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

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Supporting Information

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-homoallylamines, under Pd(II) catalysis. In conjunction with previous findings, we demonstrate regiodivergent hydrofunctionalization of 3-butenoic 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.

Substrate directivity is a powerful and well-established approach in organic synthesis and transition-metal catalysis.[1] In coordination-controlled reactions, the kinetics and thermodynamics of metallacycle formation dictate stereo- and regioselectivity. In the context of Pd(II) catalysis, directed functionalization of C−H bonds and C−C π-bonds, including hydrofunctionalization of alkenes,[2] has received significant attention. With reactions involving alkyl palladacycles, there is a preference for formation of a 5-membered ring, which has limited such reactions to substrates containing functional groups in close proximity to the reaction site. Remote functionalization involving larger alkyl palladacycles is a less well-established approach. For instance, 6-membered palladacycles have only been implicated when the 5-membered intermediate is sterically disfavored.[3] Overcoming innate reactivity preferences to achieve cyclometalation control through specifically tailored directing groups or ligands 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-butenoic acid derivatives bearing Daugulis's 8-aminoquinoline (AQ) directing group.[2b,4] The mechanism of this reaction involves γ-selective addition to a Pd(II)-bound alkene to form a 5-membered palladacycle. When we attempted to extend this concept to 6-membered palladacycles, only 11% of the desired product **2** was formed, with the remainder of the starting material being consumed by pathways involving β-hydride (β-H) elimination or alkene isomerization followed by functionalization (Figure 1A).[5] Since β-H elimination requires

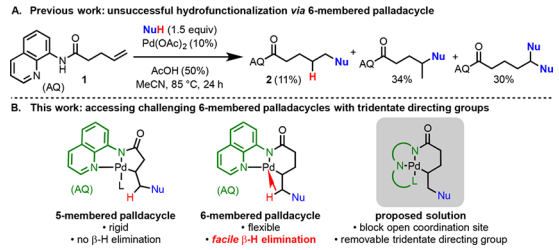

Figure 1. Design of tridentate directing groups to stabilize 6-membered palladacycles.

an open coordination site on the metal catalyst, we hypothesized that a tridentate directing group,[6] inspired by the well-known family of pincer ligands,[7] would suppress these undesired side-reactions and stabilize the 6-membered palladacycle (Figure 1B). At the outset, we realized we would need to tune steric and electronic properties of the third binding site to allow for nucleopalladation, while still ensuring binding to the metal catalyst was reversible.[8]

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 (Table 1). AQ-containing substrate **IA** afforded 13% of the desired product **II** 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 an increase in formation of **II** with 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 AQ. While thiophene (**G**) and pyrimidine (**H**) were ineffective, we were pleased that a 2-pyridyl group (**J**) successfully minimized detrimental side-reactions, furnishing 97% of the desired product by ^{1}H 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 g scale and easily recycled (*vide infra*).

With this optimized directing group in hand, we proceeded to investigate the substrate scope of this method (Scheme 1). 4-

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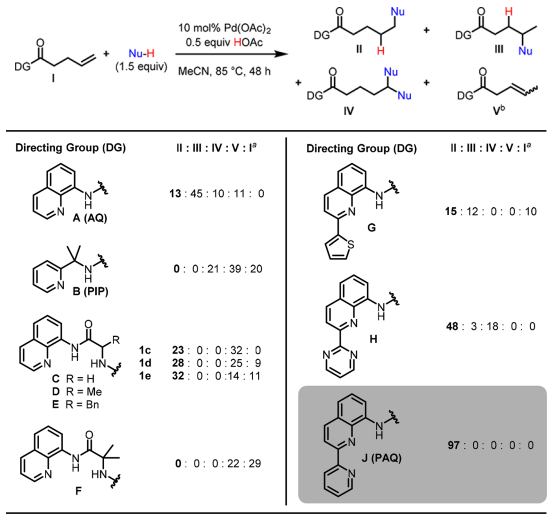
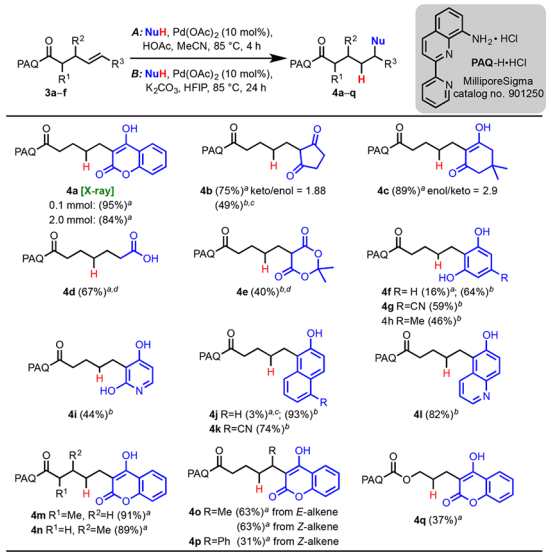
Table 1. Optimization of Tridentate Directing Group*



