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An Umpolung Approach to Alkene Carboamination: Palladium Catalyzed 1,2-Amino-Acylation, -Carboxylation, -Arylation, -Vinylation, and -Alkynylation

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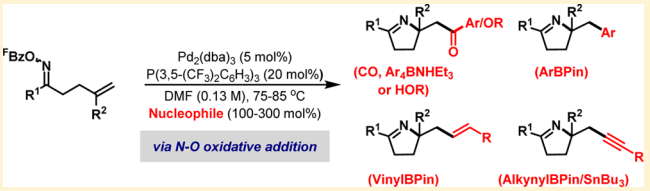
Supporting Information

ABSTRACT: Conventional approaches to Pd-catalyzed alkene 1,2-carboamination rely upon the combination of a *nucleophilic* nitrogen-based component and an internal C-based or external oxidant. In this study, we outline an umpolung approach, which is triggered by oxidative initiation at an *electrophilic* N-based component and employs "standard" organometallic nucleophiles to introduce the new carbon-based fragment. Specifically, oxidative addition of a Pd(0)-catalyst into the N−O bond of *O*-pentafluorobenzoyl oxime esters generates imino-Pd(II) intermediates, which undergo 5-*exo* cyclization with sterically diverse alkenes. The resultant alkyl-Pd(II) intermediates are intercepted by organometallic nucleophiles or alcohols, under carbonylative or noncarbonylative conditions, to provide 1,2-carboamination products. This approach provides, for the first time, a unified strategy for achieving alkene 1,2-amino-acylation, -carboxylation, -arylation, -vinylation, and -alkynylation. For carbonylative processes, orchestrated protodecarboxylation of the pentafluorobenzoate leaving group underpins reaction efficiency. This process is likely a key feature in related Narasaka−Heck cyclizations and accounts for the efficacy of *O*-pentafluorobenzoyl oxime esters in aza-Heck reactions of this type.



INTRODUCTION

Palladium-catalyzed 1,2-carboaminations of alkenes are valuable but challenging processes.[1] In most cases, intramolecular C−N bond formation is coupled with intermolecular C−C bond formation to provide 5-ring *N*-heterocycles (e.g., pyrrolidines). Within this area, two distinct strategies have emerged (Scheme 1). Oxidative processes were pioneered by the groups of Hegedus, Tamaru and Yoshida (Approach A).[2−4] Here, Pd(II)-triggered aminopalladation generates intermediates **1** that undergo carbonylative trapping with alcohols to provide esters. Recent contributions have outlined related 1,2-amino-acylation[5] and -arylation[6] protocols. A conceptually distinct approach has been pursued by the Wolfe group, who have developed 1,2-carboaminations that rely upon oxidative addition of Pd(0)-catalysts into the incoming C-based fragment (Approach B).[7] This enables 1,2-amino-arylation, -vinylation, and -alkynylation reactions.[7−9] Both existing strategies rely upon a *nucleophilic* N-based component and usually require relatively strongly coordinating monosubstituted or cyclic alkenes. In certain cases 1,1-disubstitution on the alkene is tolerated, but in general, this is limited to small alkyl substituents (e.g., methyl/ethyl groups).[7f] Additionally, organometallic reagents are not compatible with Approach A, and so, for associated amino-acylation protocols, C-based nucleophiles are constrained by Friedel−Crafts reactivity patterns.[5]

An attractive, but unrealized, alternative approach involves oxidative initiation at *electrophilic* nitrogen followed by intramolecular engagement of the olefin to provide intermediates **1** (Approach C). In principle, two key benefits emerge from this umpolung strategy. First, because alkene coordination to Pd is intramolecular, relatively hindered 1,1-disubstituted olefinic partners should be compatible, which would complement existing carboamination approaches.[10] Second, as the site of oxidative addition is at the N-based fragment, a wide range of C−C bond formations should be accessible by trapping of common intermediate **1** with "standard" organometallic nucleophiles.[11] In this report, we show that this approach can be achieved by harnessing the oxidative addition of Pd(0)-catalysts into N−O bond of *O*-pentafluorobenzoyl oxime esters, a process that is the basis of the Narasaka−Heck reaction (Scheme 1, gray box).[12−15] The versatility of this strategy is highlighted by prototypical methods for five distinct classes of alkene carboamination: 1,2-amino-acylation, -carboxylation, -arylation, -vinylation, and -alkynylation.

