JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Asymmetric Markovnikov Hydroaminocarbonylation of Alkenes Enabled by Palladium-Monodentate Phosphoramidite Catalysis

Ya-Hong Yao, Hui-Yi Yang, Ming Chen, Fei Wu, Xing-Xing Xu, and Zheng-Hui Guan*

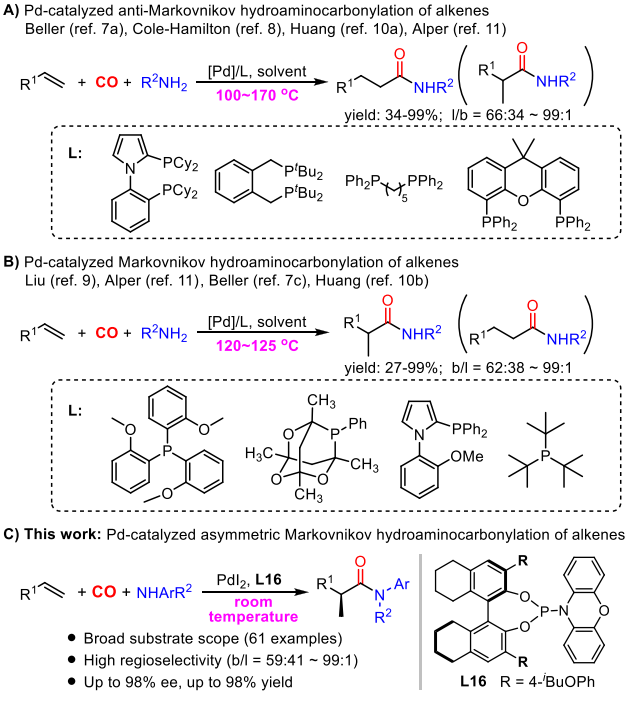
Cite This: J. Am. Chem. Soc. 2021, 143, 85−91
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A palladium-catalyzed asymmetric Markovnikov hydroaminocarbonylation of alkenes with anilines has been developed for the atom-economical synthesis of 2-substituted propanamides bearing an α-stereocenter. A novel phosphoramidite ligand **L16** was discovered which exhibited very high reactivity and selectivity in the reaction. This asymmetric Markovnikov hydroaminocarbonylation employs readily available starting materials and tolerates a wide range of functional groups, thus providing a facile and straightforward method for the regio- and enantioselective synthesis of 2-substituted propanamides under ambient conditions. Mechanistic studies revealed that the reaction proceeds through a palladium hydride pathway.

Hydrocarbonylation of alkenes is one of the most fundamental and ideal reactions for the synthesis of carbonyl compounds from readily available feedstocks.[1] Whereas hydroalkoxycarbonylations[2,3] and hydrothiocarbonylations[4] have been extensively developed over the past decades and the state-of-the-art Pd-catalyzed methoxycarbonylation of ethylene has been conducted on a >300,000 ton per annum scale,[5] hydroaminocarbonylation, a reaction analogous with hydroalkoxycarbonylation and hydrothiocarbonylation, has been far less well established. The original catalytic systems for hydroaminocarbonylations based on Co, Ni, Fe, and Ru complexes are operated at high temperatures and often accompanied by aminoformylation side reactions, thus resulting in limited substrate scope and fewer applications.[6] Recently, ligand-controlled regiodivergent Pd-catalyzed hydroaminocarbonylations, which were promising approaches to access either linear or branched amides, have been developed by the groups of Beller,[7] Cole-Hamilton,[8] Liu,[9] Huang,[10] and Alper[11] (Scheme 1 A,B).[12] Despite these advances, Pd-catalyzed asymmetric Markovnikov hydroaminocarbonylations of alkenes with simultaneous control of the regio- and enantioselectivity of the reaction, as well as a straightforward and atom-economical approach to pharmaceutically interesting chiral amides with an α-stereocenter, have not been realized so far.

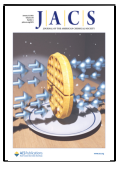
In general, the use of bidentate ligands favors Pd-catalyzed *anti*-Markovnikov hydroaminocarbonylations for the formation of linear amides,[7a,b,8,10a] while Pd-catalyzed Markovnikov hydroaminocarbonylation prefers resorting to a monodentate ligand.[7c,9,10b,11,13] Nevertheless, as a result of there being no "chelate effect", enantioselective monodentate ligand-assisted carbonylations with competitively coordinative CO are always tough issues.[14] In addition, the high temperatures and pressures that are generally required in this type of reactions would make enantiocontrol much more difficult.[15] With the goal of simultaneous control of regio- and enantioselectivities of hydroaminocarbonylation, we present herein a novel Pd-catalyzed asymmetric Markovnikov hydroaminocarbonylation

Scheme 1. Pd-Catalyzed Hydroaminocarbonylation of Alkenes with Amines



of alkenes with anilines (Scheme 1 C). By utilizing a new PdI_2-phosphoramidite ligand catalytic system, the features of the reaction include the following: (i) *Effectiveness*. The

