinc additives[20] often improved the reaction efficiency. Indeed, combination of $Zn(OAc)_2$ and CCA resulted in acceptable efficiency but poor enantioselectivity. To address this challenge, we prepared a series of zinc chiral carboxylates (**Zn1**−**Zn8**). Match and mismatch of chiral zinc salts were observed, and the (*R*) salt proved to be superior (entries 9 and 11). Both the efficiency and *s*-values were significantly improved when the **Zn6** (25 mol %) was used as an additive (entries 6−14). Thus, an optimal *s*-value of 75 was obtained in DCE solvent, with the ee's of product **3aa** and the resolved **2a** being 91% and 94%, respectively (entry 11).

With the optimized reaction conditions in hand, we next examined the scope of the benzamide substrate toward resolution of alcohol **2a** (Scheme 3). *N*-Methoxybenzamides

Scheme 3. Scope of the Benzamide in Allenylation via Kinetic Resolution



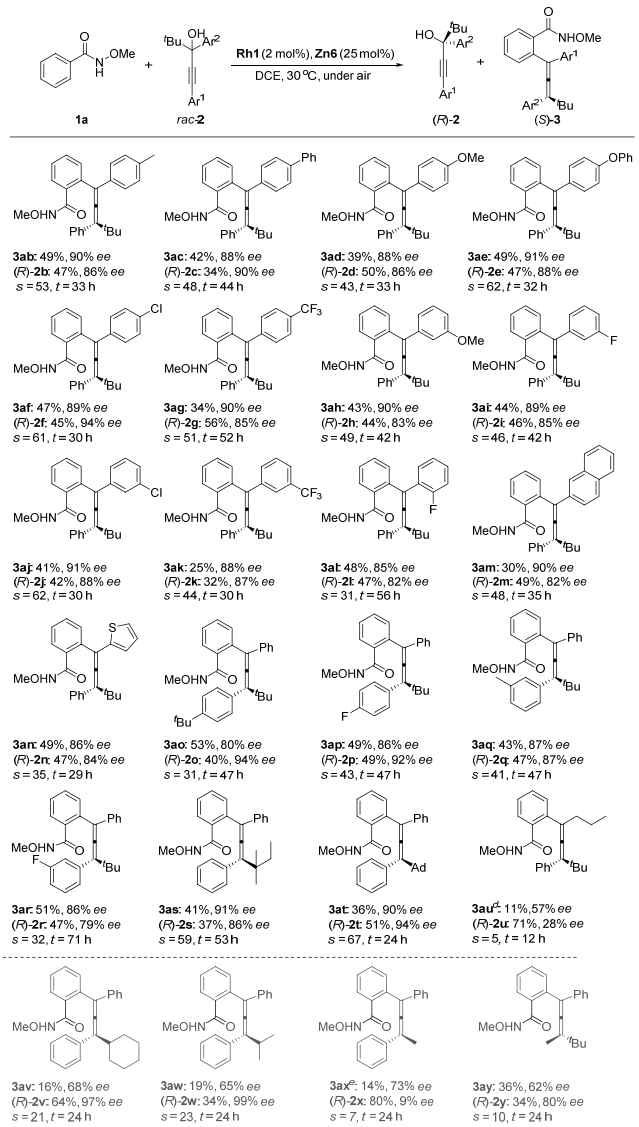
[a]Reaction conditions: **1** (0.11 mmol), *rac*-**2a** (0.2 mmol), **Rh1** (2 mol %), **Zn6** (25 mol %) in 3 mL of DCE, 30 °C without exclusion of air or moisture. [b]Isolated yield. [c]Determined by chiral HPLC. [d]**3ia** was isolated in 48% yield and 87% ee and **2a** was recovered in 52% yield and 94% ee (*s* = 51) under the condition of 45 °C and 24 h.

