Mapping Ambiphile Reactivity Trends in the *Anti*-(Hetero)annulation of Non-Conjugated Alkenes via Pd(II)/Pd(IV) Catalysis

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Abstract: In this study, we systematically evaluate different ambiphilic organohalides for their ability to participate in *anti*-selective carbo- or heteroannulation with non-conjugated alkenyl amides under Pd catalysis. Detailed optimization of reaction conditions has led to protocols for synthesizing tetrahydropyridines, tetralins, pyrrolidines, and other carbo/heterocyclic cores via [*n*+2] (*n* = 3–5) (hetero)annulation. Expansion of scope to otherwise unreactive ambiphilic haloketones through Pd(II)/amine co-catalysis is also demonstrated. Compared to other annulation processes, this method proceeds via a distinct Pd(II)/Pd(IV) mechanism involving Wacker-type directed nucleopalladation. This distinction results in unique reactivity and selectivity patterns, as revealed through assessment of reaction scope and competition experiments.

Introduction

Heterocycles and carbocycles, such as tetrahydropyridines, tetralins, pyrrolidines and lactams, are common substructures in pharmaceuticals and natural products.[1] During the past few decades, several powerful synthetic methods to access these core structures have emerged.[2] Of special importance are Larock-type annulations, palladium(0)-catalyzed couplings of ambiphilic aryl (pseudo)halides with C=C π-bonds. This type of reaction was first reported by Dieck and co-workers in 1984[3] and was later expanded and popularized by seminal contributions from the Larock group.[4]

By applying the Larock reactivity paradigm, researchers have discovered numerous methods to synthesize 5-, 6-, and in rare cases ≥7-membered hetero- and carbocycles.[5] Generally speaking, [≥4+2] reactions are far less common than [3+2] reactions. To the best of our knowledge, only one example of medium-sized ring formation ([5+2], [6+2], [7+2]) has been reported,[6] and all known methods to prepare 6-membered rings are restricted to substrates with activated C=C bonds, such as 1,3-dienes,[4a, 4b, 7] allenes,[4c, 8] and strained alkenes.[9] (Figure 1A) During the past five years, we and others have reported various palladium-catalyzed functionalizations of non-conjugated alkenes by leveraging strongly coordinating bidentate directing auxiliaries, such as 8-aminoquinoline (AQ)-based amides.[10, 11] By applying the substrate directivity strategy, we recently described a Pd(II)-catalyzed [3+2] annulation method to prepare dihydrobenzofurans, indolines and indanes.[12] (Figure 1B) In contrast to classical Larock-type Pd(0) chemistry, which nearly always results in *syn*-selective addition,[5] this reaction proceeds in an *anti*-selective fashion as a consequence of its nucleopalladation-first mechanism.

Given the unique mechanistic features of this Pd(II)-mediated annulation, much remains unknown regarding reactivity patterns, particularly the structural requirements of the ambiphilic organohalide coupling partners. In the present study, we generalize Pd(II)-mediated alkene annulation to a broad array of ambiphilic reagents and elucidate relative reactivity trends with respect to nucleophile identity, product ring size, and C–X hybridization, among other features.

