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Pd-Catalyzed Enantioselective Double Heck Reaction

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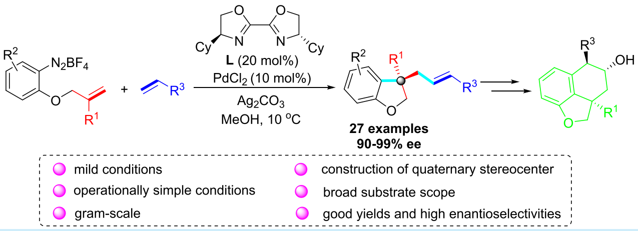
Supporting Information

ABSTRACT: An asymmetric Pd-catalyzed intramolecular followed by an intermolecular double Heck reaction of arenediazonium salts with simple alkenes is disclosed. This reaction features mild reaction conditions, simple operation, and excellent functional group tolerance and provides a rapid access to functionalized dihydrobenzofurans bearing all-carbon quaternary centers in good regioselectivity (>95/5) and enantioselectivity (90−99% ee).



The fused tricyclic dihydrobenzofuran framework represents a prevalent core structure present in a large number of natural products such as Isoabietenin A, Parviflorene J, Morphine, and its derivatives (Codeine, Thebaine, and Codeinone), which show a wide range of important biologically activities (Figure 1).[1] Therefore, it is not surprising that enormous efforts have been devoted to developing new transformations to synthesize this privileged structural skeleton.[2] Nevertheless, efficient methods for their enantioselective preparation are still rare. Therefore, it is highly desirable to develop new strategies to access these scaffolds.

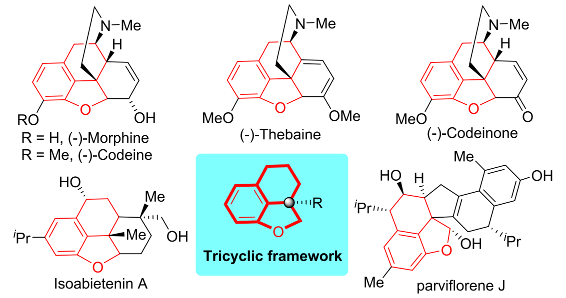
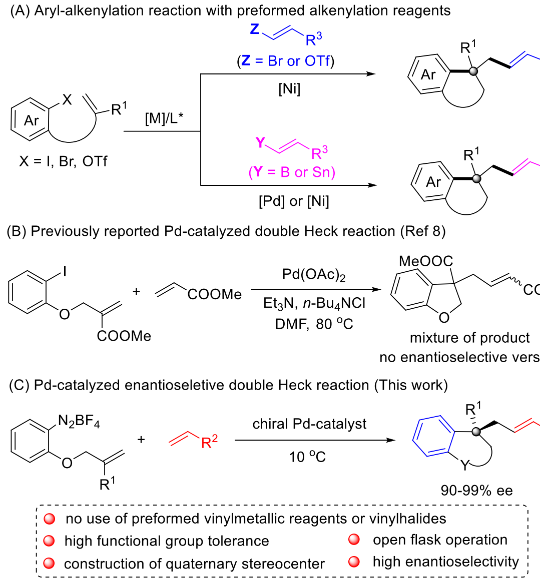


Figure 1. Representative examples of biologically active molecules and natural products.

On the other hand, catalytic asymmetric dicarbofunctionalization of alkenes by simultaneously installing two carbon groups on each side of the double bond has experienced remarkable progress and emerged as a powerful synthetic tool for constructing molecules containing quaternary stereocenters.[3] Among them, the double Heck reaction is a particularly appealing transformation, since it not only offers a facile route to diverse cyclic scaffolds having all-carbon quaternary centers, but also the introduced alkenyl group can be further functionalized. Our group recently reported the first example of a highly enantioselective aryl-alkenylation reaction by Ni-catalyzed reductive cyclizative cross-coupling of an aryl bromide with a vinyl bromide (Scheme 1A, top).[4] In addition, transition metal catalyzed redox-neutral aryl-alkenylation reaction of aryl halides with vinylmetallic reagents has also been well investigated (Scheme 1A, bottom).[5] However, asymmetric transformation has not been reported.[6] Only recently, the Zhang group reported the Pd-catalyzed enantioselective aryl-alkenylation reaction of aryl halides with vinyl boronic acids.[7] However, the above-mentioned methods are limited to the use of pregenerate coupling partners (the vinylmetallic reagents or vinylhalides), which require many stoichiometric transformations for their preparation.