RESULTS AND DISCUSSION

Our initial studies were guided by observations made in our laboratory during the development of efficient protocols for Narasaka−Heck cyclizations. We have established that electron deficient Pd-catalysts enhance these processes and this led to the identification of $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ as a privileged ligand.[15a−c] The use of *O*-pentafluorobenzoyl oxime esters is also important as this component offers a balance between

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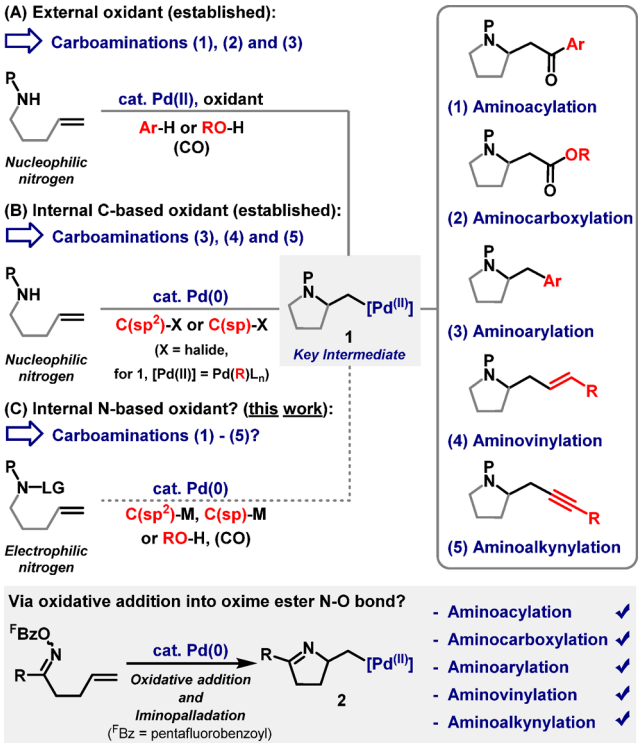
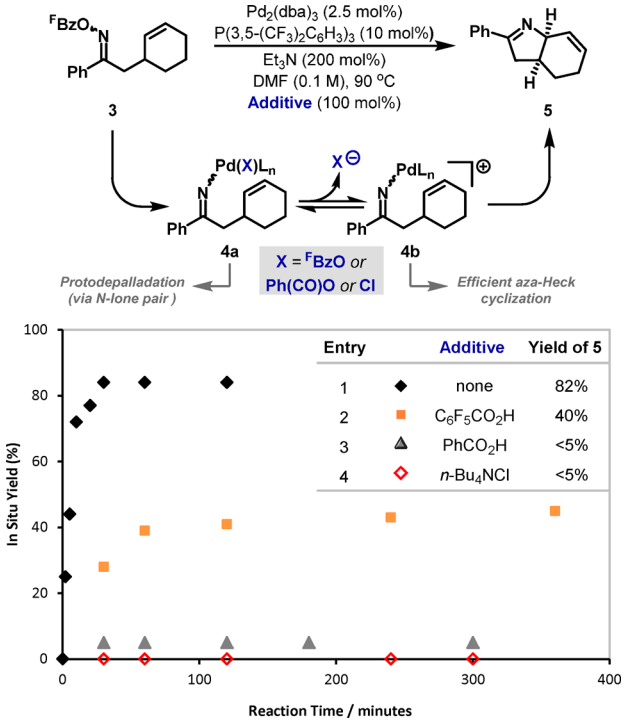
Scheme 1. Pd-Catalyzed 1,2-Carboamination of Alkenes



Scheme 2. Additive Effects for the Cyclization of 3 to 5



starting material stability and efficient cyclization. Strongly polarizing activating groups (e.g., OTs) are problematic due to competing Beckmann rearrangement and hydrolysis.[12] Conversely, less activated and more stable *O*-benzoyl oxime esters do not undergo efficient cyclization, even though it has been shown in other settings that they are effective for N−O oxidative addition.[16]