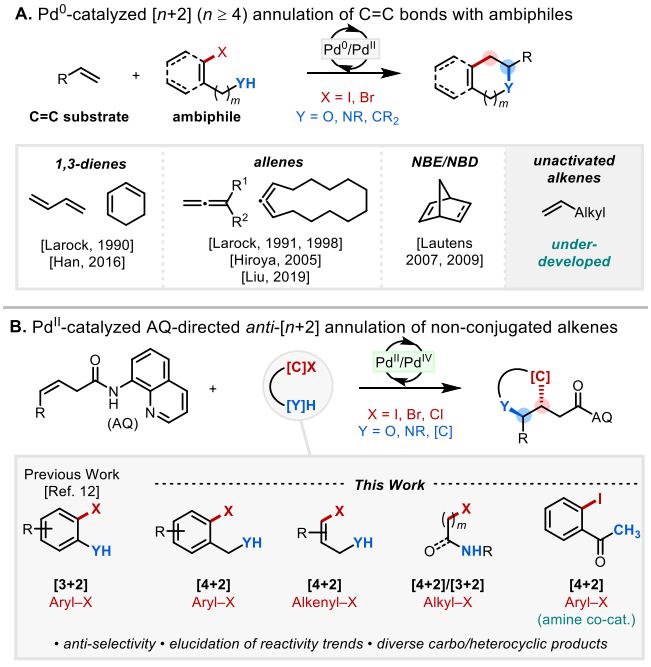


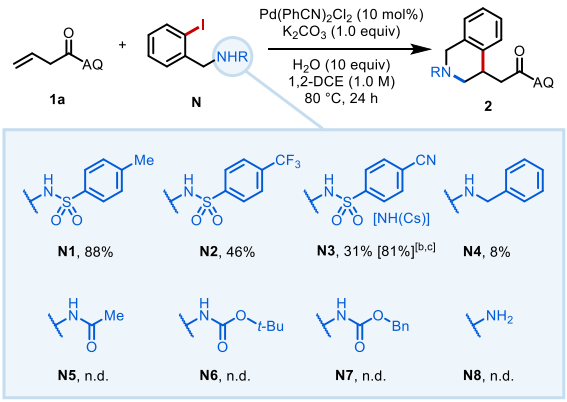
Figure 1. Background and project summary.

Results and Discussion

The study commenced with optimization of a [4+2] coupling between representative alkene substrate*: N*-(quinolin-8-yl)but-3-enamide (**1a**), and *ortho*-iodobenzylamine (**N8**) and derivatives thereof (**N1–N7**).This reaction was low-yielding under previously reported conditions for *ortho*-haloaniline substrates (entry 2, Table 1). Though at first glance the insertion of a CH_2 spacer into the ambiphile going from an aniline to a benzylamine appears to be a modest structural change, the significant changes in the nucleophilicity, Lewis-basicity, and pK_a[13, 14] of the aliphatic nitrogen atom (AlkylNH_2) presents new challenges. In addition to differences in nucleopalladation, susceptibility to oxidation by Pd(II) and stronger coordination to the Pd(II) center leading to off-cycle sequestration of the catalyst. For these reasons, (Alkyl)(R)NH nucleophiles are recognized as classically challenging coupling partners in Pd(II)-catalyzed aza-Wacker-type reactions,[15, 16] with *N*-(arenesulfonyl) protection used as a common strategy to overcome these difficulties.[17]

Systematic evaluation of key variables led to identification of an optimal combination using sulfonamide-based coupling partners (**N1–N3**), $Pd(PhCN)_2Cl_2$ (10 mol%) as the catalyst, K_2CO_3 (1.0 equiv) as the base, H_2O (10 equiv) as an additive, and 1,2-DCE (1.0 M) as the solvent. The desired product **2a** was formed in 88% yield when a 4-methylbenzenesulfonyl (Ts) (**N1**) protecting group was used. The introduction of electron-withdrawing groups, such as $–CF_3$ or –CN (Cs), led to lower yields (**N2**, **N3**). In the case of **N3**, the yield could be improved from 31% to 81% with higher palladium loading. This is advantageous because of the precedented ease of removal of the Cs group by the use of 1-dodecanethiol.[18] *N*-Benzyl (**N4**), -acetyl (**N5**), -Boc (**N6**), -Cbz (**N7**), and free NH_2 (**N8**) coupling partners were low yielding (<10% yield). With **N1** as the ambiphile, $Pd(OAc)_2$ was a less effective precatalyst (entry 3). Additionally, other solvents (entries 4–8) including commonly used HFIP, were lower-yielding compared with 1,2-DCE. Inclusion of H_2O as an additive proved to be essential for reproducibility, with a potential role of solubilizing the inorganic base. Without added H_2O, yields were highly variable, likely reflecting variable water content in the reagents employed or subtle differences in rates of mixing (entry 9, 0–68% yield).

Table 1. Optimization of the [4+2] annulation.



