Published in final edited form as:

J Am Chem Soc. 2017 November 08; 139(44): 15576–15579. doi:10.1021/jacs.7b08383.

Tridentate Directing Groups Stabilize 6-Membered Palladacycles in Catalytic Alkene Hydrofunctionalization

Miriam L. O'Duill[†], Rei Matsuura[†], Yanyan Wang[‡], Joshua L. Turnbull[†], John A. Gurak[†], De-Wei Gao[†], Gang Lu[‡], Peng Liu^{‡,*}, and Keary M. Engle^{†,*}

[†]Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Rd., La Jolla, California 92037, USA

[‡]Department of Chemistry, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, Pennsylvania 15260, USA

Abstract

Removable tridentate directing groups inspired by pincer ligands have been designed to stabilize otherwise kinetically and thermodynamically disfavored 6-membered alkyl palladacycle intermediates. This family of directing groups enables regioselective remote hydrocarbofunctionalization of several synthetically useful alkene-containing substrate classes, including 4-pentenoic acids, allylic alcohols, homoallyl amines, and bis-homoallyl amines, under Pd(II) catalysis. In conjunction with previous findings, we demonstrate regiodivergent hydrofunctionalization of 3-butenic acid derivatives to afford either Markovnikov or anti-Markovnikov addition products depending on directing group choice. Preliminary mechanistic and computational data are presented to support the proposed catalytic cycle.

Graphical Abstract

Substrate directivity is a powerful and well-established approach in organic synthesis and transition-metal catalysis.[1] In reactions that are coordination controlled, the kinetics and thermodynamics of metalacycle formation dictate stereo- and regiochemical outcomes. In the context of Pd(II) catalysis, directed functionalization of C–H bonds and C–C π -bonds

*Corresponding Author: pengliu@pitt.edu; keary@scripps.edu.

Notes

The authors declare no competing financial interests.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, analytical data, NMR spectra, computational methods and Cartesian coordinates (PDF)

X-ray crystallographic data for **4a** (CIF)

X-ray crystallographic data for **15** (CIF)

X-ray crystallographic data for **18** (CIF)

NMR spectra in MNOVA format (ZIP)

has received significant attention in the past decade. With reactions involving alkyl palladacycles, there is a strong preference for formation of 5-membered palladacycles, which has limited such reactions to substrates containing functional groups in close proximity to the reaction site. Coordination through more distal functional groups involving larger alkyl palladacycles is a less well-established approach. For instance, the thermodynamically and kinetically less favored 6-membered palladacycles have only been implicated when formation of the 5-membered intermediate is conformationally or sterically disfavored.[2,3] Overcoming innate reactivity preferences to achieve control of cyclometalation through use of a specifically tailored directing group or ancillary ligand remains a significant challenge.

This limitation is illustrated by a recent report from our group. We described a method for Pd(II)-catalyzed hydrocarbofunctionalization of 3-butenic acid derivatives bearing Daugulis's 8-aminoquinoline (AQ) directing group.[4–6] The mechanism of this reaction involves γ -selective addition to a Pd(II)-bound alkene to form a 5-membered palladacycle. Attempting to extend this concept to substrate **1**, which would be expected to react *via* a 6-membered palladacycle, only 11% of the desired product **2** was formed, with the remainder of the material succumbing to *beta*-hydride (β -H) elimination or alkene isomerization (Fig. 1A). Since β -H elimination requires an open coordination site on the metal catalyst, we hypothesized that a tridentate directing group, inspired by the well-known family of pincer ligands,[7] would suppress these undesired side-reactions and stabilize the 6-membered palladacycle (Fig. 1B). At the outset, we realized that two challenges would need to be overcome. First, we would need to tune the steric and electronic properties of the third binding site to allow for nucleopalladation. Second, the directing group's coordination strength would need to be modulated such that it would bind reversibly to the metal catalyst despite being tridentate.[8]