*NuH = 4-hydroxycoumarin. [a]^{1}H NMR yields and ratios. [b]In most reactions, **V** is a 3:1 mixture of the depicted compound and its conjugated isomer.

Scheme 1. δ-Functionalization of Carboxylic Acid Derivatives*

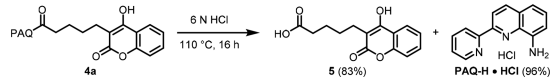


*Conditions (0.1 mmol scale): ***A*** 1.5 equiv NuH, 10% Pd(OAc)$_2$, 0.5 equiv HOAc, MeCN, 85 °C, 4 h; ***B*** 1.5 equiv NuH, 10% Pd(OAc)$_2$, 1.0 equiv K_2CO_3, HFIP, 85 °C, 24 h. All yields are of isolated products unless otherwise noted. [a]Reaction conditions ***A***. [b]Reaction conditions ***B***. [c]^{1}H NMR yield. [d]NuH = Meldrum's acid.

Hydroxycoumarin and cyclic 1,3-dicarbonyl compounds reacted readily under conditions ***A*** (HOAc/MeCN), giving the corresponding products **4a–c** in high yields. Meldrum's acid was hydrolyzed *in situ* to give decarboxylated product **4d**;[9] however, under conditions ***B*** (K_2CO_3/HFIP) the 1,3-dicarbonyl moiety remained intact (**4e**). Electron-rich aromatics were competent nucleophiles under these conditions as well (**4f–l**). Electron-donating or -withdrawing groups on the arene did not affect the yields substantially (**4g–h**, **4k**), and the reaction tolerated heteroaromatic nucleophiles (**4i**, **4l**). On the alkene side, α- and β-substituents on the carbon chain are tolerated (**4m**, **4n**). Gratifyingly, internal alkenes also show moderate reactivity (**4o**, **4p**), and allyl alcohol, when masked as the PAQ carbamate, also underwent hydrofunctionalization in moderate yield (**4q**).

To demonstrate scalability, product **4a** was synthesized on 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 PAQ group in 96% yield (Scheme 2).

Scheme 2. Directing Group Removal and Recovery



Next, we sought to extend this concept from carboxylic acids to amine substrates (Figure 2). A brief optimization (see SI) revealed 2,2′-bipyridylamide (PPA), a directing group conveniently prepared on 10 gram scale, to be most effective for this substrate class. Like PAQ, this directing group contains three nitrogen-based binding sites, one X-type and two L-type, forming a pincer-like ligand system around the metal center. Both PAQ and PPA are electron-donating and strongly coordinating, stabilizing the partially positively charged Pd during proto-depalladation (*vide infra*). 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*-methylindole, which was unreactive with **3**, afforded **7f** in moderate yield.

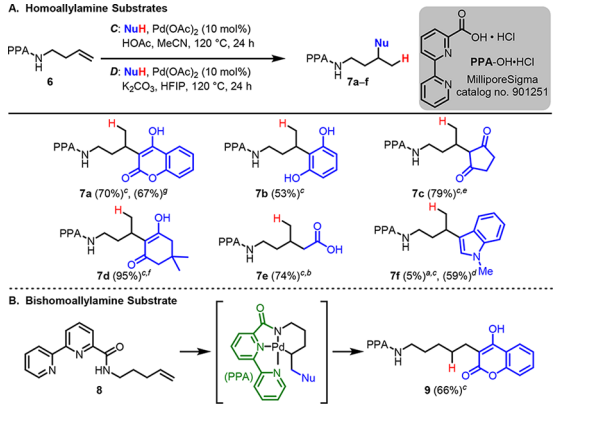
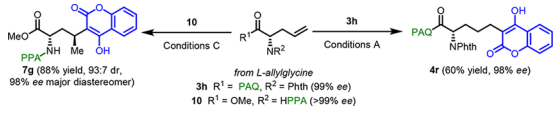


