JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Palladium-Catalyzed Regioselective C–H Iodination of Unactivated Alkenes

Benedikt Schreib, and Erick M Carreira

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 14 May 2019

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Palladium-Catalyzed Regioselective C–H Iodination of Unactivated Alkenes

Benedikt S. Schreib, Erick M. Carreira*

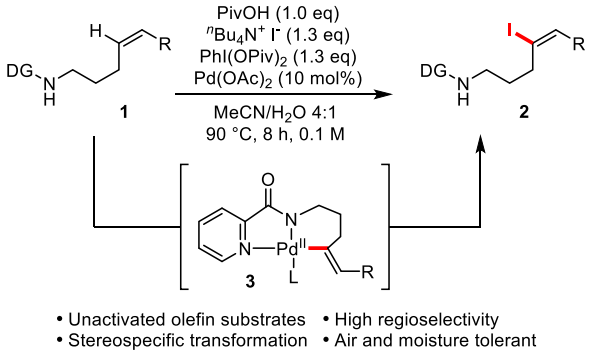
ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland

Supporting Information Placeholder

ABSTRACT: A palladium-catalyzed C–H iodination of unactivated alkenes is reported. A picolinamide directing group enables the regioselective functionalization of a wide array of olefins to furnish iodination products as single stereoisomers. Mechanistic investigations suggest the reversible formation of a six-membered alkenyl palladacycle intermediate through a turnover-limiting C–H activation.

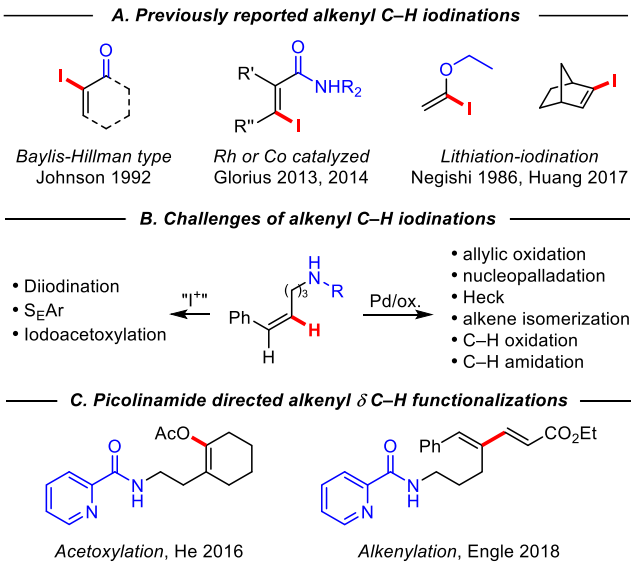
The selective transformation of C–H bonds has been a long-standing goal in organic synthesis.[1] The functionalization of unbiased and unactivated hydrocarbons with high positional selectivity remains a challenging problem, and possible overfunctionalization often necessitates use of substrates in excess, even as solvent.[2a] Coordinating groups which direct a metal to the desired site of functionalization have emerged as a powerful tool to overcome these issues.[2] While palladium-catalyzed, direct activation of aromatic and aliphatic C–H bonds has been at the forefront of this development,[3] reports of olefinic C–H functionalization have not enjoyed the same level of development.[4,5] Herein, we report a palladium-catalyzed, picolinamide directed alkenyl C–H functionalization to access the corresponding alkenyl iodides with excellent regio- and stereoselectivity (Scheme 1).

Scheme 1. Palladium-Catalyzed Alkenyl C–H Iodination



Alkenyl iodides constitute a valuable class of building blocks that are routinely used in organic synthesis.[6,7] Commonly employed methods for the synthesis of alkenyl iodides include Barton or Takai olefination of the corresponding carbonyl compounds, metallation-iodination sequence of acetylenes, or the Hunsdiecker reaction on α,β-unsaturated carboxylic acids.[8,9] However, the successful implementation of these established methods can be hampered by poor regio- and stereoselectivity, and it often necessitates the use appropriately functionalized starting materials. Arguably the simplest class of precursors for alkenyl iodides would be the corresponding olefin. However, only few examples for the direct C–H iodination of olefins have been reported in the literature (Scheme 2A).[10-13] Synthetically useful methods of this type are limited to the functionalization of Michael acceptors, and the most commonly employed approach is the nucleophile-catalyzed iodination of cyclic enones. More recently, Glorius and co-workers have reported the rhodium- or cobalt-catalyzed alkenyl C–H iodination of acrylamides.[11] However, general methods for the direct and regioselective C–H iodination of unactivated olefins remain elusive, yet highly desirable.