To test this idea, we prepared a series of 4-pentenoic acid derivatives **I** bearing different tridentate directing groups, along with bidentate controls, and submitted these to Pd(II)-catalyzed hydrofunctionalization (10 mol% Pd(OAc)₂, 0.5 equiv HOAc, MeCN, 85 °C, 48 h) (Table 1). AQ-containing substrate **IA** afforded 13% of the desired product **II** (cf. 11% after 24 h) along with substantial amounts of byproducts from β -H elimination (**IV**) and isomerization (**III** and **IV**). Shi's bidentate PIP directing group **B** was similarly ineffective. When we examined tridentate amino-acid-derived directing groups **C–F**, we were encouraged by a slight increase in formation of **II** with complete suppression of β -H elimination, though isomerization remained problematic. We next examined an alternative tridentate scaffold in which coordinating heterocycles were introduced to the C2 position of the AQ core structure. While thiophene (**G**) was ineffective, and pyrimidine (**H**) caused a high amount of substrate decomposition, we were pleased to see that a 2-pyridyl group (**J**) successfully minimized detrimental side-reactions, furnishing 97% of the desired product by ¹H NMR. It was further possible to shorten the reaction time to 4 h without a significant drop in yield. Notably, this novel 2-pyridyl-8-aminoquinoline (PAQ) auxiliary can be conveniently prepared on >5-gram scale and can be removed and recycled (*vide infra*).

With this optimized directing group in hand, we proceeded to investigate the substrate scope of this method (Scheme 2).[9] 4-Hydroxycoumarin and cyclic 1,3-dicarbonyl compounds

reacted readily under the standard conditions (Conditions A), giving the corresponding products **4a–c** in high yields. Meldrum's acid was hydrolyzed *in situ* to give decarboxylated product **4d**,[10] however under basic conditions (Conditions B) the 1,3-dicarbonyl moiety remained intact (**4e**). Electron-rich aromatics, such as resorcinols and naphthols, were competent nucleophiles under basic conditions as well (**4f–l**). Electron-donating or -withdrawing groups on the arene did not affect the yields substantially (**4g–h**, **4l**), and the reaction tolerated heteroaromatic nucleophiles (**4i**, **4k**). On the alkene side, α - and β -substituents on the carbon chain are well tolerated (**4m–4n**). Gratifyingly, internal alkenes also show moderate reactivity (**4o**). Lastly, we were pleased to find that allyl alcohol, when masked as its corresponding PAQ carbamate, underwent hydrofunctionalization in moderate yields (**4p**).

To demonstrate scalability, product **4a** was synthesized on a 2 mmol scale, affording 784 mg (84% yield). Removal of the directing group with 6 N HCl yielded 83% of carboxylic acid **5** and allowed for recovery of the directing group in 96% yield (Scheme 1).

Next, we sought to extend this concept from carboxylic acids to amine substrates (Fig. 2). A brief optimization (see SI) revealed 2,2'-bipyridylamide (PPA), a directing group that can be conveniently prepared on a 10-gram scale, to be most effective for this substrate class. Under optimal conditions, the reaction afforded 82% of product **7a**, consistent with a 6-membered palladacycle intermediate. The nucleophile scope for homoallylamine **6** was similar to that observed for carboxylic acid substrates **3**. Interestingly, *N*-methyl indole, which was unreactive with substrates **3**, afforded product **7f** in moderate yield.

By employing these two directing groups, we were able to hydrofunctionalize L-allylglycine derivatives in a regiodivergent manner (Scheme 3). Masking the carboxylic acid moiety with the PAQ directing group allowed for anti-Markovnikov selectivity, providing hydrofunctionalized product **4q** in 60% yield. Using the PPA directing group to mask the amine moiety, on the other hand, we were able to obtain 88% of the Markovnikov product **7g** without erosion of stereochemistry in the major diastereoisomer.[11]

Having established that tridentate directing groups are capable of stabilizing 6-membered palladacycles, we next questioned whether these directing groups could override the innate regioselectivity preference of 3-butenic acid substrates for 5-membered nucleopalladation. If successful, we envisioned that end-users would be able to control the regiochemical course of the reaction through choice of the directing group, without the need for other biasing factors in the starting material. As previously reported, substrate **11** bearing the bidentate AQ directing group affords anti-Markovnikov addition product **13**. [4] Under the same reaction conditions, the tridentate PAQ directing group instead affords primarily Markovnikov product **14** (85:15 r.r.) (Scheme 4). These results indicate that the innate selectivity for products derived from 5-membered palladacycle can be overridden by directing group choice.