bearing electron-donating (OMe and OEt), electron-withdrawing (CF_3), and halogen groups at the *para* position all coupled in good efficiency, affording the allenylated product in 90−95% ee (**3ba**-**3ia**), and the *s*-value ranged from 58 to 139. The presence of a *meta* Me, Ph, F, and CF_3 group was also tolerated, and the allenylated product was obtained in 91−93% ee, while the ee's of the resolved **2a** were slightly lower (*s*-factor 67−85). Lower enantioselectivity was observed when an *ortho* substituent was present or in the case of 2-naphthyl-substituted amide (**3na** and **3oa**, *s* = 15−31), likely due to steric effect. Of note, different reaction times ranging from 24 to 84 h were adopted for different substrates to compromise the conversion and enantioselectivities of the product and the recovered alcohol.

The scope of the propargyl alcohol was next examined using **1a** as the arene substrate (Scheme 4). Introduction of electron-withdrawing (Ph and CF_3) and -donating (Me, OMe, and OPh) groups into the *para* position of the alkyne-attached Ar^1 group all gave smooth reactions (**3ab**−**3ag**, 88−91% ee). Comparable ee values were also obtained for the resolved alcohols, which corresponds to *s*-values of 43−62. The

https://doi.org/10.1021/acs.orglett.1c02398
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Scope of the Propargyl Alcohols in Kinetic Resolution

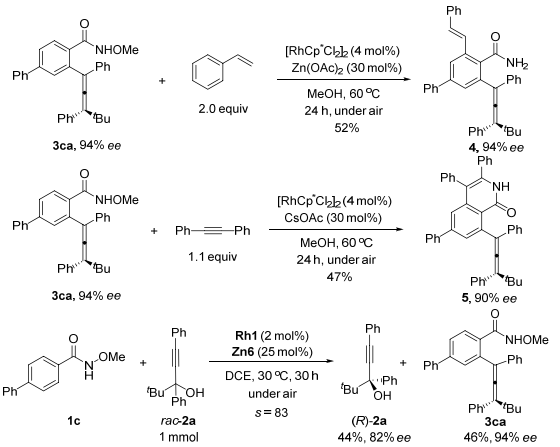


[a]Reaction conditions: **1** (0.11 mmol), *rac*-**2a** (0.2 mmol), **Rh1** (2 mol %), **Zn6** (25 mol %) in DCE 3 (mL) at 30 °C without exclusion of air or moisture. [b]Isolated yield. [c]Determined by chiral HPLC. [d]0 °C and 0.1 mmol scale. [e]$Zn(OAc)_2$ (25 mol %) and acic **A1** (50 mol %) were used.

absolute configuration of the product **3ae** was determined to be (*S*) by X-ray crystallography (CCDC 2067510). Similar enantioselectivity was also obtained for *meta*-substituted propargyl alcohols (**3ah**−**3ak**). Introduction of an *ortho* F group led to lower enantioselectivity of both the alcohol and the coupled product (**3al**, *s* = 31). Besides phenyl ring, a thienyl group was also tolerated (**3an**, *s* = 35). Variation of the propargylic aryl ring (Ar^2) was also made (**3ao**−**3ar**), and these reactions tend to give a lower *s*-factor (31−43). In addition, the tertiary alkyl group was extended to a *tert*-Amyl (**3as**) and to an Ad group (**3at**) with comparably high enantioselectivity. In contrast, replacing the bulky alkyl group with a secondary or a methyl group (**3au**−**3aw**) only gave moderate or low enantioselectivity of the coupled product, indicating significance of the steric bias between these two propargylic substituents. Switching the propargylic phenyl group to a methyl also gave poor enantioselectivity (**3ax**).

