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Pd-catalyzed anti-Markovnikov selective oxidative amination

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Abstract

In recent years the synthesis of amines and other nitrogen containing motifs has been a major area of research in organic chemistry due to their being widely represented in biologically active molecules. Current strategies rely on a multistep approach and require one reactant to be activated prior to the carbon-nitrogen bond formation. This leads to reaction inefficiency and functional group intolerance. As such, a general approach to the synthesis of nitrogen-containing compounds from readily available and benign starting materials is highly desirable. Here we present a Pd-catalyzed oxidative amination reaction, where the addition of the nitrogen occurs at the less substituted carbon of a double bond, in what is known as anti-Markovnikov selectivity. Alkenes are shown to react with imides in the presence of a palladate catalyst to generate the terminal imide via *trans*-aminopalladation. Subsequently, olefin isomerization occurs to afford the thermodynamically favored products. Both the scope of the transformation and mechanistic investigations are reported.

Alkene amination reactions, including hydro- and oxidative amination, are atom-economical approaches to the synthesis of ubiquitous C–N bonds.[1–7] Oxidative amination, also known as the aza-Wacker oxidation, differs from hydroamination reactions in that it retains the degree of unsaturation in the product, allowing for further elaboration of this functionality.[3–7] As terminal amines are prevalent in pharmaceuticals, especially distal to polar functionalities,[8] the development of an anti-Markovnikov selective aza-Wacker oxidation of unactivated alkenes would represent a significant advance. Such a process would constitute a novel approach to the remote, anti-Markovnikov amination of organic molecules, and represent a new, powerful disconnection in organic synthesis. Additionally, when performed aerobically, this transformation would couple two easily accessible starting materials and would generate only an equivalent of H_2O as waste.

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Author Contributions

D.G.K. and K.L.H. conceived and designed the experiments and wrote the manuscript. D.G.K. and P.J.W. discovered the reaction. D.G.K., J.L.K, and S.N.G. performed the experiments.

Data availability

Synthetic procedures, NMR spectra and characterization for all new compounds, kinetic plots, deuterium labelling data, and X-ray diffraction data, are available within this Article and its Supplementary Information. X-Ray structural data for the tetrachloropalladate have also been deposited with the Cambridge Crystallographic Data Centre under numbers 1548343and are available from CCDC in cif format. Data are also available from the corresponding author upon request.

The primary challenge in generating the anti-Markovnikov product is biasing the aminometalation step to afford the branched [M]–C and terminal N–C bonds. Due to both steric repulsion and the inherent electronic bias of nucleophile addition to alkenes, known as Markovnikov's rule, this selectivity is not generally favored for an intermolecular aminometalation.[6,7] However, several strategies have been successfully employed to reverse this inherent selectivity. One approach uses activated alkenes that can form π-benzyl or [M]-enolate intermediates (Figure 1a).[9–16] A second approach utilizes an allylic C–H activation followed by nucleophilic attack at the terminal carbon on the resulting π-allyl.[17–20] Alternatively, proximal Lewis basic groups can direct functionalization of the alkene to afford the favored metallacycle (Figure 1b).[21–27] Finally, in stoichiometric investigations, the combination of a palladate complex and sterically hindered amine nucleophiles, promoted a *trans*-aminopalladation to functionalize the terminal carbon and produce the anti-Markovnikov constitutional isomer (Figure 1c).[28,29] However, conditions that afford the anti-Markovnikov aza-Wacker product, with simple aliphatic alkenes, have not been reported in catalytic amination reactions.

We envisioned utilizing a palladate catalyst, which could promote a selective *trans*-nucleopalladation by saturating the coordination sites with excess halide, as seen in the Wacker oxidation (Figure 1d).[7,30] During the *trans*-aminopalladation step, a relatively large nucleophile would be kinetically biased to approach the alkene to form the less hindered C–N bond, leading to the desired anti-Markovnikov product.[28,29,31–33] While the *trans*-aminopalladation with cationic palladium catalysts are known to occur to afford the Markovnikov constitutional isomer,[34,35] we hypothesized that the electronic differentiation between the double bond carbons, which leads to Markovnikov's rule, would be minimized with a less electrophilic anionic palladate catalyst, leading to a more sterically biased transformation.[28] The successful development of an anti-Markovnikov selective aminopalladation of simple alkenes would have implications that reach far beyond the aza-Wacker reaction, as aminopalladation is the regioselectivity-determining step in many olefin difunctionalization reactions.[34,35] Thus, the principles we have learned from the studies reported herein could find future applications in other anti-Markovnikov aminofunctionalizations of simple alkenes, enabling single-step access to a wide class of products.[36,37]

Results and Discussion

Reaction discovery and optimization.

Our initial investigation focused on developing an anti-Markovnikov selective oxidative amination of homoallyl benzene. As seen in Table 1 and further elaborated in the Supplementary Section B, employing known oxidative amination conditions affords the expected Markovnikov isomer exclusively (88% yield).[4] However, in the presence of 10 mol % $Pd(OAc)_2$, addition of either 40 mol % Bu_4NCl (Table 1, Entry 2) or 20 mol % Bu_4NOAc (Table 1, Entry 6) the regioselectivity is reversed to favor the anti-Markovnikov products, in 95% (3.0:1 a-M:M) and 59% (1.3:1 a-M:M) total yields, respectively. The *in situ* generation of a palladate complex is supported by the independent synthesis and crystallographic characterization of $[PdCl_4](Bu_4N)_2$ (see Supplementary Section I). The significant increase