Scheme 2. Prior Art and Challenges



Palladium catalysis offers a powerful tool for the halogenation of hydrocarbons, and it has been explored for the iodination of arenes and aliphatic hydrocarbons.[14] Yet, a palladium-catalyzed C–H iodination of olefins has not been documented. The use of palladium for the direct iodination of alkenes is complicated by competing reactivity, such as palladium-catalyzed allylic oxidation,[15] Wacker-type nucleopalladation,[16] or Heck-type reactions[17] (Scheme 2B). Additionally, significant undesired background reactivity, such as olefin diiodination or competing electrophilic aromatic iodination can take place under the oxidizing conditions typically employed for iodination reactions. To address these reactivity challenges, we envisioned a chelation assisted cyclopalladation strategy, which would enable the direct selective iodination of unactivated olefins. We surmised that picolinamides may function as

a suitable directing group, owing to their ability to facilitate the formation of 6-membered alkenyl-palladacycles **3** through a concerted metallation-deprotonation (CMD) pathway,[18] as demonstrated by He[5h] and Engle[4] (Scheme 2C). Subsequent reaction with an electrophilic iodine source is envisioned to afford alkenyl iodide **2** with retention of olefin configuration, either through a redox-neutral electrophilic cleavage pathway or a stepwise oxidative addition/reductive elimination mechanism.[19]

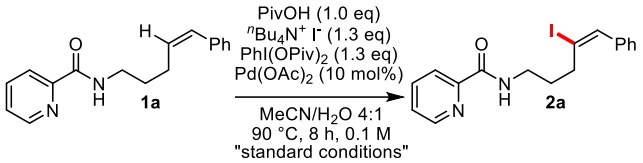
We set out to identify optimal reaction conditions using (*Z*)-5-phenylpent-4-en-1-amine derived olefin **1a** as model substrate, which bears the bidentate picolinamide directing group. Originally introduced by Daugulis, picolinamides are conveniently prepared from inexpensive picolinic acid, and can be readily cleaved through hydrolytic or reductive procedures.[20,21] After evaluating a wide array of reaction parameters, we found that a system comprising of palladium acetate (10 mol%), pivalic acid (1.0 equiv), and the combination of tetrabutylammonium iodide (1.3 equiv) and di-(pivaloyloxy)iodobenzene (1.3 equiv) as oxidative iodinating agent in aqueous acetonitrile afforded the desired alkenyl iodide **2a** in 64% isolated yield (Table 1, entry 1). The olefin configuration was retained, as evidenced by NOESY experiments. The major side products included the formation of a regioisomeric mixture of the corresponding enol pivalates, which may form either through oxidation of palladacycle **3** or Wacker-type pathways. The combination of an iodide salt and an oxidizing agent proved to be more efficient than common electrophilic iodinating reagents such as *N*-iodosuccinimide (entries 2 and 3). Initial attempts to achieve bromination or chlorination under similar conditions were unsuccessful.

A screening of picolinamide derivatives showed that substitution adjacent to the aromatic nitrogen is not tolerated (entry 4). Of note, quinoline containing directing group **B** showed modest selectivity for the undesired C–H oxidation products (ca 60% NMR yield). Only traces of the iodination product were formed when pyridine N-oxide-containing directing group **E** – a potential side-product under the oxidizing reaction conditions – was employed (entry 4). Using pharmaceutically relevant pyrazine **F** and β-carboline **G**[5j] as directing groups furnished the corresponding alkenyl iodides in 56% and 60% isolated yields, respectively (entries 5, 6). When the corresponding 4-pentenoic acid derived substrate bearing well-established 8-aminoquinoline directing group **H**[20] was subjected to our standard conditions, a complex mixture of products was obtained (entry 7). Employing Shi's PIP directing group **I**[22] allowed for isolation of the desired vinyl iodide in 26% yield (entry 8), demonstrating that the iodination of 4-pentenoic acids is possible.

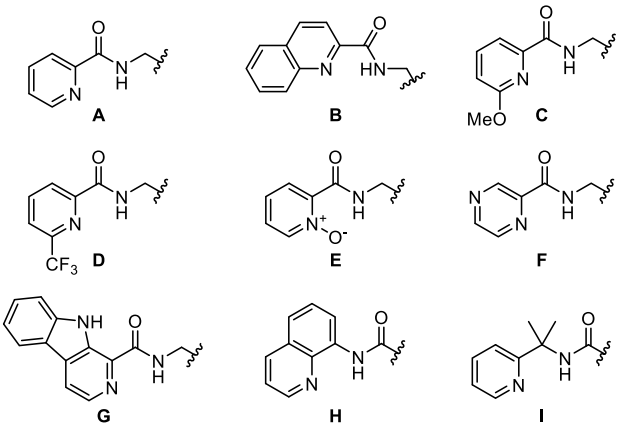
As a control experiment, in the absence of palladium catalyst alkenyl iodide **2a** was not observed (entry 9). The reactions described in Table 1 are conducted in aqueous acetonitrile as solvent under ambient atmosphere, and execution of the reaction under inert atmosphere (dry N_2) has no impact on the yield. The use of anhydrous acetonitrile decreases slightly the yield of **2a** (70 vs 60%) and leads to an increased amount of enol pivalate formation, as determined by NMR (entry 10).