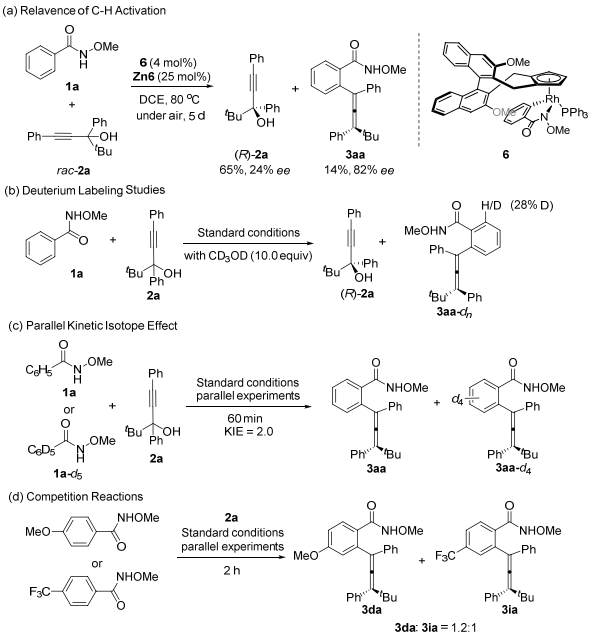
Several experiments have been conducted to explore the synthetic transformations (Scheme 5). Redox-neutral olefination of **3ca** with styrene afforded the product **4** in 52% yield. Rhodium-catalyzed [4 + 2] annulation of **3ca** and diphenylacetylene gave product **5** in moderate yield. In all cases, essentially no erosion of enantiopurity was detected. The synthesis of product **3ca** at a 1 mmol scale was also realized without deterioration of the enantioselectivity.

Scheme 5. Scale-Up Synthesis and Transformations of an Allenylation Product



Mechanistic studies have been conducted to probe the reaction mechanism (Scheme 6). A chiral rhodacyclic complex **6** was prepared and was designated as a catalyst for the coupling of **1a** and **2a** (Scheme 6a), affording the product at a higher temperature with 82% ee, suggesting relevancy of C−H bond activation. H/D exchange experiments between amide **1a** and CD_3OD under the standard conditions afforded product

Scheme 6. Experimental Mechanistic Studies



https://doi.org/10.1021/acs.orglett.1c02398
Org. Lett. XXXX, XXX, XXX−XXX

3aa-d_n with deuteration at the *ortho* position (Scheme 6b), indicating reversibility of the C−H activation. To further study the C−H activation, parallel kinetic isotope effect was measured using **1a** and **1a**-d_5. A moderate value of KIE = 2.0 seems to suggest that C−H cleavage might be involved in the turnover-limiting process (Scheme 6c). Parallel competitive reactions of electronically distinguishable benzamides **1d** (*para* OMe) and **1i** (*para* CF_3) have been conducted, and the more electron-rich benzamide tends to react with slightly higher reactivity (Scheme 6d). In time-resolved studies of the coupling of **1a** and (*rac*)-**2a**, the product **3aa** was initially detected in ca. 95% ee and the enantioselectivity decayed slowly to 91% ee. Meanwhile, the ee of the recovered product increases rapidly to 95% (Figure S1).

In this coupling system, either alkyne insertion or the subsequent β-OH elimination can be stereodiscriminating. Thus, computational studies at the DFT level were then conducted to explore the chiral induction mode (Figure S2). The coupling of **1a** and **2a** in the absence of the Zn(II) additive was examined as the starting point (Figure S2a). It was found that the ligation of (*R*) and (*S*)-**2a** to the C−H activation-derived chiral rhodacyclic intermediate is slighty exogernic, affording two corresponding alkyne complexes **Int1**-*R* and **Int1**-*S*. The subsequent migratory insertion of the Rh−C(aryl) into the alkyne constitutes the stereodetermining step. Indeed, the activation barrier for this step is only slightly different for the (*R*)- and (*S*)-configured alkynes (20.5 kcal/mol for the *R* pathway and 20.4 kcal/mol for the *S* pathway). The observed selectivity agrees with our initial optimization studies (Table S1, entry 1). Following the alkyne insertion, the subsequent β-OH elimination carries a lower kinetic barrier and will not contribute to the enantioselectivity. These calculated activation barriers seem consistent with observed poor enantioselectivity in the absence of the chiral zinc additive.