in reactivity of the Bu_4N^+ salts, relative to Li^+ or Cs^+, can be attributed to the increased solubility of the resulting palladate complexes under the reaction conditions. Similarly, no product was observed when Na_2PdCl_4 or K_2PdCl_4 were used directly, with or without added acetate sources. Known aza-Wacker conditions typically form the enimide, where the double bond remains unmoved and the nitrogen replaces one of the hydrogen atoms, as the exclusive product; however, using the palladate catalyst, mixtures of olefin isomers are observed with the (*E*)-styrenyl isomer (**2a**) as the major product.[4,5] When both additives are present, the regioselectivity is improved, affording 86% combined yield (4:1 a-M:M), with a 62% yield of **2a** (Table 1, entry 8). Excitingly, further optimization lead to the conditions employed in Table 1, Entry 9, which afforded **2a** in 60% GC and 57% isolated yield as a single isomer; the combined yield of all isomers was 75% (8:1 a-M:M) (Table 1, Entry 9).

Reaction generality.

With optimized conditions identified, we investigated the anti-Markovnikov amination of other olefinic substrates. Substitution on the aryl group of homoallylbenzene showed a minimal effect on yield and regioselectivity (**2a-2e)**. The functionalization of allylbenzene (**1f**) afforded **2f** with significantly higher selectivity (47:1) and moderate yield (47%). Interestingly, it was observed that electron poor *p*-CF_3-allylbenzene (**1j**) gave **2j** in a much higher selectivity (57:1 a-M:M) than electron rich *p*-MeO-allylbenzene (**1g**) for **2g** (6:1 a-M:M). Overall, the selectivity is generally lower for the homologated products (**2a**-**2e**) compared to the allyl benzenes (**2f**-**2j**), with greater quantities of Markovnikov and double bond isomers observed. Increasingly distal functionality, such as a phenyl ring three methylene units away, **1k**, affords the primary amine derivative **2k** in modest yield and good (8:1 a-M:M) selectivity. However, when substrates lack an inductively withdrawing aryl ring (**1l**), reactivity and regioselectivity are poor.

These studies suggest that proximal electron-withdrawing groups improve the selectivity for the anti-Markovnikov isomer. Given this observation, we became interested in investigating homoallylic alcohols as substrates. The alcohol would presumably increase the regioselectivity by acting as an electron withdrawing group and would, *via* formation of the ketone, favor a single isomeric product.[34,38–42] Moreover, the reaction would afford the thermodynamic γ-aminoketone product – a common motif and intermediate in biologically active molecules and their synthetic precursors.[8] Excitingly, when homoallylic alcohol **1m** is combined with phthalimide in the presence of 5 mol % $Pd(OAc)_2$ and 20 mol % Bu_4NCl, a 77% yield of the γ-aminoketone **2m** is observed. The regioselectivity is also significantly enhanced, favoring the *anti*-Markovnikov product in a 14:1 ratio. It is notable that this aerobic oxidation reaction can be conducted at ambient pressures, as high pressure is a common requirement for other aza-Wacker processes.[5] The reaction is also readily scalable, providing **2m** in 75% yield on 0.5 mmol scale and 77% yield on 5.0 mmol scale. Given the presence of the electron withdrawing oxygen atom, Bu_4NOAc is no longer required to achieve excellent levels of selectivity in most cases. Importantly, the thermodynamically driven isomerization process indeed occurred to exclusively generate the ketone product; i.e., no enimide or allyl imide products are observed.

Under the modified conditions identified for these alcohol-containing substrates, both electron-withdrawing and donating groups were well tolerated. It was found that substituting the aryl ring with electron withdrawing substituents (**1q**-**1u**) generally gave higher yields and regioselectivities of **2q**-**2u** compared to unsubstituted or electron-rich substrates **2m**-**2p**; for example **2t** bearing a *p*-CF_3 substituent was formed in 72% yield and 19:1 a-M:M selectivity while **2n**, bearing a *p*-MeO, was afforded in 56% yield and 14:1 a-M:M. Steric hindrance on the aryl ring has a deleterious effect on the yield, but results in an increase in the regioselectivity of the reaction. For example, the *o*-tolyl (**2o**) and mesityl (**2p**) products were obtained with improved selectivities (20:1 and 18:1 a-M:M, respectively) as compared with **2m** (14:1 a-M:M) in albeit lower isolated yields (64% for **2o** and 31% for **2p**). Overall, the reaction offers very good functional group tolerance. For example, ethers (**2b, 2g, 2n**), chlorides (**2d, 2i, 2s**), trifluoromethyl groups (**2t** and **2u**), and heterocycles (**2v** and **2w**) were all well tolerated. Additionally, a triflate (**2r**), an α,β-unsaturated ketone (**2x**), and a silyl ether (**2ab**) were unaffected under the reaction conditions. Substrates with free primary alcohols do not afford any of the desired products, as the primary alcohol oxidizes under the reaction conditions.

Interestingly, in the case of alkyl substitution α to the alcohol, we observed high yield but significantly diminished *anti*-Markovnikov selectivity under the conditions optimized for the α-aryl alcohols. This is likely due to the diminished inductive effect of alkyl substituents relative to aryl groups. As with the simple alkenes, the addition of Bu_4NOAc (5 mol %) restores the regioselectivity. It was observed that the size of the aliphatic group had an impact on regioselectivity, with larger substituents affording a more selective transformation (**2y**-**2ab**).