With optimal conditions in hand, we explored the scope of the directed C–H iodination reaction (Scheme 3). Changing the phenyl substituent for a larger 2-naphthyl had a negligible effect on the reaction outcome and **2b** was afforded in 63% yield. Styrenes carrying electron-neutral or electron-withdrawing substituents in the *meta* or *para* positon were well tolerated and furnished the desired alkenyl iodide in 57 to 72% yield (**2d**–**2h**). Notably, substrates containing an oxidation sensitive benzaldehyde (**1d**) or an aryl bromide (**1h**) undergo iodination successfully in 66 and 72% yield, respectively. Increasing steric bulk at the *ortho*-position of the arene proved beneficial for the reaction, affording the desired products in 75 to 85% yield (**2i**–**2l**). The electronic nature of the arene only has a minor influence, with electron rich 2,6-dimethylstyrene **1j** and electron deficient 2,6-dichlorostyrene **1k** undergoing iodination with comparable yields (83 and 85%).

Table 1. Selected Optimization Results[a]



Entry	Variation from "standard conditions"	Yield[b]
1	None	70 (64[c])
2	NIS, MeCN, 70 °C	<10
3	Oxone, MeCN, 70 °C	63[d]
4	Directing group **B**-**E**	<15[e]
5	Directing group **F**	56[c,e]
6	Directing group **G**	60[c,e]
7	Directing group **H**	Complex mixture
8	Directing group **I**	26[c,e]
9	No Pd	0
10	No water, 70 °C	60

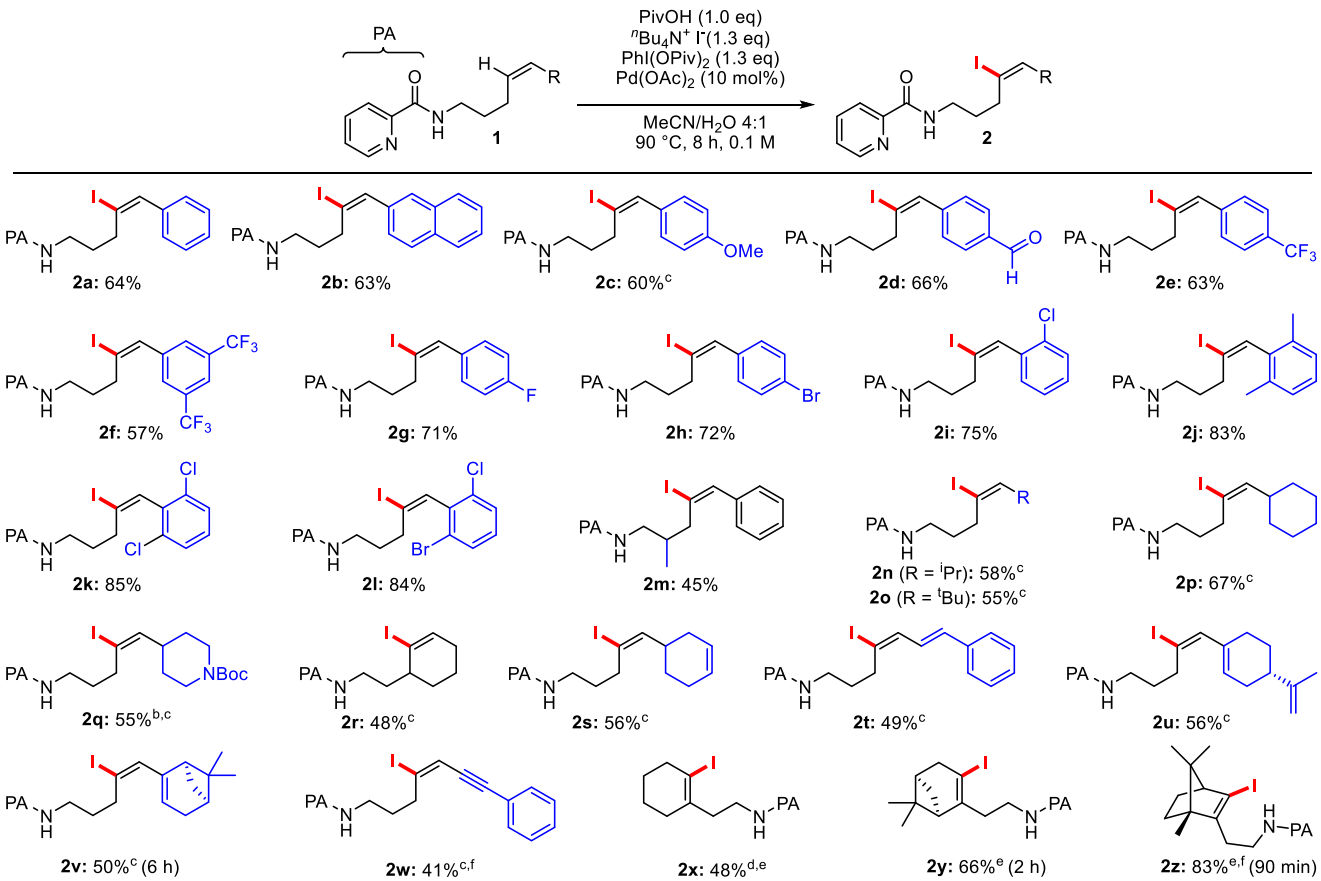


[a] Reactions conducted on 0.2 mmol scale. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c] Isolated yield after purification. [d] 15 mol% $Pd(OAc)_2$. [e] 0.1 mmol scale.