Given the unique reactivity enabled by the tridentate PAQ and PPA directing groups, it is important to understand the mechanistic similarities and differences between these groups and bidentate variants in order to determine where and how such groups can be effectively

exploited. To this end, several preliminary mechanistic and computational experiments were performed (Fig. 3).[12,13] When we exposed alkene **6** to 1 equiv Pd(OAc)₂ in MeCN at room temperature, complex **15** was formed in 86% yield (Fig. 3A), a process that was calculated to be highly exergonic by 17.1 kcal/mol (Fig. 3D). Notably, the corresponding processes involving bidentate directing groups are much less exergonic.[2,14] In our previous results with AQ, the corresponding π -alkene complex is formed under analogous conditions.[4] Tridentate π -alkene complex **16**, in contrast, was not observed experimentally (see SI), presumably since its formation by dissociation of acetate from **15** is endergonic by 5.8 kcal/mol.

When complex **15** was treated with 4-hydroxycoumarin, we expected to observe the corresponding nucleopalladated alkylpalladium(II) species **17** in analogy to our earlier report.[4] However, in practice, we were surprised to observe product-bound Pd(II) complex **18** (Fig. 3A). Previously, using an AQ directing group, we found that nucleopalladation occurs at room temperature, but protodepalladation requires elevated temperatures.[4] In this case, both steps take place at room temperature. Furthermore, no external acid is necessary in this case, suggesting that the nucleophile's hydroxy group may play a role in the protodepalladation step. This hypothesis is supported computationally: intramolecular protodepalladation [8] via a 6-membered cyclic transition state (**TS2**) requires a relatively low activation energy (12.8 kcal/mol with respect to **17**) and is highly exergonic. The observation that all of the early steps in the catalytic cycle take place at room temperature but that the catalytic system requires elevated temperature is consistent with a mechanism in which ligand exchange is slow, which would be unsurprising considering the directing group's pincer-like structure. Indeed, dissociation of the tridentate directing group was calculated to be highly endergonic by 18.6 kcal/mol.

When complex **18** was used as a pre-catalyst under otherwise standard reaction conditions, 81% of hydrofunctionalized product **7a** was obtained. When 1,3-cyclopentanedione was used as a nucleophile, 79% **7c** was isolated together with 7% **7a** (Fig. 3A). These two results establish that **18** is catalytically competent. The latter result further demonstrates that ligand exchange takes place during the catalytic cycle.

We next computationally investigated the role of the tridentate directing group in suppressing β -H elimination. Experimental results in Table 1 demonstrated that in the hydrocarbofunctionalization of 4-pentenoic acid derivatives, the use of PAQ directing group completely prevents the formation of side products from β -H elimination. We calculated the activation free energies of the competing intramolecular protodepalladation (**TS3**, **TS5**) and β -H elimination (**TS4**, **TS6**) pathways from 6-membered palladacycle intermediates bearing the AQ and PAQ groups (Fig. 3B). With the PAQ group, **TS3**, which eventually leads to the experimentally observed hydrocarbofunctionalization product, is 7.1 kcal/mol more stable than the β -H elimination transition state **TS4**. **TS4** is destabilized due to the dissociation of the pyridine group to accommodate the hydride that is being transferred to the square planar Pd. In contrast, the intramolecular protodepalladation (**TS3**) does not require the partial dissociation of the tridentate directing group. In addition, the strongly electron-donating PAQ directing group stabilizes the partial positive charge on the Pd center in the protodepalladation transition state. With the AQ directing group, the selectivity is

completely switched to favor β -H elimination (**TS6**). These computational results highlight the important role of the tridentate directing group in suppressing the β -H elimination and promoting the protodepalladation.

Based on the data presented above, we propose the mechanism in Fig. 3C. Pd(II) first coordinates to the substrate (**15**), acting as a π -Lewis acid activator to the alkene (**16**), which undergoes nucleopalladation to form a 5-5-6 tricyclic palladacycle intermediate (**17**). Intramolecular protodepalladation (**18**), followed by dissociation of the Pd(II) catalyst from the directing group affords the hydrofunctionalized product. This mechanism was confirmed by the DFT-computed reaction energy profile shown in Fig. 3D.