The increase in regioselectivity observed with substrates bearing a homoallylic alcohol suggest that it may be acting as a directing group during the aminopalladation step.[21–27] Although this was not observed in related reactions, it has been proposed in the Wacker oxidation of β-substituted homoallylic alcohols[43] but not unsubstituted homoallylic alcohols or ethers.[44] When **1ac** was subjected to the optimized reaction conditions, **2ac** was afforded in 58% yield as a 3.6:1 mixture of *Z*/*E* isomers and 9:1 mixture of **2ac** to all other constitutional and stereoisomers. These experiments indicate that the coordination of the alcohol to the catalyst is not necessary for an *anti*-Markovnikov selective transformation, though we cannot eliminate the possibility that it is participating in the reaction for these substrates. Similarly, inductively withdrawing imides and amides at the allylic or homoallylic position promoted the *anti*-Markovnikov selective oxidative amination. These substrates, lacking the thermodynamic sink of a styrene or carbonyl, afford the enimides **2ad** and **2ae** with the allylic substrate and the allyl imide **2af** with the homoallylic substrate. It is important to note that the resulting terminal phthalimides are easily deprotected. **2a** has been shown to react with NH_2NH_2 to afford **2a'** in 85% yield (Table 2).[45] Additionally, under similar condition we were able to remove the phthalimide from **2s** to afford cyclic imine **6s** in 78% yield (Table 2).

Next, we sought to explore the scope of the reaction. Cyclic, other acidic amine nucleophiles, including succinimide, saccharine, and 4-nitrophthalimide were all effective under the reaction conditions, affording **3m**-**5m** in good to very good yields.

Mechanistic Investigations.

The dramatic selectivity difference between this transformation and that of other oxidative amination reactions[4,5] led us to probe whether this reaction is, in fact, going through an aminopalladation mechanism or if it is going through π-allyl Pd intermediates formed *via* an allylic C–H activation event, as has been demonstrated in related reactions.

To gain mechanistic insight into the nature of the catalytic cycle, we performed kinetic analyses on the optimized reaction conditions for homoallyl benzene. The concentrations of additives were kept constant, relative to the Pd for all the investigations, as a certain concentration is required to form the active catalyst and then additional AcO^- has an inhibitory effect on the rate (Figure 2a). Interestingly, results indicate that the reaction is zero order in nucleophile, first order in olefin, and 1.4 order in [Pd]. The non-integer order in [Pd] is likely due to an equilibrium between monomeric and dimeric palladate complexes, with both being competent catalysts for the reaction at low concentrations and generating less active complexes at high concentrations. A similar effect has previously been reported by Henry.[46] The addition of Bu_4NOAc first shifts the equilibrium towards the dimeric species and thus reduces the concentration of active [Pd] catalysts.[47] To support this conclusion, we determined the order in catalyst in the absence of additional Bu_4NOAc and found an order of 1.1 (Figure 2b). The oxidative amination of homoallylic alcohols have similar orders in reagents (see Supplementary Section C): zero order in phthalimide, first order in homoallyl alcohol, and first order in [Pd]. The order in [Pd] suggests that a monomeric palladate complexes is the active catalysts for the homoallylic alcohol system where Bu_4NOAc is not added to the reaction. These order experiments are consistent with either coordination of the olefin or allylic C–H activation being the turnover limiting step.

As the optimized conditions are related to the Jeffery's conditions for the Heck reaction, which under similar conditions are thought to involve Pd nanoparticles, we sought to determine if the catalyst was homogeneous or heterogeneous.[48] When the reaction is run in the presence of Hg^0 the product is still generated, albeit in lower yield (12–14%). However, an induction period is observed for the Heck reaction, and no induction period was observed in our oxidative amination reaction.[48,49] These studies suggest that the Pd^{II} catalytic intermediate is homogeneous, though Pd^0 species may be stabilized as transient nanoparticles prior to oxidation by O_2.

The requirement for the olefin to bear an electron withdrawing group was investigated by performing a Hammett study. A ρ-value of 0.878 was observed for a series of homoallylbenzene derivatives, indicating that electron withdrawing groups increase the rate of the oxidative amination reaction. This is consistent with either aminopalladation or C–H activation mechanism. In the first, reducing the electrostatic repulsion between the olefin and electron-rich anionic palladate complex would accelerate the rate of the ligand exchange. A similar effect was reported by Hartwig in computationally comparing the $\Delta\Delta G^{\neq}$ for of styrene derivatives undergoing ligand exchange with a neutral Pd(II) complex, where *m*-MeO-styrene was predicted to have a lower barrier than *p*-Me-styrene.[50] Alternatively, electron-withdrawing groups would stabilize the anionic charge build-up and therefore accelerate the rate of C–H allylic activation via deprotonation.

The order in reagents and Hammett investigations demonstrate that the alkene and the catalysts are both involved during the rate determining step but does not allow us to distinguish between aminopalladation or C–H activation, as this would be consistent with the turnover limiting step being either olefin coordination, for the aminopalladation mechanism,[6,7] or allylic C–H activation,[17–19] with C–N bond formation occurring after the rate determining step (Figure 3a). To eliminate one of the two possible mechanisms, we isotopically labeled the substrate at the allylic position. Subjecting substrate **1a-*d*$_2$** to the reaction conditions allows us to distinguish between the two mechanistic pathways. If the reaction were proceeding through the aminometalation pathway, it is expected that **2a-*d*$_2$** would be the primary product of the reaction, where one of the deuterium atoms migrates to C3. Additionally, as no C–H bond cleavage would occur until after the turnover-limiting step, no kinetic isotope effect is expected. Alternatively, if the reaction was proceeding through an allylic C–H activation pathway, **2a-*d*$_1$** would be formed, with only a single deuterium atom in the product, as the second would have been deprotonated during the C–H activation step. Further, if allylic C–H activation is the turnover limiting step, a primary kinetic isotope effect would be observed. Subjecting **1a-*d*$_2$** to the reaction conditions afforded **2a-*d*$_2$** selectively and a k_H/k_D of 1.0 was observed, consistent with the reaction occurring *via* aminopalladation and not C–H activation (Figure 3b).