It is worth noting that the *trans*-isomer of **1j** did not show any reactivity under these conditions, with the starting material being recovered. Introduction of a branching substituent at the tether was unfavourable to the reaction outcome and methyl substituted product **2m** was isolated in 45% yield. The robustness and scalability of this protocol was demonstrated through the iodination of **1i** on a 1 mmol scale, which afforded the desired product **2i** in 75% yield, even when the catalyst loading was lowered to 5 mol%.

During the investigations on the substrate scope of the directed C–H iodination, cyclohexyl substituted olefin **1p** was found to oxidize to a mixture of enol pivalate and ketone side-products. Thus, re-evaluation of the reaction conditions revealed inexpensive Oxone to be an efficient oxidant in anhydrous acetonitrile, providing **2p** in 67% isolated yield. Under these conditions the remaining material was identified as starting material and enol-pivalate side-products. A variety of aliphatic disubstituted olefins

Scheme 3. Scope of the Alkenyl C–H Iodination[a]



[a] Reactions were conducted on 0.3 mmol scale unless indicated otherwise. Yields refer to the isolated product after purification. [b] Yield determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c] Reaction was conducted in anhydrous acetonitrile at 70 °C, using 1.3 equiv of Oxone instead of PhI(OPiv)$_2$ and 15 mol% Pd(OAc)$_2$. [d] 20 mol% Pd(OAc)$_2$. [e] Reaction was conducted in anhydrous acetonitrile at 70 °C. [f] Reaction was conducted on a 0.1 mmol scale.

underwent iodination in moderate yields under these conditions (**2n**–**2q**, 55–67%). The yield of the reaction drops dramatically for unbranched alkyl substituents. Boc-protected amines are tolerated under the acidic reaction conditions and vinyl-piperidine **1q** underwent iodination in 55% yield. Substituted cyclohexene **2q** showcases that selective iodination at the sterically less accessible C–H of the olefin is possible in 48% yield. Switching the oxidant from di-(pivaloyloxy)iodobenzene to Oxone also enabled the iodination of electron rich styrene **1c** in 60% yield, which had decomposed under the previous conditions.

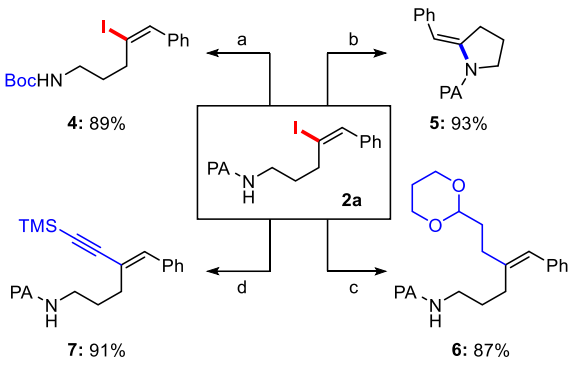
Importantly, all olefins subjected to iodination conditions afforded the alkenyl iodide as a single regioisomer, as determined by ^{1}H-NMR analysis of the crude reaction mixture. To further assess the selectivity imparted by the directing group, we evaluated several substrates bearing additional olefins and alkynes. The C–H iodination reaction allows for a highly regioselective functionalization of polyenes, as demonstrated by non-conjugated diene **2s** and phenylbutadiene derivative **2t**, which were obtained in 56 and 49% yield, respectively. In addition, (*S*)-(–)-perillaldehyde derived triene **2u** (56%) and (1*R*)-(–)-myrtenal derived diene **2v** (50%) were obtained as single regio- and diastereoisomers.

In order to explore substrates bearing a shorter tether (cyclohexenyl)ethylamine derived substrate **1x** was subjected to the iodination conditions. This would require the olefin to be endocyclic instead of exocyclic in the putatively operating palladacycle intermediate **3**. While an aqueous solvent system was found to be detrimental for the reaction outcome, the desired iodocyclohexene **2x** was obtained in 48% yield in anhydrous acetonitrile with di-(pivaloyloxy)iodobenzene as oxidant. This result showcases that trisubstituted olefins are suitable substrates for the reaction. Similar to the styrenes discussed above, an increase in steric bulk around the olefin proves beneficial, as demonstrated by the increased yields for (*R*)-(–)-nopol derived product **2y** (66%) and (1*R*)-(+)-camphor derived product **2z** (83%). No rearrangement of the vinylcyclobutane **1y** and the norbornene skeleton in **1z** were observed during the iodination reaction. This stands in contrast to the classical Barton vinyl iodide synthesis on camphor, where 1-iodocamphene is obtained after a Wagner-Meerwein rearrangement of the proposed iodocarbonium intermediate.[23]

To demonstrate the synthetic versatility of the alkenyl iodides we subjected **2a** to a variety of transformations (Scheme 4). The picolinamide auxiliary can be easily removed through a one pot Boc-activation/hydrolysis sequence, affording Boc-protected amine **4** in 89% yield. Intramolecular Ullman amidation using Buchwald's conditions[24] yields pyrrolidine derivative **5** (93%). Despite the strongly coordinating picolinamide auxiliary, palladium catalyzed alkylation and alkynylation readily furnish 1,3-dioxane **6** and TMS-alkyne **7** in 87 and 91% yield, respectively.