To rationalize the efficacies of different N-based leaving groups (particularly pentafluorobenzoate vs benzoate), we studied the cyclization of oxime ester **3** to bicycle **5** in the presence of carboxylate and halide additives (Scheme 2). Cyclization of **3** at 90 °C, under our previously reported conditions, provided adduct **5** in 82% yield (entry 1). When the cyclization was conducted in the presence of 100 mol % $C_6F_5CO_2H$ or $PhCO_2H$, which both undergo in situ deprotonation to the corresponding carboxylates, **5** was formed in 40% and <5% yield, respectively (entries 2 and 3). Addition of chloride (n-Bu_4NCl) completely suppressed the formation of **5** (entry 4). For entries 2−4, formal hydrolysis of oxime ester **3** to the corresponding ketone predominated. Overall, these studies indicate that, after oxidative addition, efficient cyclization requires dissociation of the N-based leaving group to access cationic imino-Pd(II) intermediate **4b**. This is more challenging for processes involving anionic additives or weakly dissociating leaving groups, and consequently, cyclization is less efficient. In these cases, our studies suggest that competitive protodepalladation of neutral imino-Pd(II) intermediate **4a** to the corresponding NH imine is followed by hydrolysis to the observed ketone byproduct. Notably, the studies in Scheme 2 show that even a pentafluorobenzoate leaving group inhibits cyclization; however, as outlined later, we have found that this inhibitor undergoes self-clearance from the reaction system by surprisingly facile protodecarboxylation.[17]

Because CO is a strong π-acceptor ligand that can mimic the effects of electron deficient phosphines (e.g., P(3,5-$(CF_3)_2C_6H_3)_3$), carbonylative processes became an appealing starting point for the development of 1,2-carboamination reactions and our initial studies sought a method for alkene 1,2-aminoacylation.[18] This required the identification of a suitable class of C-nucleophile and guiding considerations for the conversion of **6a** to **10a** are outlined in Scheme 3A. Following oxidative addition, dissociation of pentafluorobenzoate is required to access a cationic imino-Pd(II) intermediate **7a**, which is effective for cyclization. This restricts the choice of organometallic partner because chloride or hydroxide additives, which typically are employed to accelerate transmetalation from weakly nucleophilic organo-tin or -boron reagents,[19] were found to suppress cyclization, presumably by coordination to Pd at the stage of **7a**.[20] Two mechanistic options therefore emerged: (a) rely upon the pentafluorobenzoate ligand of **8b** to trigger transmetalation or (b) identify reagents that are sufficiently nucleophilic to attack directly the Pd(II)-center of **8a**/**b** (only attack via **8a** is depicted). In the event, reagents that can engage in 4-centered Suzuki-type transmetalations (i.e., via **TS-8b**), such as $PhB(OH)_2$ and PhBPin, were not successful (Scheme 3B, entries 1−3).[20a,b] This prompted the investigation of the use of tetraarylborates, which are a class of "preactivated" boron-based nucleophile.[20c−e] Sodium, potassium or tetramethylammonium salts of tetraphenylborate were not effective (entries 4−6), but ammonium and triethylammonium derivatives delivered **10a** in 29% and 62% yield, respectively (entries 7 and 8).[21] The efficiency of this latter protocol is notable given that this partially intramolecular 4-component coupling[22] generates one new C−N and two new C−C bonds. Substoichiometric quantities of the tetraarylborate can be employed, but the process is less efficient. For example, when 30 mol % Ph_4BNHEt_3 was used, **10a** was generated in only 51% yield (vs 62% with 110 mol % Ph_4BNHEt_3) (entry 9). This result suggests that BPh_3, which is generated during the first cycle, is sufficiently Lewis acidic to engage in transmetalation via **8b**.[23] However, employment of BPh_3 at the outset of the

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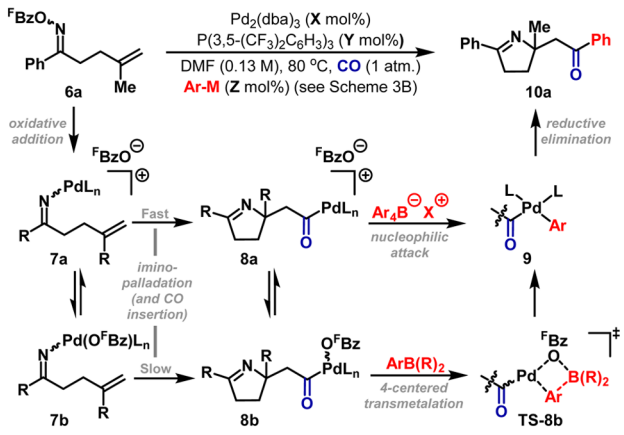
Scheme 3. Optimization of the Conversion of 6a to 10a and Key Mechanistic Considerations

(A) Mechanistic considerations for 1,2-aminoacylation processes:

