Palladium Catalysis

International Edition: DOI: 10.1002/anie.201911961
German Edition: DOI: 10.1002/ange.201911961

Asymmetric Wacker-Type Oxyallenylation and Azaallenylation of Cyclic Alkenes

*Shenghan Teng, Zhiwei Jiao, Yonggui Robin Chi, and Jianrong Steve Zhou**

Abstract: *Palladium-catalyzed three-component carboetherification of cyclic alkenes proceeded to give trans adducts exclusively with excellent enantioselectivity through a Wacker-type pathway. The reaction is also applicable to other oxygen nucleophiles, such as water, phenols, and carboxylic acids, as well as some electron-poor aryl amines.*

Catalytic carboetherification and carboamination of alkenes allows the construction of a new C–C bond and a new C–O/N bond in a single reaction.[1] The three-component reaction is particularly attractive in terms of convergence and the possibility to establish two new stereocenters. Many existing three-component examples involve carbon-radical addition to alkenes as the key step.[2] The development of such an asymmetric radical reaction still remains a challenge. Until now, most examples of asymmetric carboetherification and carboamination have been limited to two-component reactions initiated by intramolecular heteropalladation[3] or heterocupration[4] (Figure 1a). In a similar strategy, Mazet and co-workers strategically placed hydroxy and sulfonamide groups at *ortho* positions of aryl palladium species, which set the stage for intramolecular *syn* attack at a bound cycloalkene, 2,3-dihydrofuran.[5] In an oxy-Heck-Matsuda reaction developed by Correia et al.,[6] aryl insertion produced an η^3-benzyl complex, which, in turn, was intercepted by a pendant phenol to produce dihydrobenzofurans. The tethering strategy was also utilized by Wolfe and co-workers for asymmetric *anti* attack of external amines on an allylphenyl Pd species to form 2-amidoindanes.[7] Furthermore, Liu and co-workers recently disclosed a truly three-component copper-catalyzed asymmetric arylsulfonamidation of styrene, which proceeded by amino-radical addition to styrene and subsequent formation of a new stereocenter at the benzylic position.[8]

Herein, we report the first three-component example of asymmetric oxyallenylation,[9] using propargylic acetates and oxygen nucleophiles, such as alcohols, phenol, carboxylic acids, and water (Figure 1b). The reactivity can also be extended to electron-deficient aryl amines. The reaction led to exclusive *trans* heteroallenylation in excellent enantioselectivity. Allenes are important intermediates in organic synthesis, especially so with the advent of many metal-catalyzed stereoselective and/or regioselective reactions to prepare substituted allenes.[10]

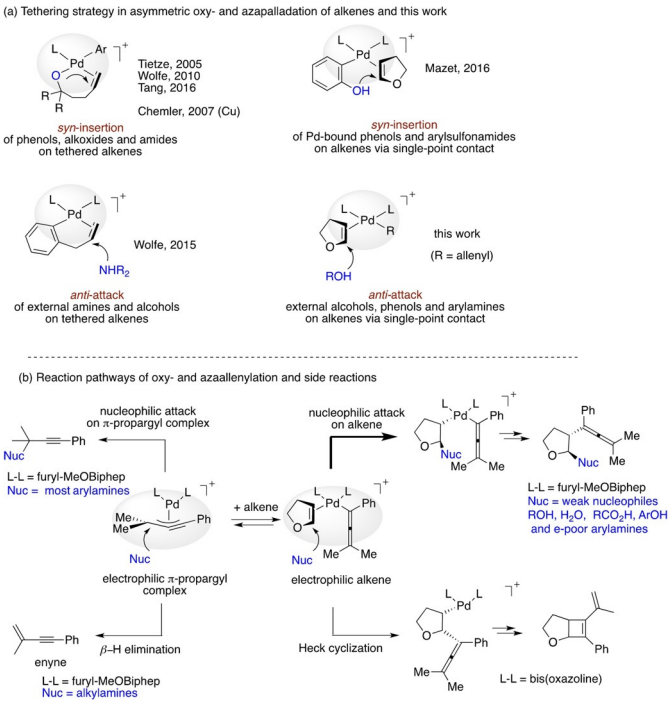


Figure 1. a) Use of tethering for asymmetric induction in the oxy- or azapalladation of alkenes. b) Plausible pathways of oxy- and azaallenylation and side reactions.