To probe the mechanism of the reaction β-substituted styrene **1k** was treated with pivalic acid (1 equiv) and $Pd(OAc)_2$ (10 mol%) in CD_3CN/D_2O 4:1 at 90 °C. After 6 hours selective

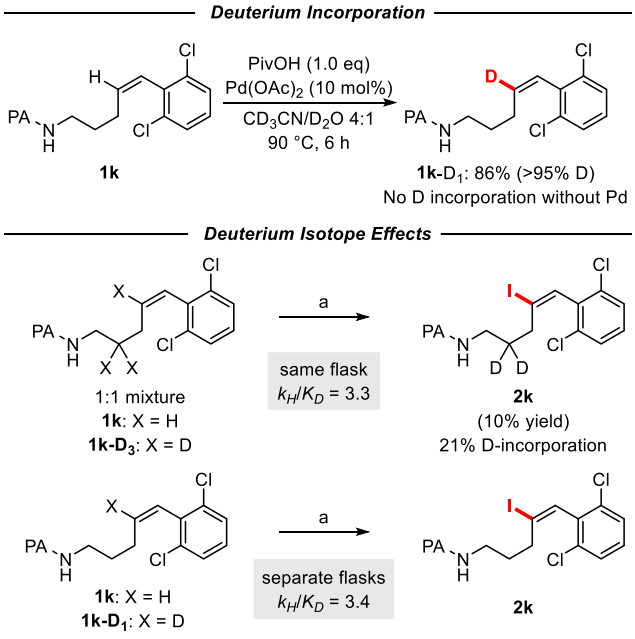
Scheme 4. Derivatization of 2a



Reagents and conditions: (a) Boc_2O (8 equiv), DMAP (1 equiv), MeCN, 50 °C, 24 h, then aq LiOH, 50 °C, 3 h; (b) CuI (20 mol%), 1,2-bis(methylamino)ethane (40 mol%), Cs_2CO_3 (1.5 equiv), THF, 50 °C, 90 min; (c) $Pd(PPh_3)_4$ (10 mol%), (2-(1,3-dioxan-2-yl)ethyl)zinc(II) bromide (3 equiv, 0.5 M in THF), THF, 50 °C, 4 h; (d) $Pd(PPh_3)_4$ (10 mol%), ethynyltrimethylsilane (3 equiv), lithium diisopropylamide (3 equiv), $ZnBr_2$ (3.3 equiv), THF, 50 °C, 2 h.

deuterium incorporation at the β-carbon was observed (>95% D), which is consistent with reversible formation of palladacycle **3** (Scheme 5). Notably, this result demonstrates the synthetically useful, efficient and highly selective β-deuteration of styrenes enabled through this method. Measurement of the initial rate constant for the iodination of **1k** and **1k-D₁** in two parallel reactions, as well as an intermolecular competition experiment, provided a k_H/k_D value of 3.4 and 3.3 respectively, showing that C–H cleavage is the turnover-limiting step of the reaction.[25] The magnitude of the observed kinetic isotope effect is in the expected range for a C–H bond cleavage based on a CMD mechanism.[26]

Scheme 5. Mechanistic Investigations



(a) $Pd(OAc)_2$ (10 mol%), $PhI(OPiv)_2$ (1.3 equiv), $[^nBu_4N^+]I^-$ (1.3 equiv), MeCN, 70 °C; see Supporting Information for detailed experimental procedures.

In summary, we developed a regio- and stereoselective palladium catalyzed C–H iodination of unactivated alkenes tolerating a wide variety of alkyl and aryl substituted olefins bearing various functional groups. The robust and operationally convenient procedure is enabled by a picolinamide auxiliary and mechanistic investigations demonstrate that the reaction proceeds via an alkenyl C–H activation as turnover limiting step. This method complements existing methods for the regio- and stereoselective synthesis of highly functionalized olefins.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization data (PDF).

AUTHOR INFORMATION

Corresponding Author

*erickm.carreira@org.chem.ethz.ch

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

ETH Zürich is gratefully acknowledged for financial support. We thank Dr. M.-O. Ebert, R. Arnold, R. Frankenstein, and S. Burkhardt for NMR measurements. Simon L. Rössler and Dr. David A. Petrone (all ETH Zürich) are thanked for helpful discussions.

REFERENCES

(1) (a) Gutekunst, W. R.; Baran, P. S. C–H Functionalization Logic in Total Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1976; (b) Hartwig, J. F. Evolution of C–H Bond Functionalization from Methane to Methodology. *J. Am. Chem. Soc.* **2016**, *138*, 2; (c) Crabtree, R. H.; Lei, A. Introduction: CH Activation. *Chem. Rev.* **2017**, *117*, 8481.

