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

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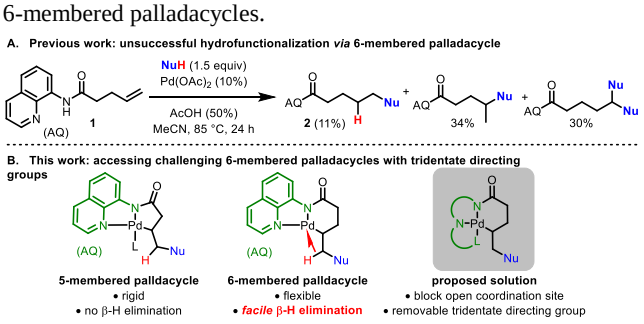
Supporting Information Placeholder

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 strong 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.[3–4] Overcoming innate reactivity preferences to achieve cyclometallation control through specifically tailored directing groups or ligands remains a significant challenge.

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



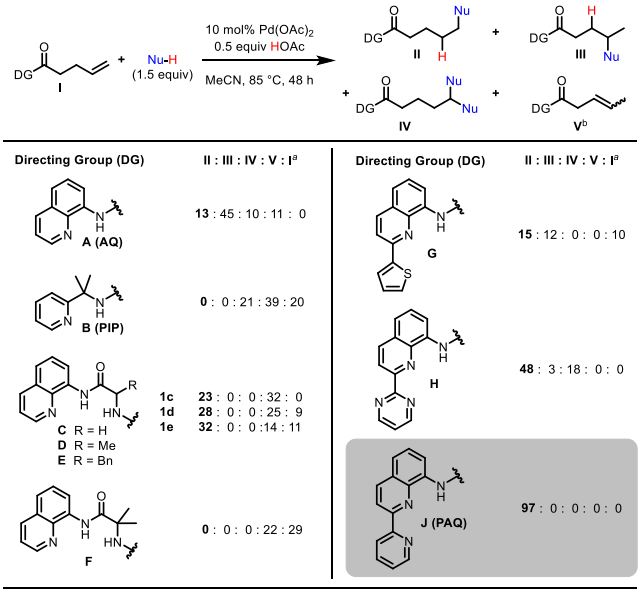
This limitation is illustrated by a recent report from our group. We described a method for Pd(II)-catalyzed hydrocarbofunctionalization of 3-butenoic acid derivatives bearing Daugulis's 8-aminoquinoline (AQ) directing group.[2b–c,5] The mechanism of this reaction involves γ-selective addition to a Pd(II)-bound 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 *beta*-hydride (β-H) elimination or alkene isomerization followed by functionalization (Fig. 1A).[3] Since β-H elimination requires 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 (Fig. 1B). At the outset, we realized that we would need to tune the steric and electronic properties of the third binding site to allow for nucleopalladation, while still ensuring that 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 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 AQ. While thiophene (**G**) and pyrimidine (**H**) were ineffective, we were pleased to see 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-gram scale and easily recycled (*vide infra*).

With this optimized directing group in hand, we proceeded to investigate the substrate scope of this method (Scheme 2). 4-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

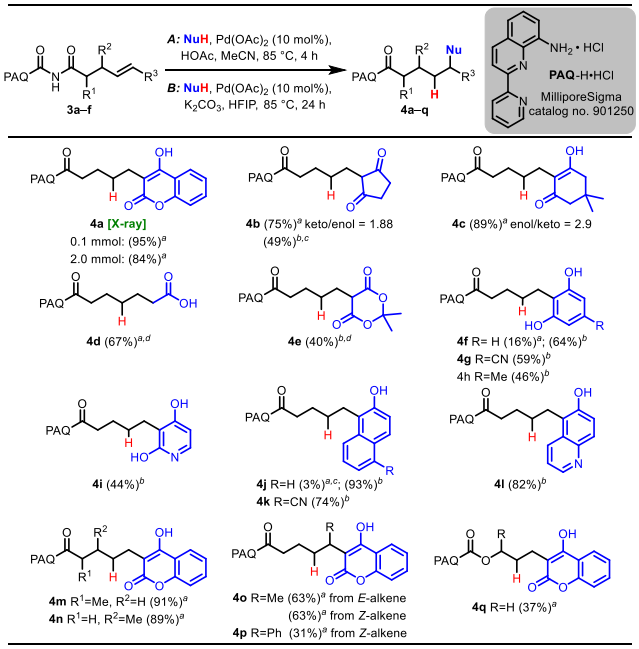
these conditions as well (**4f**–**l**). Electron-donating or -withdrawing groups on the arene did not affect the yields substantially (**4g**–**h**, **4k**), and the reaction tolerated heteroaromatic nucleophiles (**4i**, **4l**). On the alkene side, α- and β-substituents on the carbon chain are well tolerated (**4m**–**n**). Gratifyingly, internal alkenes also show moderate reactivity (**4o**–**p**). Pleasingly, allyl alcohol—when masked as its corresponding PAQ carbamate—underwent hydrofunctionalization in moderate yields (**4q**).