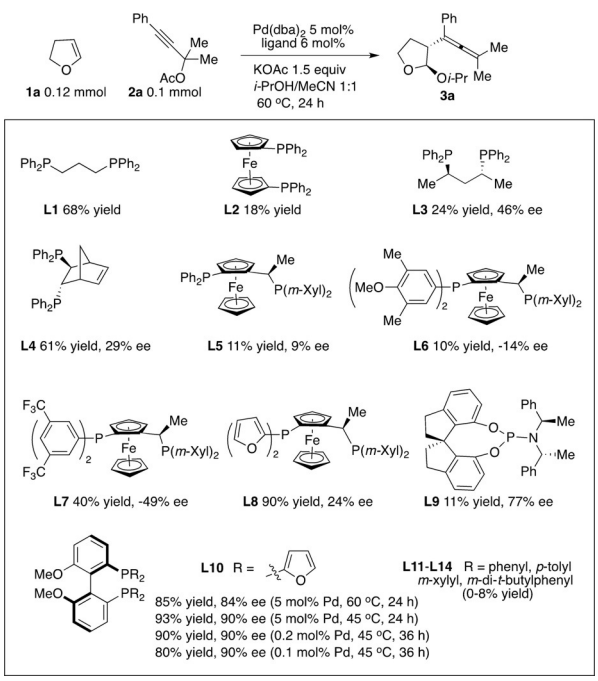
To produce the Wacker-type adducts, several side reactions must be prevented (Figure 1b): 1) The σ-allenyl complex of palladium must undergo fast Wacker-type *anti* heteropalladation of alkenes instead of *syn* insertion[11] or Heck *syn* carbopalladation, the latter leading to fused cyclobutenes, which we reported previously.[12] 2) The allenyl complex may exist in equilibrium with the π-propargyl complex, which can eliminate a β-hydrogen atom to give an enyne. 3) The π-propargyl complex is electrophilic and can undergo propargylic substitution if nucleophilic amines are used.

Tethering of alkenes to the inserting heteroatoms or metal-bound aryl rings is a commonly employed strategy to facilitate asymmetric insertion (see Figure 1a).[13] For simple alkenes that bind to catalysts through a single point of

[*] Prof. Dr. J. S. Zhou
State Key Laboratory of Chemical Oncogenomics, Key Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology
Peking University Shenzhen Graduate School
2199 Lishui Road, Room F-312, Nanshan District, Shenzhen 518055 (China)
E-mail: jrzhou@pku.edu.cn
S. Teng, Dr. Z. Jiao, Prof. Dr. Y. R. Chi
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University,
21 Nanyang Link, Singapore 637371 (Singapore)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.201911961.

contact, stereocontrol by catalysts still remains a challenge. Therefore, there has been no asymmetric example of the archetypical Wacker *anti* attack on simple monoolefins.

In our recent study of a model Heck annulation of 3-phenylpropargyl acetate **2a** and 2,3-dihydrofuran (Scheme 1), a new product of alkoxyallenylation **3a** was obtained in 68% yield through the reaction of the cosolvent, isopropanol in the presence of $Pd(dba)_2$ and dppp. A small amount of the enyne by-product was also detected.



Scheme 1. Effect of bisphosphines on a model alkoxyallenylation of 2,3-dihydrofuran (yields and *ee* values of **3a** are indicated). dba = dibenzylideneacetone, Xyl = *m*-xylyl.