Scheme 1. Transition-Metal-Catalyzed Double Heck Reaction



The direct double Heck reaction with nonfunctionalized olefins is a significantly more efficient and atom-economical

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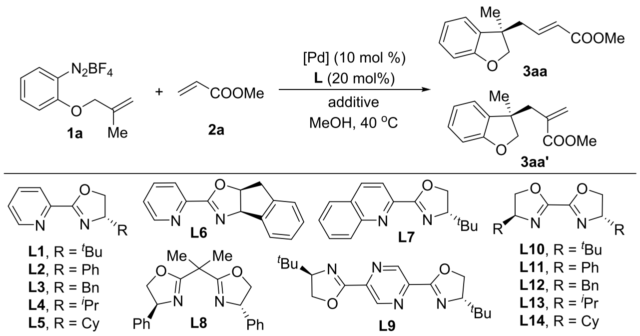
strategy. A single racemic example of a double Heck reaction of aryl iodide with methyl acrylate has been reported; however, a mixture of products was obtained (Scheme 1B),[8] which draws into question the generality of this approach. To solve this problem, we anticipated that a mild generation of active arylmetallic species is critical for success. Inspired by the seminal contributions by Correia[9] as well as Sigman and Toste[10] on enantioselective Heck–Matsuda reactions, we expected to achieve an enantioselective double Heck reaction of aryldiazonium salts with simple alkenes by utilizing the ability of aryldiazonium salts to be easily available and highly reactive.[11] Herein, we report the first catalytic enantioselective double Heck reaction that provides access to functionalized dihydrobenzofurans bearing all-carbon quaternary centers (Scheme 1C). This protocol reported in this work proceeds under open flask and mild conditions without requiring anhydrous solvents and air-sensitive chiral phosphines ligands.

Our investigations commenced with the coupling of arenediazonium salt **1a** and methyl acrylate **2a**. Gratefully, the desired *E*-configuration dihydrobenzofuran **3aa** was obtained exclusively in 74% yield using $Pd(OAc)_2$ (10 mol %) as a catalyst in the absence of ligand (Table 1, entry 1). This result may indicate that controlling the enantioselectivity of the reaction is challenging because of the background reaction. Facing the challenge, we decided to employ the same protocol to test the asymmetric transformation using (*S*)-^{t}Bu-Pyrox (**L1**) as a chiral ligand, affording **3aa** in 75% yield, albeit with only 9% *ee* (entry 2). Subsequently, we found that the anions in palladium catalysts had a great influence on both the efficiency and enantioselectivity (entries 3–5). $PdCl_2$ was found to be particularly effective in terms of enantioselectivity (entry 5, 77% *ee*), albeit with a lower yield. Attempts to add DTBMP, a highly efficient organic base in asymmetric Heck–Matsuda reaction,[12] or the addition of carbonates such as Na_2CO_3 or K_2CO_3 as base,[13] inhibited the desired domino process (entries 6–8). To our surprise, noteworthy improvement of the yield to 90% was observed when Ag_2CO_3 was used as an additive (entry 9). Next, the chiral ligands **L2**–**L14** were examined (entries 11–23), and **L14** proved to be the most effective, delivering **3aa** in 65% yield with 82% *ee* (entry 23). Gratefully, when lowering the reaction temperature to 10 °C, the enantioselectivity of **3aa** could be improved to 94% (**3aa**/**3aa′** > 95/5, entry 24).[14] We assume that the cationic pathway might be established by removing chloride ions through Ag_2CO_3, so only catalytic amounts of silver salt are sufficient. To our surprise, the enantioselectivity was significantly reduced with 10 mol % of Ag_2CO_3 (entry 25, 60% *ee*). Obviously, the addition of Ag_2CO_3 was beneficial for both the reactivity and enantioselectivity. Although the role of Ag_2CO_3 is unclear, we suspect that it may play a dual role, not only as a Lewis acid to promote the oxidative addition of Pd(0) to arenediazonium salt but also as a chloride scavenger.

Table 1. Optimization of the Reaction Conditions[a]