The chiral zinc(II) additive was next included and its role was examined. A reasonably simplified model that employs the cationic Zn(II) mono carboxylate species of **Zn6** was applied (Figure S2b). The interaction/assembly of the chiral rhodacycle intermediate, the propargyl alcohols, and the Zn(II) cation affords a tridentate O−O−O chelation Zn-stabilized alkyne intermediate **Int1**-*R*-**Zn6**$^+$ or **Int1**-*S*-**Zn6**$^+$ as the catalyst resting state. In line with the Zn-free scenarios, the migratory insertion remains enantio-discriminating. The (*S*) pathway (blue) is clearly kinetically favored (18.5 kcal/mol activation free energy for the (*S*)-selectivity). The resulting **Int2-Zn** then undergoes tridentate to bidentate rearrangement, affording a thermodynamically more stable intermediate **Int3-Zn** upon release of the strain energy. The calculated selectivity is qualitatively in line with the observed selectivity of the (*S*)-configured coupled product.

In summary, we have realized kinetic resolution of propargyl alcohols in Cp^XRh(III)-catalyzed asymmetric C−H allenylation of benzamides. The reaction was enabled by judicious choice of a chiral zinc carboxylate additive in addition to the chiral Rh(III) catalyst. The reaction proceeded with a decent scope of substrates, and both the coupled products and the recovered propargyl alcohols were generally obtained in high enantioselectivity (*s*-factor up to 139). The high enantioselectivity is related to the steric bias of the two propargylic groups and is also assisted by a chiral zinc additive. DFT studies indicate that the alkyne insertion constitutes the stereodiscriminating step of this coupling system, and chiral zinc carboxylate plays an important role during chiral induction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02398.

Detailed experimental procedures, characterization of new compounds, and copies of NMR spectra (PDF)

Accession Codes

CCDC 2067510 and 2074822 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Wei-Qiao Deng − *Institute of Molecular Science and Engineering, Institute of Frontier and Interdisciplinary Sciences, Shandong University, Qingdao 266237, China;* orcid.org/0000-0002-3671-5951; Email: dengwq@sdu.edu.cn

Xingwei Li − *School of Chemistry and Chemical Engineering, Shaanxi Normal University (SNNU), Xi'an 710062, China; Institute of Molecular Science and Engineering, Institute of Frontier and Interdisciplinary Sciences, Shandong University, Qingdao 266237, China;* orcid.org/0000-0002-1153-1558; Email: lixw@snnu.edu.cn

Authors

Ruxia Mao − *School of Chemistry and Chemical Engineering, Shaanxi Normal University (SNNU), Xi'an 710062, China*

Yanliang Zhao − *Institute of Molecular Science and Engineering, Institute of Frontier and Interdisciplinary Sciences, Shandong University, Qingdao 266237, China*

Xiaohan Zhu − *School of Chemistry and Chemical Engineering, Shaanxi Normal University (SNNU), Xi'an 710062, China*

Fen Wang − *School of Chemistry and Chemical Engineering, Shaanxi Normal University (SNNU), Xi'an 710062, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02398

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the NSFC (21525208 and 22101167), the Fundamental Research Funds for the Central Universities (2020CSLZ005 and GK202103031), and the research fund from the Natural Science Basic Research Plan in Shaanxi Province of China (2021JQ-303) is gratefully acknowledged.

■ REFERENCES

(1) (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. Ru-, Rh-, and Pd-Catalyzed C-C Bond Formation Involving C-H Activation and Addition on Unsaturated Substrates: Reactions and Mechanistic Aspects. *Chem. Rev.* **2002**, *102*, 1731−1770. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. Palladium- and Copper-Catalyzed Arylation of Carbon-Hydrogen

