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Pd-Catalyzed Alkene Diamination Reactions of Nitrogen Electrophiles. Synthesis of Cyclic Guanidines and Ureas Bearing Dialkylaminomethyl Groups.

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Abstract

The Pd-catalyzed coupling of *N*-allylguanidines or *N*-allylureas with *O*-benzoylhydroxylamine derivatives affords cyclic guanidines or cyclic ureas bearing dialkylaminomethyl groups. The desired products are obtained in good yield, and substrates bearing substituents at the allylic position are transformed with moderate diastereoselectivity. The mechanism of these reactions appears to involve *anti*-aminopalladation of the alkene, followed by a rare sp^3C – sp^3N bond-forming reductive elimination from an alkylpalladium complex that contains β -hydrogen atoms.

Graphical Abstract

Over the past fourteen years, our group has reported a series of Pd-catalyzed alkene difunctionalization reactions between aryl or alkenyl halides or triflates and alkenes bearing pendant nucleophiles.¹ For example, treatment of an *N*-allyl urea or guanidine derivative (**1**) with an aryl halide or triflate affords heterocyclic product **2** in good yield (eq 1).² These transformations are effective with a broad range of nucleophiles, the reactions are stereospecific with respect to alkene geometry, and substrates bearing substituents on the alkene or the alkyl tether are generally transformed with good to excellent levels of diastereoselectivity. Despite the utility of these transformations, to date, all reactions have involved the use of carbon-centered electrophiles, which leads to the formation of one C–C bond and one carbon-heteroatom bond during the alkene addition.

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Supporting Information

Experimental procedures, characterization data, and copies of ¹H and ¹³C NMR spectra for all new compounds (PDF). The Supporting Information is available free of charge on the ACS Publications website.

Notes

The authors declare no competing financial interest.

(1)

(2)

In recent years, the use of O-acylated hydroxylamine derivatives as nitrogen-centered electrophiles **3** in metal-catalyzed reactions has attracted considerable attention.³ We were interested in investigating the utility of these electrophiles in heterocycle-forming alkene diamination reactions^{4,5,6} of substrates such as **1** that are mechanistically related to our Pd-catalyzed alkene carboamination reactions (eq 2). These transformations would provide heterocyclic products bearing an appended dialkylaminomethyl group (**4**), which are subunits displayed in some biologically active compounds.⁷ The final step in the alkene diamination catalytic cycle would be an sp³C–sp³N bond-forming reductive elimination from an alkylpalladium complex, which is a very rare organometallic transformation,⁸ and was expected to be challenging to achieve. However, recent studies on alkane C–H functionalization with these electrophiles suggested that this reductive elimination step may be possible.^{8a,9} In addition, although Wang has reported an analogous, Cu-catalyzed alkene diamination reaction involving N-alkoxypentamides or N¹-allyl-N²-methoxyureas as substrates,^{10,11,12} the Cu-catalyzed reactions reported thus far are not stereospecific with respect to alkene geometry due to the radical character of an intermediate alkylcopper complex (eq 3).¹⁰ Thus, it appeared that the Pd-catalyzed process could have advantages over the Cu-catalyzed reactions, as our Pd-catalyzed alkene carboamination reactions are stereospecific, and we anticipated the new diamination reactions would also be stereospecific.

(3)

In order to explore the feasibility of Pd-catalyzed alkene diamination reactions involving nitrogen electrophiles, we first examined the coupling of **7a** with morpholino benzoate (**3a**) to afford cyclic guanidine product **8a** (Table 1). Initially, we employed catalysts derived from Pd(OAc)₂ and the ligands DPE-Phos, CPhos, and XantPhos, as these ligands provided good to excellent results in alkene carboamination reactions of **7a** and related nucleophiles.^{1,2} No desired product was obtained with the CPhos or XantPhos ligands, but we were gratified to find that use of DPE-Phos led to the formation of the desired product in a measurable, but low yield.¹³ Subsequently, we turned our attention to electron-poor monodentate phosphines, as ligands such as P(C₆F₅)₃ have provided good results in other Pd-catalyzed transformations of nitrogen electrophiles,^{9a,14} and it seemed that the electron-poor ligand may accelerate the sp³C–sp³N bond-forming reductive elimination step.¹⁵ Use of P(C₆F₅)₃ as ligand resulted in an improved 30% yield of **8a**, and after surveying several palladium sources, we found that use of Pd(acac)₂ led to a further increase to 60% yield. The combination of P[3,5-(CF₃)₂C₆H₃]₃ as ligand and Pd(acac)₂ as precatalyst was even better, with **8a** generated in 80% yield. Finally, we examined the biarylphosphine JackiePhos, which contains two 3,5-(CF₃)₂C₆H₃ groups on the phosphorous atom and has previously been shown to promote challenging sp²C–N bond-forming reductive elimination;¹⁶ we were delighted to obtain a 95% NMR yield of **8a**. With this catalyst system we were able to decrease the amount of electrophile used from 4 equiv to 3 equiv, but use of 2 equiv or less of the electrophile resulted in diminished yields.