Next, we sought to distinguish between *cis*- and *trans*-aminopalladation pathways. As the stereochemical outcome of this transformation cannot be determined by examining the stereochemistry of the products after the olefin isomerization has occurred, we chose to investigate styrene as a substrate because it cannot undergo an olefin isomerization and can only afford the enimide product (Figure 3c). Subjecting (*Z*)-β-deuterostyrene (**1ag-*d*$_1$**) to the standard reaction conditions affords **2ag-*d*$_1$**, with 79% deuterium α to the phthalimide and 13% x to the phenyl ring (see Supplementary Section E). As shown in Figure 3d, the major isomer is indeed consistent with the reaction occurring via *trans*-aminopalladation followed by β-hydride elimination. The minor isomer, where the deuterium has migrated, may be the result of initial *trans*-aminopalladation/β-hydride elimination to afford the *cis*-diastereomer and subsequent isomerization to the *trans* product by the Pd–D. A kinetic isotope effect could also account for some of the preference toward hydride elimination if a *cis*-aminopalladation was occurring; however, if this were the case the *cis*-diastereomer (*Z*-**2ag-*d*$_1$**) would be the expected product.

Combining the mechanistic information garnered from the kinetic data and the isotope labeling studies, the catalytic cycle shown in Figure 4 is proposed. Either the Pd(0) or the Pd(II) palladate complex is the catalyst resting state, with loss of either an anionic ligand being required during or prior to the turnover limiting olefin coordination. Outer-sphere nucleophilic attack by the phthalimide and olefin isomerization of the Pd(0) all occur between the turn over limiting step and the catalyst resting state, as supported by the absence of a kinetic isotope effect. As the reaction does not work in the absence of $^{-}$OAc, we propose that it is required to act as a catalytic base under the reaction conditions, both serving to deprotonate the phthalimide and to undergo reductive elimination from Pd(H)OAc to generate AcOH and Pd(0). The two equivalents of H^+ are eventually used in the aerobic oxidation of Pd(0) to Pd(II) to generate H_2O_2 or H_2O and regenerate the $^{-}$OAc.

Conclusion

In conclusion, we have demonstrated a palladate catalyst promotes an anti-Markovnikov selective aza-Wacker oxidation. Additionally, under the reaction conditions, olefin isomerization occurs to translocate the unit of unsaturation to the most thermodynamically favored position in the molecule. Further, we have demonstrated that this reaction occurs through a *trans*-aminopalladation mechanism with rate determining olefin coordination. This report represents a major advance in oxidative amination technology, and constitutes a unique approach to conceptualizing remote amination disconnections in organic synthesis. Our current efforts seek to develop an in-depth mechanistic understanding of the regioselectivity-determining step, as well as exploring the intermediacy and capture of alkylpalladium species for the development of alkene difunctionalization reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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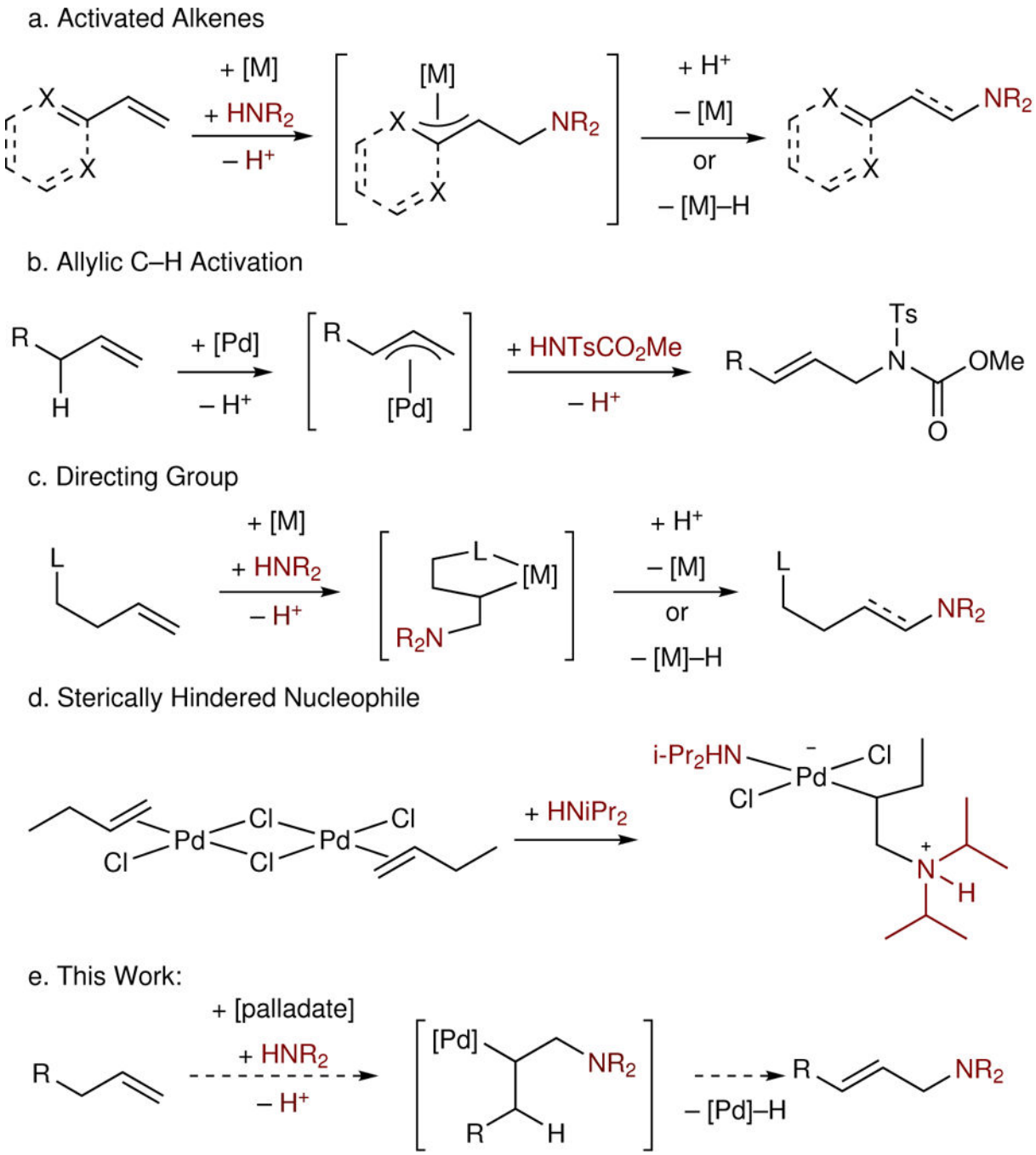