Received: October 26, 2020
Published: December 29, 2020

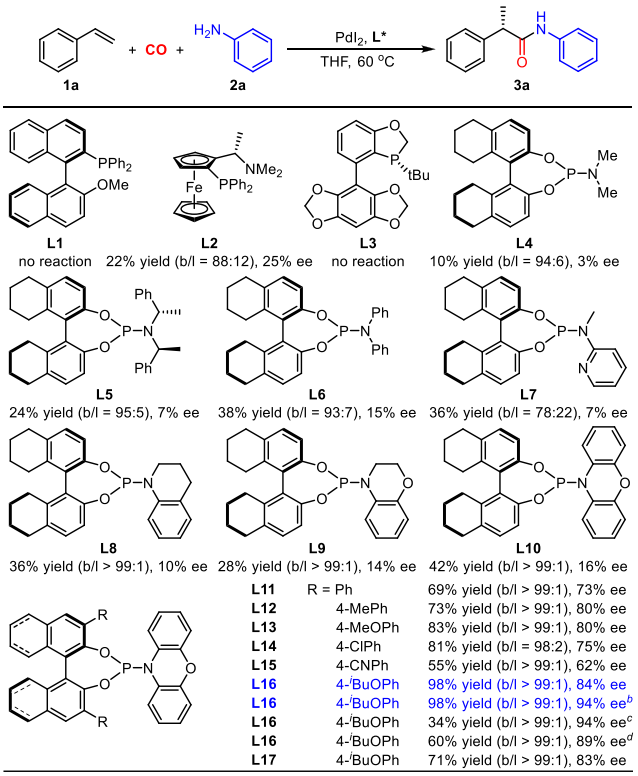


https://dx.doi.org/10.1021/jacs.0c11249
J. Am. Chem. Soc. 2021, 143, 85−91

hydroaminocarbonylation was operated under mild ambient conditions and achieved in a regio- and enantioselective manner. (ii) *Generality*. The reaction was suitable for a range of substrates including alkenylarenes and aliphatic alkenes, and primary and secondary anilines, and exhibited good compatibility with sensitive functional groups such as bromo, phenolic hydroxyl, and nitro. (iii) *Utility*. The utility the reaction is demonstrated in the synthesis of the anti-inflammatory new chemical entity (NCE) **5t** in one step and in the syntheses of ibuprofen, naproxen, and flurbiprofen in two steps.

We initiated our investigations with Pd-catalyzed Markovnikov hydroaminocarbonylation of styrene **1a** and aniline **2a** at 60 °C under CO atmosphere (50 atm) in THF (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



[a]Conditions: unless otherwise noted, **1a** (0.15 mmol), **2a** (0.1 mmol), PdI_2 (10 mol%), ligand (11 mol%), CO (50 atm), THF (1.0 mL), 60 °C, 48 h. Isolated yields. The ratios of branched to linear isomers shown within parentheses were determined by GC-MS analysis of the crude products. Enantiomeric excess was determined by chiral HPLC analysis. [b]The reaction was performed at room temperature (rt) for 72 h. [c]10 °C, 72 h. [d]CO (30 atm), rt, 72 h. **L17** was based on BINOL framework.

Owing to the unique advantages of monophosphine ligands in this type of reactions, a variety of privileged monodentate chiral ligands (**L1**−**L5**) were screened first. The reaction occurred at low temperature (60 °C) with ferrocenylphosphine **L2** and phosphoramidite **L4** or **L5** as the ligand, albeit in low yields and low enantiomeric excess (ee). These primary results inspired us to further search for an effective monodentate ligand for the reaction. In this context, various phosphoramidite ligands (**L6**−**L10**) with different amino substituents were screened. It was found that phenoxazinyl (**L10**) was the best choice in terms of the reactivity, regioselectivity, and enantioselectivity of the reaction. Subsequently, various phosphoramidite ligands with a range of electronic variation at the 3,3′-positions of the H_8-BINOL framework were prepared and screened (**L11**−**L16**). Encouragingly, the yield and ee of **3a** achieved important improvement in these cases, with 4-^{i}BuOPh and phenoxazinyl (POA) substituents **L16** being the most optimal. Due to the high reactivity of the new ligand **L16** (98% yield), the optimal reaction conditions to afford the corresponding **3a** with 94% ee in 98% yield (branched-to-linear (b/l) ratio >99:1) were obtained by lowering the reaction temperature to ambient conditions. Notably, further lowering the reaction temperature to 10 °C and also the pressure of CO to 30 atm, or employing BINOL-type **L17** as the ligand, gave rise to inferior results.

