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Directed, Regiocontrolled Hydroamination of Unactivated Alkenes via Protodepalladation

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Supporting Information

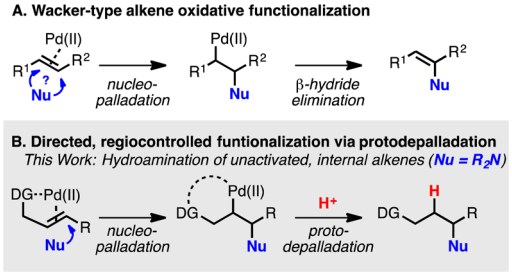
ABSTRACT: A directed, regiocontrolled hydroamination of unactivated terminal and internal alkenes is reported. The reaction is catalyzed by palladium(II) acetate and is compatible with a variety of nitrogen nucleophiles. A removable bidentate directing group is used to control the regiochemistry, prevent β-hydride elimination, and stabilize the nucleopalladated intermediate, facilitating a protodepalladation event. This method affords highly functionalized γ-amino acids in good yields with high regioselectivity.

Since its discovery in 1956, the Wacker oxidation has transformed the field of synthetic chemistry, ushering in the modern era of homogeneous palladium catalysis. The Wacker process involves a key nucleopalladation step to generate an alkylpalladium(II) intermediate, which then undergoes β-hydride elimination to give the oxidized alkene product.[1] Though nucleopalladation has been extensively studied and found to take place with many different classes of nucleophiles,[2] significant challenges remain in realizing the full potential of this elementary reaction as a synthetic tool for functionalizing alkenes into versatile building blocks. First, the regioselectivity of nucleophilic addition is typically highly dependent on the steric and electronic properties of the alkene. Second, the nucleopalladated intermediate is very short-lived when there is a *syn* hydrogen at the β position, as it undergoes facile β-hydride elimination to generate an alkene. Although some success has been achieved in trapping these intermediates with oxidants,[2a,b,3] achieving selective protonation of the resultant C−Pd(II) bond[4] to give hydrofunctionalized products, while highly appealing, remains underdeveloped. Here, we describe a new catalytic intermolecular hydroamination method for unactivated alkene substrates, wherein a removable bidentate directing group enables regioselective aminopalladation and facilitates subsequent protodepalladation.

Hydroamination provides an efficient method for installing amines across an alkene in an atom-economical fashion, making it a highly appealing reaction with numerous strategic benefits in synthesis; however, classical methods have suffered from limitations, including harsh reaction conditions, poor chemo-, regio-, and stereoselectivity, and limited alkene and nitrogen nucleophile scope. Numerous transition-metal-catalyzed approaches have been developed to address these issues.[5] Three main reaction categories include: (1) "umpolung" metal-hydride addition followed by trapping with an N−O electrophile;[5e,6] (2) H• radical transfer followed by interception of the resulting alkyl radical with an electrophilic nitrogen source;[7] and (3) π-Lewis acid activation of an alkene to enable aminometalation, followed by protodemetalation (or in some cases, reductive demetalation).[8,9] One attractive aspect of the third approach is the ability to use simple nitrogen nucleophiles (i.e., N−H bonds) as both the source of the N and H atoms. In this context, excellent strides have been made with intramolecular reactions and with intermolecular reaction with activated alkenes (e.g., styrenes and norbornenes).[4a,8,9] Metal-catalyzed intermolecular reactions with unactivated alkenes have proven more challenging,[10] both in terms of reactivity and regiocontrol. Recently, Hull et al. have made significant progress on this front, reporting directed, regiocontrolled rhodium(I)-catalyzed hydroaminations of terminal allylic and homoallylic amines with secondary amines.[11] Developing approaches to enable regiocontrolled hydroamination with other alkene substrate classes (particularly with internal alkenes) and with alternative nitrogen nucleophiles (especially those that can be subsequently deprotected) remains a tremendous challenge.

In our reaction design, we were inspired by the versatility and applicability of nucleopalladation for functionalizing alkenes. Therefore, we sought to intercept an aza-Wacker aminopalladated intermediate[12] with a proton in a protodepalladation event to provide the hydroaminated product (Scheme 1). As mentioned above, two major challenges with this approach are regioselectivity and competing β-hydride elimination to form the enamine or allylic amine, which generally occurs much faster than protodemetalation. We hypothesized that both obstacles could be overcome by employing a removable bidentate directing group. We envisioned that the directing group would guide regioselective addition of the nucleophile and would

Scheme 1. Comparison of Wacker-Type Alkene Oxidation and Hydrofunctionalization via Nucleopalladation



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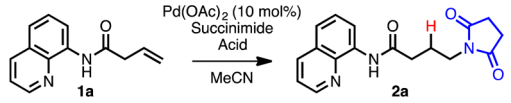
stabilize the nucleopalladated intermediate, thereby preventing β-hydride elimination.[13] As a result, the aminopalladated intermediate would have a sufficiently long lifetime to undergo protodepalladation.