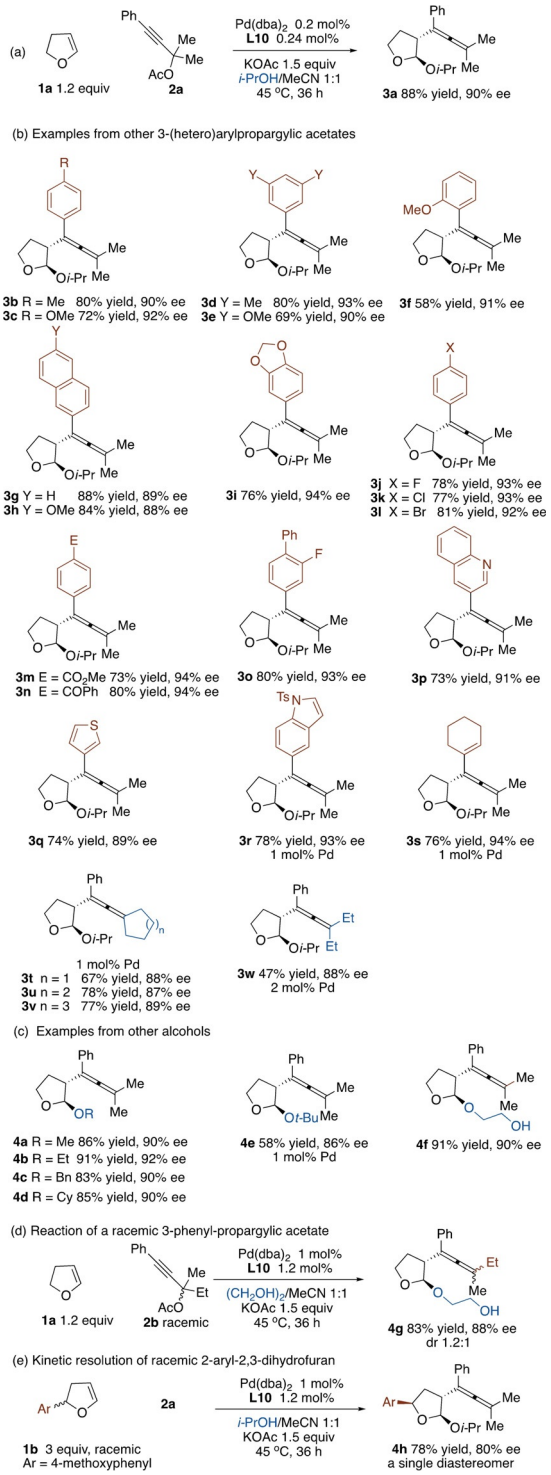
Encouraged by this finding, we then screened chiral bisphosphines to develop an enantioselective variant. In most cases, β-elimination to the enyne was the main side reaction, whereas Heck annulation was rarely seen, except with the ligand Norphos **L4** (23% yield). For example, biaryl diphosphines, such as BINAP, Segphos and Difluorphos gave the desired product **3a** in less than 5% yield. Notably, the trifluoromethylated Josiphos ligand **L7** provided **3a** in 40% yield with 49% *ee* (and 28% elimination). Josiphos ligand **L8** bearing electron-withdrawing 2-furyl groups afforded **3a** in 90% yield with 24% *ee*, and notably without any elimination. Gratifyingly, a palladium catalyst with furyl-MeOBIPHEP **L10** afforded **3a** in 85% yield with 84% *ee* at 60 °C. Moreover, 90% *ee* and 80% yield were observed at 45 °C in the presence of 0.1 mol% Pd catalyst. Importantly, no enyne was detected. In comparison, catalysts formed by other MeOBIPHEP ligands **L11**–**L14** containing parent *P*-phenyl and electron-donating *P*-aryl substituents had almost no activity, and elimination was the main side reaction. As compared to triphenylphosphine, 2-furylphosphines are much weaker σ-donors to transition metals and better π-acceptors.[14] They form an electronically deficient allenyl palladium center, which activates the bound alkene for Wacker attack by nucleophiles. This trend is consistent with the higher Wacker reactivity observed with electron-deficient Josiphos **L7** and **L8** as compared to **L6**. Notably, both MeOBIPHEP and Josiphos form quite large bite angles of 94° and 97°, respectively, at palladium(II) centers,[15] which may also help to prevent elimination. The corresponding monoxide of bisphosphine **L10** was also prepared and tested, but it only led to **3a** in low yield with less than 10% *ee*.[16]