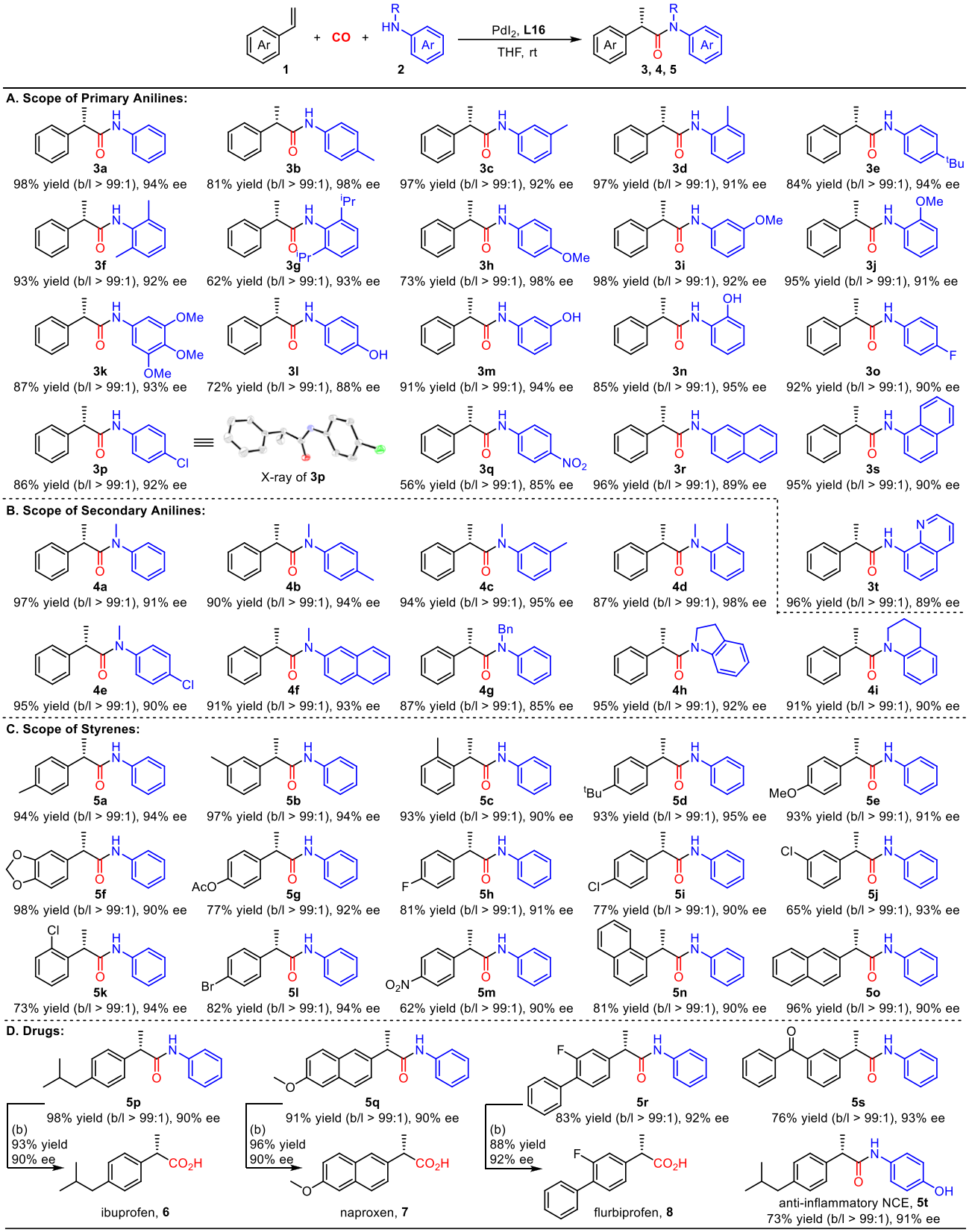
With the optimal reaction conditions in hand, we focused our effort on the reaction scope (Table 2). First, the scope of anilines was investigated (Table 2A). Anilines with electron-donating substituents, such as alkyl and methoxy, underwent the Pd-catalyzed Markovnikov hydroaminocarbonylation smoothly to afford the desired products in high yields and high ee values (**3a**−**3k**, 62−98% yield, 91−98% ee). Notably, the sterically bulky 2,6-dimethylaniline and 2,6-diisopropylaniline were compatible with the above conditions, implying that the reaction is insensitive to the steric effect of anilines.[16] Owing to the stronger nucleophilicity of anilines than that of phenols,[11,17] simultaneous chemo-, regio-, and enantioselective reactions were observed to afford the corresponding single isomers **3l**−**3n** in 72−91% yields and 88−95% ee when aminophenols were used as the substrates. Anilines with halide substituents, such as F and Cl, and strong electron-withdrawing groups, such as NO_2, were tolerated in the reaction to deliver the desired products **3o**−**3q** in high yields and ee's. Additionally, naphthylamines and even coordinative 8-aminoquinoline were also tolerated in the reactions (**3r**−**3t**).

Secondary anilines were tested in the reaction as well. As depicted in Table 2B, various *N*-alkylanilines, including indoline and tetrahydroquinoline, were compatible with the conditions to give rise to the corresponding 2-phenylpropanamides **4a**−**4i** in high yields and ee values. The substrate scope with respect to alkenylarenes was also investigated (Table 2C). All of the *para*-, *meta*-, and *ortho*-methyl-substituted styrenes gave the corresponding 2-arylpropanamides **5a**−**5c** in high yields and ee values, thus indicating that the reaction is insensitive to the sterics of the styrenes. Styrenes with electron-donating groups on aryl rings displayed higher reactivity than those with electron-withdrawing groups in the reaction, but all of the MeO-, AcO-, F-, Cl-, Br-, and NO_2-substituted styrenes afforded the desired 2-arylpropanamides **5d**−**5m** in high ee values. The compatibility of aryl chloride (**5i**−**5k**) and aryl bromide (**5l**) not only indicates that there was no reactive Pd(0) species in the reaction but they could also facilitate further functionalization reactions at the retained carbon−halogen bond. In addition, enantioenriched 2-naphthylpropanamides **5n** and **5o** could be synthesized in high yields through our reactions where alkenylnaphthalenes were employed as the starting materials.

To demonstrate the utility of this Pd-catalyzed asymmetric Markovnikov hydroaminocarbonylation (Table 2D), ibuprofen, naproxen, flurbiprofen and ketoprofen-derived 2-arylpropanamides **5p**−**5s** were synthesized in high yields and ee values with the respective alkenylarenes and aniline as the starting materials. As a result, a series of enantioenriched non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen **6**, naproxen **7**, flurbiprofen **8**, and ketoprofen, were

https://dx.doi.org/10.1021/jacs.0c11249
J. Am. Chem. Soc. 2021, 143, 85−91

Table 2. Palladium-Catalyzed Asymmetric Markovnikov Hydroaminocarbonylation of Alkenylarenes with Anilines[a]



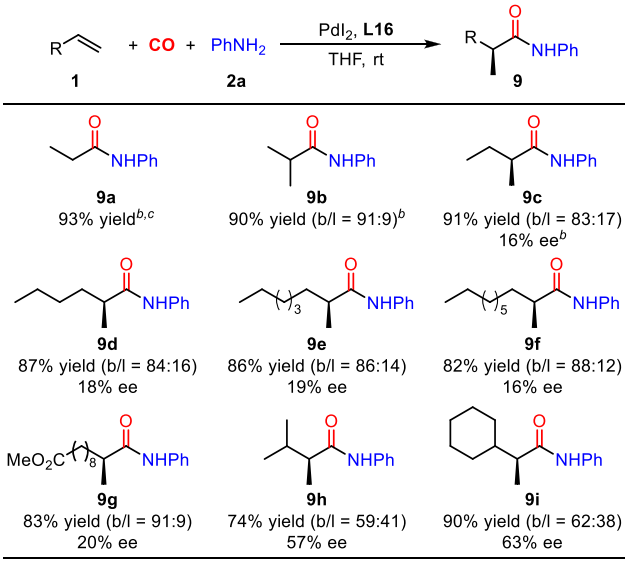
[a]Conditions: alkenylarene **1** (0.15 mmol), aniline **2** (0.10 mmol), PdI_2 (10 mol%), **L16** (11 mol%), CO (50 atm), THF (1.0 mL), rt, 72 h. Isolated yields. The ratios of branched to linear isomers (b/l) were determined by GC-MS analysis of the crude products. [b]Conditions: 1 M H_2SO_4 (aq, 1.0 mL), 1,4-dioxane (1.0 mL), 80 °C, 8 h.