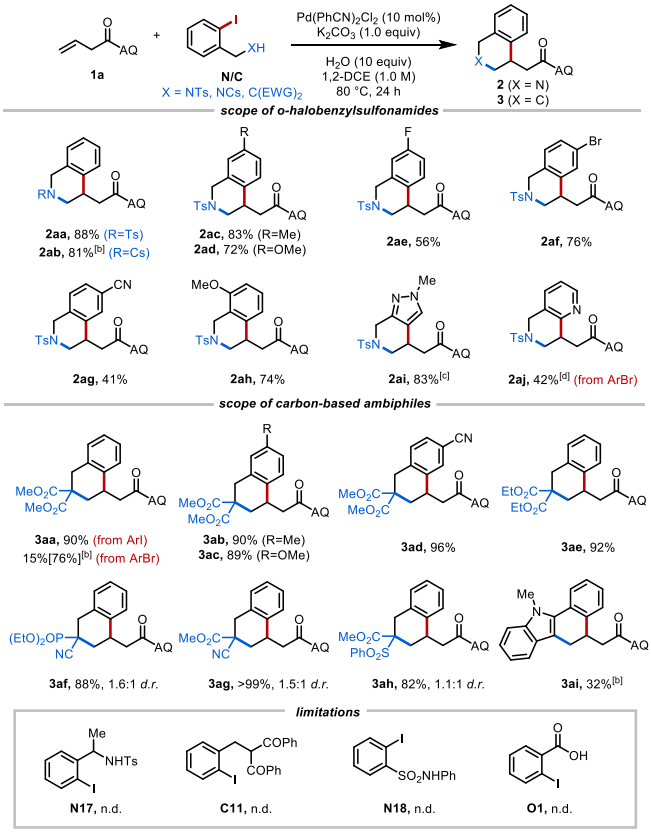
Entry	Deviation from standard conditions	Yield (R = Ts)
1	none	84% (88%)[b]
2	standard conditions in ref. 10	30%[d]
3	$Pd(OAc)_2$ as catalyst	55%
4	HFIP as solvent	37%
5	MeCN as solvent	29%
6	toluene as solvent	58%
7	PhCl as solvent	58%
8	DCM as solvent	59%
9	dry solvent, N_2	0–68%

[a] Reaction conditions: **1a** (0.2 mmol), **N** (1.5 equiv), $Pd(PhCN)_2Cl_2$ (10 mol%), K_2CO_3 (1.0 equiv), H_2O (10 equiv), 1,2-DCE (1.0 M), 80 °C, 24 h. Values correspond to ^1H NMR yields using $Cl_2CHCHCl_2$ as internal standard. [b] Isolated yield. [c] $Pd(PhCN)_2Cl_2$ (20 mol%). [d] **1a** (0.1 mmol), **N** (1.2 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (1.0 equiv), HFIP (1.0 M), 80 °C, 24 h.

With the optimized conditions in hand, we first examined the scope of ambiphilic aryl halides (Table 2). The [4+2] annulation with benzyl-amine-derived coupling partners proceeded well with electron-donating groups (**2ac**, **2ad**, **2ah**) or halides (**2ae**, **2af**) at 4-, 5- or 6-positions of the arene, giving 56–83% yields. An electron-withdrawing –CN (**2ag**) group was also tolerated, though in this case lower yield was obtained (41%). We were pleased that two representative heteroaryl coupling partners (**2ai**, **2aj**), which typically pose challenges in palladium(II) catalysis, were also compatible under our reaction conditions. While most examples in Table 2 employed aryl iodides, **2aj** demonstrates that (hetero)aryl bromides are also competent, though higher catalyst and/or coupling partner loading is typically needed (for a head-to-head comparison, see **3aa**). The ability to use aryl bromides is advantageous because they are easier to prepare and more widely available from commercial suppliers compared to analogous aryl iodides. Next, a series of carbon-based coupling partners were tested. Both electron-rich and electron-poor aryl iodides (**3aa**–**3ad**) provided the desired products in excellent yields (89–96%). Synthesis of **3aa** from the aryl bromide provided 76% yield using 20% palladium loading. Different electron withdrawing groups on the carbon pronucleophile were then tested (**3ae**–**3ah**). Excellent yields (82–99%) and moderate diastereoselectivities (1.1:1–1.6:1) were obtained in all cases. An indole-derived coupling partner gave the desired cyclized product in 32% yield (**3ai**). A number of limitations were also identified. First, coupling partners bearing a substituent α to the nucleophilic atom, even a sterically small –Me group (**N17**), were unreactive.

Second, ambiphiles derived from 1,3-diketones (**C11**) or oxopropanenitriles (**C12**, see SI), two classes of nucleophiles previously shown to be effective in AQ-directed functionalization,[10b] only led to isomerized alkene starting material without any cyclized product. Third, 2-iodobenzoic acid (**O1**) , or the more conformationally rigid coupling partner, 2-iodo-*N*-phenylbenzenesulfonamide (**N18**), was not compatible.