Figure 2. Functionalization of amine derivatives. Conditions (0.1 mmol scale): ***C*** 1.5 equiv NuH, 10% Pd(OAc)$_2$, 0.5 equiv HOAc, MeCN, 120 °C, 24 h; ***D*** 1.5 equiv NuH, 10% Pd(OAc)$_2$, 1.0 equiv K_2CO_3, HFIP, 120 °C, 24 h; Yields are of isolated products unless otherwise stated. [a]^{1}H NMR yield. [b]NuH = Meldrum's acid. [c]Reaction conditions ***C***. [d]Reaction conditions ***D***. [e]keto/enol = 6.8. [f]enol/keto = 3.6. [g]Reaction conditions ***A***.

By employing these two directing groups, we were able to hydrofunctionalize L-allylglycine in a regiodivergent manner (Scheme 3). Masking the carboxylic acid moiety with the PAQ directing group allowed for anti-Markovnikov selectivity,

Scheme 3. Hydrofunctionalization of L-Allylglycine Derivatives



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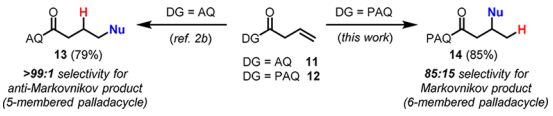
providing hydrofunctionalized product **4r** in 60% yield. Using the PPA directing group to mask the amine moiety, on the other hand, we obtained 88% of the Markovnikov product **7g** without erosion of stereochemistry in the major diastereoisomer.[10]

Having established that tridentate directing groups are capable of stabilizing 6-membered palladacycles, we next questioned whether they could override the regioselectivity preference for 5-membered nucleopalladation with 3-butenoic acid substrates. As reported, substrate **11** bearing the bidentate AQ group affords anti-Markovnikov addition product **13**.[2b] Under the same reaction conditions, the tridentate PAQ directing group instead affords primarily Markovnikov product **14** (85:15 r.r.) (Scheme 4). Our working hypothesis that is PAQ favors the 6-membered

Scheme 4. Directing-Group-Controlled Regioselectivity of Alkene Hydrofunctionalization*



*Conditions: 4-hydroxycoumarin (1.5 equiv), 10% $Pd(OAc)_2$, HOAc, MeCN, 120 °C, 4 h. Yields are of isolated products.

nucleopalladation pathway in this case due to strain release in the 5−5−6 square-planar palladatricycle compared to the alternative 5−5−5 palladatricycle in the 5-membered pathway. Broadly speaking, these results indicate end-users could control the regiochemical course of their reactions through choice of directing group, without need for other biasing factors in the starting material.

Given the unique reactivity enabled by these directing groups, it is vital 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 mechanistic and computational experiments were performed (Figure 3).[11] When we exposed alkene **6** to 1 equiv $Pd(OAc)_2$ in MeCN at room temperature, complex **15** was formed in 86% yield (Figure 3A), a process that was calculated to be highly exergonic by 17.1 kcal/mol (Figure 3D). Notably, the corresponding processes involving bidentate directing groups are much less exergonic.[12] In our previous results with AQ, the corresponding π-alkene complex is formed under analogous conditions.[2b]

When complex **15** was treated with 4-hydroxycoumarin, we expected to observe the corresponding nucleopalladated alkylpalladium(II) species **17**.[2b] However, we were surprised to observe product-bound Pd(II) complex **18** instead (Figure 3A). With the AQ directing group, nucleopalladation occurs at room temperature, but protodepalladation requires elevated temperatures.[2b] For PAA, both steps take place at room temperature, consistent with a mechanism in which ligand exchange is slow; unsurprisingly, dissociation of the pincer-like tridentate directing group was calculated to be highly endergonic by 18.6 kcal/mol (Figure 3D). Furthermore, no external acid is necessary, suggesting 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 and is highly exergonic.

When complex **18** was used as a precatalyst with 1,3-cyclopentanedione as the nucleophile, 79% hydrofunctionalized product **7c** was isolated together with 7% **7a** (Figure 3A). This result establishes **18** is catalytically competent and that ligand exchange takes place during the catalytic cycle.