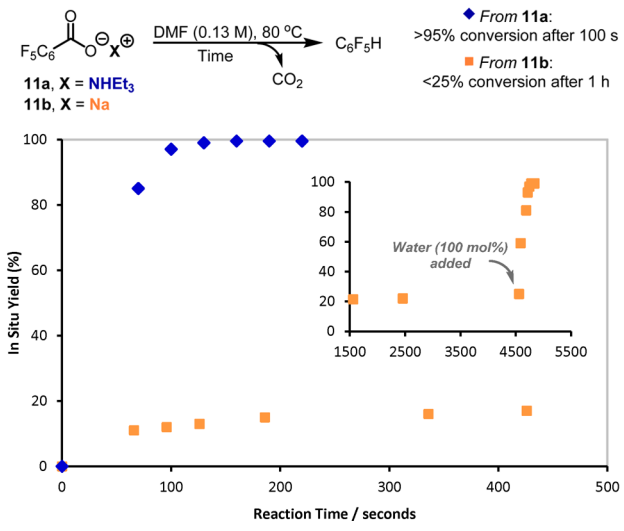


(B) Selected optimisation results for the synthesis of 10a:

Entry	X	Y	Ar-M	Z	Additive	Yield of 10a[a]
1	5	20	$PhB(OH)_2$	110	none	<5%
2	5	20	$PhB(OH)_2$	110	$K_3PO_4{\cdot}H_2O$ (200 mol%)	11%[a]
3	5	20	PhBPin	110	none	<5%
4	5	20	Ph_4BNa	110	none	<5%
5	5	20	Ph_4BK	110	none	12%[a]
6	5	20	Ph_4BNMe_4	110	none	<5%
7	5	20	Ph_4BNH_4	110	none	29%[a]
8	5	20	Ph_4BNHEt_3	110	none	62%[a]
9	5	20	Ph_4BNHEt_3	30	none	51%[a]
10	3.75	15	Ph_4BNHEt_3	110	none	48%[a]
11	5	20	Ph_3B	110	none	14%

[a] Isolated yield. All other yields were determined by ^1H NMR analysis of crude material vs 1,3,5-trimethoxybenzene as a standard.

(C) Decarboxylation experiments:



reaction was not effective, and **10a** was formed in only 14% yield (entry 11).

The results shown in Scheme 3B highlight the importance of a borate counterion that incorporates an acidic proton. A possible rationalization is based upon the observation that DMF solutions of pentafluorobenzoate undergo facile protodecarboxylation to C_6F_5H in the presence of protic ammonium counterions (Scheme 3C). For example, decarboxylation of triethylammonium salt **11a** was greater than 95% complete after 100 s at 80 °C, whereas sodium analogue **11b** reached less than 25% conversion after 1 h. In this latter case, protodecarboxylation is likely promoted by adventitious water. In support of this, subsequent wetting of the reaction mixture triggered rapid and complete conversion to C_6F_5H (Scheme 3C, inset).[24,25] The formation of C_6F_5H was observed by ^1H and ^{19}F NMR during the conversion of **6a** to **10a** and **3** to **5**, which confirms that, in both cases, decarboxylation occurs during catalysis. Upon the basis of the data and mechanistic considerations outlined in Scheme 2, we suggest that, for **10a**, the decarboxylation process enforces access to cationic imino-Pd(II) intermediate **7a** (at the expense of **7b**), which, in turn, accelerates C−N bond formation. Additionally, simultaneous clearance of the pentafluorobenzoate and triethylammonium counterions at the stage of **8a** would provide "naked", and presumably more reactive, nucleophilic and electrophilic components, which may accelerate transmetalation to **9**. For conventional Narasaka−Heck cyclizations (e.g., **3** to **5**), the equivalent of acid generated by the β-hydride elimination step (which is not operative for **6a** to **10a**) clears pentafluorobenzoate from the reaction system and minimizes its inhibitory effect on cyclization. Schroeder and co-workers have conducted detailed studies on the decarboxylation of fluorobenzoic acids by N-bases, where it was shown that pentafluorobenzoic acid undergoes protodecarboxylation 1−3 orders of magnitude faster than 2,3,5,6-tetrafluorobenzoic acid.[24,26] These studies, in combination with the results outlined here, provide a rationalization for the special role of pentafluorobenzoyl oxime esters in Narasaka−Heck cyclizations.