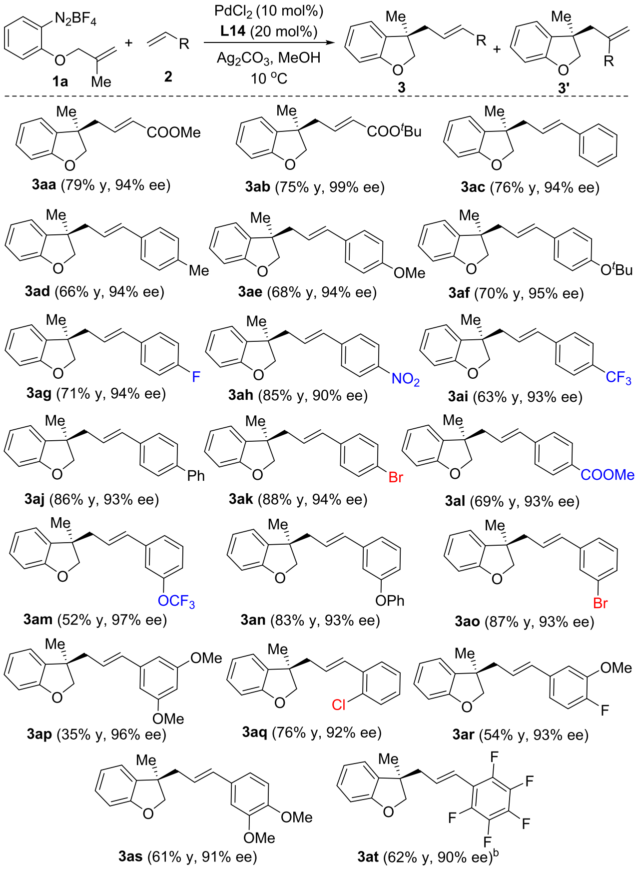
entry	[Pd]	additive	ligand	yield of **3aa** (%)[b]	*ee* of **3aa** (%)[c]
1	$Pd(OAc)_2$	–	–	74	–
2	$Pd(OAc)_2$	–	**L1**	75	9
3	$Pd(TFA)_2$	–	**L1**	26	20
4	$Pd(dba)_2$	–	**L1**	28	37
5	$PdCl_2$	–	**L1**	9	77
6	$PdCl_2$	DTBMP	**L1**	trace	–
7	$PdCl_2$	Na_2CO_3	**L1**	trace	–
8	$PdCl_2$	K_2CO_3	**L1**	trace	–
9	$PdCl_2$	Ag_2CO_3	**L1**	90	74
10	$PdCl_2$	Ag_3PO_4	**L1**	83	69
11	$PdCl_2$	Ag_2CO_3	**L2**	trace	–
12	$PdCl_2$	Ag_2CO_3	**L3**	14	67
13	$PdCl_2$	Ag_2CO_3	**L4**	71	69
14	$PdCl_2$	Ag_2CO_3	**L5**	56	70
15	$PdCl_2$	Ag_2CO_3	**L6**	31	73
16	$PdCl_2$	Ag_2CO_3	**L7**	83	67
17	$PdCl_2$	Ag_2CO_3	**L8**	89	1
18	$PdCl_2$	Ag_2CO_3	**L9**	57	79
19	$PdCl_2$	Ag_2CO_3	**L10**	62	17
20	$PdCl_2$	Ag_2CO_3	**L11**	85	48
21	$PdCl_2$	Ag_2CO_3	**L12**	87	69
22	$PdCl_2$	Ag_2CO_3	**L13**	52	81
23	$PdCl_2$	Ag_2CO_3	**L14**	65	82
24[d]	$PdCl_2$	Ag_2CO_3	**L14**	79	94
25[e]	$PdCl_2$	Ag_2CO_3	**L14**	76	60

[a] **1a** (0.1 mmol), **2a** (0.2 mmol), Pd-catalyst (10 mol %), ligand (20 mol %), additive (0.1 mmol) in solvent (1 mL) at 40 °C for 24 h, **3aa**/**3aa′** > 95/5. [b] Isolated yields. [c] Determined by HPLC analysis with a chiral column. [d] Reaction was performed at 10 °C for 4 days. [e] Reaction was conducted with 10 mol % of Ag_2CO_3. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

With the optimized reaction conditions in hand (Table 1, entry 24), the substrate scope of alkenes **2** was first explored (Scheme 2). Gratifyingly, the reaction showed excellent regioselectivity to produce the *E*-configuration linear product **3** rather than the branched product **3′** in almost all cases (**3**/**3′** > 95/5). In addition to acrylates, both the electron-rich and electron-deficient styrenyl derivatives can undergo cyclizative cross-coupling to provide the desired dihydrobenzofurans **3ac**–**at** in good yields with high enantioselectivities (90%–97% *ee*). Notably, the inclusion of an ortho-substituent did not hinder the reaction (**3aq**). The reaction was rather general and distinguished by an exquisite chemoselectivity profile, as methoxyl (**3ae**, **3ap**, and **3as**), fluoro (**3ag**, **3ar**, and **3at**), nitro (**3ah**), trifluoromethyl (**3ai**), trifluoromethoxyl (**3am**), ester (**3al**), or chloro (**3aq**) could all be perfectly accommodated. Particularly interesting was the observation that the presence of bromo atom on the aromatic ring did not interfere, affording **3ak** and **3ao** in good yields without traces of the further competing Heck coupling product being observed, thus providing opportunities for further derivatization by cross-couplings.

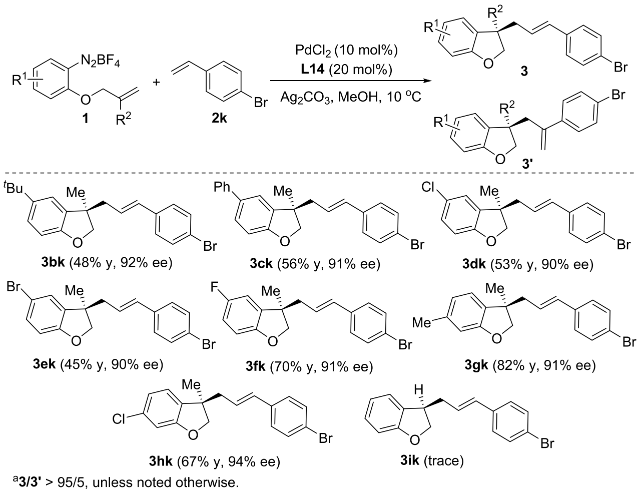
The substrate scope of arenediazonium salts **1** was examined next (Scheme 3). Dihydrobenzofurans **3bk**–**fk** were obtained in good yields and high enantioselectivities (90%–92% *ee*) regardless of whether the para-substitutions of arenediazonium salts are electron-donating or electron-withdrawing groups. The meta-substituted arenediazonium salts all posed no