In Table 1, we showed the tridentate PAQ directing group completely suppresses β-H elimination. We calculated the

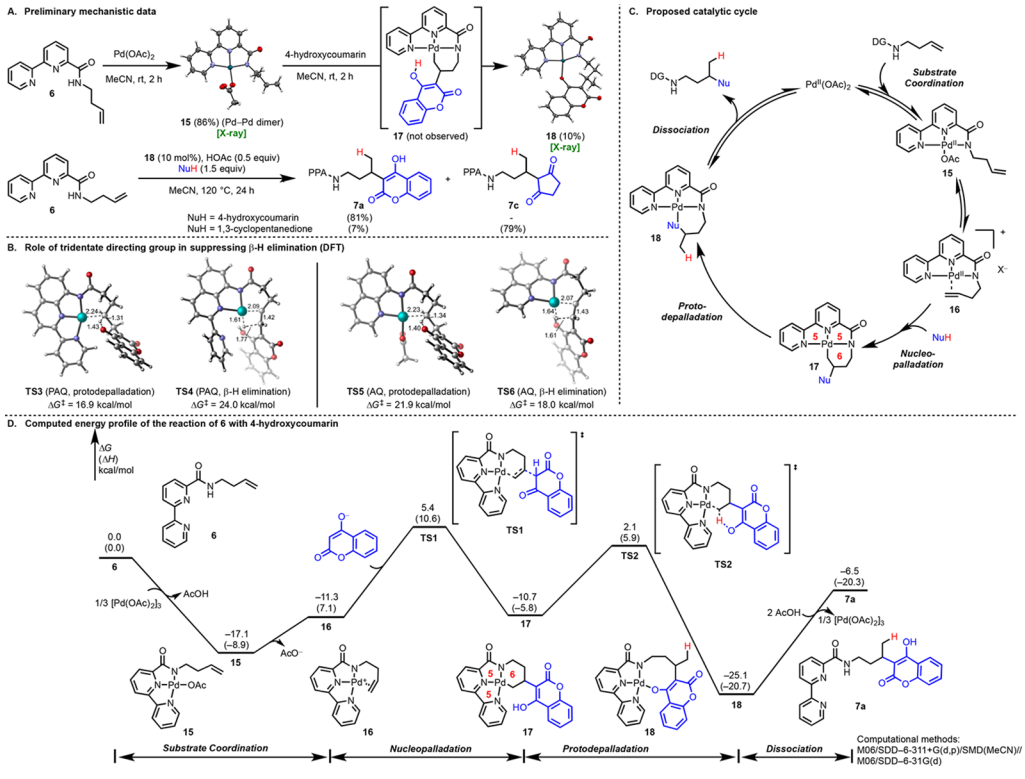


Figure 3. Mechanistic and computational data.

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activation free energies of the competing intramolecular protodepalladation (**TS3**, **TS5**) and β-H elimination (**TS4**, **TS6**) pathways from 6-membered palladacycle intermediates bearing AQ and PAQ groups (Figure 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**, which is destabilized due to dissociation of pyridine to accommodate the hydride being transferred to Pd. In contrast, intramolecular protodepalladation (**TS3**) does not require partial dissociation of the directing group. With AQ, the selectivity is reversed to favor β-H elimination (**TS6**). These computational results highlight the important role of the tridentate directing group in suppressing β-H elimination and promoting protodepalladation.

On the basis of the data presented, we propose the mechanism in Figure 3C: Pd(II) 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 palladatricycle intermediate (**17**). Intramolecular protodepalladation (**18**), followed by dissociation of the Pd(II) catalyst from the directing group affords the hydrofunctionalized product. This mechanism is supported by the DFT-computed reaction energy profile shown in Figure 3D.

In conclusion, we have demonstrated use of pincer-like tridentate directing groups for stabilization of elusive 6-membered palladacycles. We postulate this stabilization may result from strain release in going from a 5−5−5-tricyclic system around a square-planar, central Pd atom to a 5−5−6 system. These new directing groups enable remote alkene functionalization (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 metallacycle size that could find broad utility in synthesis and catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b08383.

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

NMR spectra in MNOVA format (ZIP)

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

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

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

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Notes

The authors declare no competing financial interest.

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