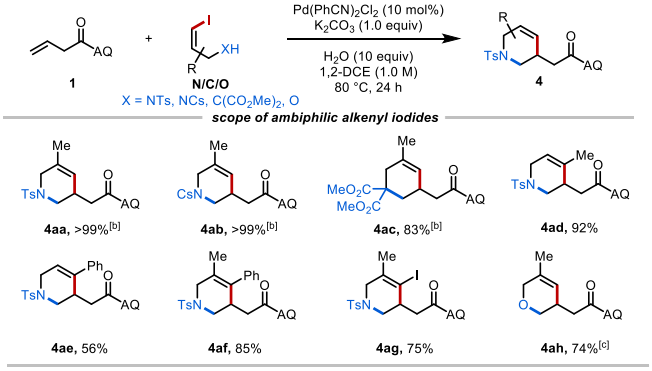
Table 2. Scope of [4+2] annulations with *N*-/*C*-based coupling partners.[a]



[a] Reaction conditions: **1a** (0.2 mmol), **N/C** (1.5 equiv for [NTs], 1.2 equiv for [C]), $Pd(PhCN)_2Cl_2$ (10 mol%), K_2CO_3 (1.0 equiv), H_2O (10 equiv), 1,2-DCE (0.2 mL), 80 °C, 24 h. Values correspond to isolated yields. [b] $Pd(PhCN)_2Cl_2$ (20 mol%). [c] **1a** (1.2 equiv), **N** (0.2 mmol). [c] **N** (1.2 equiv), $Pd(PhCN)_2Cl_2$ (20 mol%), 100 °C, 72 h.

Various ambiphilic alkenyl iodides were then synthesized and tested (Table 3). To our delight, reactions with these coupling partners proved to extremely efficient and typically higher yielding, which we attribute to their attenuated steric hindrance.[11b] For nitrogen-based coupling partners bearing a terminal alkenyl iodide, full conversion could be achieved within a short reaction time (2 h) leading to quantitative yields (**4aa**, **4ab**). With a carbon-based coupling partner (**4ac**), we obtained a slightly diminished yield (83%). More hindered internal alkenyl iodides (**4ad**–**4ag**) were also well tolerated under the standard reaction conditions, although a longer reaction time was required in these cases (24 h). Notably, we were able to prepare **4ah** from an oxygen-based coupling partner, expanding the types of heterocyclic products that can be accessed.[19]

Table 3. Scope of [4+2] annulations with alkenyl iodides.

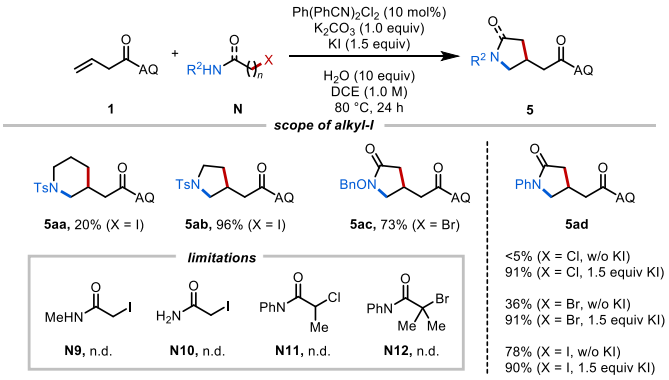


[a] Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv), $Pd(PhCN)_2Cl_2$ (10 mol%), K_2CO_3 (1.0 equiv), H_2O (10 equiv), 1,2-DCE (0.2 mL), 80 °C, 24 h. Values correspond to isolated yields. [b] 2 h. [c] $Pd(PhCN)_2Cl_2$ (20 mol%)

Having established that both aryl and alkenyl electrophiles were effective, we next moved on to evaluate alkyl electrophiles. Only two reports have described use of alkyl electrophiles in Pd(II)-catalyzed AQ-directed alkene functionalization (three examples, 11–53% yield).[11b, 11g] Among the challenges that we anticipated in this system were competitive E2 elimination and sluggish Alkyl–X oxidative addition.

Under slightly modified conditions with added KI, we were able to prepare piperidine, pyrrolidine, and lactam products (Table 4). Although the precise role of KI is unclear at this time, it likely serves to generate the more reactive alkyl iodide *in situ* via an S_N2 reaction when alkyl bromides and chlorides are used.[20] Both [4+2] (**5aa**) and [3+2] (**5ab**) annulation were viable in 20% and 96% yields, respectively. α-Haloacetamides are a n important class of ambiphilic molecules and can be used in a variety of domino and cycloaddition reactions.[21] Although commonly used in the synthesis of aza-heterocycles *via* copper catalysis or simple basic media, such compounds have rarely been used in palladium catalysis.[22] In the presence of KI, high conversion could be achieved with *N*-Ph-α-haloacetamides bearing different halides (X = I, Br, Cl, **5ad**). An *N*-benzyloxy-α-bromoacetamide coupling partner (**5ac**) was also compatible, giving 73% yield. In contrast, *N*-Me protected amide (**N9**), free NH_2 amide (**N10**) and coupling partners with a more substituted 2° or 3° Alkyl–X electrophiles (**N11**, **N12**) were ineffective. In summary, these results represent the first successful annulations between Alkyl–X ambiphiles and non-conjugated alkenes under palladium catalysis.