Scheme 2. Substrate Scope of Alkenes 2[a]



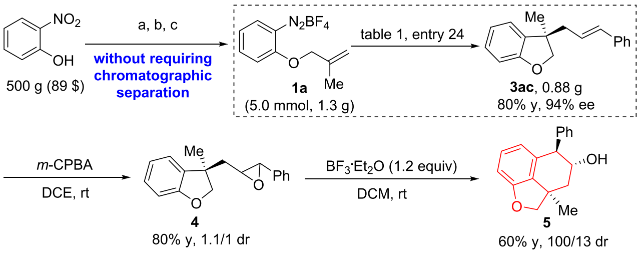
[a] $3/3' > 95/5$, unless noted otherwise. [b] 5 equiv of **2t** were used; **3at**/**3at′** = 92/8.

Scheme 3. Substrate Scope of Arenediazonium Salts 1[a]



[a] $3/3' > 95/5$, unless noted otherwise.

Scheme 4. Gram-Scale Reaction and Synthetic Applications



[a] 3-Chloro-2-methylprop-1-ene (1.5 equiv), K_2CO_3 (3 equiv), acetone, 65 °C. [b] Zn^0, MeOH/NH_4Cl. [c] HBF_4, $NaNO_2$ (2.5 equiv), H_2O, 0 °C, 68% (three steps). *m*-CPBA = *meta*-chloroperbenzoic acid.

problems (**3gk–hk**). However, the reaction of arenediazonium salt with a monosubstituted olefin was unsuccessful (**3ik**).

Given the wide structural diversity of chiral fused tricyclic dihydrobenzofurans in target compounds as illustrated in Figure 1, a further synthetic application of this catalytic double Heck reaction was proven by efficient synthesis of fused tricyclic dihydrobenzofuran **5** (Scheme 4). The arenediazonium salt **1a** was synthesized from inexpensive and commercially available 2-nitrophenol in three steps without the need for column chromatographic separation. The preparative utility of this key double Heck reaction was evaluated using 1.3 g of substrate **1a** to afford the desired product **3ac** in 80% yield with 94% *ee* value. The double bond was then epoxidized in the presence of *m*-CPBA to afford the corresponding epoxide **4** in 80% yield (1.1/1 *dr*). Further investigations with other Brønsted or Lewis acids found that $BF_3{\cdot}Et_2O$ was the best to furnish product **5** with high diastereoselectivity (100/13).[15]

In summary, we have demonstrated a facile and efficient protocol for the construction of functionalized dihydrobenzofurans through the Pd-catalyzed double Heck reaction of arenediazonium salts with simple alkenes. This reaction features mild reaction conditions, simple operation, and excellent functional group tolerance and exhibits exquisite regioselectivity (>95/5) and enantioselectivity (90%−99% ee). In addition, this reaction has been applied to efficient synthesis of athe enantiopure tricyclic dihydrobenzofuran scaffold from commercially available and inexpensive 2-nitrophenol.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03517.

Experimental procedures and spectra data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Gomez, F.; Quijano, L.; Calderon, J. S.; Rodriquez, C.; Rios, T. Prenylflavans from Tephrosia watsoniana. *Phytochemistry* **1985**, *24*, 1057−1059. (b) Tamaki, M.; Sadhu, S. K.; Ohtsuki, T.; Toume, K.; Koyano, T.; Kowithayakorn, T.; Hayashi, M.; Komiyama, K.; Ishibashi, M. Parviflorene J, a Cytotoxic Sesquiterpene Dimer with a New Rearranged Skeleton from Curcuma parviflora. *Heterocycles* **2007**, *72*, 649−654. (c) Yang, J.-H.; Du, X.; He, F.; Zhang, H.-B.; Li, X.-N.; Su, J.; Li, Y.; Pu, J.-X.; Sun, H.-D. Bioactive Abietane and ent-Kaurane Diterpenoids from Isodon tenuifolius. *J. Nat. Prod.* **2013**, *76*, 256−264.