Bonds. *Acc. Chem. Res.* **2009**, *42*, 1074−1086. (c) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. Palladium(II)-Catalyzed C-H Activation/C-C Cross-Coupling Reactions: Versatility and Practicality. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (d) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C-H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147−1169. (e) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C-H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315−1345. (f) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon-Carbon Bonds by Oxidizing Two Carbon-Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215−1292. (g) McMurray, L.; O'Hara, F.; Gaunt, M. J. Recent developments in natural product synthesis using metal-catalysed C-H bond functionalisation. *Chem. Soc. Rev.* **2011**, *40*, 1885−1898. (h) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. Towards mild metal-catalyzed C-H bond activation. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761. (i) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C-H bond activation strategy for C-C and C-N bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083. (j) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C-H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009. (k) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Transition metal-catalyzed ketone-directed or mediated C-H functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764−7786. (l) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. Transition-Metal-Catalyzed C-H Bond Addition to Carbonyls, Imines, and Related Polarized π Bonds. *Chem. Rev.* **2017**, *117*, 9163−9227. (m) Leitch, J. A.; Frost, C. G. Ruthenium-catalysed σ-activation for remote *meta*-selective C-H functionalisation. *Chem. Soc. Rev.* **2017**, *46*, 7145−7153.

(2) (a) Song, G.; Wang, F.; Li, X. C-C, C-O and C-N bond formation via rhodium(III)-catalyzed oxidative C-H activation. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678. (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Rhodium Catalyzed Chelation-Assisted C-H Bond Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 814−825. (c) Kuhl, N.; Schroder, N.; Glorius, F. Formal S_N-Type Reactions in Rhodium(III)-Catalyzed C-H Bond Activation. *Adv. Synth. Catal.* **2014**, *356*, 1443−1460. (d) Wang, F.; Yu, S.; Li, X. Transition metal-catalysed couplings between arenes and strained or reactive rings: combination of C-H activation and ring scission. *Chem. Soc. Rev.* **2016**, *45*, 6462−6477. (e) Zhu, W.; Gunnoe, T. B. Advances in Rhodium-Catalyzed Oxidative Arene Alkenylation. *Acc. Chem. Res.* **2020**, *53*, 920−936.

(3) (a) Ye, B.; Cramer, N. Chiral Cyclopentadienyl Ligands as Stereocontrolling Element in Asymmetric C-H Functionalization. *Science* **2012**, *338*, 504−506. (b) Hyster, T. K.; Knorr, L.; Ward, T. R.; Rovis, T. Biotinylated Rh(III) Complexes in Engineered Streptavidin for Accelerated Asymmetric C-H Activation. *Science* **2012**, *338*, 500−503. (c) Zheng, J.; Cui, W.-J.; Zheng, C.; You, S.-L. Synthesis and Application of Chiral Spiro Cp Ligands in Rhodium-Catalyzed Asymmetric Oxidative Coupling of Biaryl Compounds with Alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 5242−5245.

(4) (a) Zheng, C.; You, S.-L. Recent development of direct asymmetric functionalization of inert C-H bonds. *RSC Adv.* **2014**, *4*, 6173−6214. (b) Ye, B.; Cramer, N. Chiral Cyclopentadienyls: Enabling Ligands for Asymmetric Rh(III)-Catalyzed C-H Functionalizations. *Acc. Chem. Res.* **2015**, *48*, 1308−1318. (c) Newton, C. G.; Kossler, D.; Cramer, N. Asymmetric Catalysis Powered by Chiral Cyclopentadienyl Ligands. *J. Am. Chem. Soc.* **2016**, *138*, 3935−3941. (d) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C-H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908−8976. (e) Mas-Rosello, J.; Herraiz, A. G.; Audic, B.; Laverny, A.; Cramer, N. Chiral Cyclopentadienyl Ligands: Design, Syntheses, and Applications in Asymmetric Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 13198. (f) Yoshino, T.; Satake, S.; Matsunaga, S. Diverse Approaches for Enantioselective C-H Functionalization Reactions Using Group 9 Cp^xM^{III} Catalysts. *Chem. - Eur. J.* **2020**, *26*, 7346−7357. (g) Achar, T. K.; Maiti, S.; Jana, S.; Maiti, D. Transition Metal Catalyzed Enantioselective C(sp^2)-H Bond Functionalization. *ACS Catal.* **2020**, *10*, 13748−13793.