https://dx.doi.org/10.1021/jacs.0c11249
J. Am. Chem. Soc. 2021, 143, 85−91

obtained in high yields by an additional hydrolysis step from **5p**−**5s**. The *p*-amidophenol-derived NSAIDs, which were recognized as NCEs, displayed reduced ulcerogenic potential compared to their parent NSAIDs and enhanced anti-pyretic activity compared to paracetamol.[18] In this context, the anti-inflammatory NCE **5t** was synthesized in one step under our conditions by employing 1-isobutyl-4-vinylbenzene and 4-aminophenol as the starting materials.

Furthermore, the scope and limitations of aliphatic alkenes were explored (Table 3). Ethylene was well compatible with

Table 3. Palladium-Catalyzed Hydroaminocarbonylation of Aliphatic Alkenes with Aniline[a]

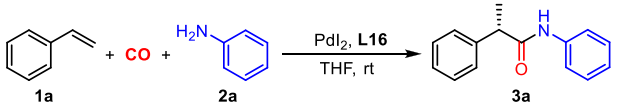


[a]Conditions: alkene **1** (0.30 mmol), aniline **2a** (0.20 mmol), PdI_2 (10 mol%), **L16** (11 mol%), CO (50 atm), THF (2.0 mL), rt, 72 h. Isolated yields. The ratios of branched to linear isomers (b/l) were determined by GC-MS analysis of the crude products. [b]Alkene (ethylene, propene, 1-butene) (1 atm). [c]60 °C.

the conditions to afford the desired propionanilide **9a** in 93% yield, although the regio- and enantioselectivities were not involved in the reaction. In general, the transition-metal-catalyzed Markovnikov hydrocarbonylations (hydroformylation, hydroalkoxycarbonylation, and hydroaminocarbonylation) of aliphatic alkenes toward branched carbonyl compounds are particularly not favored because of the increasing steric effects for both the step of alkene insertion into the [M−H] to form the secondary carbon−metal species and the step of CO insertion into the secondary carbon−metal species.[3a,15a,19] Meanwhile, the Pd-catalyzed Markovnikov hydroaminocarbonylation of propene for the formation of isobutyrylanilide **9b** with b/l = 91:9 was achieved in 90% yield under our conditions. Encouraged by this result, we then evaluated various alkenes. Non-functionalized bulk aliphatic alkenes, such as 1-butene, 1-hexene, 1-octene, 1-decene, and methyl 10-undecenoate were tolerated under the conditions to afford the corresponding branched amides **9c**−**9g** with b/l = 83:17 to 91:9 in high yields. Presumably due to the lack of functional groups that can provide binding or affinity interaction with the catalyst as well as the very small differentiation of the two prochiral faces of aliphatic alkenes, low ee values were obtained in these cases. However, the situation can be partially improved by utilizing sterically hindered substrates. For example, the alkenes substituted with more sterically demanding isopropyl or cyclohexanyl group produced their desired amides **9h** and **9i** with moderate regioselectivities in high yields and with 57−63% ee values.

To gain mechanistic insight into the reaction, control experiments were performed (Table 4). First, it was found that

Table 4. Control Experiments



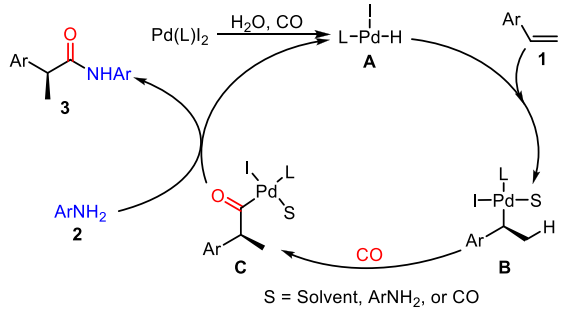
entry	variation from standard conditions[a]	yield of **3a** (%)
1	none	98
2	anhydrous THF as the solvent	<10
3	anhydrous THF as the solvent + H_2O (1.0 equiv)	95
4	Pd/C (10 mol%) and HI (10 mol%) instead of PdI_2	81
5	Na_2CO_3 (1.0 equiv) was added as a base	0
6	K_2CO_3 (1.0 equiv) was added as a base	0

[a]Conditions: styrene **1a** (0.15 mmol), aniline **2a** (0.10 mmol), PdI_2 (10 mol%), **L16** (11 mol%), CO (50 atm), THF (1.0 mL), rt, 72 h. Isolated yields.

the trace amount of H_2O played a vital role in the reaction. The reaction was significantly suppressed when anhydrous THF was used as the solvent, while a 95% yield of **3a** was obtained when 1.0 equiv of H_2O was employed as the additive (entries 2 and 3). The replacement of PdI_2 by Pd/C and HI resulted in **3a** in 81% yield (entry 4). And the reaction was completely suppressed by a base, such as Na_2CO_3 or K_2CO_3 (entries 5 and 6). These experimental results suggest that the Pd-catalyzed hydroaminocarbonylation reaction proceeded most likely through a palladium hydride pathway.