Table 1. Optimization of tridentate directing group structure



NuH = 4-hydroxycoumarin. [a]^{1}H NMR yields and ratios. [b]In most reactions, **V** is a 0.75 : 0.25 mixture of the depicted compound and its conjugated isomer.

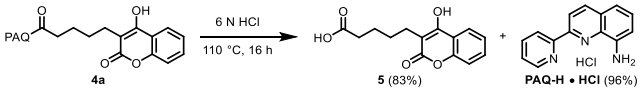
Scheme 2. δ-Functionalization of carboxylic acid derivatives



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.

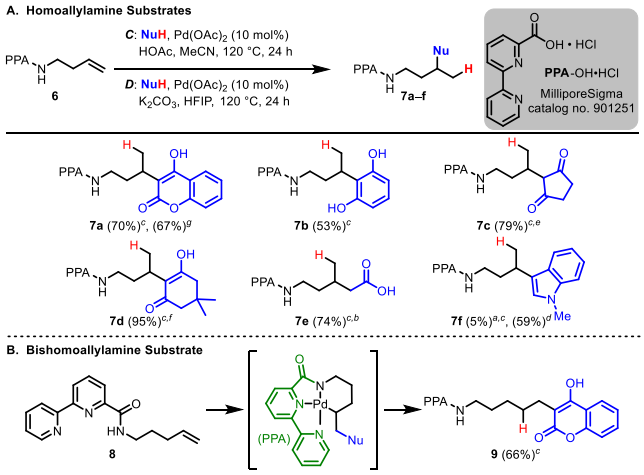
To demonstrate scalability, product **4a** was synthesized on a 2 mmol scale, affording 784 mg (84% yield). Removal of the directing group with 6 N HCl yielded 83% of carboxylic acid **5** and allowed for recovery of the directing group in 96% yield (Scheme 1).

Scheme 1. Directing group removal and recovery



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. Like PAQ, this directing group presents 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 protodepalladation (*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*-methyl indole, which was unreactive with **3**, afforded **7f** in moderate yield.

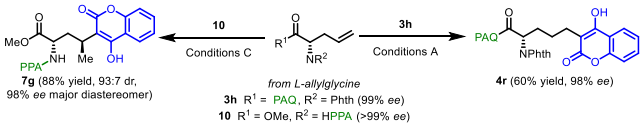
Figure 2. Functionalization of amine derivatives



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, 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.[10]

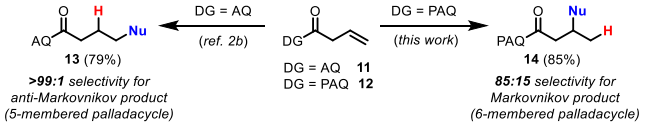
Scheme 3. Hydrofunctionalization of L-allylglycine derivatives



Having established that tridentate directing groups are capable of stabilizing 6-membered palladacycles, we next questioned

whether they could override the regioselectivity preference of 3-butenoic acid substrates for 5-membered nucleopalladation. As previously 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 Our working hypothesis is that PAQ favors the six-membered 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 five-membered pathway. Broadly speaking, these results indicate that end-users could control the regiochemical course of their reactions through choice of directing group, without the need for other biasing factors in the starting material.