(2) (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C–H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788; (b) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-Catalyzed C–H Activation: Examples and Concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900; (c) Gandeepan, P.; Ackermann, L. Transient Directing Groups for Transformative C–H Activation by Synergistic Metal Catalysis. *Chem* **2018**, *4*, 199.

(3) (a) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147; (b) He, G.; Wang, B.; Nack, W. A.; Chen, G. Syntheses and Transformations of α-Amino Acids via Palladium-Catalyzed Auxiliary-Directed sp^3 C–H Functionalization. *Acc. Chem. Res.* **2016**, *49*, 635; (c) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C–H Bonds. *Chem. Rev.* **2017**, *117*, 8754.

(4) Liu, M.; Yang, P.; Karunananda, M. K.; Wang, Y.; Liu, P.; Engle, K. M. C(Alkenyl)–H Activation via Six-Membered Palladacycles: Catalytic 1,3-Diene Synthesis. *J. Am. Chem. Soc.* **2018**, *140*, 5805.

(5) For selected examples see: (a) Wen, Z.-K.; Xu, Y.-H.; Loh, T.-P. Palladium-Catalyzed Cross-Coupling of Unactivated Alkenes with Acrylates: Application to the Synthesis of the C13–C21 Fragment of Palmerolide A. *Chem. Eur. J.* **2012**, *18*, 13284; (b) Shang, X.; Liu, Z.-Q. Transition Metal-Catalyzed C_{vinyl}–C_{vinyl} Bond Formation via Double C_{vinyl}–H Bond Activation. *Chem. Soc. Rev.* **2013**, *42*, 3253; (c) Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. Mild and Versatile Nitrate-Promoted C–H Bond Fluorination. *Angew.*

Chem. Int. Ed. **2014**, *53*, 10330; (d) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. Ligand-Promoted Alkylation of C(sp^3)–H and C(sp^2)–H Bonds. *J. Am. Chem. Soc.* **2014**, *136*, 13194; (e) Wang, C.; Zhang, L.; Chen, C.; Han, J.; Yao, Y.; Zhao, Y. Oxalyl Amide Assisted Palladium-Catalyzed Synthesis of Pyrrolidones via Carbonylation of γ-C(sp^3)–H Bonds of Aliphatic Amine Substrates. *Chem. Sci*. **2015**, *6*, 4610; (f) Kong, W.-J.; Liu, Y.-J.; Xu, H.; Chen, Y.-Q.; Dai, H.-X.; Yu, J.-Q. Pd-Catalyzed α-Selective C–H Functionalization of Olefins: En Route to 4-Imino-β-Lactams. *J. Am. Chem. Soc.* **2016**, *138*, 2146; (g) Hu, T.-J.; Zhang, G.; Chen, Y.-H.; Feng, C.-G.; Lin, G.-Q. Borylation of Olefin C–H Bond via Aryl to Vinyl Palladium 1,4-Migration. *J. Am. Chem. Soc.* **2016**, *138*, 2897; (h) Zang, Z.-L.; Zhao, S.; Karnakanti, S.; Liu, C.-L.; Shao, P.-L.; He, Y. Catalytic Multisite-Selective Acetoxylation Reactions at sp^2 vs sp^3 C–H Bonds in Cyclic Olefins. *Org. Lett.* **2016**, *18*, 5014; (i) Liang, Q.-J.; Yang, C.; Meng, F.-F.; Jiang, B.; Xu, Y.-H.; Loh, T.-P. Chelation versus Non-Chelation Control in the Stereoselective Alkenyl sp^2 C−H Bond Functionalization Reaction. *Angew. Chem. Int. Ed.* **2017**, *56*, 5091; (j) Viart, H. M.-F.; Bachmann, A.; Kayitare, W.; Sarpong, R. β-Carboline Amides as Intrinsic Directing Groups for C(sp^2)–H Functionalization. *J. Am. Chem. Soc.* **2017**, *139*, 1325; (k) Parella, R.; Babu, S. A. Pd(II)-Catalyzed, Picolinamide-Assisted, *Z* -Selective γ-Arylation of Allylamines To Construct *Z* -Cinnamylamines. *J. Org. Chem.* **2017**, *82*, 6550; (l) Luo, Y.-C.; Yang, C.; Qiu, S.-Q.; Liang, Q.-J.; Xu, Y.-H.; Loh, T.-P. Palladium(II)-Catalyzed Stereospecific Alkenyl C–H Bond Alkylation of Allylamines with Alkyl Iodides. *ACS Catal.* **2019**, 4271.

(6) Hoyle, J. Some Synthetic Uses of Halides. In *Supplement D2; The Chemistry of Halides, Pseudo-Halides and Azides*; John Wiley & Sons, Ltd, **2004**; pp 709–785.

(7) *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, **2004**.

(8) Science of Synthesis, 32.4.2 Product Subclass 2: Chloro-, Bromo-, and Iodoalkenes, Pollex, A., **2008**, *32*, 462.