The scope of the aminoacylation protocol is outlined in Table 1. A range of oxime esters (**6a−c**) and sterically diverse 1,1-disubstituted alkenes (**6d−g**) participate to provide the cyclization products (**10a−g**) in good yields, especially given the complexity of the cascade. The tolerance to relatively hindered 1,1-disubstituted alkenes is notable and contrasts existing carboamination strategies where internal substitution on acyclic alkenes is poorly tolerated.[11] Pleasingly, monosubstituted alkenes also participate and cyclization of **6h−l** delivered targets **10h−l** in 42−78% yield. In these cases, migratory insertion of CO at the stage of **2** (see Scheme 1, gray box) is seemingly faster than β-hydride elimination to the alkene, which, for **6h** and **6l** (R^4 = H), would lead to the corresponding pyrroles. In the case of **6h**, small quantities of pyrrole were observed (10:1 **10h**/pyrrole),[27] but in other cases, 1,2-carboacylation occurred exclusively. For **6l**, cyclization was highly diastereoselective and *trans*-disubstituted adduct **10l** was formed in good yield; the stereochemistry of this adduct was determined by NOE studies (see the Supporting Information). At the present stage of development, 1,2-dialkylated alkenes are not tolerated, and, in these cases, β-hydride elimination dominates to afford, ultimately, the corresponding pyrrole, even if elevated pressures of CO are employed. A key benefit of this carboamination strategy is that the oxime ester starting materials are easily accessed from the corresponding carbonyl compounds, which, in turn, are prepared by simple and established chemistry (see the Supporting Information). Consequently, regiocontrolled access to pyrrolidine derivatives bearing substitution at any of the ring positions is readily achieved. We have not exhaustively assessed the scope of the R^1 group, but pertinent limitations have already been delineated in our earlier work on conventional Narasaka−Heck cyclizations.[15a]

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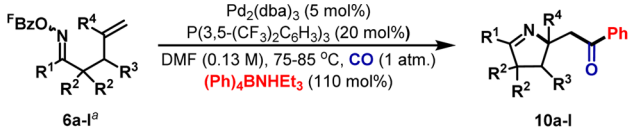
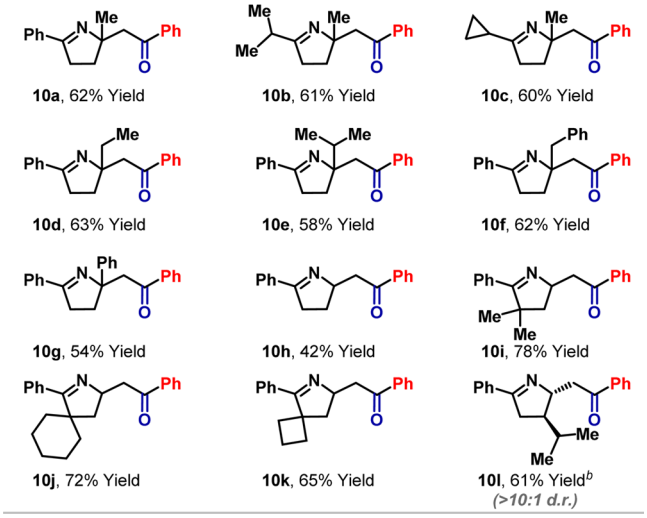
Table 1. 1,2-Aminoacylation Reactions: Scope of the Oxime Ester and Alkene



6a-l[a] 10a-l

6a, R^1=Ph, R^4 = Me	**6b**, R^1=*i*-Pr, R^4=Me	**6c**, R^1=*c*-Pr, R^4 =Me
6d, R^1=Ph, R^4=Et	**6e**, R^1=Ph, R^4= *i*-Pr	**6f**, R^1=Ph, R^4=Bn
6g, R^1=Ph, R^4=Ph	**6h**, R^1=Ph	**6i**, R^1=Ph, R^2=Me
6j, R^1=Ph, R^2=-$(CH_2)_5$-	**6k**, R^1=Ph, R^2=-$(CH_2)_3$-	**6l**, R^1=Ph, R^3= *i*-Pr



10a, 62% Yield; **10b**, 61% Yield; **10c**, 60% Yield

10d, 63% Yield; **10e**, 58% Yield; **10f**, 62% Yield

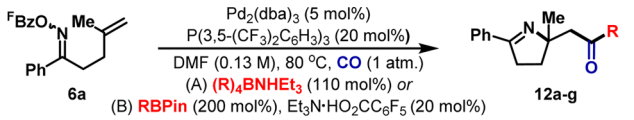
10g, 54% Yield; **10h**, 42% Yield; **10i**, 78% Yield

10j, 72% Yield; **10k**, 65% Yield; **10l**, 61% Yield[b] (>10:1 d.r.)