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

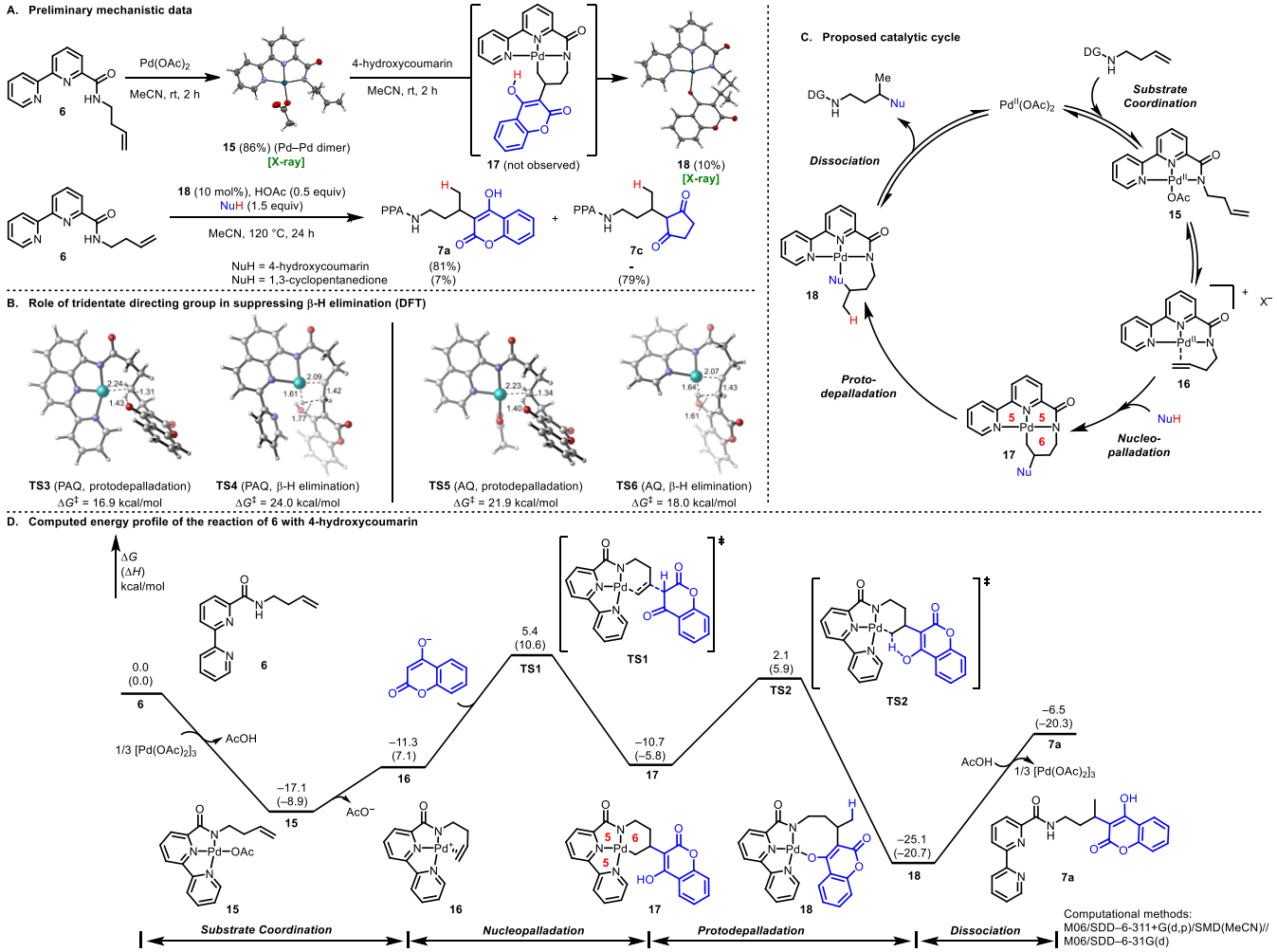


Conditions: 4-hydroxycoumarin (1.5 equiv), 10% $Pd(OAc)_2$, HOAc, MeCN, 120 °C, 4 h. Yields are of isolated products.

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 (Fig. 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 (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.[12] In our previous results with AQ, *e.g.*, 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 (Fig. 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 which is 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 (Fig. 3D). Furthermore, no external acid is necessary, 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 and is highly exergonic.

Figure 3. Proposed reaction mechanism



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

In Table 1 we showed that the tridentate PAQ directing group completely suppresses 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 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**, 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.

Based on the data presented above, we propose the mechanism in Fig. 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 Fig. 3D.

In conclusion, we have demonstrated the use of pincer-like tridentate directing groups for stabilization of elusive 6-membered palladacycles. We believe that 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.

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)

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Notes

The authors declare no competing financial interests.

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