On the basis of the above preliminary observations and the known reports on Pd-catalyzed hydrocarbonylations,[7−11,20] a tentative mechanism is proposed in Scheme 2. Initially, a

Scheme 2. Tentative Reaction Mechanism

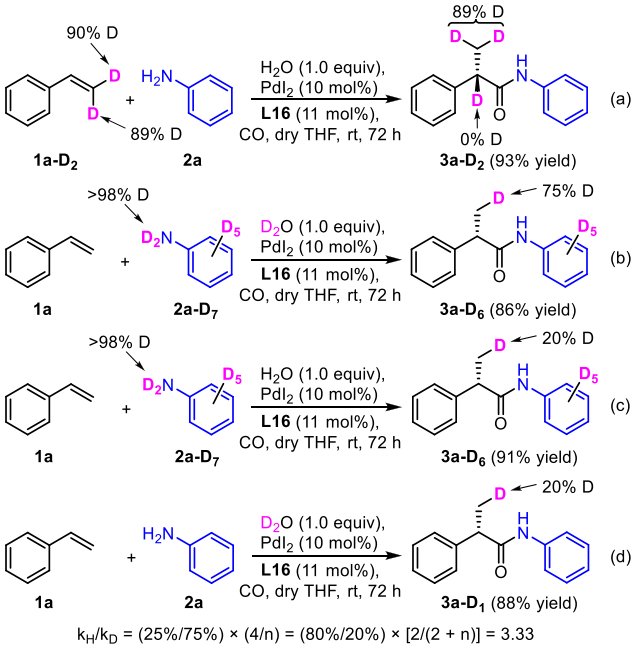


palladium hydride species **A** is generated from the reaction of PdI_2, H_2O, and CO. Coordination and insertion of alkene **1** into palladium hydride **A** afford the alkyl-Pd intermediate **B**. The alkyl-Pd **B** undergoes CO coordination and insertion to give the acyl-Pd intermediate **C**. Finally, aminolysis of acyl-Pd **C** results in the desired amide and regenerates the active palladium hydride catalyst **A**.

To gain further insight into the catalytic cycle, deuterium-labeling experiments were conducted under the standard conditions. First, when the deuterium-labeled **1a-D$_2$** was used as the substrate and 1.0 equiv of H_2O was used as the additive,

https://dx.doi.org/10.1021/jacs.0c11249
J. Am. Chem. Soc. 2021, 143, 85−91

Scheme 3. Deuterium-Labeling Studies



H/D scrambling was not observed (Scheme 3a). This result suggested that the hydropalladation process from palladium hydride **A** to intermediate **B** is irreversible and should be the regio- and enantiodetermining step of the reaction. However, when the deuterium-labeled **2a-D$_7$** (>98% D on nitrogen) was used as the substrate, an important deuterium loss was observed, even in the presence of 1.0 equiv of D_2O (Scheme 3b). This result indicated that a trace amount of active H (maybe in the form water) is still contained in the reaction. For comparison, the control experiments were carried out by using either **2a-D$_7$**/H_2O (1:1) or **2a**/D_2O (1:1) as the substrates (Scheme 3c,d). In both cases, similar results (20% D in **3a-D$_1$**) were obtained. These two experiments indicated that H/D exchange on aniline and water is fast under the conditions. Since these experiments were operated under identical conditions (Scheme 3b–d), we then concluded that the kinetic isotope effect (KIE) on the hydrogen of aniline was 3.33, thus indicating that aminolysis is probably the rate-limiting step of the reaction.

In summary, we have developed the first Pd-catalyzed asymmetric Markovnikov hydroaminocarbonylation of alkenes with anilines. A new catalytic system of PdI_2-phosphoramidite ligand **L16** was discovered. The reaction proceeded under mild ambient conditions and exhibited good functional group compatibility. A diverse array of 2-substituted propanamides was obtained straightforwardly in high yields and enantioselectivities, several of which could be easily converted to nonsteroidal anti-inflammatory drugs. Mechanistic investigations revealed that the reaction proceeds through a palladium-hydride mechanism, and the hydropalladation is irreversible and is the regio- and enantiodetermining step, while aminolysis is probably the rate-limiting step. Further scope and mechanistic studies of such reactions are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11249.

Experimental procedure and characterization data for all the products (PDF)

Crystallographic data for **3p** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Zheng-Hui Guan − *Key Laboratory of Synthetic and Nature Molecule of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, P.R. China;* orcid.org/0000-0003-4901-5951; Email: guanzhh@nwu.edu.cn

Authors

Ya-Hong Yao − *Key Laboratory of Synthetic and Nature Molecule of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, P.R. China*

Hui-Yi Yang − *Key Laboratory of Synthetic and Nature Molecule of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, P.R. China*

Ming Chen − *Key Laboratory of Synthetic and Nature Molecule of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, P.R. China*

Fei Wu − *Key Laboratory of Synthetic and Nature Molecule of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, P.R. China*

Xing-Xing Xu − *Key Laboratory of Synthetic and Nature Molecule of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, P.R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c11249

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by generous grants from the National Natural Science Foundation of China (NSFC-21971204, 21622203, 21702161) and the Innovation Capability Support Program of Shaanxi Province (No. 2020TD-022). We thank Prof. Xi Chen for her helpful polishing of the paper. This paper is dedicated to Prof. Xumu Zhang on the occasion of his 60th birthday.

■ REFERENCES

(1) (a) For selected reviews, see: Ali, B. E.; Alper, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 113–132. (b) Brennführer, A.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylation Reactions of Alkenes and Alkynes. *ChemCatChem* **2009**, *1*, 28–41. (c) Peng, J.-B.; Wu, F.-P.; Wu, X.-F. First-Row Transition-Metal-Catalyzed Carbonylative Transformations of Carbon Electrophiles. *Chem. Rev.* **2019**, *119*, 2090–2127. (d) Matsubara, H.; Kawamoto, T.; Fukuyama, T.; Ryu, I. Applications of Radical Carbonylation and Amine Addition Chemistry: 1,4-Hydrogen Transfer of 1-Hydroxylallyl

Radicals. *Acc. Chem. Res.* **2018**, *51*, 2023−2035. (e) Kalck, P.; Urrutigoïty, M. Recent Improvements in the Alkoxycarbonylation Reaction Catalyzed by Transition Metal Complexes. *Inorg. Chim. Acta* **2015**, *431*, 110−121. (f) Franke, R.; Selent, D.; Börner, A. Applied Hydroformylation. *Chem. Rev.* **2012**, *112*, 5675−5732. (g) Kiss, G. Palladium-Catalyzed Reppe Carbonylation. *Chem. Rev.* **2001**, *101*, 3435−3456.