The palladium catalyst (0.2 mol%) of **L10** was then applied to reactions of 2,3-dihydrofuran with other propargylic acetates bearing both electron-rich and electron-deficient aryl rings in the 3-position (Scheme 2b). Esters, ketones, acetals, aryl bromides, fluorides, and chlorides were well tolerated. Furthermore, the reaction tolerated quinoline, thiophene, and indole (products **3p**–**r**). When 3-aryl propargylic acetates containing 1,1-diethyl and cycloalkyl substituents were used, 1–2 mol% of the Pd catalyst was enough to give full conversion (products **3t**–**w**). Unfortunately, 3-alkyl propargylic acetates only afforded the adducts in low yields. Other alcohols, including benzyl alcohol, cyclohexanol, *tert*-butyl alcohol, and ethylene glycol also reacted smoothly (Scheme 2c, products **4a**–**f**). The reaction of racemic propargylic acetate **2b** led to a mixture of two allenyl isomers **4g**, both with 88% *ee* (Scheme 2d). However, primary and secondary propargylic acetates did not react at all. The racemic 2,3-dihydrofuran **1b** substituted with a *p*-methoxyphenyl ring afforded the single diastereomer **4h** with 80% *ee*. The observed enantiofacial selectivity translates to an *s* value of 9 (Scheme 2e). Unfortunately, in the reaction of 2,3-dihydropyran, only simple addition of isopropanol to the alkene group was detected.

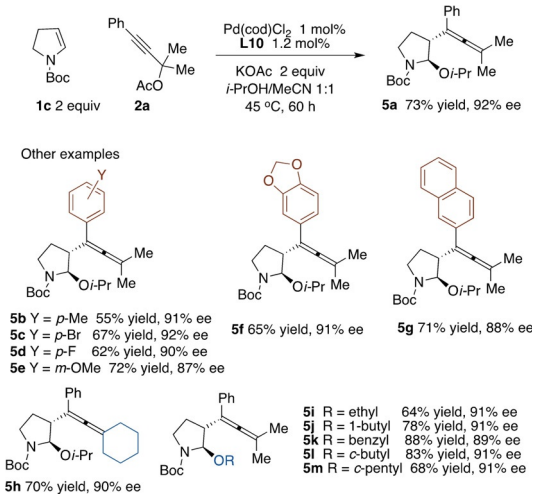
N-*tert*-butoxycarbonyl-2,3-dihydropyrrole (**1c**) was another reactive alkene in this transformation (Scheme 3), whereby different aryl rings at the 3-position of the propargylic acetate were tolerated (products **5b**–**f**), and both primary and secondary alcohols coupled in good yields (products **5i**–**m**). Notably, simple addition of alcohols to the double bond was also detected, accounting for the rest of the material. Reactions of cyclopentene afforded only a small amount of the desired products, however.

When **1a** was treated with acetic acid and phenol in acetonitrile, the *trans* adducts **6a** and **6b** were also generated exclusively (Scheme 4a,b). The reaction with water generated **6c** as both *trans* and *cis* isomers in a ratio of 4:1 (Scheme 4c), whereas a similar reaction of *N*-Boc-substituted dihydropyrrole **1c** afforded exclusively *trans* isomer **6d** (Scheme 4d). The minor *cis*-lactol **6c** was probably formed through reversible ring opening of the initially formed *trans* lactol. Notably, adduct **6a** was also detected in small amounts in reaction mixtures of alkoxyallenylation in Scheme 2, but purified **6a** remained unreactive when subjected to the conditions of catalytic alkoxyallenylation. Thus, **6a** was chemically incompetent as an intermediate for the alkoxyallenylation process.