(5) (a) Zheng, J.; You, S.-L. Construction of Axial Chirality by Rhodium-Catalyzed Asymmetric Dehydrogenative Heck Coupling of Biaryl Compounds with Alkenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 13244−13247. (b) Jia, Z.-J.; Merten, C.; Gontla, R.; Daniliuc, C. G.; Antonchick, A. P.; Waldmann, H. General Enantioselective C-H Activation with Efficiently Tunable Cyclopentadienyl Ligands. *Angew. Chem., Int. Ed.* **2017**, *56*, 2429−2434. (c) Trifonova, E. A.; Ankudinov, N. M.; Mkhaylov, A. A.; Chusov, D. A.; Nelyubina, Y. V.; Perekalin, D. S. A Planar-Chiral Rhodium(III) Catalyst with a Sterically Demanding Cyclopentadienyl Ligand and Its Application in the Enantioselective Synthesis of Dihydroisoquinolones. *Angew. Chem., Int. Ed.* **2018**, *57*, 7714−7718. (d) Wang, S.-G.; Cramer, N. An Enantioselective $Cp^xRh(III)$-Catalyzed C-H Functionalization /Ring-Opening Route to Chiral Cyclopentenylamines. *Angew. Chem., Int. Ed.* **2019**, *58*, 2514−2518. (e) Duchemin, C.; Cramer, N. Chiral cyclopentadienyl Rh^{III}-catalyzed enantioselective cyclopropanation of electron-deficient olefins enable rapid access to UPF-648 and oxylipin natural products. *Chem. Sci.* **2019**, *10*, 2773−2777. (f) Audic, B.; Wodrich, M. D.; Cramer, N. Mild complexation protocol for chiral Cp^xRh and Ir complexes suitable for in situ catalysis. *Chem. Sci.* **2019**, *10*, 781−787. (g) Phipps, E. J. T.; Rovis, T. Rh(III)-Catalyzed C-H Activation-Initiated Directed Cyclopropanation of Allylic Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, 6807−6811. (h) Hassan, I. S.; Ta, A. N.; Danneman, M. W.; Semakul, N.; Burns, M.; Basch, C. H.; Dippon, V. N.; McNaughton, B. R.; Rovis, T. Asymmetric δ-Lactam Synthesis with a Monomeric Streptavidin Artificial Metalloenzyme. *J. Am. Chem. Soc.* **2019**, *141*, 4815−4819. (i) Mi, R.; Zheng, G.; Qi, Z.; Li, X. Rhodium-Catalyzed Enantioselective Oxidative [3 + 2] Annulation of Arenes and Azabicyclic Olefins through Twofold C-H Activation. *Angew. Chem., Int. Ed.* **2019**, *58*, 17666−17670. (j) Yang, X.; Zheng, G.; Li, X. Rhodium(III)-Catalyzed Enantioselective Coupling of Indoles and 7-Azabenzonorbornadienes by C-H Activation/Desymmetrization. *Angew. Chem., Int. Ed.* **2019**, *58*, 322−326. (k) Maity, S.; Potter, T. J.; Ellman, J. A. α-Branched amines by catalytic 1,1-addition of C-H bonds and aminating agents to terminal alkenes. *Nat. Catal.* **2019**, *2*, 756−762. (l) Duchemin, C.; Cramer, N. Enantioselective Cp^xRh^{III}-Catalyzed Carboaminations of Acrylates. *Angew. Chem., Int. Ed.* **2020**, *59*, 14129−14133.

(6) (a) Ye, B.; Cramer, N. A Tunable Class of Chiral Cp Ligands for Enantioselective Rhodium(III)-Catalyzed C-H Allylations of Benzamides. *J. Am. Chem. Soc.* **2013**, *135*, 636−639. (b) Wang, S.-G.; Liu, Y.; Cramer, N. Asymmetric Alkenyl C-H Functionalization by Cp^xRh^{III} forms 2H-Pyrrol-2-ones through [4 + 1]-Annulation of Acryl Amides and Allenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 18136−18140. (c) Wang, S.-G.; Cramer, N. Asymmetric $Cp^xRh(III)$-Catalyzed Acrylic Acid C-H Functionalization with Allenes Provides Chiral γ-Lactones. *ACS Catal.* **2020**, *10*, 8231−8236.