(2) For reviews on the total synthesis of morphine and its derivatives, see: (a) Chida, N. Recent Advances in the Synthesis of Morphine and Related Alkaloids. *Top. Curr. Chem.* **2010**, *299*, 1−28. (b) Rinner, U.; Hudlicky, T. Synthesis of Morphine Alkaloids and Derivatives. *Top. Curr. Chem.* **2011**, *309*, 33−66. (c) Li, Q.; Zhang, H. Research Progress on the Synthesis of Morphine Alkaloids. *Youji Huaxue* **2017**, *37*, 1629−1652. For references on total synthesis of morphine and its derivatives by intramolecular Heck reaction, see: (d) Hong, C. Y.; Kado, N.; Overman, L. E. Asymmetric Synthesis of Either Enantiomer of Opium Alkaloids and Morphinans. Total Synthesis of (−)- and (+)-Dihydrocodeinone and (−)- and (+)-Morphine. *J. Am. Chem. Soc.* **1993**, *115*, 11028−11029. (e) Liou, J. P.; Cheng, C. Y. Total synthesis of (±)-desoxycodeine-D: a novel route to the morphine skeleton. *Tetrahedron Lett.* **2000**, *41*, 915−918. (f) Trost, B. M.; Tang, W. P. Enantioselective Synthesis of (−)-Codeine and (−)-Morphine. *J. Am. Chem. Soc.* **2002**, *124*, 14542−14543. (g) Trost, B. M.; Tang, W. P.; Toste, F. D. Divergent Enantioselective Synthesis of (−)-Galanthamine and (−)-Morphine. *J. Am. Chem. Soc.* **2005**, *127*, 14785−14803. (h) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. Total Synthesis of (±)-Morphine. *Org. Lett.* **2006**, *8*, 5311−5313. (i) Omori, A. T.; Finn, K. J.; Leisch, H.; Carroll, R. J.; Hudlicky, T. Chemoenzymatic Total Synthesis of (+)-Codeine by Sequential Intramolecular Heck Cyclizations via C-B-D Ring Construction. *Synlett* **2007**, *2007*, 2859−2862. (j) Varin, M.; Barre, E.; Iorga, B.; Guillou, C. Diastereoselective Total Synthesis of (±)-Codeine. *Chem. - Eur. J.* **2008**, *14*, 6606−6608.

(3) For reviews on asymmetric alkene dicarbofunctionalization reactions, see: (a) Ping, Y.; Li, Y.; Zhu, J.; Kong, W. Construction of Quaternary Stereocenters by Palladium-Catalyzed Carbopalladation-Initiated Cascade Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 1562−1573. (b) DeLuca, R. J.; Stokes, B. J.; Sigman, M. S. The Strategic Generation and Interception of Palladium-Hydrides for Use in Alkene Functionalization Reactions. *Pure Appl. Chem.* **2014**, *86*, 395−408. (c) Giri, R.; KC, S. Strategies toward Dicarbofunctionalization of Unactivated Olefins by Combined Heck Carbometalation and Cross-Coupling. *J. Org. Chem.* **2018**, *83*, 3013−3022. (d) Dhungana, R. K.; KC, S.; Basnet, P.; Giri, R. Transition Metal-Catalyzed Dicarbofunctionalization of Unactivated Olefins. *Chem. Rec.* **2018**, *18*, 1314−1340. For selected examples, see: (e) Cong, H.; Fu, G. C. Catalytic Enantioselective Cyclization/Cross-Coupling with Alkyl Electrophiles. *J. Am. Chem. Soc.* **2014**, *136*, 3788−3791. (f) Stokes, J. B.; Liao, L.; de Andrade, A. M.; Wang, Q.; Sigman, M. S. A Palladium-Catalyzed Three-Component-Coupling Strategy for the Differential Vicinal Diarylation of Terminal 1,3-Dienes. *Org. Lett.* **2014**, *16*, 4666−4669. (g) Shen, C.; Liu, R.-R.; Fan, R.-J.; Li, Y.-L.; Xu, T.-F.; Gao, J.-R.; Jia, Y.-X. Enantioselective Arylative Dearomatization of Indoles via Pd-Catalyzed Intramolecular Reductive Heck Reactions. *J. Am. Chem. Soc.* **2015**, *137*, 4936−4939. (h) Yue, G.; Lei, K.; Hirao, H.; Zhou, J. S. Palladium-Catalyzed Asymmetric Reductive Heck Reaction of Aryl Halides. *Angew. Chem., Int. Ed.* **2015**, *54*, 6531−6535. (i) You, W.; Brown, M. K. Catalytic Enantioselective Diarylation of Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 14578−14581. (j) Kong, W.; Wang, Q.; Zhu, J. Palladium-Catalyzed Enantioselective Domino Heck/Intermolecular C-H Bond Functionalization: Development and Application to the Synthesis of (+)-Esermethole. *J. Am. Chem. Soc.* **2015**, *137*, 16028−16030. (k) Kong, W.; Wang, Q.; Zhu, J. Water as a Hydride Source in Palladium-Catalyzed Enantioselective Reductive Heck Reactions. *Angew. Chem., Int. Ed.* **2017**, *56*, 3987−3991. (l) Liu, R.; Wang, Y.; Li, Y.; Huang, B.; Liang, R.; Jia, Y.-X. Enantioselective Dearomative Difunctionalization of Indoles by Palladium-Catalyzed Heck/Sonogashira Sequence. *Angew. Chem., Int. Ed.* **2017**, *56*, 7475−7478. (m) Zhang, Z.; Xu, B.; Qian, Y.; Wu, L.; Wu, Y.; Zhou, L.; Liu, Y.; Zhang, J. Palladium-Catalyzed Enantioselective Reductive Heck Reactions: Convenient Access to 3,3-Disubstituted 2,3-Dihydrobenzofuran. *Angew. Chem., Int. Ed.* **2018**, *57*, 10373−10377. (n) Zhang, Z.; Xu, B.; Wu, L.; Zhou, L.; Ji, D.; Liu, Y.; Li, Z.; Zhang, J. Palladium/XuPhos-Catalyzed Enantioselective Carboiodination of Olefin-Tethered Aryl Iodides. *J. Am. Chem. Soc.* **2019**, *141*, 8110−8115. (o) Shen, C.; Zeidan, N.; Wu, Q.; Breuers, C. B. J.; Liu, R.; Jia, Y.-X.; Lautens, M. Pd-catalyzed dearomative arylborylation of indoles. *Chem. Sci.* **2019**, *10*, 3118−3122.