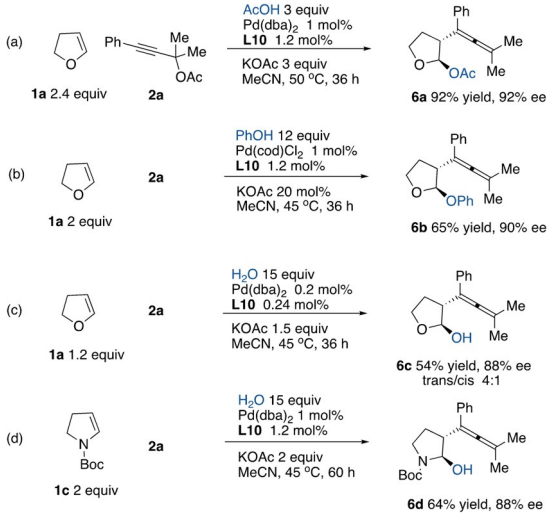
We also attempted to replace alcohols with amine nucleophiles in acetonitrile. When aniline and indoline were used, propargylic amination of **2a** was the main side reaction (see Figure 1b). Moreover, aliphatic amines, such as diethyl-



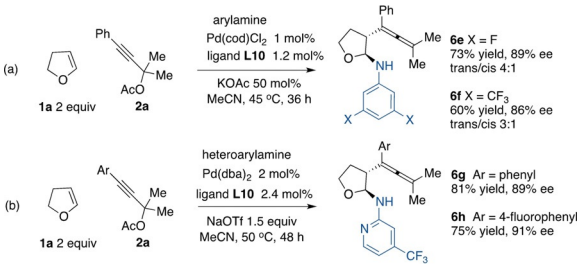
Scheme 2. Alkoxyallenylation of 2,3-dihydrofuran.



Scheme 3. Alkoxyallenylation of *N*-Boc-2,3-dihydropyrrole.



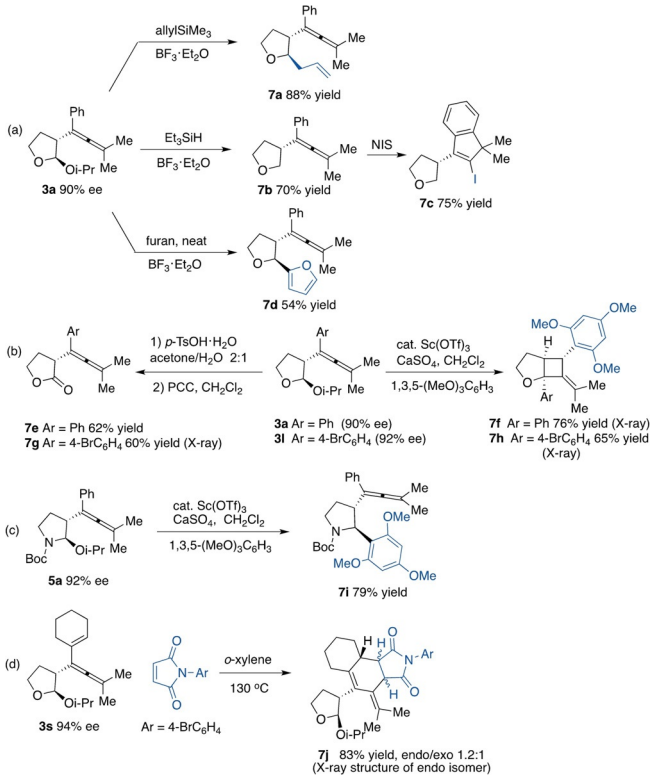
Scheme 4. Wacker-type oxyallenylation using acetic acid, phenol, and water.



Scheme 5. Wacker-type azaallenylation triggered by the attack of an aryl amine. Tf = trifluoromethanesulfonyl.

amine and pyrroline, led to elimination of **2a** to give the enyne. However, fluorinated aryl amines and pyridyl amines of attenuated nucleophilicity reacted smoothly to provide azaallenylation adducts (Scheme 5a,b). The initially formed *trans N,O*-acetals **6e**,**f** probably underwent reversible ring opening to generate the minor *cis* isomers. NaOTf accelerated the addition of pyridyl amines to give products **6g**,**h** (Scheme 5b); without this additive, no conversion was detected.