In conclusion, we have demonstrated the use of pincer-like tridentate directing groups for stabilization of elusive 6-membered palladacycle intermediates. These new directing groups enable alkene functionalization remote to existing functional groups (e.g. δ -functionalization of alkenyl carboxylic acid derivatives). This fundamental study of regioselectivity in alkene functionalization led to the development of a new family of auxiliaries for controlling metalacycle size that could find broad utility in synthesis and catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was financially supported by The Scripps Research Institute (TSRI), Pfizer, Inc., the National Institutes of Health (1R35GM125052) and the NSF (CHE-1654122). We gratefully acknowledge the DAAD for a postdoctoral fellowship (M.L.O.), the Chemistry Department at King's College, London, for an Alumni Overseas Summer Studentship (J.L.T.), and the Donald E. and Delia B. Baxter Foundation and the National Science Foundation (NSF/DGE-1346837) for graduate fellowships (J.A.G.). We thank Prof. Arnold L. Rheingold and Dr. Milan Gembicky (UCSD) for X-ray crystallographic analysis, Dr. Dee-Hua Huang and Dr. Laura Pasternack for assistance with NMR spectroscopy, and Dr. Jason S. Chen for ee determination of compound **7g**.

References

1. Evans DA, Fu GC, Hoveyda AH. *J Am Chem Soc.* 1992; 114:6671–6679.
2. Yang YF, Chen G, Hong X, Yu JQ, Houk KN. *J Am Chem Soc.* 2017; 139:8514–8521. [PubMed: 28578572]
3. (a) Reddy BVS, Reddy LR, Corey EJ. *Org Lett.* 2006; 8:3391–3394. [PubMed: 16836413] (b) Ano Y, Tobisu M, Chatani N. *J Am Chem Soc.* 2011; 133:12984–12986. [PubMed: 21790123] (c) He G, Zhao Y, Zhang S, Lu C, Chen G. *J Am Chem Soc.* 2012; 134:3–6. [PubMed: 22191666] (d) Nades ET, Daugulis O. *J Am Chem Soc.* 2012; 134:7–10. [PubMed: 22206416] (e) Zhang SY, He G, Nack WA, Zhao Y, Li Q, Chen G. *J Am Chem Soc.* 2013; 135:2124–2127. [PubMed: 23350845] (f) He G, Zhang SY, Nack WA, Li Q, Chen G. *Angew Chem Int Ed.* 2013; 52:11124–11128. (g) Cui W, Chen S, Wu JQ, Zhao X, Hu W, Wang H. *Org Lett.* 2014; 16:4288–4291. [PubMed: 25089912] (h) He G, Zhang SY, Nack WA, Pearson R, Rabb-Lynch J, Chen G. *Org Lett.* 2014; 16:6488–6491. [PubMed: 25487778] (i) Li S, Zhu RY, Xiao KJ, Yu JQ. *Angew Chem Int Ed.* 2016; 55:4317–4321. (j) Xu JW, Zhang ZZ, Rao WH, Shi BF. *J Am Chem Soc.* 2016; 138:10750–10753. [PubMed: 27529372]
4. Yang K, Gurak JA Jr, Liu Z, Engle KM. *J Am Chem Soc.* 2016; 138:14705–14712. [PubMed: 27709911]
5. Daugulis O, Roane J, Tran LD. *Acc Chem Res.* 2015; 48:1053–1064. [PubMed: 25756616]
6. For earlier examples of intramolecular hydrocarbofunctionalization, see: Pei T, Widenhoefer RA. *J Am Chem Soc.* 2001; 123:11290–11291. [PubMed: 11697972]