(7) (a) Ye, B.; Cramer, N. Asymmetric Synthesis of Isoindolones by Chiral Cyclopentadienyl-Rhodium(III)-Catalyzed C-H Functionalizations. *Angew. Chem., Int. Ed.* **2014**, *53*, 7896−7899. (b) Chen, X.; Yang, S.; Li, H.; Wang, B.; Song, G. Enantioselective C-H Annulation of Indoles with Diazo Compounds through a Chiral Rh(III) Catalyst. *ACS Catal.* **2017**, *7*, 2392−2396. (c) Sun, Y.; Cramer, N. Enantioselective Synthesis of Chiral-at-Sulfur 1,2-Benzothiazines by Cp^xRh^{III}-Catalyzed C-H Functionalization of Sulfoximines. *Angew. Chem., Int. Ed.* **2018**, *57*, 15539−15543. (d) Kong, L.; Han, X.; Liu, S.; Zou, Y.; Lan, Y.; Li, X. Rhodium(III)-Catalyzed Asymmetric Access to Spirocycles through C-H Activation and Axial-to-Central Chirality Transfer. *Angew. Chem., Int. Ed.* **2020**, *59*, 7188−7192.

(8) (a) Tian, M.; Bai, D.; Zheng, G.; Chang, J.; Li, X. Rh(III)-Catalyzed Asymmetric Synthesis of Axially Chiral Biindolyls by Merging C-H Activation and Nucleophilic Cyclization. *J. Am. Chem. Soc.* **2019**, *141*, 9527−9532. (b) Wang, F.; Qi, Z.; Zhao, Y.; Zhai, S.; Zheng, G.; Mi, R.; Huang, Z.; Zhu, X.; He, X.; Li, X. Rhodium(III)-Catalyzed Atroposelective Synthesis of Biaryls by C-H Activation and