We chose the simple alkene 3-butenoic acid and the masked ammonia nucleophile succinimide for our optimization studies (Table 1). After initial screening revealed promising results with the removable bidentate 8-aminoquinoline auxiliary developed by Daugulis (see Supporting Information (SI)),[13a,b] we elected to use this directing group for further optimization. Our attention first turned to identifying a suitable reaction temperature to overcome the potentially high activation energy for the directed aminopalladation step.[14] No product was observed at room temperature (entry 1), but trace amounts of products were observed upon heating to 80 °C (entry 2). At 120 °C (entry 3), the product was formed in 16% yield. We then turned our attention to screening acids, anticipating that the installation of the hydrogen might occur by protodepalladation. Acids with lower pK_a values performed worse, and, in many cases, promoted the isomerization of the substrate to the α,β-unsaturated amide (entries 4–6). With this in mind, we next tested weaker acids (entries 7–9) and found benzoic acid to be quite effective, providing the desired product in 47% yield. We continued our optimization efforts by evaluating the effect of concentration (entries 10 and 11) and discovered that higher concentrations increased yield, with a concentration of 1.0 M leading to 94% yield of the desired product. Upon further optimization of succinimide and benzoic acid equivalents, palladium loading, and reaction time, the final optimized conditions gave quantitative yield of the desired product in only 4 h (entry 12).

Having finished optimization, we next investigated the scope of compatible nitrogen nucleophiles (Table 2). To our delight, a broad range of nucleophiles underwent hydroamination, many in moderate to high yields, showcasing the generality of this method. These nucleophiles included masked ammonia compounds that can easily be converted to primary amines upon deprotection. Succinimide (**2a**) gave nearly quantitative yield, while phthalimide (**2b**) was also converted cleanly to product in 89% yield. Tetrachlorophthalimide (**2c**) was slightly lower yielding than phthalimide, giving 78% yield. Increasing the ring size of the nucleophile from a five- to a six-membered ring (**2d**) decreased the yield. With hydantoin, which contains two potentially nucleophilic nitrogens, only one hydroamination product (**2e**) was observed. Peculiarly, the addition occurred at the less nucleophilic nitrogen, indicating that N–H bond acidity and/or attenuated nucleophilicity are important properties for nitrogen nucleophiles in this reaction. Importantly, other electron-deficient azaheterocycles (**2f**, **2g**, and **2j**) were also reactive. Some nitrogen nucleophiles performed slightly better with an alternative Brønsted acid promoter. For instance, by using pivalic acid instead of benzoic acid, Boc- and tosyl-protected amines (**2h** and **2i**) underwent hydroamination in 48% and 44% yields, respectively. Lastly, the reaction also performed well with hydroxamic acid derivatives (**2k** and **2l**).

Next, we explored the alkene substrate scope for this transformation (Table 3). We were pleased to find that a variety of unactivated terminal alkenes underwent *anti*-Markovnikov hydroamination in good to excellent yields. Monosubstitution at the α-position did not hinder addition across the alkene, even with bulkier groups such as isopropyl (**3c**) and benzyl (**3d**) substituents. Hydroamination of the sterically congested α,α-disubstituted substrate proceeded in relatively good yield, although higher palladium loading and concentration were required (**3e**). The presence of a pendant tertiary alcohol was well tolerated (**3f**). With a substrate containing two alkenes, the reaction proved to be chemoselective with preferential functionalization of the β-γ olefin over the δ-ε olefin (**3g**). Likely, the chemoselectivity arises from both the difference in the relative rates of formation of the five- vs seven-membered palladacycle and the fact that the distal olefin is more substituted