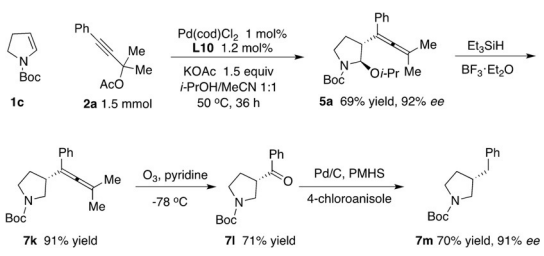
To demonstrate the synthetic utility of the transformation, we subjected adduct **3a** to Friedel–Crafts allylation and heteroarylation with an allylsilane[17] and furan (Scheme 6a). Acetal **3a** was also reduced to **7b** by triethylsilane, and then underwent facile iodocyclization to **7c** upon treatment with



Scheme 6. Transformations of alkoxyallenylation adducts. Ts = toluenesulfonyl.

N-iodosuccinimide (NIS).[18] Acidic hydrolysis of **3a** and PCC oxidation furnished butyrolactone **7e** (Scheme 6b). In all cases, no erosion of enantiopurity was observed. Next, we attempted arylation of the oxonium species derived from **3a** under Friedel–Crafts conditions. Surprisingly, scandium triflate efficiently catalyzed the addition of 1,3,5-trimethoxybenzene to **3a** but giving a highly strained, fused cyclobutane **7f** through an unprecedented sequence of cationic reactions (Scheme 6b). A bromophenylated acetal **3l** was also readily converted into **7h**, whose configuration was established by X-ray diffraction analysis (Scheme 6b).[19] However, the analogous Friedel–Crafts reaction of **5a** resulted in simple arylation (Scheme 6c). A thermal Diels–Alder reaction of **3s** with an *N*-aryl maleimide produced a mixture of two isomers of **7j** (Scheme 6d).

Adduct **5a** was also subjected to silane reduction and selective ozonolysis to give ketone **7l** (Scheme 7).[20] Subsequent palladium-catalyzed reduction with polymethylhydrosiloxane (PMHS) afforded *N*-(*tert*-butoxycarbonyl)benzylpyrrolidine **7m**.[21] Chiral 3-benzylpyrrolidines are one type of heterocyclic amines used in drug discovery,[22] but few efficient stereoselective methods for their synthesis exist to date.[23]



Scheme 7. Synthesis of chiral 3-benzoyl- and 3-benzylpyrrolidine. cod = 1,5-cyclooctadiene.

In summary, we have reported an asymmetric Wacker-type coupling of propargylic acetates, cyclic alkenes, and external nucleophiles, such as alcohols, phenols, carboxylic acids, water, and electron-deficient aryl amines. For the first time, asymmetric Wacker-type attack of truly external nucleophiles on monoolefins proceeded without any aid of directing groups. Notably, the use of electron-deficient furyl-MeOBIPHEP proved crucial to both the reactivity and stereoselectivity of the asymmetric Wacker-type process.

Acknowledgements

We acknowledge financial support from Peking University Shenzhen Graduate School, Shenzhen Bay Laboratory (21230011-Scripps), Nanyang Technological University, the GSK-EDB Trust Fund (2017 GSK-EDB Green and Sustainable Manufacturing Award), and A*STAR Science and Engineering Research Council (AME IRG A1783c0010). We thank Dr. Li Yongxin for X-ray diffraction analysis of several compounds.

Conflict of interest

The authors declare no conflict of interest.

Keywords: allenes · asymmetric catalysis · carboetherification · palladium catalysis · Wacker reaction

How to cite: *Angew. Chem. Int. Ed.* **2020**, *59*, 2246–2250
Angew. Chem. **2020**, *132*, 2266–2270

[1] For reviews, see: a) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981; b) Z. J. Garlets, D. R. White, J. P. Wolfe, *Asian J. Org. Chem.* **2017**, *6*, 636; c) J.-S. Zhang, L. Liu, T. Chen, L.-B. Han, *Chem. Asian J.* **2018**, *13*, 2277.