Figure 1: Current strategies for anti-Markovnikov oxidative amination of simple alkenes.

a, Use of activated alkenes gives rise to stabilized alkyl-Pd intermediates, providing a basis for anti-Markovnikov selectivity. **b**, Allylic C–H bond activation can afford a **π**-allyl intermediate, which can be intercepted by a nucleophile to afford allylic amines. **c**, A tethered directing group can direct functionalization at the terminal position through formation of a more stable metallacyclic intermediate. **d**, Use of a palladate catalyst with sterically encumbered nucleophiles can kinetically favor anti-Markovnikov functionalization in stoichiometric studies and in the present work.

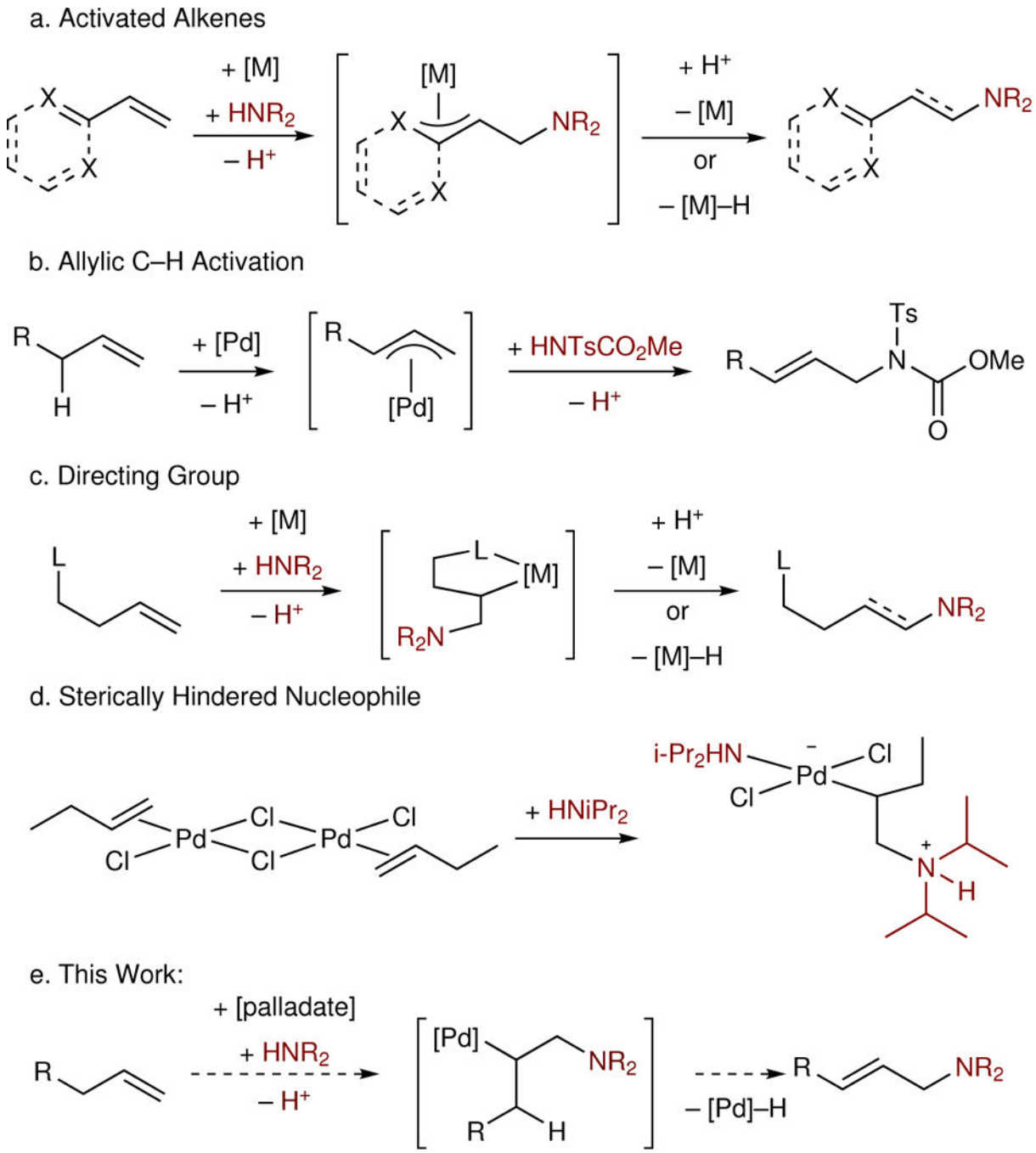


Figure 2: Mechanistic investigation of the anti-Markovnikov oxidative amination through reagent order determination and Hammett plot analysis.