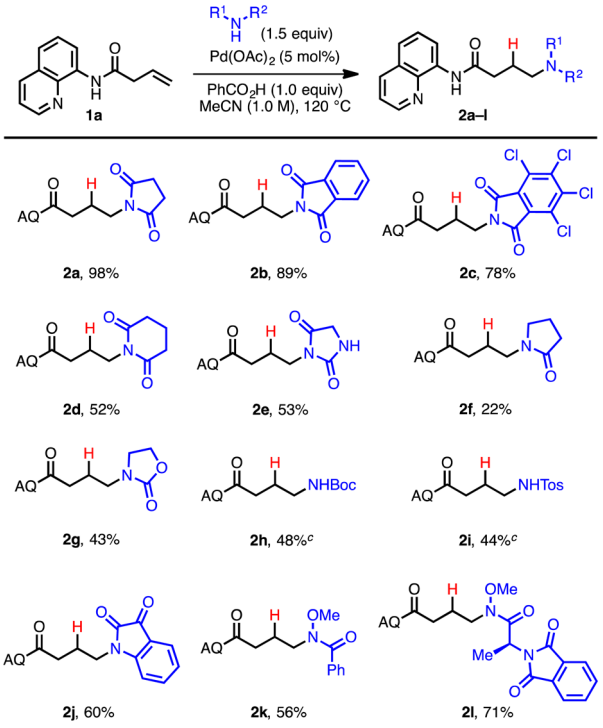
Table 1. Optimization of Regioselective Hydroamination[a]



entry	temp. (°C)	acid	conc. (M)	**1a** (%)[b]	**2a** (%)[b]
1	rt	none	0.1	90	ND
2	80	none	0.1	77	4
3	120	none	0.1	67	16
4	120	TFA	0.1	ND	1
5	120	TsOH	0.1	ND	ND
6	120	HCl	0.1	ND	ND
7	120	Meldrum's acid	0.1	24	18
8	120	pivalic acid	0.1	35	43
9	120	benzoic acid	0.1	26	47
10	120	benzoic acid	0.3	ND	79
11	120	benzoic acid	1.0	ND	94
12[c]	120	benzoic acid	1.0	ND	>99

[a]Alkene (1.0 equiv), succinimide (1.0 equiv), $Pd(OAc)_2$ (10 mol %), acid (1.0 equiv), 15 h. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with dibromomethane as an internal standard (ND = not detected). [c]Succinimide (1.5 equiv), $Pd(OAc)_2$ (5 mol %), 4 h.

Table 2. Scope of Nitrogen Nucleophiles[a,b]



[a]Alkene (1.0 equiv), nitrogen nucleophile (1.5 equiv), $Pd(OAc)_2$ (5 mol %), $PhCO_2H$ (1 equiv), MeCN (1.0 M), 120 °C, 4–48 h, AQ = 8-aminoquinoline. [b]Isolated yields. [c]Pivalic acid (1.0 equiv) instead of $PhCO_2H$.

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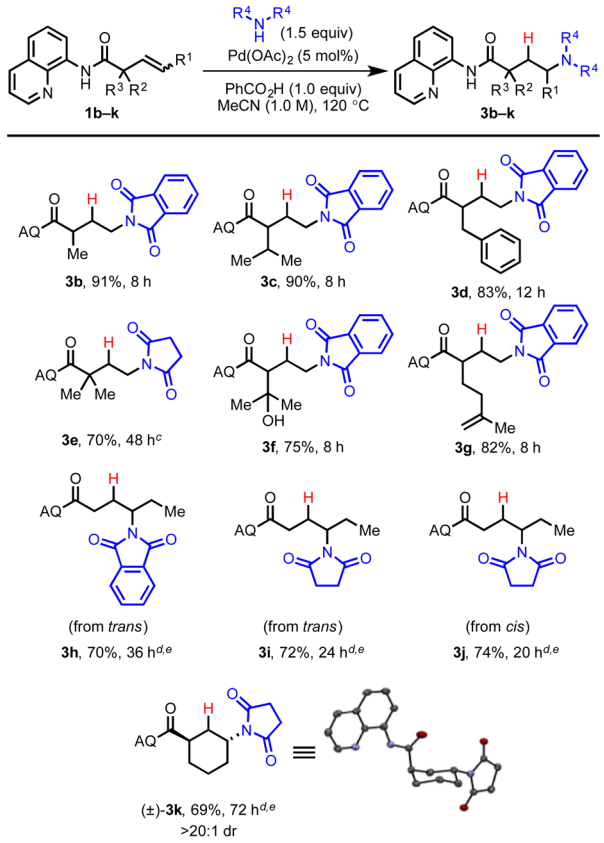
Table 3. Scope of Unactivated Alkenes[a,b]