(4) (a) Wang, K.; Ding, Z.; Zhou, Z.; Kong, W. Ni-Catalyzed Enantioselective Reductive Diarylation of Activated Alkenes by Domino Cyclization/Cross-Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 12364−12368. (b) Li, Y.; Ding, Z.; Lei, A.; Kong, W. Ni-Catalyzed enantioselective reductive aryl-alkenylation of alkenes: application to the synthesis of (+)-physovenine and (+)-physostigmine. *Org. Chem. Front.* **2019**, *6*, 3305−3309. (c) Tian, Z.; Qiao, J.; Xu, G.; Pang, X.; Qi, L.; Ma, W.; Zhao, Z.; Duan, J.; Du, Y.; Su, P.; Liu, X.; Shu, X. Highly Enantioselective Cross-Electrophile Aryl-Alkenylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 7637−7643.

(5) (a) Seashore-Ludlow, B.; Somfai, P. Domino Carbopalladation-Cross-Coupling for the Synthesis of 3,3-Disubstituted Oxindoles. *Org. Lett.* **2012**, *14*, 3858−3861. (b) Zhou, M.-B.; Huang, X.-C.; Liu, Y.-Y.; Song, R.-J.; Li, J.-H. Alkylation of Terminal Alkynes with Transient σ-Alkylpalladium(II) Complexes: A Carboalkynylation Route to Alkyl-Substituted Alkynes. *Chem. - Eur. J.* **2014**, *20*, 1843−1846. (c) Packer, G.; Lepre, K.; Kankanala, J.; Sridharan, V. Bimetallic (Cu/Pd) catalytic cascade reactions to 3,3-disubstituted oxindole analogues. *RSC Adv.* **2014**, *4*, 3457−3460. (d) Vachhani, D. D.; Butani, H. H.; Sharma, N.; Bhoya, U. C.; Shah, A. K.; Van der Eycken, E. V. Domino Heck/borylation sequence towards indolinone-3-methyl boronic esters: trapping of the σ-alkylpalladium intermediate with boron. *Chem. Commun.* **2015**, *51*, 14862−14865. (e) Liu, R.-R.; Xu, T.-F.; Wang, Y.-G.; Xiang, B.; Gao, J.-R.; Jia, Y.-X. Palladium-catalyzed dearomative arylalkynylation of indoles. *Chem. Commun.* **2016**, *52*, 13664−13667. (f) You, W.; Brown, M. K. Diarylation of Alkenes by a Cu-Catalyzed Migratory Insertion/Cross-Coupling Cascade. *J. Am. Chem. Soc.* **2014**, *136*, 14730−14733. (g) Wu, L.; Wang, F.; Wan, X.; Wang, D.; Chen, P.; Liu, G. Asymmetric Cu-Catalyzed Intermolecular Trifluoromethylarylation of Styrenes: Enantioselective Arylation of Benzylic Radicals. *J. Am. Chem. Soc.* **2017**, *139*, 2904−2907. (h) Gao, P.; Chen, L.; Brown, M. K. Nickel-Catalyzed Stereoselective Diarylation of Alkenylarenes. *J. Am. Chem. Soc.* **2018**, *140*, 10653−10657. (i) Shrestha, B.; Basnet, P.; Dhungana, R. K.; KC, S.; Thapa, S.; Sears, J. M.; Giri, R. Ni-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Olefins by Intercepting Heck Intermediates as Imine-Stabilized Transient Metallacycles. *J. Am. Chem. Soc.* **2017**, *139*, 10653−10656. (j) Li, W.; Boon, J. K.; Zhao, Y. Nickel-catalyzed difunctionalization of allyl moieties using organoboronic acids and halides with divergent regioselectivities. *Chem. Sci.* **2018**, *9*, 600−607. (k) Derosa, J.; Tran, V. T.; Boulous, M. N.; Chen, J. S.; Engle, K. M. Nickel-Catalyzed β,γ-Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Conjunctive Cross-Coupling. *J. Am. Chem. Soc.* **2017**, *139*, 10657−10660. (l) Liu, Z.; Zeng, T.; Yang, K. S.; Engle, K. M. β,γ-Vicinal Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Directed Nucleopalladation. *J. Am. Chem. Soc.* **2016**, *138*, 15122−15125.