(9) Petrone, D. A.; Ye, J.; Lautens, M. Modern Transition-Metal-Catalyzed Carbon–Halogen Bond Formation. *Chem. Rev.* **2016**, *116*, 8003.

(10) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskoković, M. R. Direct α-Iodination of Cycloalkenones. *Tetrahedron Letters* **1992**, *33*, 917.

(11) (a) Kuhl, N.; Schröder, N.; Glorius, F. Rh(III)-Catalyzed Halogenation of Vinylic C–H Bonds: Rapid and General Access to Z-Halo Acrylamides. *Org. Lett*. **2013**, *15*, 3860; (b) Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. Co(III)-Catalyzed C–H Activation/Formal SN-Type Reactions: Selective and Efficient Cyanation, Halogenation, and Allylation. *J. Am. Chem. Soc.* **2014**, *136*, 17722.

(12) Negishi, E.; Takahashi, T. The Origin of the Configurational Instability of 1-Silyl-1-Alkenyllithiums and Related Alkenylmetals. *J. Am. Chem. Soc*. **1986**, *108*, 3402.

(13) Wang, Y.; Liu, J.; Huang, L.; Zhu, R.; Huang, X.; Moir, R.; Huang, J. KOtBu-Catalyzed Lithiation of PMDTA and the Direct Functionalization of Bridged Alkenes under Mild Conditions. *Chem. Commun*. **2017**, *53*, 4589.

(14) For selected examples of Pd-catalyzed C–H iodinations see: (a) Andrienko, O. S.; Goncharov, V. S.; Raida, V. S. Catalytic Iodination of Aromic Compounds via *ortho*-Palladated Complexes. *Russ. J. Org. Chem.* **1996**, *32*, 79; (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. A Highly Selective Catalytic Method for the Oxidative Functionalization of C−H Bonds. *J. Am. Chem. Soc.* **2004**, *126*, 2300; (c) Giri, R.; Chen, X.; Yu, J.-Q. Palladium-Catalyzed Asymmetric Iodination of Unactivated C–H Bonds under Mild Conditions. *Angew. Chem. Int. Ed.* **2005**, *44*, 2112; (d) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. A Simple Catalytic Method for the Regioselective Halogenation of Arenes. *Org. Lett*. **2006**, *8*, 2523; (e) Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Burrell, R.; Yu, J.-Q. Pd(II)-Catalyzed C–H Iodination Using Molecular I_2 as the Sole Oxidant. *J. Am. Chem. Soc.* **2013**, *135*, 10326; (f) Chu, L.; Xiao, K.-J.; Yu, J.-Q. Room-Temperature Enantioselective C–H Iodination via Kinetic Resolution. *Science* **2014**, *346*, 451; (g) Lu, C.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. Palladium-Catalyzed Picolinamide-Directed Halogenation of Ortho C–H Bonds of Benzylamine Substrates. *Tetrahedron* **2014**, *70*, 4197; (h) Zhu, R.-Y.; Liu, L.-Y.; Yu, J.-Q. Highly Versatile β-C(sp^3)–H Iodination of Ketones Using a Practical Auxiliary. *J. Am. Chem. Soc.* **2017**, *139*, 12394.

(15) For a recent review see: Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. Direct Allylic Functionalization Through Pd-Catalyzed C–H Activation. *Eur. J. Org. Chem.* **2014**, *2014*, 5863.

(16) For selected examples see: (a) Keith, J. A.; Henry, P. M. The Mechanism of the Wacker Reaction: A Tale of Two Hydroxypalladations. *Angew. Chem. Int. Ed.* **2009**, *48*, 9038; (b) McDonald, R. I.; Liu, G.; Stahl, S. S. Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev*. **2011**, *111*, 2981. (c) Gurak, J. A.; Yang, K. S.; Liu, Z.; Engle, K. M. Directed, Regiocontrolled Hydroamination of Unactivated Alkenes via Protodepalladation. *J. Am. Chem. Soc.* **2016**, *138*, 5805; (d) 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; (e) O'Duill, M. L.; Matsuura, R.; Wang, Y.; Turnbull, J. L.; Gurak, J. A.; Gao, D.-W.; Lu, G.; Liu, P.; Engle, K. M. Tridentate Directing Groups Stabilize 6-Membered Palladacycles in Catalytic Alkene Hydrofunctionalization. *J. Am. Chem. Soc.* **2017**, *139*, 15576; (f) Wang, H.; Bai, Z.; Jiao, T.; Deng, Z.; Tong, H.; He, G.; Peng, Q.; Chen, G. Palladium-Catalyzed Amide-Directed Enantioselective Hydrocarbofunctionalization of Unactivated Alkenes Using a Chiral Monodentate Oxazoline Ligand. *J. Am. Chem. Soc.* **2018**, *140*, 3542; (g) Shen, H.-C.; Zhang, L.; Chen, S.-S.; Feng, J.; Zhang, B.-W.; Zhang, Y.; Zhang, X.; Wu, Y.-D.; Gong, L.-Z. Enantioselective Addition of Cyclic Ketones to Unactivated Alkenes Enabled by Amine/Pd(II) Cooperative Catalysis. *ACS Catal*. **2019**, *9*, 791.