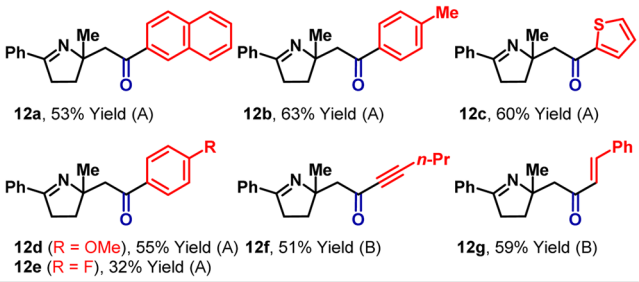
[a]R^{2-4} = H unless specified otherwise. [b]Isolated yield of the major diastereomer.

The 1,2-carboacylation methodology described here enables the introduction of a variety of C-based nucleophiles. Variation of the tetraarylborate component provides modular access to aryl analogues **12a–d**, where a range of electron rich arenes are transferred with similar levels of efficiency (53–63% yield) (Table 2). Electron-deficient arenes can also be introduced, but the processes are less efficient, presumably due to the diminished nucleophilicity of the tetraarylborate. For example, 1,2-carboacylation of **6a** with tetra(*p*-fluorophenyl)borate delivered **12e** in only 32% yield. The development of protocols that address this limitation will be a focus of future studies. Transfer of alkynyl- or vinyl-groups cannot be achieved using an analogous protocol because the requisite tetraalkynyl- and tetravinyl-borates are not synthetically accessible. Fortunately, in these cases, pinacol organoboronates are effective and introduction of alkynyl- (**6a** to **12f**) and alkenyl-groups (**6a** to **12g**) was achieved in 51% and 59% yield, respectively. Here, the organometallic component is apparently sufficiently reactive such that transmetalation via a 4-centered transition state (cf. **TS-8b**) is effective. Upon the basis of the hypothesis that additional pentafluorobenzoate may enhance the rate of this step (by increasing access to **8b**, vide infra), we have noted that addition of 20 mol % $Et_3N{\cdot}HO_2CC_6F_5$ often has a small but reproducible benefit to reaction efficiency. For example, in the absence of this additive, **12f** was generated in only 43% yield (vs 51% yield with 20 mol % $Et_3N{\cdot}HO_2CC_6F_5$). Established Pd-catalyzed protocols for alkene 1,2-carboacylation do not allow the direct installation of ynones or enones, thereby highlighting the value of the umpolung approach outlined here.

Table 2. 1,2-Aminoacylation Reactions: Scope of the C-Based Nucleophile



6a 12a-g



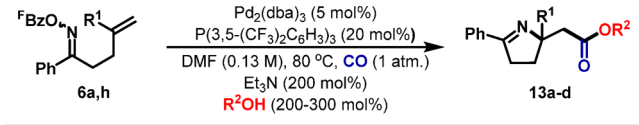
12a, 53% Yield (A); **12b**, 63% Yield (A); **12c**, 60% Yield (A)

12d (R = OMe), 55% Yield (A) **12f**, 51% Yield (B)
12e (R = F), 32% Yield (A)

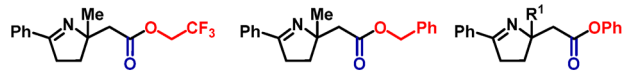
12g, 59% Yield (B)

Replacement of the organoboron component with alcohol nucleophiles provides 1,2-aminocarboxylation reactions (Table 3). The catalysis system is analogous to that used in Table 1,

Table 3. 1,2-Aminocarboxylation Reactions



6a,h 13a-d



13a, 66% Yield; **13b**, 60% Yield; **13c**, 65% Yield[a] (R^1 = Me)
13d, 58% Yield[a] (R^1 = H)

[a]The reaction was run without Et_3N.

and adducts **13a–d** were isolated in good yield, especially given the complexity of the process. The successful cyclization of **6h** to **13d** is particularly noteworthy, and again, only traces of pyrrole were observed in this case (cf. **6h** to **10h**). Because a molar equivalent of acid is liberated over the course of the cascade, it is likely that protodecarboxylation of the activating group is also relevant to these processes. For **13c** and **13d**, S_NAr attack of phenolate onto the *para*-position of the pentafluorobenzoyl oxime ester of **6a**/**h** was problematic when Et_3N was employed, and consequently, this additive was omitted in these cases.[28] Aminocarboxylation products **13a–c** provide a representative range of activated or protected ester derivatives that are available from a common starting point.