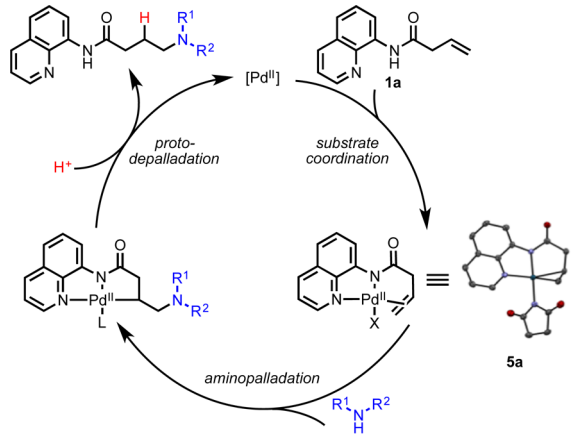


[a]Unless otherwise specified, reaction conditions are identical to those used in Table 2. [b]Isolated yields. [c]20 mol % $Pd(OAc)_2$ and 2.0 M MeCN. [d]10 mol % $Pd(OAc)_2$ and 4-OMe-$C_6H_4CO_2H$ (1 equiv). [e]The other potential regioisomer was not observed.

and thus more sterically hindered. We were excited to find that this method was also effective with unactivated internal alkenes under slightly reoptimized conditions with higher palladium loading (10 mol %) and 4-methoxybenzoic acid in lieu of benzoic acid. As expected, both the *trans*- and *cis*-3-hexenoic acids (**3i** and **3j**) yielded the same hydroamination product. To probe the mechanism of the aminopalladation step, we tested a *cis*-locked cyclohexyl olefin (**3k**) and found that succinimide added *trans* to the directing group, as confirmed by X-ray crystallography and NOE analysis (see Supporting Information). Assuming that palladium coordinates to the same face of the alkene as the directing group, this result is consistent with an *anti*-aminopalladation via outer-sphere attack.

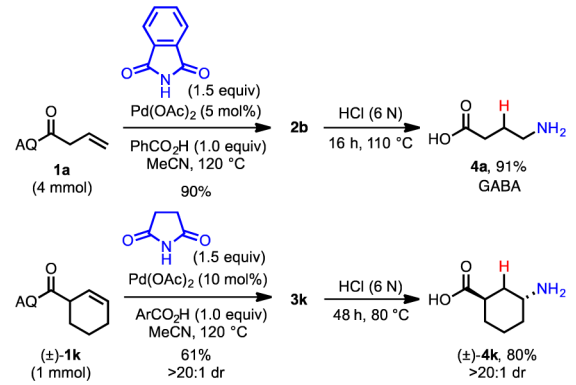
A plausible catalytic cycle is shown in Scheme 2. To begin, palladium(II) binds to the directing group, which brings it in close proximity to the olefin, facilitating π-Lewis acid activation. Indeed, by combining stoichmetric $Pd(OAc)_2$ with **1a** and succinimide, we were able to independently prepare and characterize complex **5a**.[15] Next, nucleopalladation takes place, which, at least in the case of **3k**, occurs via an outer-sphere mechanism to give the *trans*-nucleopalladated intermediate.[15,16] Because of the stability and conformational rigidity imparted by the directing group, the palladacycle does not undergo β-hydride elimination and instead is sufficiently long-lived to be intercepted with a proton in a protodepalladation step[4,13b] to form the hydroaminated product and regenerate the active palladium catalyst.

Scheme 2. Proposed Catalytic Cycle



To establish the preparative utility of this hydroamination method for accessing functionalized γ-amino acids, we performed two representative reactions on larger scale (Scheme 3). Gratifyingly, both provided yields consistent with the small-

Scheme 3. Hydroamination Scale-Up and Directing Group Removal



scale trials. The hydroaminated products were subsequently treated with acid to promote hydrolysis of both the directing group and the imide protecting group in a single step. Both substrates underwent double hydrolysis smoothly to provide **4a** and **4k** in 91% and 80% yields, respectively. The unmasked products are γ-aminobutyric acid derivatives, demonstrating that this method can expedite access to highly functionalized bioactive compounds.

In summary, we have demonstrated a regiocontrolled hydroamination reaction of unactivated olefins that is compatible with a range of nitrogen nucleophiles. The removable 8-aminoquinoline directing group dictates the regioselectivity and prevents β-hydride elimination. The mechanism appears to involve nucleopalladation followed by protodepalladation. Future work will focus on further mechanistic investigations as well as expanding the nucleophile scope.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02718.

Experiment details, spectral data, copies of ^1H and ^{13}C NMR spectra (PDF)

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X-ray crystallographic data (CIF)
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Notes

The authors declare no competing financial interest.

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(16) At this stage, we have not confirmed whether all of the examples in this manuscript proceed via *anti*-nucleopalladation or whether the mechanism of this step is dependent on the identity of the alkene and/or nitrogen nucleophile.

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