a, Determination of the order in all reagents for the anti-Markovnikov selective oxidative amination of **1a**, showing first order kinetics for alkene, non-integer 1.4 order for catalyst, and zero order for nucleophile. **b**, Determination in the order of [Pd] when no Bu_4NOAc is added, indicating first order in catalyst with lower acetate equivalence and implicating palladium oligomerization. **c**, Hammett investigation for the effect of electronics on the aryl ring on the rate of the oxidative amination reaction, demonstrating the rate enhancement of

electron withdrawing groups, even several bonds from the reactive alkene. Error bars represent the standard deviation of the measured values across multiple independent runs.

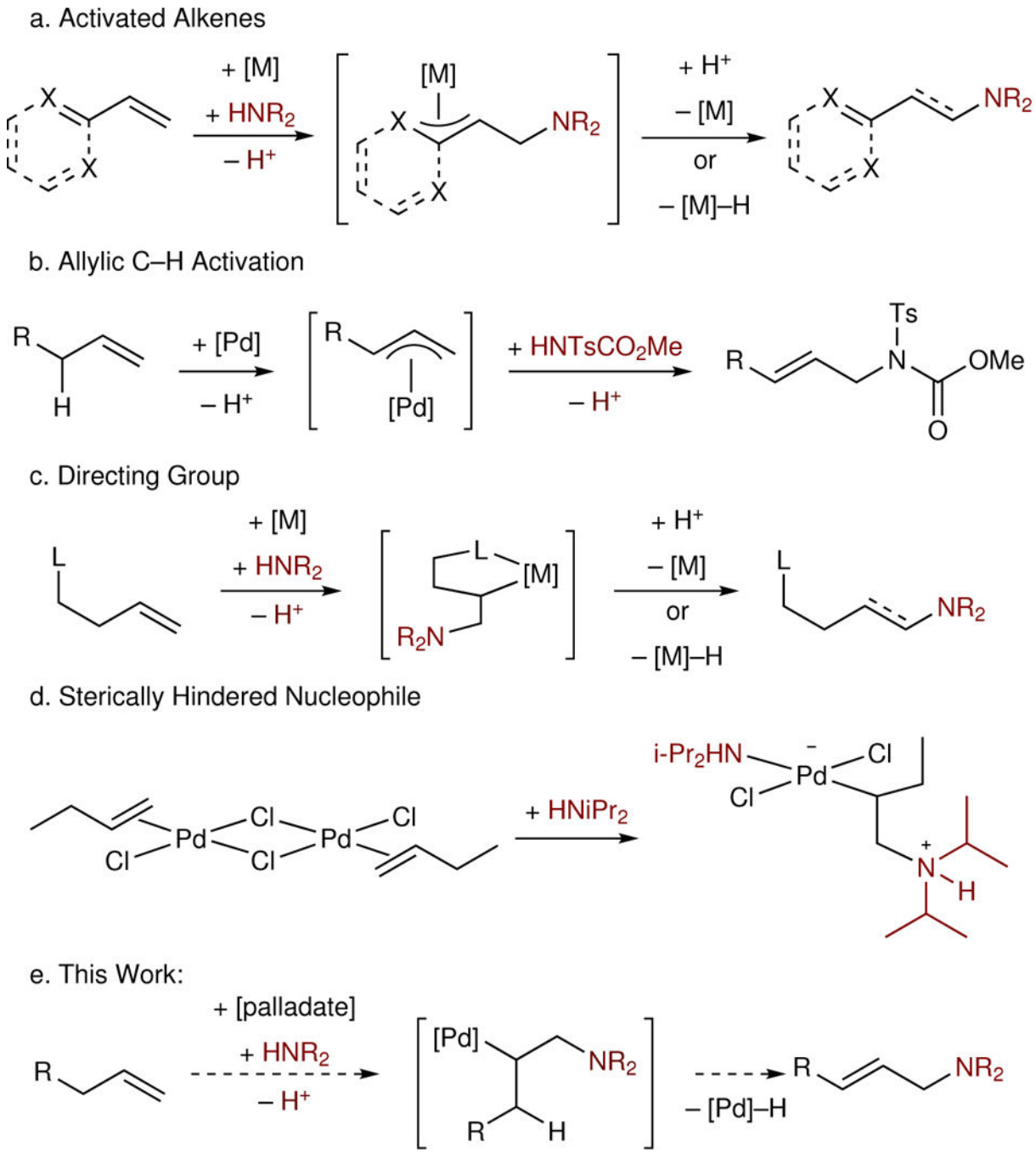


Figure 3: Deuterium labelling studies as probes to distinguish between multiple mechanistic pathways.

a, Potential C–H activation and aminopalladation mechanisms. **b**, Isotopic labeling experiments to test the two possible mechanisms, showing full deuterium retention and no kinetic isotope effect as evidence for aminopalladation and against C–H activation. **c**, Possible outcomes for *cis*- and *trans*-aminopalladation pathways. **d**, Isotopic labeling study to probe the mechanism of aminopalladation, showing predominately deuterium retention at

the terminal carbon and thereby indicating an *anti*-aminopalladation pathway (see Supplementary Figure 32).