[2] For examples, see: a) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 6877; *Angew. Chem.* **2010**, *122*, 7029; b) A. D. Melhado, W. E. Brenzovich, A. D. Lackner, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8885; c) G. Fumagalli, S. Boyd, M. F. Greaney, *Org. Lett.* **2013**, *15*, 4398; d) Y. Xie, J. Hu, P. Xie, B. Qian, H. Huang, *J. Am. Chem. Soc.* **2013**, *135*, 18327; e) M. N. Hopkinson, B. Sahoo, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 2794; f) T. Itoh, Y. Shimizu, M. Kanai, *Org. Lett.* **2014**, *16*, 2736; g) H. Yi, X. Zhang, C. Qin, Z. Liao, J. Liu, A. Lei, *Adv. Synth. Catal.* **2014**, *356*, 2873; h) C. Chatalova-Sazepin, Q. Wang, G. M. Sammis, J. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 5443; *Angew. Chem.* **2015**, *127*, 5533; i) Z. Liao, H. Yi, Z. Li, C. Fan, X. Zhang, J. Liu, Z. Deng, A. Lei, *Chem. Asian J.* **2015**, *10*, 96; j) A. Tlahuext-Aca, R. A. Garza-Sanchez, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 3708; *Angew. Chem.* **2017**, *129*, 3762; k) S. Zheng, Á. Gutiérrez-Bonet, G. A. Molander, *Chem* **2019**, *5*, 339.

[3] For examples, see: a) L. F. Tietze, K. M. Sommer, J. Zinngrebe, F. Stecker, *Angew. Chem. Int. Ed.* **2005**, *44*, 257; *Angew. Chem.* **2005**, *117*, 262; b) Y. Kawamura, Y. Kawano, T. Matsuda, Y. Ishitobi, T. Hosokawa, *J. Org. Chem.* **2009**, *74*, 3048; c) D. N.

Mai, J. P. Wolfe, *J. Am. Chem. Soc.* **2010**, *132*, 12157; d) B. A. Hopkins, J. P. Wolfe, *Angew. Chem. Int. Ed.* **2012**, *51*, 9886; *Angew. Chem.* **2012**, *124*, 10024; e) B. A. Hopkins, Z. J. Garlets, J. P. Wolfe, *Angew. Chem. Int. Ed.* **2015**, *54*, 13390; *Angew. Chem.* **2015**, *127*, 13588; f) N. Hu, K. Li, Z. Wang, W. Tang, *Angew. Chem. Int. Ed.* **2016**, *55*, 5044; *Angew. Chem.* **2016**, *128*, 5128.

[4] a) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948; b) L. Miao, I. Haque, M. R. Manzoni, W. S. Tham, S. R. Chemler, *Org. Lett.* **2010**, *12*, 4739; c) Y. Miller, L. Miao, A. S. Hosseini, S. R. Chemler, *J. Am. Chem. Soc.* **2012**, *134*, 12149; d) M. T. Bovino, T. W. Liwosz, N. E. Kendel, Y. Miller, N. Tyminska, E. Zurek, S. R. Chemler, *Angew. Chem. Int. Ed.* **2014**, *53*, 6383; *Angew. Chem.* **2014**, *126*, 6501; e) S. D. Karyakarte, C. Um, I. A. Berhane, S. R. Chemler, *Angew. Chem. Int. Ed.* **2018**, *57*, 12921; *Angew. Chem.* **2018**, *130*, 13103.

[5] a) V. Bizet, G. M. Borrajo-Calleja, C. Besnard, C. Mazet, *ACS Catal.* **2016**, *6*, 7183; b) G. M. Borrajo-Calleja, V. Bizet, C. Mazet, *J. Am. Chem. Soc.* **2016**, *138*, 4014.

[6] C. R. Correia, A. Ribeiro, E. Polo, N. Martins, *Adv. Synth. Catal.* **2018**, *360*, 346.

[7] D. R. White, J. T. Hutt, J. P. Wolfe, *J. Am. Chem. Soc.* **2015**, *137*, 11246.

[8] D. Wang, L. Wu, F. Wang, X. Wan, P. Chen, Z. Lin, G. Liu, *J. Am. Chem. Soc.* **2017**, *139*, 6811.

[9] T. H. Graham, C. M. Jones, N. T. Jui, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 16494.

[10] a) S. Yu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 3074; *Angew. Chem.* **2012**, *124*, 3128; b) B. Alcaide, P. Almendros, *Chem. Soc. Rev.* **2014**, *43*, 2886; c) J. Ye, S. Ma, *Acc. Chem. Res.* **2014**, *47*, 989; d) R. Santhoshkumar, C.-H. Cheng, *Asian J. Org. Chem.* **2018**, *7*, 1151.

