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 alkyl amides under Pd catalysis. Detailed optimization of reaction conditions has led to protocols for synthesizing tetrahydropyridines, tetralins, pyrrolines, 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, pyrrolines 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, [2+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,[7] allenes,[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-aminonaphthoquinone (AQ)-based amidines.[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,[13] 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.

A. Pd^2+ catalyzed [n+2] (n ≥4) annulation of C=C bonds with ambiphiles

B. Pd^0 catalyzed AQ-directed anti-[n+2] annulation of non-conjugated alkenes

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 CH2 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 pKa of the aliphatic nitrogen atom (AlkylNH2) 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(PPh3)Cl2 (10 mol%) as the catalyst, K2CO3 (1.0 equiv) as the base, H2O (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 –CF3 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 precedent 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 NH2 (N8) coupling partners were low yielding (<10% yield). With N1 as the ambiphile, Pd(OAc)2 was 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 H2O as an additive proved to be essential for reproductibility, with a potential role of solubilizing the inorganic base. Without added H2O, 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).

With the optimized conditions in hand, we first examined the scope of ambiphilic aryl halides (Table 2). The [4+2] annihilation 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,[10] 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]

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2a (X = N) 2b (X = C)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1a (0.2 mmol), NC (1.5 equiv for N(Ts)), 1.5 equiv for (C), PO(PPh3)2Cl2 (10 mol%), K2CO3 (1.0 equiv), H2O (10 equiv), 1.2-OCE (1.0 mL), 60 °C, 24 h. Values correspond to isolated yields.

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

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a, 90%[R] 4b, 90%[R] 4c, 83%[R] 4d, 92%</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1 (0.2 mmol), PO(PPh3)2Cl2 (10 mol%), K2CO3 (10 mol%), H2O (15 equiv), 1.2-OCE (0.2 mL), 80 °C, 24 h. Values correspond to isolated yields. [b] 2 h. [c] PO(PPh3)2Cl2 (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 SN2 reaction when alkyl bromides and chlorides are used.[20] Both [4+2] (5a)[a] and [3+2] (5b) annulation were viable in 20% and 96% yields, respectively. α-Haloacetamides are an 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 azaheterocycles 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-phenyloxy-α-bromoacetamide coupling partner (5ac) was also compatible, giving 73% yield. In contrast, N-Me protected amide (N9), free NH2 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.

Various ambiphilic alkényl 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 alkényl 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 alkényl 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]
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, 2b 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, 5f) and –CH2CH2Ar (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.

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 alkenes, as described in 1998.[6, 23] Given that ambiphile reactivity was found to critically depend on the properties of the nucleophilic atom (e.g., pKa 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 orthiodenzophenone, 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 diminished yield (13–19%).

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

<table>
<thead>
<tr>
<th>Ambiphile</th>
<th>( \text{R} )</th>
<th>( \text{R}’ )</th>
<th>( \text{N} )</th>
<th>( \text{X} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>N25</td>
<td>CH2</td>
<td>Ph</td>
<td>Ph</td>
<td>I3</td>
</tr>
<tr>
<td>N19</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>I3</td>
</tr>
<tr>
<td>N21</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>I3</td>
</tr>
<tr>
<td>N30</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>I3</td>
</tr>
</tbody>
</table>

Scheme 2. Competition experiments.

The reaction mechanism is similar to the previous [3+2] annulation reaction, involving reversible nucleopalladation, intramolecular Pd(II)/Pd(IV) oxidative addition, and reductive elimination. We carried out control experiments to exclude the alternative functionalization/C–H cyclization pathway that could be envisioned (Scheme 3). When the iodo group was removed from the coupling partner (N39), the corresponding functionalized product 6ab was not observed. Along these lines, when independently prepared 2aa’ was subjected to the standard conditions, intramolecular cyclization was not observed.
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 arybonic acid using a modified Suzuki–Miyaura reaction. In this way various multi-substituted tetrahydropridine, which are valuable core structures in drug discovery could be accessed.

Scheme 4 Deprotection and derivatization.

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 tetrahydropridines, tetralins, pyrrolidin and lactams. This reaction is effective with challenging α-substituted alkenyl carbonyl substrates as well as alkenes bearing 1,2-diaryl-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 2iodoacetophenone 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 pKa (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 alkenne annulation reactions and facilitate further development of this reaction system.

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Keywords: palladium • directing group • annulation • heterocycle • alkenne functionalization


[19] Reaction using 2-iodobenzylalcohol led to 10% yield of the cyclized product under the standard condition. (‘H NMR yield using CH3ClCHClCl as internal standard)


[23] The analogous 5+2 a–i coupling partner led to an intractable mixture.


[27] The C:N product ratio in C6-versus-N1 trials increased at extended reaction time for reasons that remain unclear (see Supporting Information).

[28] In an additional series of competition experiments, we found that activated Alkyl-i ambiphiles (i.e., α-haloamides) were much more reactive, behaving similarly to α-l ambiphiles (see Supporting Information).


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 or-ortho-haloacetophenones can be activated using an amine co-catalyst.

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