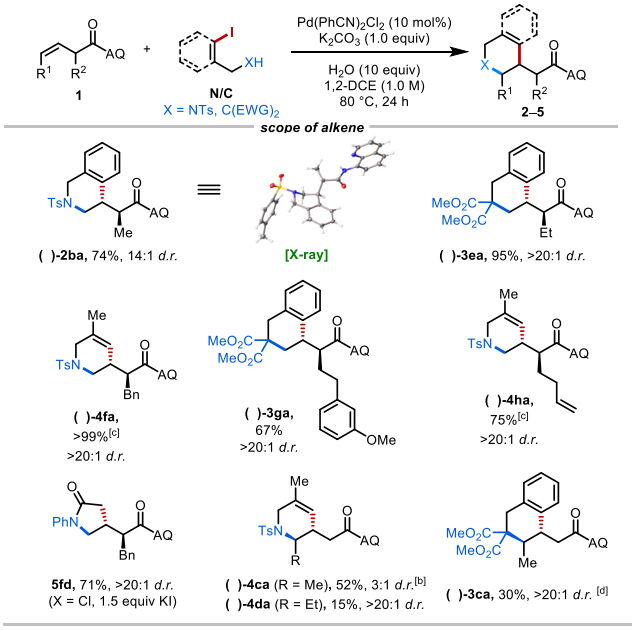
Table 4. Scope of [3+2] and [4+2] annulation using ambiphilic alkyl halides.



[a] Reaction conditions: **1** (0.2 mmol), **N** (1.5 equiv), $Pd(PhCN)_2Cl_2$ (10 mol%), K_2CO_3 (1.0 equiv), KI (1.5 equiv), H_2O (10 equiv), 1,2-DCE (0.2 mL), 80 °C, 24 h. Values correspond to isolated yields.

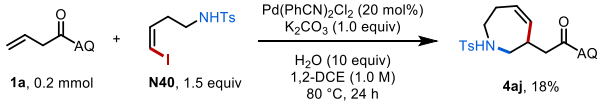
Next, we examined the alkene scope with a representative collection of ambiphiles (Table 5). To our delight, reactions with α-substituted alkenyl amides proceeded efficiently and with high diastereoselectivity. With a small –Me group at the α-position, **2ba** was obtained in 74% yield and 14:1 *d.r.* using a nitrogen-based Ar–I coupling partner. An X-ray crystal structure of **2ba** confirmed that the *trans* relationship between the Me and Ar groups in the major product. With a slightly larger –Et group at the α-position (**3ea**), >20:1 d.r. and 95% yield were obtained using carbon-based Ar–I coupling partner. Other larger groups at the α-position, such as –Bn (**4fa**, **5fd**) and $–CH_2CH_2Ar$ (**3ga**) substituents, gave the desired products in good to excellent yields and excellent diastereoselectivity. A diene substrate (**4ha**) reacted exclusively at the β,γ-alkene rather than at the δ,ε-alkene, showcasing chemoselectivity that arises from substrate directivity. Acyclic, non-conjugated internal alkenes are a challenging substrate class in alkene functionalization and have not previously been employed in [4+2] heteroannulations. *Z*-Configured alkenes reacted in moderate yields (15–52%) and with good to excellent diastereoselectivity (3:1–20:1) (**4ca**, **4da**, **3ca**). The *anti*-selectivity of the annulation reaction was confirmed by NOESY analysis of **4ca** (for NMR spectra, see SI).

Table 5. Scope of alkenes in [4+2] annulations with representative ambiphilic coupling partners.



[a] Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv for [NTs], 1.2 equiv for [C]), $Pd(PhCN)_2Cl_2$ (10 mol%), K_2CO_3 (1.0 equiv), H_2O (10 equiv), 1,2-DCE (0.2 mL), 80 °C, 24 h. Values correspond to isolated yields. Stereochemistry assignments of **3ea**, **4fa**, **3ga**, **4ha**, **5fc** are by analogy to **2ba**. Stereochemistry assignments of **4ca**, **4da**, **3ca** are by NOESY. [b] 48 h. [c] 2 h. [d] $Pd(PhCN)_2Cl_2$ (20 mol%), 48 h.