The accessibility of the key alkyl-Pd(II) intermediate **2** suggests that a range of distinct *noncarbonylative* 1,2-amino-functionalizations should also be viable by trapping of this species. 1,2-Aminoarylation reactions are achieved readily by using the corresponding pinacol arylboronate as the nucleophile (Table 4). Exposure of **6a** to a selection of these reagents afforded the corresponding aminoarylation products **14a–g** in 53–72% yield, with electron rich arylboronates proving most effective. As observed earlier, the protocol is relatively insensitive to the steric demands of the alkene and adducts **6d–f** also cyclized efficiently in the presence of pinacol 2-furylboronate to afford the targets **14h–j** in 66–73% yield. In these noncarbonylative processes, trapping of intermediate **2** is slower and so *β*-hydride elimination to the corresponding pyrrole dominates in cases involving monosubstituted alkenes

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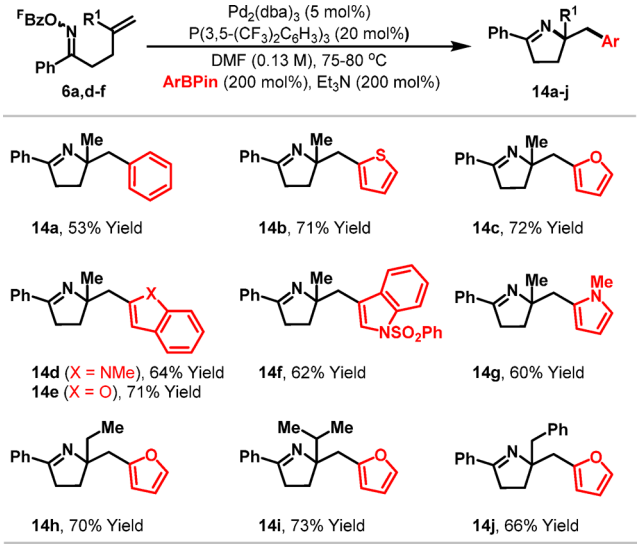
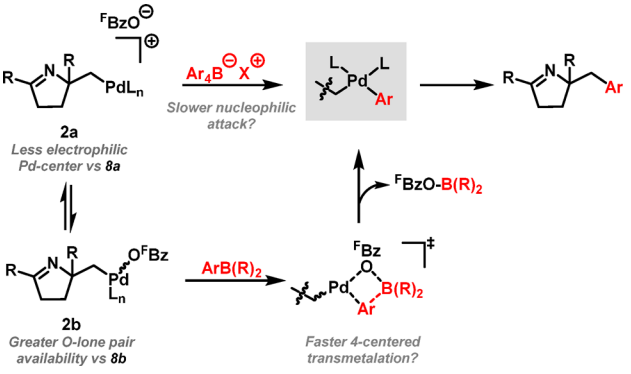
Table 4. 1,2-Aminoarylation Reactions



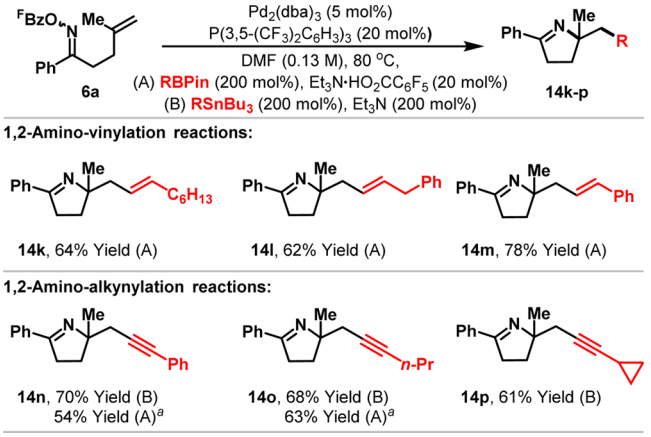
(cf. **6h** to **13d**). It is interesting to note that, although pinacol arylboronates are not suitable for the carbonylative processes described in Table 1, they are competent nucleophiles for 1,2-aminoarylation. A possible explanation is that pentafluorobenzoate assisted transmetalation involving the key alkyl-Pd(II) intermediate **2b** is easier than via the analogous acyl-Pd(II) intermediate **8b** because of greater O-lone pair availability (Scheme 4). In this scenario, pentafluorobenzoate is presumably cleared from the reaction system as ^{F}BzO-BPin. Intriguingly, tetraarylborates, which were effective earlier, are not suitable for these noncarbonylative processes, perhaps due to decreased electrophilicity of alkyl-Pd(II) intermediates **2a**/**b** relative to analogous acyl-Pd(II) intermediates **8a**/**b**.