7. For recent reviews, see: Selander N, Szabó KJ. Chem Rev. 2011; 111:2048–2076. [PubMed: 21087012] van Koten G, Milstein D. Organometallic Pincer Chemistry. Springer-Verlag 2013 O'Reilly ME, Veige AS. Chem Soc Rev. 2014; 43:6325–6369. [PubMed: 24927219]
8. PNP pincer ligands have previously been used in Pd(II)-catalyzed intramolecular hydroamination: Cochran BM, Michael FE. J Am Chem Soc. 2008; 130:2786–2792. [PubMed: 18254623]
9. For substrates that gave only moderate yields, the major by-product observed was usually isomerized starting material V.
10. For similar hydrolysis/decarboxylation transformations of substituted Meldrum's Acid derivatives, see: Knoepfel TF, Carreira EM. J Am Chem Soc. 2003; 125:6054–6055. [PubMed: 12785825] Nutaitis CF, Schultz RA, Obaza J, Smith FX. J Org Chem. 1980; 45:4606–4608.
11. The major diastereoisomer was tentatively assigned by analogy to previously observed stereocontrol in the nucleopalladation step: Liu Z, Zeng T, Yang KS, Engle KM. J Am Chem Soc. 2016; 138:15122. [PubMed: 27779861]
12. Due to low solubility of substrates bearing the PAQ directing group, our mechanistic experiments focused on amine-derived substrates bearing the PPA group, which were easier to handle.
13. See SI for computational methods.
14. (a) Omer HM, Liu P. J Am Chem Soc. 2017; 139:9909–9920. [PubMed: 28664728] (b) Deb A, Hazra A, Peng Q, Paton RS, Maiti D. J Am Chem Soc. 2017; 139:763–775. [PubMed: 27997801]

A. Previous work: unsuccessful hydrofunctionalization via 6-membered palladacycle **B. This work: accessing challenging 6-membered palladacycles with tridentate directing groups** **Figure 1.**

Development of a tridentate directing group to stabilize 6-membered palladacycle intermediates.

A. Homoallylamine Substrates **B. Bishomoallylamine Substrate** **Figure 2.**

Functionalization of amine derivatives

PPA = 2,2'-bipyridylamide. Reaction conditions (0.1 mmol scale): **C** NuH (1.5 equiv), Pd(OAc)₂ (10 mol%), HOAc (0.5 equiv), MeCN, 120 °C, 24 h; **D** NuH (1.5 equiv), Pd(OAc)₂ (10 mol%), K₂CO₃ (1.0 equiv), HFIP, 120 °C, 24 h; Yields are of isolated products unless otherwise stated. ^a¹H NMR yield. ^bNuH = Meldrum's acid. ^cReaction conditions C. ^dReaction conditions D. ^eketo/enol = 6.8. ^fenol/keto = 3.6. ^gReaction conditions A.

Figure 3.
Proposed Reaction Mechanism

Scheme 1.
Directing group removal and recovery

Scheme 2.**8-Functionalization of carboxylic acid derivatives**

PAQ = 2-pyridyl-8-aminoquinoline. Reaction conditions (0.1 mmol scale): **A** 10% Pd(OAc)₂, 0.5 equiv HOAc, 2 M MeCN, 85 °C, 4 h; **B** 10% Pd(OAc)₂, 1.0 equiv K₂CO₃, 2 M HFIP, 85 °C, 24 h. All yields are of isolated products unless otherwise noted. ^aReaction conditions A. ^bReaction conditions B. ^c¹H NMR yield. ^dNuH = Meldrum's acid.

Scheme 3.

Hydrofunctionalization of L-allylglycine derivatives

Scheme 4. Directing-group-controlled regioselectivity of alkene hydrofunctionalization^a

^aReaction conditions: 4-hydroxycoumarin (1.5 equiv), Pd(OAc)₂ (10 mol%), HOAc (0.5 equiv), MeCN, 120 °C, 4 h. Yields are of isolated products.

Table 1

Optimization of tridentate directing group structure

Directing Group (DG)	II : III : IV : V : I ^a
A (AQ)	13 : 45 : 10 : 11 : 0
B (PIP)	0 : 0 : 21 : 39 : 20
C R = H	23 : 0 : 0 : 32 : 0
D R = Me	28 : 0 : 0 : 25 : 9
E R = Bn	32 : 0 : 0 : 14 : 11
F	0 : 0 : 0 : 22 : 29
Directing Group (DG)	II : III : IV : V : I ^a
G	15 : 12 : 0 : 0 : 10
H	48 : 3 : 18 : 0 : 0
J (PAQ)	97 : 0 : 0 : 0 : 0

AQ = 8-aminoquinoline, PIP = 2-(pyridin-2-yl)isopropyl amine, PAQ = 2-pyridyl-8-aminoquinoline, NuH = 4-hydroxycoumarin.

^a¹H NMR yields and ratios.^bIn most reactions, V is a 0.75 : 0.25 mixture of the depicted compound and its conjugated isomer.