Interestingly, preliminary investigation of a [5+2] reaction indicated the possibility to form medium-sized rings (Scheme 1). To the best of our knowledge, the only example of medium-sized ring synthesis using Larock-type Pd(0)-catalyzed annulation involved allenes, as described in 1998.[6, 23]

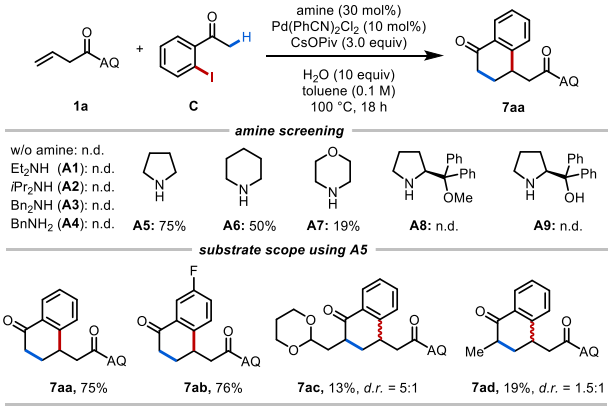


Scheme 1. Medium-sized ring synthesis via [5+2] annulation.

Given that ambiphile reactivity was found to critically depend on the properties of the nucleophilic atom (*e.g.*, pK_a of the Y–H bond), we questioned whether otherwise unreactive ambiphiles could become competent coupling partners through use of a suitable dual catalytic activation strategy. In particular we targeted *ortho*-iodobenzophenone, which was found to be unreactive under various reaction conditions, including those in Table 2. A dual palladium(II)/organocatalytic activation strategy[10h, 10i] was applied to enhance the nucleophilicity of the α-carbon (Table 6). A high-throughput screen identified CsOPiv and toluene as the base and solvent of choice (see SI). A control experiment indicated that the reaction did not take place in the absence of the amine catalyst. Various amines were then examined, and acyclic amines proved to be ineffective (**A1**–**A4**). Cyclic amines, such as pyrrolidine (**A5**), piperidine (**A6**), and morpholine (**A7**), afforded the desired product in 19–75% yield. No desired product was observed with chiral amines **A8** and **A9** that contain a bulky group α to nitrogen. A coupling partner containing a fluoro group at the *para*-position with respect to the iodo group gave 76% yield (**7ab**)

with the presence of **A5**. Substitution at the α-carbon of the ketone (**7ac**, **7ad**) led to a significantly diminised yield (13–19%).

Table 6. Pd(II)/amine dual activation strategy for employing *ortho*-iodoacetophenone ambiphiles.

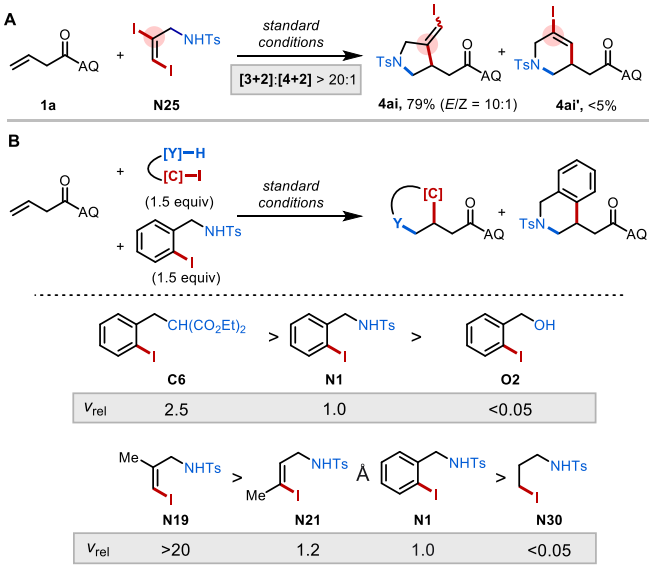


[a] Reaction conditions: **1a** (0.2 mmol), **2** (2.0 equiv), amine (30 mol%), $Pd(PhCN)_2Cl_2$ (10 mol%), CsOPiv (3.0 equiv), H_2O (10 equiv), toluene (1.0 M), 100 °C, 18 h. Isolated yields.

A series of competition studies were then designed to better understand the relative reactivity of different types of coupling partners. We initiated the study with **N25**, a 1,2-diiodo alkenyl compound, which has the potential to react in a [3+2] or [4+2] manner. Under the standard reaction conditions, 79% of the [3+2] product was obtained as 10:1 *E/Z* mixture.[11b, 24] Meanwhile, the putative [4+2] product could not be detected by ^{1}H NMR analysis of the crude reaction mixture (Scheme 2A). Given that the C2(alkenyl) is more substituted than the C3(alkenyl) position in **N25** (see below), exclusive reaction of the C2(alkenyl)–I bond indicates a strong preference for [3+2] annulation versus [4+2] annulation, likely due to reflecting the kinetic and thermodynamic preference for Pd(II)/Pd(IV) oxidative addition and reductive elimination via a 6-membered rather than 7-membered palladacycle intermediate.[25] This line of reasoning can be extended to explain why [5+2] couplings are low-yielding (Scheme 1).