(2) For selected examples of anti-Markovnikov hydroesterification, see: (a) Yang, J.; Liu, J.; Neumann, H.; Franke, R.; Jackstell, R.; Beller, M. Direct Synthesis of Adipic Acid Esters via Palladium-Catalyzed Carbonylation of 1,3-Dienes. *Science* **2019**, *366*, 1514−1517. (b) Dong, K.; Fang, X.; Gülak, S.; Franke, R.; Spannenberg, A.; Neumann, H.; Jackstell, R.; Beller, M. Highly Active and Efficient Catalysts for Alkoxycarbonylation of Alkenes. *Nat. Commun.* **2017**, *8*, 14117. (c) Williams, D. B. G.; Shaw, M. L.; Green, M. J.; Holzapfel, C. W. Aluminum Triflate as a Highly Active and Efficient Nonprotic Cocatalyst in the Palladium-Catalyzed Methoxycarbonylation Reaction. *Angew. Chem., Int. Ed.* **2008**, *47*, 560−563. (d) Amézquita-Valencia, M.; Alper, H. Regioselective Alkoxycarbonylation of Allyl Phenyl Ethers Catalyzed by Pd/dppb Under Syngas Conditions. *J. Org. Chem.* **2016**, *81*, 3860−3867. (e) Vieira, T. O.; Green, M. J.; Alper, H. Highly Regioselective Anti-Markovnikov Palladium-Borate-Catalyzed Methoxycarbonylation Reactions: Unprecedented Results for Aryl Olefins. *Org. Lett.* **2006**, *8*, 6143−6145. (f) Reynhardt, J. P. K.; Alper, H. Hydroesterification Reactions with Palladium-Complexed PAMAM Dendrimers Immobilized on Silica. *J. Org. Chem.* **2003**, *68*, 8353−8360. (g) Rodriguez, C. J.; Foster, D. F.; Eastham, G. R.; Cole-Hamilton, D. J. Highly Selective Formation of Linear Esters from Terminal and Internal Alkenes Catalysed by Palladium Complexes of Bis-(di-tert-butylphosphinomethyl)benzene. *Chem. Commun.* **2004**, 1720−1721.

(3) For selected examples of Markovnikov hydroesterification, see: (a) Li, H.; Dong, K.; Jiao, H.; Neumann, H.; Jackstell, R.; Beller, M. The Scope and Mechanism of Palladium-Catalysed Markovnikov Alkoxycarbonylation of Alkenes. *Nat. Chem.* **2016**, *8*, 1159−1166. (b) Nielsen, D. B.; Wahlqvist, B. A.; Nielsen, D. U.; Daasbjerg, K.; Skrydstrup, T. Utilizing Glycerol as an Ex Situ CO-Source in Pd-Catalyzed Alkoxycarbonylation of Styrenes. *ACS Catal.* **2017**, *7*, 6089−6093. (c) Li, J.; Chang, W.; Ren, W.; Dai, J.; Shi, Y. Palladium-Catalyzed Highly Regio- and Enantioselective Hydroesterification of Aryl Olefins with Phenyl Formate. *Org. Lett.* **2016**, *18*, 5456−5459. (d) Konrad, T. M.; Durrani, J. T.; Cobley, C. J.; Clarke, M. L. Simultaneous Control of Regioselectivity and Enantioselectivity in the Hydroxycarbonylation and Methoxycarbonylation of Vinyl Arenes. *Chem. Commun.* **2013**, *49*, 3306−3308. (e) Amézquita-Valencia, M.; Alper, H. PdI_2-Catalyzed Regioselective Cyclocarbonylation of 2-Allyl Phenols to Dihydrocoumarins. *Org. Lett.* **2014**, *16*, 5827−5829. (f) Lee, C.; Alper, H. Hydroesterification of Olefins Catalyzed by $Pd(OAc)_2$ Immobilized on Montmorillonite. *J. Org. Chem.* **1995**, *60*, 250−252.

(4) (a) Wang, X.; Wang, B.; Yin, X.; Yu, W.; Liao, Y.; Ye, J.; Wang, M.; Hu, L.; Liao, J. Palladium-Catalyzed Enantioselective Thiocarbonylation of Styrenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 12264−12270. (b) Hirschbeck, V.; Gehrtz, P. H.; Fleischer, I. Regioselective Thiocarbonylation of Vinyl Arenes. *J. Am. Chem. Soc.* **2016**, *138*, 16794−16799. (c) Xiao, W.-J.; Alper, H. First Examples of Enantioselective Palladium-Catalyzed Thiocarbonylation of Prochiral 1,3-Conjugated Dienes with Thiols and Carbon Monoxide: Efficient Synthesis of Optically Active β,γ-Unsaturated Thiol Esters. *J. Org. Chem.* **2001**, *66*, 6229−6233.

(5) (a) Nagai, K. New Developments in the Production of Methyl Methacrylate. *Appl. Catal., A* **2001**, *221*, 367−377. (b) Clegg, W.; Eastham, G. R.; Elsegood, M. R. J.; Tooze, R. P.; Wang, X. L.; Whiston, K. Highly Active and Selective Catalysts for the Production of Methyl Propanoate via the Methoxycarbonylation of Ethene. *Chem. Commun.* **1999**, 1877−1878. (c) Eastham, G. R.; Cameron, P. A.; Tooze, R. P.; Cavell, K. J.; Edwards, P. G.; Coleman, D. L. A Phospha-Adamantane Catalytic System. Patent WO2004014552 A1, 2004.

