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Synthesis of Cyclic Guanidines Bearing *N*-Arylsulfonyl and *N*-Cyano Protecting Groups via Pd-Catalyzed Alkene Carboamination Reactions

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Abstract

Palladium-catalyzed carboamination reactions of *N*-allylguanidines bearing cleavable *N*-cyano or *N*-arylsulfonyl protecting groups are described. The reactions afford cyclic guanidine products in good yield, and transformations of substrates bearing internal alkenes proceed with high diastereoselectivity. Deuterium labeling studies indicate these transformations proceed via *anti*-aminopalladation pathways.

Graphical abstract

The synthesis of cyclic guanidines has attracted considerable attention due to the presence of cyclic guanidine subunits in a variety of biologically active natural products.^{i,ii} Many recent approaches to the construction of these motifs have focused on the use of metal catalysts to effect formation of carbon-nitrogen bonds.^{iii,iv} However, aside from our prior studies in the area,^{v,vi} no existing methods effect formation of both a C–N, a C–C bond, and the ring in a single transformation.

Our group previously described a new approach to the preparation of cyclic guanidines via Pd-catalyzed alkene carboamination reactions between PMP-protected *N*-allylguanidines **1** and aryl bromides (eq 1).^v These transformations afforded the desired cyclic guanidines (e.g., **2**) in good chemical yield. However, efforts to cleave the PMP-protecting groups were unsuccessful. We have also reported a related series of Pd-catalyzed alkyne carboamination

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ASSOCIATED CONTENT

Supporting Information

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

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reactions of tosyl-protected *N*-propargyl guanidines **3**, which also proceed in good yield under appropriate conditions to afford 2-aminoimidazoles such as **4** (eq 2), and the *N*-tosyl group proved to be readily cleavable.^{vi} However, the conditions that provided high yields in reactions of *N*-propargylguanidines did not work with analogous *N*-allylguanidines; efforts to couple **5** with 4-methoxyphenyl triflate afforded little or none of the desired product. In this communication we describe a significant expansion in the scope of this method that allows for transformation of substrates bearing cleavable *N*-arylsulfonyl or *N*-cyano groups.

In order to develop Pd-catalyzed carboamination reactions of *N*-allylguanidines bearing cleavable protecting groups, we elected to explore the reactivity of two different substrates, **6a** and **7a**, which contain benzyl groups on two nitrogen atoms and either a cyano group or a tosyl group on the third. Our prior studies had indicated it should be possible to cleave the *N*-tosyl group from the products, and *N*-cyano groups can be cleaved from guanidines via treatment with strong acids. Moreover, the *N*-cyanoguanidines appeared to be particularly attractive products to target, as many *N*-cyanoguanidines have interesting biological activities.^{vii}

(1)

(2)

(3)

Our initial optimization studies were focused on the coupling of **6a** and **7a** with bromobenzene. As shown in Table 1, the coupling of **6a** afforded good yields of **8a** using a number of different phosphine ligands under conditions that have provided good results in many other alkene carboamination reactions.^{viii} Optimal yields were obtained with the biaryl

phosphine XPhos (entry 4). However, efforts to employ these conditions for the coupling of **7a** with bromobenzene were not successful, as the desired product **9a** was generated in low yield (25%) along with a complex mixture of side products (entry 5). Fortunately, simply employing reaction conditions that previously provided optimal results with *N*-tosyl *N*-propargyl guanidine **3** (aryl triflate in place of aryl bromide, Pd(OAc)₂ as palladium source, LiO^tBu as base, and PhCF₃ as solvent) afforded the desired product **9a** in 92% yield (entry 7).

We then explored the scope of the Pd-catalyzed carboamination reactions of *N*-cyano and *N*-tosylguanidine substrates. As shown in Table 2, the transformations are effective with a range of different aryl halide coupling partners, including electron-rich, and electron-poor derivatives. The reaction of **7a** with *o*-methylphenyl triflate also proceeded in good yield, but ca 10% of an inseparable impurity resulting from competing Heck arylation of the alkene was also generated (entry 7). In most instances comparable yields were obtained when either **6** or **7** were coupled with the same aryl bromide/triflate (entries 1–2, 3–4, 8–9, 11–12, and 14–15). The reactions were amenable to the construction of both five- and six-membered cyclic guanidines, and substrates **6b** and **7b** bearing a methyl group at the internal alkene carbon were also efficiently converted to the desired products.