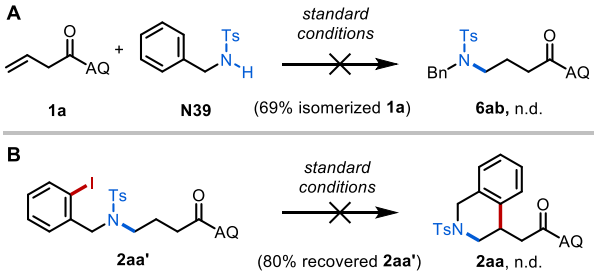
We then performed experiments in which ambiphile **N1** was competing against an equimolar amount of a second ambiphile with different nucleophilic or electrophilic component. (Scheme 2B) Notably, use of a series of ambiphiles containing a common CH_2 spacer allowed the electrophilic and nucleophilic character to be varied independently. Product ratios were assayed at two time points, low (<40%) conversion and full (>95%) conversion, and the data shown in Scheme 2B is calculated based on the product ratio at low conversion. Consistent with reactivity trends seen in Tables 2–4, a carbon-pronucleophile (–$CH(CO_2Et)_2$) was incorporated in preference to nitrogen nucleophile (–NTs), which in turn was incorporated in preference to an oxygen nucleophile (–OH).[12,26,27] Ambiphile **N1** was next competed against **N19**, **N21**, and **N30**, where the relative reactivities were found to be Alkenyl–I (terminal) > Alkenyl–I (internal) ≈ Ar–I > Alkyl–I. The difference in reactivity between isomeric terminal and internal Alkenyl–I ambiphiles reflects the sensitivity of the oxidative addition and reductive elimination steps to the steric properties of the carbogenic group.[11b] The low reactivity of the Alkyl–I ambiphile may also be explained by the sterically hindered nature of the Pd(II)/Pd(IV) oxidative addition step with C(sp^3)–I coupling partners.[28]

Collectively these results illustrate the complex origins of reactivity and product selectivity in this reaction system. In previous computational studies of [3+2] annulation, we found that nucleopalladation, oxidative addition, and reductive elimination all have similar energy barriers, meaning that the turnover-limiting step likely changes as a function of the alkene and ambiphile (and further as a function of the nucleophilic and electrophilic portions of this coupling partner). Hence across these competition experiments the product-determining step likely changes from nucleopalladation (**C6** > **N1** > **O2**) to oxidative addition or reductive elimination (**N19** > **N21** ≈ **N1** > **N30**). Knowledge of these reactivity trends can be applied to predict the likelihood of success of a given ambiphile. For example, a less reactive nucleophilic portion (–OH) can be compensated for with a more reactive electrophilic portion (terminal Alkenyl–I), as in **4ah** (Table 3).



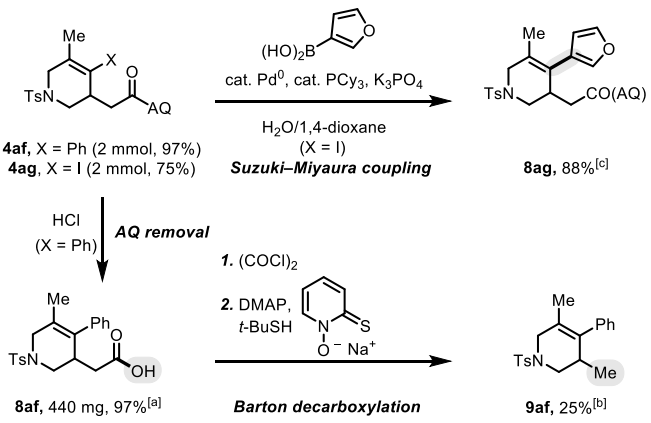
Scheme 2. Competition experiments.

The reaction mechanism is similar to the previous [3+2] annulation reaction,[12] involving reversible nucleopalladation, intramolecular Pd(II)/Pd(IV) oxidative addition, and reductive elimination. We carried out control experiments to exclude the alternative hydrofunctionalization/C–H cyclization pathway that could be envisioned (Scheme 3). When the iodo group was removed from the coupling partner (**N39**), the corresponding hydrofunctionalized product **6ab** was not observed. Along these lines, when independently prepared **2aa'** was subjected to the standard conditions, intramolecular cyclization was not observed.