(6) (a) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. Palladium Catalysed Tandem Cyclisation−Anion Capture Processes. Part 4: Organotin-(IV) Transfer Agents. *Tetrahedron* **2000**, *56*, 7525−7539. (b) Li, Y.; Wang, K.; Ping, Y.; Wang, Y.; Kong, W. Nickel-Catalyzed Domino Heck Cyclization/Suzuki Coupling for the Synthesis of 3,3-Disubstituted Oxindoles. *Org. Lett.* **2018**, *20*, 921−924. (c) Piou, T.; Neuville, L.; Zhu, J. Spirocyclization by Palladium-Catalyzed Domino Heck-Direct C-H Arylation Reactions: Synthesis of

Spirodihydroquinolin-2-ones. *Org. Lett.* **2012**, *14*, 3760−3763. (d) Liu, X.; Ma, X.; Huang, Y.; Gu, Z. Pd-Catalyzed Heck-Type Cascade Reactions with N-Tosyl Hydrazones: An Efficient Way to Alkenes via in Situ Generated Alkylpalladium. *Org. Lett.* **2013**, *15*, 4814−4817. (e) Gao, Y.; Wu, W.; Jiang, H.; Yang, X.; Liu, W.; Li, C.-J. Palladium-Catalyzed Tandem Oxidative Arylation/Olefination of Aromatic Tethered Alkenes/Alkynes. *Chem. - Eur. J.* **2017**, *23*, 793−797. (f) Schempp, T. T.; Daniels, B. E.; Staben, S. T.; Stivala, C. E. A General Strategy for the Construction of Functionalized Azaindolines via Domino Palladium-Catalyzed Heck Cyclization/Suzuki Coupling. *Org. Lett.* **2017**, *19*, 3616−3619 and references therein.

(7) Zhang, Z.; Xu, B.; Wu, L.; Wu, Y.; Qian, Y.; Zhou, L.; Liu, Y.; Zhang, J. Enantioselective Dicarbofunctionalization of Unactivated Alkenes by Palladium-Catalyzed Tandem Heck/Suzuki Coupling Reaction. *Angew. Chem., Int. Ed.* **2019**, *58*, 14653−14659.

(8) Szlosek-Pinaud, M.; Diaz, P.; Martinez, J.; Lamaty, F. Efficient synthetic approach to heterocycles possessing the 3,3-disubstituted-2,3-dihydrobenzofuran skeleton via diverse palladium-catalyzed tandem reactions. *Tetrahedron* **2007**, *63*, 3340−3349.

(9) (a) Correia, C. R. D.; Oliveira, C. C.; Salles, A. G., Jr.; Santos, E. A. F. The first examples of the enantioselective Heck−Matsuda reaction: arylation of unactivated cyclic olefins using chiral bisoxazolines. *Tetrahedron Lett.* **2012**, *53*, 3325. (b) Oliveira, C. C.; Angnes, R. A.; Correia, C. R. D. Intermolecular Enantioselective Heck−Matsuda Arylations of Acyclic Olefins: Application to the Synthesis of β-Aryl-γ-lactones and β-Aryl Aldehydes. *J. Org. Chem.* **2013**, *78*, 4373−4385. (c) Oliveira, C. C.; Pfaltz, A.; Correia, C. R. D. Quaternary Stereogenic Centers through Enantioselective Heck Arylation of Acyclic Olefins with Aryldiazonium Salts: Application in a Concise Synthesis of (*R*)-Verapamil. *Angew. Chem., Int. Ed.* **2015**, *54*, 14036−14039. (d) de Azambuja, F. de; Carmona, R. C.; Chorro, T. H. D.; Heerdt, G.; Correia, C. R. D. Noncovalent Substrate-Directed Enantioselective Heck Reactions: Synthesis of S-and P-Stereogenic Heterocycles. *Chem. - Eur. J.* **2016**, *22*, 11205−11209. (e) Khan, I. U.; Kattela, S.; Hassan, A.; Correia, C. R. D. Enantioselective total synthesis of the highly selective sphingosine-1-receptor VPC01091 by the Heck desymmetrization of a non-activated cyclopentene-fused spiro-pyrrolidinone. *Org. Biomol. Chem.* **2016**, *14*, 9476−9480. (f) Silva, A. R.; Polo, E. C.; Martins, N. C.; Correia, C. R. D. Enantioselective Oxy-Heck-Matsuda Arylations: Expeditious Synthesis of Dihydrobenzofuran Systems and Total Synthesis of the Neolignan (−)-Conocarpan. *Adv. Synth. Catal.* **2018**, *360*, 346−365. (g) Carmona, R. C.; Köster, O. D.; Correia, C. R. D. Chiral N,N Ligands Enabling Palladium-Catalyzed Enantioselective Intramolecular Heck-Matsuda Carbonylation Reactions by Sequential Migratory and CO Insertions. *Angew. Chem., Int. Ed.* **2018**, *57*, 12067−12070.