(6) (a) Pino, P.; Paleari, P. Synthesis of Anilides from Unsaturated Compounds, Carbon Monoxide, and Aniline. *Gazz. Chim. Ital.* **1951**, *81*, 646−653. (b) Lee, S. I.; Son, S. U.; Chung, Y. K. Catalytic One-Pot Synthesis of *N*-phenyl Alkyl Amides from Alkene and Aniline in the Presence of Cobalt on Charcoal under Carbon Monoxide. *Chem. Commun.* **2002**, 1310−1311. (c) Striegler, A.; Weber, J. Über die durch Metallcarbonylverbindungen katalysierte Umsetzung von Olefinen mit Kohlenoxyd und Ammoniak bzw. Aminen in Gegenwart von Wasserstoff. *J. Prakt. Chem.* **1965**, *29*, 281−295. (d) Tsuji, Y.; Ohsumi, T.; Kondo, T.; Watanabe, Y. Dodecacarbonyltriruthenium Catalysed Carbonylation of Amines and Hydroamidation of Olefins. *J. Organomet. Chem.* **1986**, *309*, 333−344.

(7) (a) Fang, X.; Jackstell, R.; Beller, M. Selective Palladium-Catalyzed Aminocarbonylation of Olefins with Aromatic Amines and Nitroarenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 14089−14093. (b) Li, H.; Dong, K.; Neumann, H.; Beller, M. Palladium-Catalyzed Hydroamidocarbonylation of Olefins to Imides. *Angew. Chem., Int. Ed.* **2015**, *54*, 10239−10243. (c) Liu, J.; Li, H.; Spannenberg, A.; Franke, R.; Jackstell, R.; Beller, M. Selective Palladium-Catalyzed Aminocarbonylation of Olefins to Branched Amides. *Angew. Chem., Int. Ed.* **2016**, *55*, 13544−13548.

(8) Jiménez-Rodriguez, C.; Núñez-Magro, A. A.; Seidensticker, T.; Eastham, G. R.; Furst, M. R. L.; Cole-Hamilton, D. J. Selective Formation of α,ω-Ester Amides from the Aminocarbonylation of Castor Oil Derived Methyl 10-Undecenoate and other Unsaturated Substrates. *Catal. Sci. Technol.* **2014**, *4*, 2332−2339.

(9) Liu, H.; Yan, N.; Dyson, P. J. Acid-free Regioselective Aminocarbonylation of Alkenes. *Chem. Commun.* **2014**, *50*, 7848−7851.

(10) (a) Zhang, G.; Gao, B.; Huang, H. Palladium-Catalyzed Hydroaminocarbonylation of Alkenes with Amines: A Strategy to Overcome the Basicity Barrier Imparted by Aliphatic Amines. *Angew. Chem., Int. Ed.* **2015**, *54*, 7657−7661. (b) Hu, Y.; Shen, Z.; Huang, H. Palladium-Catalyzed Intramolecular Hydroaminocarbonylation to Lactams: Additive-Free Protocol Initiated by Palladium Hydride. *ACS Catal.* **2016**, *6*, 6785−6789. (c) Gao, B.; Zhang, G.; Zhou, X.; Huang, H. Palladium-Catalyzed Regiodivergent Hydroaminocarbonylation of Alkenes to Primary Amides with Ammonium Chloride. *Chem. Sci.* **2018**, *9*, 380−386. (d) Li, J.; Wang, S.; Zou, S.; Huang, H. Palladium-Catalyzed Relay Hydroaminocarbonylation of Alkenes with Hydroxylamine Hydrochloride as an Ammonia Equivalent. *Commun. Chem.* **2019**, *2*, 14. (e) Zhu, J.; Gao, B.; Huang, H. Palladium-Catalyzed Highly Regioselective Hydroaminocarbonylation of Aromatic Alkenes to Branched Amides. *Org. Biomol. Chem.* **2017**, *15*, 2910−2913.

(11) Xu, T.; Sha, F.; Alper, H. Highly Ligand-Controlled Regioselective Pd-Catalyzed Aminocarbonylation of Styrenes with Aminophenols. *J. Am. Chem. Soc.* **2016**, *138*, 6629−6635.

(12) For Rh-catalyzed hydroaminocarbonylation reaction, see: (a) Dong, K.; Fang, X.; Jackstell, R.; Laurenczy, G.; Li, Y.; Beller, M. Rh(I)-Catalyzed Hydroamidation of Olefins via Selective Activation of N-H Bonds in Aliphatic Amines. *J. Am. Chem. Soc.* **2015**, *137*, 6053−6058. For Cu-catalyzed reductive hydroamidation, see: (b) Yuan, Y.; Wu, F.-P.; Schünemann, C.; Holz, J.; Kamer, P. C. J.; Wu, X.-F. Copper-Catalyzed Carbonylative Hydroamidation of Styrenes to Branched Amides. *Angew. Chem., Int. Ed.* **2020**, *59*, 22441−22445.

(13) (a) Liu, J.; Liu, Q.; Franke, R.; Jackstell, R.; Beller, M. Ligand-Controlled Palladium-Catalyzed Alkoxycarbonylation of Allenes: Regioselective Synthesis of α,β- and β,γ-Unsaturated Esters. *J. Am. Chem. Soc.* **2015**, *137*, 8556−8563. (b) Grabulosa, A.; Frew, J. J. R.; Fuentes, J. A.; Slawin, A. M. Z.; Clarke, M. L. Palladium Complexes of Bulky ortho-Trifluoromethylphenyl-Substituted Phosphines: Unusually Regioselective Catalysts for the Hydroxycarbonylation and Alkoxycarbonylation of Alkenes. *J. Mol. Catal. A: Chem.* **2010**, *330*, 18−25. (c) del Río, I.; Ruiz, N.; Claver, C.; van der Veen, L. A.; van Leeuwen, P. W. N. M. Hydroxycarbonylation of Styrene with Palladium Catalysts the Influence of the Mono- and Bidentate Phosphorus Ligand. *J. Mol. Catal. A: Chem.* **2000**, *161*, 39−48.