Scheme 3. Evaluation of an alternative cascade hydrofunctionalization/C–H cyclization pathway.

This methodology could be conveniently scaled-up (Scheme 4) and allowed for isolation of 97% yield of **4af** and 75% yield of **4ag**, respectively. The AQ directing group could be easily removed through treatment with 6M HCl, giving the desired carboxylic acid product **8af** in 97% yield, which could undergo further Barton decarboxylation[29] to give **9af**. The iodo-containing product **4ag** could be cross-coupled with arylboronic acid using a modified Suzuki–Miyaura rection.[30] In this way various multi-substituted tetrahydropyridine, which are valuable core structures in drug discovery could be accessed.



[a] **4af** (1.17 mmol), HCl (6 M, 45 mL), 110 °C, 24 h. [b] (1) **8af** (0.052 mmol), Oxalyl chloride (0.078 mmol), DMF (2 drops), DCM (1.5 mL), r.t. (2) 2-Mercaptopyridine-*N*-oxide sodium salt (0.062 mmol), DMAP (0.003 mmol), 2-methylpropane-2-thiol (0.27 mmol), THF (1.0 mL), reflux. [c] $Pd_2(dba)_3$ (10 mol%), PCy_3 (20 mol%), K_3PO_4 (2.0 equiv), H_2O (0.1 mL), 1,4-dioxane (0.3 mL), 100 °C, 18 h, Ar.

Scheme 4. Deprotection and derivatization.

Conclusion

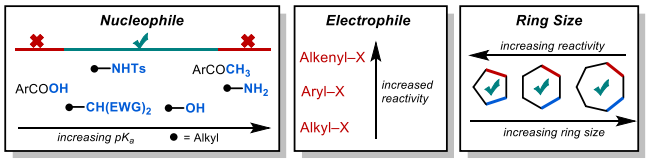


Figure 2. Overview of reactivity trends.

In conclusion, we have developed a highly versatile and selective method for [*n*+2] (*n* = 3, 4, 5) (hetero)annulation of non-conjugated alkenes via a directed nucleopalladation strategy. The transformation tolerates a diverse collection of nitrogen-/carbon-/oxygen-based coupling partners, enabling access to tetrahydropyridines, tetralins, pyrollidine and lactams. This reaction is effective with challenging α-substituted alkenyl carbonyl substrates as well as alkenes bearing 1,2-dialkyl-substitution and proceeds in a highly regioselective and diastereoselective fashion. The reaction tolerates air and does not require any special precautions to perform. A dual Pd(II)/organocatalytic activation strategy enables the use of 2-iodoacetophenone as the coupling partner.

Overall by assessing ambiphile scope and performing a series of competition studies we have shed light on general reactivity trends of ambiphiles in this Pd(II)/Pd(IV) annulation system: (1) Only nucleophiles within an appropriate pK_a (approximately 10–30 in DMSO) could be well tolerated under the reaction system we developed; (2) Nucleophilic reactivity trends: carbon > nitrogen > oxygen; (3) Electrophile reactivity trends: Alkenyl–halide (terminal) > Alkenyl–halide (internal) ≈ Aryl–halide > Alkyl–halide; (3) Reaction rate: [3+2] > [4+2] > [5+2]. This reactivity map should aid in the strategic application of Pd(II)-catalyzed alkene annulation reactions and facilitate further development of this reaction system.

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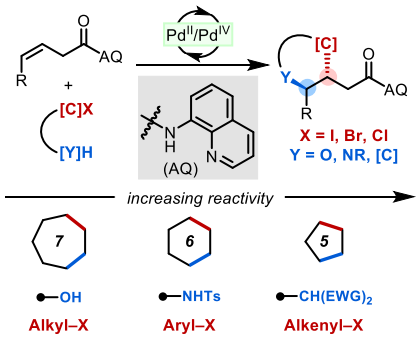

We describe a method to access 5-, 6- and 7-membered carbo- and heterocycles from non-conjugated alkenyl amides and ambiphilic organohalides. Under Pd(II)/(IV) catalysis, this [*n*+2] annulation proceeds in an *anti*-selective fashion and tolerates a wide array of ambiphiles, which are systematically benchmarked with respect to nucleophile identity, electrophile identity, and product ring-size. Otherwise unreactive ambiphilic *ortho*-haloacetophenones can be activated using an amine co-catalyst.

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