(17) (a) Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100*, 3009; (b) Wang, C.; Xiao, G.; Guo, T.; Ding, Y.; Wu, X.; Loh, T.-P. Palladium-Catalyzed Regiocontrollable Reductive Heck Reaction of Unactivated Aliphatic Alkenes. *J. Am. Chem. Soc*. **2018**, *140*, 9332; (c) Gurak, J. A.; Engle, K. M. Practical Intermolecular Hydroarylation of Diverse Alkenes via Reductive Heck Coupling. *ACS Catal*. **2018**, *8*, 8987.

(18) Lapointe, D.; Fagnou, K. Overview of the Mechanistic Work on the Concerted Metallation–Deprotonation Pathway. *Chem. Lett.* **2010**, *39*, 1118.

(19) Haines, B. E.; Xu, H.; Verma, P.; Wang, X.-C.; Yu, J.-Q.; Musaev, D. G. Mechanistic Details of Pd(II)-Catalyzed C–H Iodination with Molecular I_2: Oxidative Addition vs Electrophilic Cleavage. *J. Am. Chem. Soc.* **2015**, *137*, 9022.

(20) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. Highly Regioselective Arylation of sp^3 C−H Bonds Catalyzed by Palladium Acetate. *J. Am. Chem. Soc*. **2005**, *127*, 13154; (b) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds. *Acc. Chem. Res.* **2015**, *48*, 1053.

(21) For selected examples of the picolinamide directing group in synthesis, see: (a) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. Palladium-Catalyzed Picolinamide-Directed Alkylation of Unactivated C(sp^3)–H Bonds with Alkyl Iodides. *J. Am. Chem. Soc.* **2013**, *135*, 2124; (b) O' Donovan, D. H.; Aillard, P.; Berger, M.; de la Torre, A.; Petkova, D.; Knittl-Frank, C.; Geerdink, D.; Kaiser, M.; Maulide, N. C−H Activation Enables a Concise Total Synthesis of Quinine and Analogues with Enhanced Antimalarial Activity. *Angew. Chem. Int. Ed*. **2018**, *57*, 10737; (c) Zhan, B.-B.; Li, Y.; Xu, J.-W.; Nie, X.-L.; Fan, J.; Jin, L.; Shi, B.-F. Site-Selective δ-C(sp^3)−H Alkylation of Amino Acids and Peptides with Maleimides via a Six-Membered Palladacycle. *Angew. Chem. Int. Ed.* **2018**, *57*, 5858; (d) Guin, S.; Dolui, P.; Zhang, X.; Paul, S.; Singh, V. K.; Pradhan, S.; Chandrashekar, H. B.; Anjana, S. S.; Paton, R. S.; Maiti, D. Iterative Arylation of Amino Acids and Aliphatic Amines via δ-C(sp^3)−H Activation: Experimental and Computational Exploration. *Angew. Chem. Int. Ed*. **2019**, *58*, 5633.

(22) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. Pd(II)-Catalyzed Alkoxylation of Unactivated C(sp^3)–H and C(sp^2)–H Bonds Using a Removable Directing Group: Efficient Synthesis of Alkyl Ethers. *Chem. Sci.* **2013**, *4*, 4187.

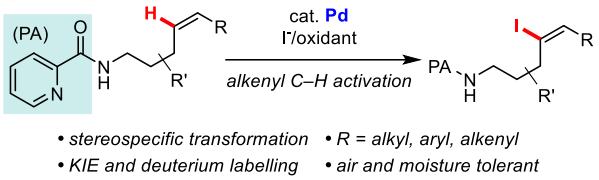
(23) (a) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. A New Reaction of Hydrazones. *J. Chem. Soc.* **1962**, 470; (b) Pross, A.; Sternhell, S. Oxidation of Hydrazones with Iodine in the Presence of Base. *Aust. J. Chem.* **1970**, *23*, 989;

(24) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. Copper-Catalyzed Coupling of Amides and Carbamates with Vinyl Halides. *Org. Lett.* **2003**, *5*, 3667.

(25) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C−H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem. Int. Ed*. **2012**, *51*, 3066.

(26) (a) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. Mechanistic Analysis of Azine N-Oxide Direct Arylation: Evidence for a Critical Role of Acetate in the $Pd(OAc)_2$ Precatalyst. *J. Org. Chem.* **2010**, *75*, 8180; (b) Liu, L.-Y.; Yeung, K.-S.; Yu, J.-Q. Ligand-Promoted Non-Directed C−H Cyanation of Arenes, *Chem. Eur. J.* **2019**, *25*, 2199.

TOC Graphic


(PA)
O
N
H
H
R
R'
N
cat. Pd
I⁻/oxidant
alkenyl C–H activation
PA
N
H
I
R
R'
• stereospecific transformation
• KIE and deuterium labelling
• R = alkyl, aryl, alkenyl
• air and moisture tolerant