Once the satisfactory conditions were in hand, we conducted a few additional experiments to further examine the influence of precatalyst structure on yield. Although the Pd(acac)₂/JackiePhos catalyst system provided excellent results (entry 10), use of Pd₂(dba)₃ as a precatalyst for this reaction completely inhibited product formation (entry 11). Addition of 6 mol % dba to the otherwise optimal conditions (entry 12) resulted in the formation of **8a** in only 25% yield. Use of the Buchwald G3-JackiePhos catalyst precursor in place of Pd(acac)₂ failed to produce significant amounts of the desired product (5%, entries 13–14). However, when 8 mol % acac (2,4-pentanedione) was added to a reaction in which the G3-JackiePhos complex was used as precatalyst, **8a** was generated in 35% yield. These results indicate that: (a) the failure of Pd₂(dba)₃ to serve as a viable precatalyst is probably due to inhibition by the dba ligand rather than the zerovalent oxidation state of that complex; and (b) acac plays a key role in these reactions, either by facilitating reactivity of an intermediate along the catalytic cycle, or more likely by inhibiting catalyst deactivation.

Then, we explored the scope of the Pd-catalyzed coupling reactions of *N*-cyano and *N*-tosylguanidine substrates **7a–d** with several different electrophiles. As shown in Table 2, these transformations are effective with *O*-benzoylhydroxylamine electrophiles derived from morpholine (**3a**), piperidine (**3b**), and *N*-boc piperazine (**3c**). However, efforts to employ an acyclic electrophile derived from *N*-methyl benzylamine led to the formation of a complex mixture of products. Reactions of substrates **7c–d** bearing an allylic methyl group proceeded to afford **8f–h** in good yield and moderate diastereoselectivity (3:1 dr). These diastereoselectivities are comparable to those obtained in analogous Pd-catalyzed carboamination reactions of **7c–d** with aryl bromides.^{2a} Attempts to employ substrates bearing either 1,1- or 1,2-disubstituted alkenes have thus far been unsuccessful.

We also briefly explored the coupling of urea substrates **9a-c** to afford **10a-f**. As shown in Table 3, the reactions of **9a** proceeded smoothly with electrophiles derived from morpholine (90% yield on a 0.1 mmol scale and 76% yield on a 1.0 mmol scale) and piperidine (83% yield). However, use of electrophile **3c** derived from *N*-boc piperazine led to a modest yield of the desired product. Although the presence of a methyl group at the allylic position was well tolerated in the reactions of guanidine nucleophiles **7c-d** (Table 1, entries 6–8), the coupling of analogous urea substrate **9b** proceeded in low yield (32%) to afford **10d** with 2:1 dr. Use of substrate **9c**, which contains an *N*-*p*-chlorophenyl group, led to lower yields than were observed in reactions of **9a** due to competing decomposition of the urea substrate to give *N*-allylbenzylamine.

In order to gain insight into the mechanism and stereospecificity of these new transformations, we examined the reactivity of deuterated substrates **d-7a-b** and **d-9a**. As shown in Table 4, the coupling of **d-7a** with **3a** afforded *anti*-addition product **d-8a** in 67% yield and 3:1 dr. The reactions of urea substrate **d-9a** and *N*-tosylguanidine **d-7b** with morpholino benzoate also proceeded via *anti*-addition to the alkene, but with higher diastereoselectivity (6:1 dr in both cases). The coupling of piperidin-1-yl benzoate **3b** with **d-7b** gave slightly higher diastereoselectivity (7:1 dr) than was obtained with morpholino benzoate. Thus, in contrast to the related copper-catalyzed diamination reactions,¹⁰ the Pd-catalyzed alkene diamination reactions are stereospecific, although the transfer of stereochemical information from substrate to product is thus far imperfect (but arguably synthetically useful).