https://doi.org/10.1021/acs.orglett.1c02398
Org. Lett. XXXX, XXX, XXX−XXX

Intermolecular Coupling with Sterically Hindered Alkynes. *Angew. Chem., Int. Ed.* **2020**, *59*, 13288−13294.
(9) Tran, D. N.; Cramer, N. Rhodium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Racemic Allenes by the [3 + 2] Annulation of Aryl Ketimines. *Angew. Chem., Int. Ed.* **2013**, *52*, 10630−10634.
(10) Sun, Y.; Cramer, N. Tailored trisubstituted chiral Cp^xRh^{III} catalysts for kinetic resolutions of phosphinic amides. *Chem. Sci.* **2018**, *9*, 2981−2985.
(11) Brauns, M.; Cramer, N. Efficient Kinetic Resolution of Sulfur-Stereogenic Sulfoximines by Exploiting Cp^XRh^{III}-Catalyzed C-H Functionalization. *Angew. Chem., Int. Ed.* **2019**, *58*, 8902−8906.
(12) (a) González, J. M.; Cendón, B.; Mascareñas, J. L.; Gulías, M. Kinetic Resolution of Allyltriflamides through a Pd-Catalyzed C-H Functionalization with Allenes: Asymmetric Assembly of Tetrahydropyridines. *J. Am. Chem. Soc.* **2021**, *143*, 3747−3752. (b) Xiao, K.-J.; Chu, L.; Chen, G.; Yu, J.-Q. Kinetic Resolution of Benzylamines via Palladium(II)-Catalyzed C-H Cross-Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 7796−7800.
(13) (a) Wu, S.; Huang, X.; Wu, W.; Li, P.; Fu, C.; Ma, S. A C-H bond activation-based catalytic approach to tetrasubstituted chiral allenes. *Nat. Commun.* **2015**, *6*, 7946−7954. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. Pd(II)-Catalyzed C-C Coupling of sp^3 C-H Bonds with sp^2 and sp^3 Boronic Acids Using Air as the Oxidant. *J. Am. Chem. Soc.* **2008**, *130*, 7190−7191.
(14) (a) Sen, M.; Dahiya, P.; Premkumar, J. R.; Sundararaju, B. Dehydrative Cp*Co(III)-Catalyzed C-H Bond Allenylation. *Org. Lett.* **2017**, *19*, 3699−3702. (b) Wu, X.; Fan, J.; Fu, C.; Ma, S. A ruthenium(II)-catalyzed C-H allenylation-based approach to allenoic acids. *Chem. Sci.* **2019**, *10*, 6316−6321. (c) Lu, Q.; Greßies, S.; Klauck, F. J. R.; Glorius, F. Manganese(I)-Catalyzed Regioselective C-H Allenylation: Direct Access to 2-Allenylindoles. *Angew. Chem., Int. Ed.* **2017**, *56*, 6660−6664.
(15) (a) Zheng, G.; Sun, J.; Xu, Y.; Zhai, S.; Li, X. Mn-Catalyzed Dehydrocyanative Transannulation of Heteroarenes and Propargyl Carbonates through C-H Activation: Beyond the Permanent Directing Effects of Pyridines/Pyrimidines. *Angew. Chem., Int. Ed.* **2019**, *58*, 5090−5094. (b) Xu, Y.; Zheng, G.; Kong, L.; Li, X. Manganese(I)-Catalyzed Synthesis of Fused Eight- and Four-Membered Carbocycles via C-H Activation and Pericyclic Reactions. *Org. Lett.* **2019**, *21*, 3402−3406. (c) Li, T.; Zhou, C.; Yan, X.; Wang, J. Solvent-Dependent Asymmetric Synthesis of Alkynyl and Monofluoroalkenyl Isoindolinones by $CpRh^{III}$-Catalyzed C-H Activation. *Angew. Chem., Int. Ed.* **2018**, *57*, 4048−4052.
(16) (a) Zhu, C.; Chu, H.; Li, G.; Ma, S.; Zhang, J. Pd-Catalyzed Enantioselective Heck Reaction of Aryl Triflates and Alkynes. *J. Am. Chem. Soc.* **2019**, *141*, 19246−19251. (b) Chu, W.-D.; Zhang, L.; Zhang, Z.; Zhou, Q.; Mo, F.; Zhang, Y.; Wang, J. Enantioselective Synthesis of Trisubstituted Allenes via Cu(I)-Catalyzed Coupling of Diazoalkanes with Terminal Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 14558−14561.
(17) (a) Chu, W.-D.; Zhang, Y.; Wang, J. Recent advances in catalytic asymmetric synthesis of allenes. *Catal. Sci. Technol.* **2017**, *7*, 4570−4579. (b) Huang, X.; Ma, S. Allenation of Terminal Alkynes with Aldehydes and Ketones. *Acc. Chem. Res.* **2019**, *52*, 1301−1312.
(18) Wu, S.; Huang, X.; Fu, C.; Ma, S. Asymmetric S_N2'-type C-H functionalization of arenes with propargylic alcohols. *Org. Chem. Front.* **2017**, *4*, 2002−2007.
(19) Jang, Y.-S.; Dieckmann, M.; Cramer, N. Cooperative Effects between Chiral Cp^x-Iridium(III) Catalysts and Chiral Carboxylic Acids in Enantioselective C-H Amidations of Phosphine Oxides. *Angew. Chem., Int. Ed.* **2017**, *56*, 15088−15092.
(20) Chen, X.; Zheng, G.; Li, Y.; Song, G.; Li, X. Rhodium-Catalyzed Site-Selective Coupling of Indoles with Diazo Esters: C4-Alkylation versus C2-Annulation. *Org. Lett.* **2017**, *19*, 6184−6187.

https://doi.org/10.1021/acs.orglett.1c02398
Org. Lett. XXXX, XXX, XXX−XXX