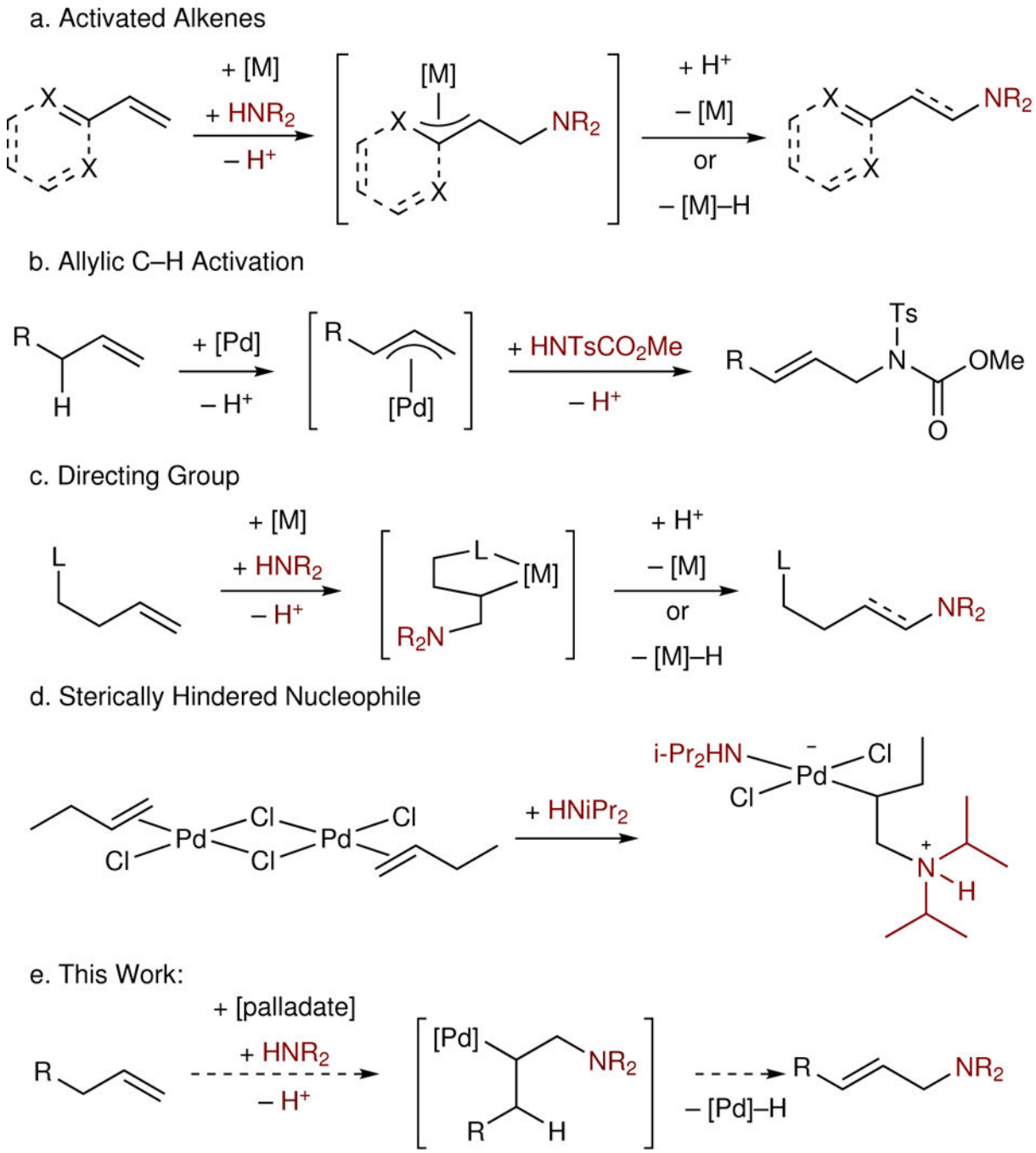


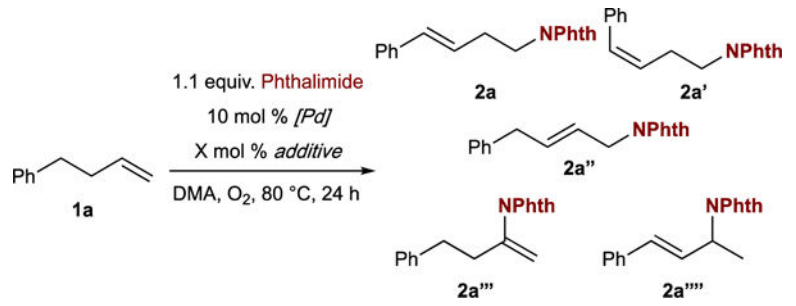
Figure 4: A catalytic cycle proposal based upon the mechanistic studies undertaken.

The order in reagents implicates the involvement of the alkene and catalyst at or before the rate determining step, while excluding the involvement of the phthalimide. This suggests that alkene binding through associative ligand dissociation is the rate determining step, and that nucleophilic attack upon the bound olefin is fast relative to this. The requirement of some catalytic quantity of acetate suggests its involvement in this process, and its function as a catalytic base is proposed, to generate a nucleophilic anionic phthalimide. Subsequent β-

hydride elimination and olefin isomerization generates the most stable olefin isomer, and the resultant Pd–H is then oxidized aerobically to regenerate the palladate.

Table 1.

Optimization of Oxidative Amination Reaction on [1a].