https://dx.doi.org/10.1021/jacs.0c11249
J. Am. Chem. Soc. 2021, 143, 85−91

(14) (a) Chen, M.; Wang, X.; Yang, P.; Kou, X.; Ren, Z.-H.; Guan, Z.-H. Palladium-Catalyzed Enantioselective Heck Carbonylation with a Monodentate Phosphoramidite Ligand: Asymmetric Synthesis of (+)-Physostigmine, (+)-Physovenine, and (+)-Folicanthine. *Angew. Chem., Int. Ed.* **2020**, *59*, 12199−12205. (b) Godard, C.; Muñoz, B. K.; Ruiz, A.; Claver, C. Pd-Catalysed Asymmetric mono- and bis-Alkoxycarbonylation of Vinylarenes. *Dalton Trans.* **2008**, 853−860. (c) Yang, B.; Qiu, Y.; Jiang, T.; Wulff, W. D.; Yin, X.; Zhu, C.; Bäckvall, J.-E. Enantioselective Palladium-Catalyzed Carbonylative Carbocyclization of Enallenes via Cross-Dehydrogenative Coupling with Terminal Alkynes: Efficient Construction of α-Chirality of Ketones. *Angew. Chem., Int. Ed.* **2017**, *56*, 4535−4539. (d) Suzuki, T.; Uozumi, Y.; Shibasaki, M. A Catalytic Asymmetric Synthesis of α-Methylene Lactones by the Palladium-Catalysed Carbonylation of Prochiral Alkenyl Halides. *J. Chem. Soc., Chem. Commun.* **1991**, 1593−1595.

(15) A large excess of ligand (400−1600:1 PPh_3:Rh) is required to minimize the ligand dissociation from metal center in Rh-catalyzed hydroformylations; see: (a) Hood, D. M.; Johnson, R. A.; Carpenter, A. E.; Younker, J. M.; Vinyard, D. J.; Stanley, G. G. Highly Active Cationic Cobalt(II) Hydroformylation Catalysts. *Science* **2020**, *367*, 542−548. (b) Yan, Y.; Zhang, X.; Zhang, X. A Tetraphosphorus Ligand for Highly Regioselective Isomerization-Hydroformylation of Internal Olefins. *J. Am. Chem. Soc.* **2006**, *128*, 16058−16061.

(16) (a) Torres, G. M.; Liu, Y.; Arndtsen, B. A. A Dual Light-Driven Palladium Catalyst: Breaking the Barriers in Carbonylation Reactions. *Science* **2020**, *368*, 318−323. (b) Quesnel, J. S.; Arndtsen, B. A. A Palladium-Catalyzed Carbonylation Approach to Acid Chloride Synthesis. *J. Am. Chem. Soc.* **2013**, *135*, 16841−16844.

(17) (a) Sha, F.; Alper, H. Ligand- and Additive-Controlled Pd-Catalyzed Aminocarbonylation of Alkynes with Aminophenols: Highly Chemo- and Regioselective Synthesis of α,β-Unsaturated Amides. *ACS Catal.* **2017**, *7*, 2220−2229. (b) Xu, T.; Alper, H. Pd-Catalyzed Chemoselective Carbonylation of Aminophenols with Iodoarenes: Alkoxycarbonylation vs Aminocarbonylation. *J. Am. Chem. Soc.* **2014**, *136*, 16970−16973.

(18) (a) Deplano, A.; Karlsson, J.; Svensson, M.; Moraca, F.; Catalanotti, F. B.; Fowler, C. J.; Onnis, V. Exploring the Fatty Acid Amide Hydrolase and Cyclooxygenase Inhibitory Properties of Novel Amide Derivatives of Ibuprofen. *J. Enzyme Inhib. Med. Chem.* **2020**, *35*, 815−823. (b) Yadav, M. R.; Nimekar, D. M.; Ananthakrishnan, A.; Brahmkshatriya, P. S.; Shirude, S. T.; Giridhar, R.; Parmar, A.; Balaraman, R. Synthesis of New Chemical Entities From Paracetamol and NSAIDs with Improved Pharmacodynamic Profile. *Bioorg. Med. Chem.* **2006**, *14*, 8701−8706.

(19) (a) Roesle, P.; Dürr, C. J.; Möller, H. M.; Cavallo, L.; Caporaso, L.; Mecking, S. Mechanistic Features of Isomerizing Alkoxycarbonylation of Methyl Oleate. *J. Am. Chem. Soc.* **2012**, *134*, 17696−17703. (b) Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. An Asymmetric Hydroformylation Catalyst that Delivers Branched Aldehydes from Alkyl Alkenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 2477−2480. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. Catalytic Markovnikov and anti-Markovnikov Functionalization of Alkenes and Alkynes: Recent Developments and Trends. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398. (d) Zhang, Y.; Torker, S.; Sigrist, M.; Bregović, N.; Dydio, P. Binuclear Pd(I)-Pd(I) Catalysis Assisted by Iodide Ligands for Selective Hydroformylation of Alkenes and Alkynes. *J. Am. Chem. Soc.* **2020**, *142*, 18251−18265.

(20) (a) Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. In Situ Generated Bulky Palladium Hydride Complexes as Catalysts for the Efficient Isomerization of Olefins. Selective Transformation of Terminal Alkenes to 2-Alkenes. *J. Am. Chem. Soc.* **2010**, *132*, 7998−8009. (b) de la Fuente, V.; Waugh, M.; Eastham, G. R.; Iggo, J. A.; Castillón, S.; Claver, C. Phosphine Ligands in the Palladium-Catalysed Methoxycarbonylation of Ethene: Insights into the Catalytic Cycle through an HP NMR Spectroscopic Study. *Chem. - Eur. J.* **2010**, *16*, 6919−6932. (c) Eastham, G. R.; Tooze, R. P.; Kilner, M.; Foster, D. F.; Cole-Hamilton, D. J. Deuterium Labelling Evidence for a Hydride Mechanism in the Formation of Methyl Propanoate from Carbon Monoxide, Ethene and Methanol Catalysed by a Palladium Complex. *J. Chem. Soc., Dalton Trans.* **2002**, 1613−1617.

https://dx.doi.org/10.1021/jacs.0c11249
J. Am. Chem. Soc. 2021, 143, 85−91