(10) (a) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. Enantioselective Heck Arylations of Acyclic Alkenyl Alcohols Using a Redox-Relay Strategy. *Science* **2012**, *338*, 1455−1458. (b) Stokes, J. B.; Liao, L.; de Andrade, A. M.; Wang, Q.; Sigman, M. S. A Palladium-Catalyzed Three-Component-Coupling Strategy for the Differential Vicinal Diarylation of Terminal 1,3-Dienes. *Org. Lett.* **2014**, *16*, 4666−4669. (c) Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P.-O.; Wu, Y.-D.; Sigman, M. S.; Wiest, O. Mechanism, Reactivity, and Selectivity in Palladium-Catalyzed Redox-Relay Heck Arylations of Alkenyl Alcohols. *J. Am. Chem. Soc.* **2014**, *136*, 1960−1967. (d) Yamamoto, E.; Hilton, M. J.; Orlandi, M.; Saini, V.; Toste, F. D.; Sigman, M. S. Development and Analysis of a Pd(0)-Catalyzed Enantioselective 1,1-Diarylation of Acrylates Enabled by Chiral Anion Phase Transfer. *J. Am. Chem. Soc.* **2016**, *138*, 15877−15880. (e) Nelson, H. M.; Williams, B. D.; Miró, J.; Toste, F. D. Enantioselective 1,1-Arylborylation of Alkenes: Merging Chiral Anion Phase Transfer with Pd Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 3213−3216. (f) Orlandi, M.; Hilton, M. J.; Yamamoto, E.; Toste, F. D.; Sigman, M. S. Mechanistic Investigations of the Pd(0)-Catalyzed Enantioselective 1,1-Diarylation of Benzyl Acrylates. *J. Am. Chem. Soc.* **2017**, *139*, 12688−12695. (g) Avila, C. M.; Patel, J. S.; Reddi, Y.; Saito, M.; Nelson, H. M.; Shunatona, H. P.; Sigman, M. S.; Sunoj, R. B.; Toste, F. D. Enantioselective Heck-Matsuda Arylations through Chiral Anion Phase-Transfer of Aryl Diazonium Salts. *Angew. Chem., Int. Ed.* **2017**, *56*, 5806−5811. (h) Reddi, Y.; Tsai, C.; Avila, C. M.; Toste, F. D.; Sunoj, R. B. Harnessing Noncovalent Interactions in Dual-Catalytic Enantioselective Heck-Matsuda Arylation. *J. Am. Chem. Soc.* **2019**, *141*, 998−1009.

(11) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. Diazonium Salts as Substrates in Palladium-Catalyzed Cross-Coupling Reactions. *Chem. Rev.* **2006**, *106*, 4622−4643.

(12) (a) Angnes, R. A.; Oliveira, J. M.; Oliveira, C. C.; Martins, N. C.; Correia, C. R. D. Stereoselective Synthesis of Aryl Cyclopentene Scaffolds by Heck-Matsuda Desymmetrization of 3-Cyclopentenol. *Chem. - Eur. J.* **2014**, *20*, 13117−13121. (b) Kattela, S.; Heerdt, G.; Correia, C. R. D. Non-Covalent Carbonyl-Directed Heck−Matsuda Desymmetrizations: Synthesis of Cyclopentene-Fused Spirooxindoles, Spirolactones, and Spirolactams. *Adv. Synth. Catal.* **2017**, *359*, 260−267. (c) de Oliveira, J. M.; Angnes, R. A.; Khan, I. U.; Polo, E. C.; Heerdt, G.; Servilha, B. M.; da Silva, V. H. M.; Braga, A. A. C.; Correia, C. R. D. Enantioselective, Noncovalent, Substrate-Directable Heck−Matsuda and Oxidative Heck Arylations of Unactivated Five-Membered Carbocyclic Olefins. *Chem. - Eur. J.* **2018**, *24*, 11738−11747.

(13) Although ZnCO$_3$ is widely used in asymmetric Heck−Matsuda reactions, it is not commercially available.

(14) Gao, Y.; Xiong, W.; Chen, H.; Wu, W.; Peng, J.; Gao, Y.; Jiang, H. Pd-Catalyzed Highly Regio- and Stereoselective Formation of C-C Double Bonds: An Efficient Method for the Synthesis of Benzofuran-, Dihydrobenzofuran-, and Indoline-Containing Alkenes. *J. Org. Chem.* **2015**, *80*, 7456−7467.

(15) Mühlthau, F.; Schuster, O.; Bach, T. High Facial Diastereoselectivity in Intra- and Intermolecular Reactions of Chiral Benzylic Cations. *J. Am. Chem. Soc.* **2005**, *127*, 9348−9349.