Scheme 4. Mechanistic Considerations for Transmetalation in Noncarbonylative Processes



In a preliminary assessment of scope, we have assayed the cyclization of adduct **6a** in the presence of other classes of C-based nucleophile (Table 5). Processes involving vinyl boronate derivatives provide access to 1,2-aminovinylation products **14k**–**m** in 62–78% yield. In these cases, the addition of $Et_3N{\cdot}HO_2CC_6F_5$ was crucial to reaction efficiency and had a more pronounced effect than that observed for **12f** and **12g**. For example, when this additive was omitted, the cyclization of **6a** to **14k** proceeded in only 34% yield (vs 64% yield with 20 mol % $Et_3N{\cdot}HO_2CC_6F_5$). The studies outlined in Scheme 3C establish that protodecarboxylation to C_6F_5H is rapid, but we

Table 5. 1,2-Amino-Vinylation and -Alkynylation Reactions



[a] $Et_3N{\cdot}HO_2CC_6F_5$ (20 mol %) was not used.

have confirmed that this component does not have an appreciable effect on cyclization efficiency when employed as an additive. Higher loadings of $Et_3N{\cdot}HO_2CC_6F_5$ or the use of $Bu_4NO_2CC_6F_5$ provided lower yields of **14k**. Presumably, any beneficial effects that carboxylate additives have on transmetalation must be balanced with their inhibitory effect on cyclization. For more nucleophilic organometallic partners, this additive effect is not operative. Indeed, 1,2-aminoalkynylation reactions are readily achieved using alkynyl-based organometallics. Here, alkynyl-stannanes were most effective, but less toxic pinacol alkynylboronates could also be employed. Cyclization of **6a** generated **14n** in 70% yield using the alkynyl-tin reagent and 54% yield using the boron-based alternative. Extension to other alkynyl-nucleophiles provides efficient access to **14o** and **14p**, thereby highlighting the flexibility of the approach.

The imine moiety of the cyclization products described here provides options for further diversification, and we have exemplified this by studying reductive manipulations (Figure 1). Hydrogenation (Pd/C) of **10l** delivered trisubstituted pyrrolidine **15** in good yield and diastereoselectivity (6:1 d.r.). Under the conditions shown, competitive reduction of the ketone was not observed. Similarly, reduction of **13d** proceeded smoothly to generate disubstituted pyrrolidine **16** in high yield and with excellent stereocontrol. Hydrogenation of **14i** was slow, but reduction using DIBAL-H was effective and adduct **17** was isolated in 85% yield and as a 4:1 mixture of diastereomers. The stereochemical assignments of the major diastereomers of **15**–**17** were supported by NOE experiments (see the Supporting Information) and, in each case, preferential

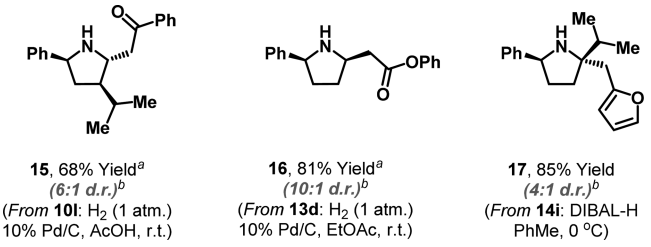


Figure 1. Reductive manipulations of the carboamination products. [a]Isolated yield of the major diastereomer. [b]Determined by ^{1}H NMR analysis of crude material.

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reduction from the less hindered face of the imine accounts for the observed diastereoselectivities.

CONCLUSIONS

The present study outlines an umpolung approach to alkene carboamination enabled by oxidative addition of Pd(0)-catalysts into the N−O bond of oxime esters. This provides a unified strategy for a wide range of amino-functionalizations, as highlighted by prototypical methods for 1,2-amino-acylation, -carboxylation, -arylation, -vinylation, and -alkynylation. For carbonylative processes, orchestrated protodecarboxylation of the pentafluorobenzoate leaving group is crucial for efficient cyclization. This process is likely a key feature in related Narasaka−Heck cyclizations, and the studies here provide important insights into the efficacy of *O*-pentafluorobenzoyl oxime esters in aza-Heck reactions of this type. Compared to established 1,2-carboamination methods, other notable features of the present approach include a tolerance to sterically demanding 1,1-disubstituted alkenes and the synthetic options provided by the imine moiety of the products. Consequently, this strategy may provide a valuable counterpoint to existing carboamination approaches. Future studies will align the development of enantioselective variants with more efficient protocols and stereocontrolled manipulations of the cyclization products. We are also developing related carboamination processes that employ other electrophilic nitrogen sources.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03732.

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Notes

The authors declare no competing financial interest.

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