On the basis of the alkene addition stereochemistry, we propose these new Pd-catalyzed alkene diamination reactions proceed via the catalytic cycle shown in Scheme 1. Initial ligation and reduction of the Pd(acac)₂ pre-catalyst leads to formation of a Pd(0) complex, which then undergoes oxidative addition to the *O*-benzoyl hydroxylamine **3a** to afford intermediate **11**.¹⁷ Coordination of the alkene to the Pd-complex followed by deprotonation and *anti*-aminopalladation of **12** then affords **13**,¹⁸ which undergoes C–N bond-forming reductive elimination to yield **d-10a** with concomitant regeneration of the Pd(0) catalyst. Although we currently favor this proposed mechanism, at this point, we cannot rule out an alternative pathway involving oxidation of **13** to Pd(IV) complex **14**, followed by reductive elimination to afford the product with formation of **11** to close the catalytic cycle.

The minor stereoisomer observed in these reactions most likely originates via one of two pathways: (a) competing *syn*-aminopalladation via a palladium bis(amido) complex; or (b) erosion of the stereochemistry of intermediate **13** (or **14**, as the case may be) via β -hydride elimination/reinsertion to generate a tertiary α -amino palladium complex, which can undergo rotation around the C–CH₂D bond followed by a second β -hydride elimination/reinsertion to invert the stereogenic center.¹⁹ In order to probe this question, we sought to slow the rate of potential β -hydride elimination from **13** by replacing the H-atom on the internal alkene carbon with a deuterium atom (R = D). We hoped that this substitution would either lead to higher stereocontrol, therefore suggesting that the minor stereoisomer originates from β -hydride elimination,²⁰ or would lead to no change in stereoselectivity, which would imply that the modest stereocontrol is due to competing *syn*- vs. *anti*-aminopalladation.²¹ As such, doubly-deuterated alkene substrate **15** was prepared and subjected to

our standard reaction conditions. As shown in eq 4, this transformation afforded **16** in 64% yield and 6:1 dr, which is comparable to that obtained in the reaction of **d-9a**. Thus, the minor stereoisomer appears to result from competing *syn*-aminopalladation.

(4)

In conclusion, we have developed a new class of Pd-catalyzed alkene diamination reactions that involve the coupling of *O*-benzoyl hydroxylamine derived electrophiles with *N*-allylguanidine or urea derivatives. The transformations proceed via stereospecific *anti*-addition of the two *N*-atoms to the alkene with up to 7:1 dr, which is in sharp contrast to previously reported Cu-catalyzed reactions.¹⁰ These transformations appear to proceed via a rare sp³C-sp³N bond-forming reductive elimination, which is facilitated by the bulky, electron-poor JackiePhos ligand. Future studies will be directed towards expanding the scope and improving the stereocontrol in these transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Catalytic Cycle – Working Hypothesis

Table 1.

Optimization Studies ^a

entry	[Pd]	ligand (L)	catalyst loading	yield (%) ^b
1	Pd(OAc) ₂	DPE-Phos	2 mol % [Pd] 4 mol % L	13
2	Pd(OAc) ₂	CPhos	2 mol % [Pd] 8 mol % L	0
3	Pd(OAc) ₂	XantPhos	2 mol % [Pd] 8 mol % L	0
4	Pd(OAc) ₂	P(C ₆ F ₅) ₃	2 mol % [Pd] 8 mol % L	30
5	Pd ₂ (dba) ₃	P(C ₆ F ₅) ₃	4 mol % [Pd] 16 mol % L	0
6	Pd(TFA) ₂	P(C ₆ F ₅) ₃	4 mol % [Pd] 16 mol % L	40
7	Pd(acac) ₂	P(C ₆ F ₅) ₃	4 mol % [Pd] 16 mol % L	60
8	Pd(acac) ₂	P[C ₆ H ₃ -3,5-(CF ₃) ₂] ₃	4 mol % [Pd] 16 mol % L	80
9	Pd(acac) ₂	JackiePhos	4 mol % [Pd] 16 mol % L	95
10	Pd(acac) ₂	JackiePhos	4 mol % [Pd] 16 mol % L	95 ^c
11	Pd ₂ (dba) ₃	JackiePhos	4 mol % [Pd] 16 mol % L	0 ^c
12	Pd(acac) ₂	JackiePhos + dba	4 mol % [Pd] 16 mol % L 6 mol % dba	25 ^c
13	G3-JackiePhos	JackiePhos	4 mol % [Pd] 16 mol % L ^d	<5 ^c
14	G3-JackiePhos	no added ligand	4 mol % [Pd]	5 ^c
15	G3-JackiePhos	JackiePhos + acac	4 mol % [Pd] 16 mol % L ^d 8 mol % acac	35 ^c