[11] For mechanistic studies on *syn* versus *anti* oxy- and azapalladation, see: a) R. M. Trend, Y. K. Ramtohul, E. M. Ferreira, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2003**, *42*, 2892; *Angew. Chem.* **2003**, *115*, 2998; b) T. Hayashi, K. Yamasaki, M. Mimura, Y. Uozumi, *J. Am. Chem. Soc.* **2004**, *126*, 3036; c) R. M. Trend, Y. K. Ramtohul, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 17778; d) A. B. Weinstein, S. S. Stahl, *Angew. Chem. Int. Ed.* **2012**, *51*, 11505; *Angew. Chem.* **2012**, *124*, 11673; e) N. J. Race, C. S. Schwalm, T. Nakamuro, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 15881; f) X. Kou, Q. Shao, C. Ye, G. Yang, W. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 7587.

[12] Z. Jiao, Q. Shi, J. S. Zhou, *Angew. Chem. Int. Ed.* **2017**, *56*, 14567; *Angew. Chem.* **2017**, *129*, 14759.

[13] For examples, see: a) Y. Zhang, M. S. Sigman, *J. Am. Chem. Soc.* **2007**, *129*, 3076; b) K. H. Jensen, J. D. Webb, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 17471; c) X. Qi, C. Chen, C. Hou, L. Fu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2018**, *140*, 7415; d) C. Chen, P. M. Pflüger, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2019**, *58*, 2392; *Angew. Chem.* **2019**, *131*, 2414.

[14] N. G. Andersen, B. A. Keay, *Chem. Rev.* **2001**, *101*, 997.

[15] For values of bite angles at palladium, see: a) C. Bolm, D. Kaufmann, S. Gessler, K. Harms, *J. Organomet. Chem.* **1995**, *502*, 47; b) A. H. Roy, J. F. Hartwig, *Organometallics* **2004**, *23*, 194.

[16] J. Hu, Y. Lu, Y. Li, J. Zhou, *Chem. Commun.* **2013**, *49*, 9425.

[17] P. Sarnpitak, K. Trongchit, Y. Kostenko, S. Sathalalai, M. P. Gleeson, S. Ruchirawat, P. Ploypradith, *J. Org. Chem.* **2013**, *78*, 8281.

[18] C. Grandclaudon, V. Michelet, P. Y. Toullec, *Org. Lett.* **2016**, *18*, 676.

[19] CCDC 1888827 (**7f**), 1937818 (**7g**), 1937817 (**7h**), and 1880117 (**7j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[20] R. Willand-Charnley, T. J. Fisher, B. M. Johnson, P. H. Dussault, *Org. Lett.* **2012**, *14*, 2242.

[21] A. Volkov, K. P. J. Gustafson, C.-W. Tai, O. Verho, J.-E. Bäckvall, H. Adolfsson, *Angew. Chem. Int. Ed.* **2015**, *54*, 5122; *Angew. Chem.* **2015**, *127*, 5211.

[22] For examples, see: a) W. Yang, Y. Wang, J. Y. Roberge, Z. Ma, Y. Liu, R. M. Lawrence, D. P. Rotella, R. Seethala, J. H. M. Feyen, J. K. Dickson, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1225; b) C. C. Musonda, G. A. Whitlock, M. J. Witty, R. Brun, M. Kaiser, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 401; c) J. Alen, M. Schade, M. Wagener, F. Christian, S. Nordhoff, B. Merla, T. R. Dunkern, G. Bahrenberg, P. Ratcliffe, *J. Med. Chem.* **2019**, *62*, 6391.

[23] For examples, see: a) E. R. Welin, A. A. Warkentin, J. C. Conrad, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 9668; *Angew. Chem.* **2015**, *127*, 9804; b) Y. Kuang, X. Wang, D. Anthony, T. Diao, *Chem. Commun.* **2018**, *54*, 2558.

Manuscript received: September 18, 2019
Accepted manuscript online: November 6, 2019
Version of record online: December 19, 2019