Entry	Additive (mol %)	Total Yield (%)[a]	Yield 2a (%)[a]	a-M/M[a]
1	None	20	< 1	0.06
2	Bu_4NCl (40 mol %)	95	68	3.0
3	LiCl (40 mol %)	32	18	1.4
4	CsCl (40 mol %)	13	2	0.2
5	Bu_4NI (40 mol %)	80	24	2.3
6	Bu_4NOAc (20 mol %)	59	26	1.3
7	NaOAc (20 mol %)	15	0	<0.01
8[b]	Bu_4NCl (10 mol %), Bu_4NOAc (20 mol %)	86	62	4.0
9[b]	Bu_4NCl (15 mol %), Bu_4NOAc (25 mol %)	75	60	8.0
10[b]	Bu_4NCl (20 mol %), Bu_4NOAc (30 mol %)	24	21	130
11[c]	None	88	0	NA

[a] *In situ* yield determined by gas chromatographic analysis and comparison to an internal standard.

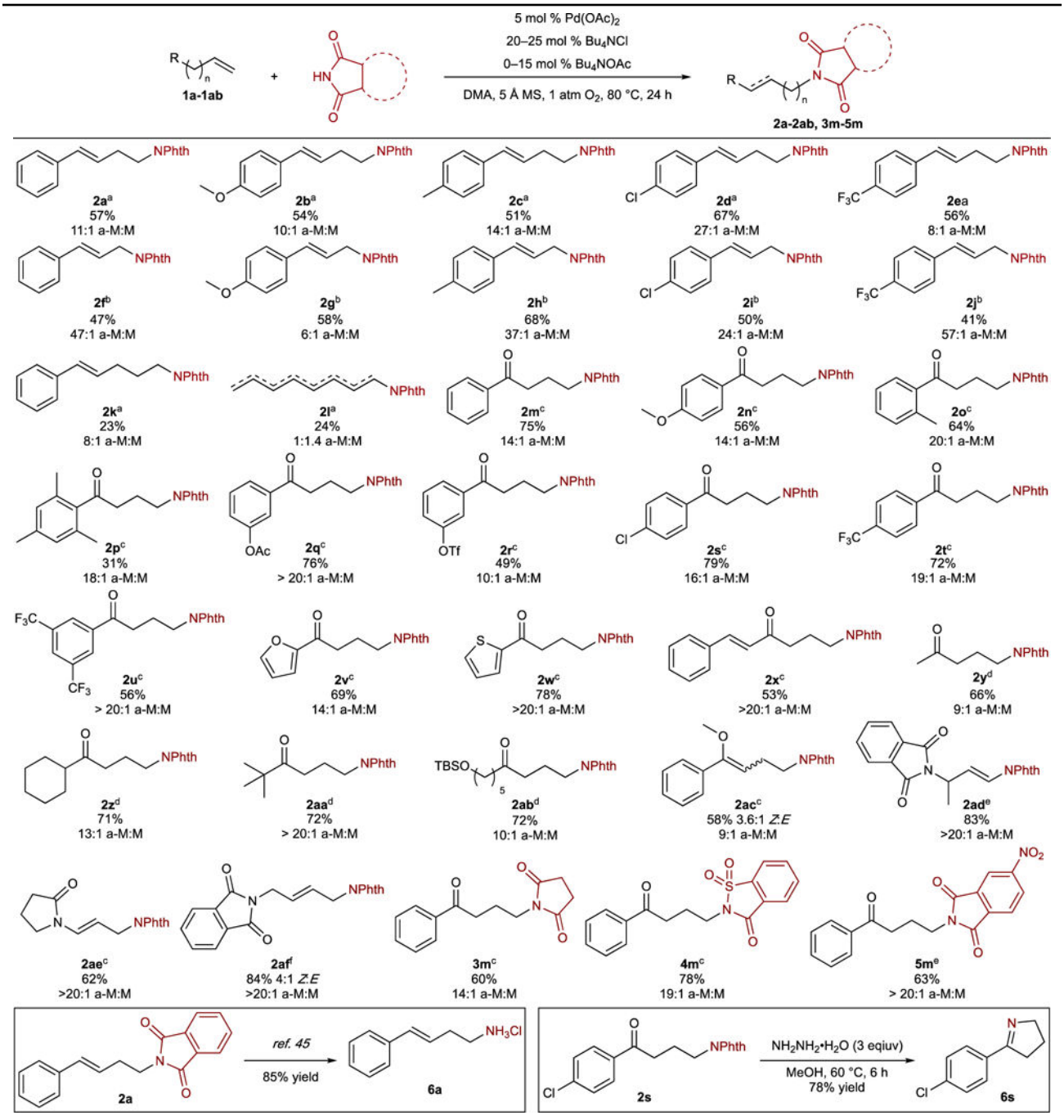
[b] 5 mol % $Pd(OAc)_2$.

[c] Literature conditions for oxidative amination used: $Pd(OAc)_2$ (5 mol %), PhCN (1 M)

[1a] (6 equiv), 60 °C, 1 atm O_2

Table 2.

Anti-Markovnikov oxidative amidation of homoallylic alcohols.



[a] Bu_4NOAc (15 mol %), Bu_4NCl (25 mol %)

[b] $Pd(OAc)_2$ (10 mol %), Bu_4NOAc (10 mol %), Bu_4NCl (40 mol %)

[c] Bu_4NCl (20 mol %)

[d] Bu_4NOAc (5 mol %), Bu_4NCl (20 mol %)

[e] Bu_4NCl (15 mol %)

[f] Bu_4NCl (25 mol %)