^aConditions: 1.0 equiv **7a**, 4.0 equiv **3a**, 2 equiv Cs₂CO₃, [Pd], ligand (L), dioxane (0.1 M), 100 °C, 16 h.

^bYields were determined by ¹H NMR using 1,10-phenanthroline as an internal standard.

^cThe reaction was conducted using 3 equiv **3a** instead of 4 equiv.

^dThe reaction was conducted with 12 mol % added JackiePhos (plus the 4 mol % of JackiePhos bound to the G3 complex).

Table 2.

Diamination of *N*-Allylguanidines^a

entry	P	X	R	dr ^b	yield (%) ^c
1	CN	O	H	—	91 (8a)
2	CN	CH ₂	H	—	92 (8b)
3	CN	NBoc	H	—	61 (8c)
4	Ts	O	H	—	86 (8d)
5	Ts	CH ₂	H	—	77 (8e)
6	CN	O	Me	3:1 (4:1)	75 (8f)
7	CN	CH ₂	Me	3:1	81 (8g)
8	Ts	O	Me	3:1	88 (8h)

^aConditions: 1.0 equiv **7**, 3.0 equiv **3**, 2 equiv Cs₂CO₃, 4 mol % Pd(acac)₂, 16 mol % JackiePhos, dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale.

^bDiastereomeric ratios were determined by ¹H NMR analysis. Numbers in parentheses are drs for the crude reaction mixture in cases where the crude and isolated dr differed.

^cIsolated yield (average of two or more experiments).

Table 3.

Diamination of *N*-Allylureas^a

entry	Y	X	R	dr ^b	yield (%) ^c
1	NO ₂	O	H	—	90 (10a)
2	NO ₂	CH ₂	H	—	83 (10b)
3	NO ₂	NBoc	H	—	46 (10c)
4	NO ₂	O	Me	2:1	32 (10d)
5 ^d	Cl	O	H	—	45 (10e)
6 ^d	Cl	CH ₂	H	—	14 (10f)

^aConditions: 1.0 equiv **7**, 3.0 equiv **3**, 2 equiv Cs₂CO₃, 4 mol % Pd(acac)₂, 16 mol % JackiePhos, dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale.

^bDiastereomeric ratios were determined by ¹H NMR analysis.

^cIsolated yield (average of two or more experiments).

^dThe reaction was conducted with 4 mol % Pd(acac)₂ and 6 mol % JackiePhos.

Table 4.

Alkene Addition Stereochemistry^a

<p> $d-7a$: R = Bn, Y = N-CN $d-7b$: R = Bn, Y = N-Ts $d-8a$: R = C₆H₄-p-NO₂, Y = O $d-8b$: R = Bn, Y = N-CN, X = O $d-8d$: R = Bn, Y = N-Ts, X = O $d-8e$: R = Bn, Y = N-Ts, X = CH₂ $d-10a$: R = C₆H₄-p-NO₂, Y = O, X = O </p>					
entry	Y	R	X	dr	yield (%) ^b
1	N-CN	Bn	O	3:1	67 (<i>d-8a</i>)
2	O	C ₆ H ₄ -p-NO ₂	O	6:1	75 (<i>d-10a</i>)
3	N-Ts	Bn	O	6:1	75 (<i>d-8d</i>)
4	N-Ts	Bn	CH ₂	7:1	77 (<i>d-8e</i>)

^aConditions: 1.0 equiv **7a-b** or **9a**, 3.0 equiv **3a** or **3b**, 2 equiv Cs₂CO₃, 4 mol % Pd(acac)₂, 16 mol % JackiePhos, dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale.

^bIsolated yield (average of two or more experiments).