Surprisingly, the diastereoselectivity obtained in reactions of substrates bearing a substituent adjacent to the N-atom was quite low (Scheme 1, **8k–m** and **9h–j**, 1.5:1 to 3:1 dr).^{ix} This is in stark contrast to results obtained in analogous reactions of *N*-allylureas,^x and *N*-allylsulfamides,^{xi} which typically proceed with ca 8:1 to >20:1 dr. In addition, although we were gratified to find that substrates bearing an internal alkene were transformed to **8n** and **9k–l**, which result from net *anti*-addition to the alkene, with good to excellent diastereoselectivity,^{xii} the stereochemistry of **8n** was rather surprising. Our prior studies on reactions of sulfamides, ureas, and PMP-protected guanidines,^{xiii} suggested that use of an aryl bromide in these guanidine carboamination reactions would lead to *syn*-addition to the double bond, whereas use of an aryl triflate was expected to favor *anti*-addition (as observed).^{xi}

Given the surprising results of these experiments, we further explored *syn*- vs. *anti*-addition pathways in transformations of deuterated substrates **10–11**. As shown in eq 4, the coupling of **10** with bromobenzene afforded *anti*-addition product **13** in 58% yield and 9:1 dr. The reaction of **11** with phenyl triflate to yield **14** also proceeded via *anti*-addition to the double bond, but with >20:1 dr. In principle the lower selectivity obtained with **10** could result either from competing *anti*- vs. *syn*-aminopalladation pathways in the catalytic cycle,^{xia} or from partial epimerization of the benzylic stereocenter via reversible β-hydride elimination processes that occur after the aminopalladation step.^{xiv} To address this question we examined the reactivity of substrate **12** and discovered its coupling with bromobenzene proceeds in 16:1 dr. Since the intermediate alkylpalladium complex derived from **12** cannot undergo β-hydride elimination, this result suggests that much of the minor diastereomer formed in the reaction of **10** is generated via β-hydride elimination side reactions.

The results of these experiments suggest the mechanism of the carboamination reactions proceeds as shown in Scheme 2. Oxidative addition of the aryl halide or triflate to the Pd(0)

catalyst affords **16**. Coordination of the pendant alkene to the metal (**17**) followed by *anti*-aminopalladation and deprotonation then generates alkylpalladium complex **18**. Reductive elimination of **18** affords the observed major stereoisomer **13** or **14**. The minor stereoisomer is formed from competing β -hydride elimination side reactions of **18**.^{xiv} The *anti*-heteropalladation mechanism is likely responsible for the modest diastereoselectivities observed for **8k–m** and **9h–j**, as the transition state for *anti*-heteropalladation is less organized than that for a *syn*-heteropalladation process.^{xv}

(4)

(5)

(6)

To further demonstrate the utility of this method we briefly explored the cleavage of the *N*-cyano or *N*-tosyl protecting groups from the guanidine products. As shown in eq 7, treatment of **7f** with concentrated HCl lead to clean deprotection of the *N*-cyano group to afford a 95% yield of **19**. However, efforts to cleave the *N*-tosyl group from **9f** with either acids or reducing agents did not provide satisfactory results. The de-tosylated product was obtained in low yield due to competing cleavage of one or both *N*-benzyl groups (eq 8).

(7)

(8)

Prior studies have shown that electron-rich arylsulfonyl groups are more readily cleaved from guanidines than tosyl groups.^{xvi} As such we prepared Mtr-protected guanidine substrate **20** (Mtr = 4-methoxy-2,3,6-trimethylbenzenesulfonyl) and subjected it to our standard reaction conditions to afford guanidine **21** in 95% yield (Scheme 3). Treatment of **21** with methanesulfonic acid and trifluoroacetic acid in the presence of thioanisole led to cleavage of the *N*-Mtr group and one *N*-benzyl group to afford **22** in 47% yield.

Due to our difficulties with cleanly removing only the *N*-arylsulfonyl group from cyclic guanidines bearing *N*-benzyl groups, we examined the preparation and deprotection of a cyclic *N*-tosyl guanidine bearing methyl groups on the other two nitrogen atoms. As shown in Scheme 4, the Pd-catalyzed coupling of **23** with 4-bromobenzophenone afforded cyclic guanidine **24** in 69% yield. We were gratified to find that cleavage of the *N*-tosyl group from **24** proceeded smoothly to provide a 70% yield of **25**.

In conclusion, we have developed a new approach to the synthesis of 5- and 6-membered cyclic guanidines bearing cleavable *N*-sulfonyl or *N*-cyano protecting groups. The Pd-catalyzed carboamination reactions proceed in generally good chemical yields, and provide products resulting from *anti*-addition to the alkene. Future studies will be directed towards improving diastereoselectivities in these reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- xii. The low yield of **8n** is due to competing base-mediated hydroamination of the starting material. This hydroamination side reaction was not observed with the less nucleophilic *N*-tosyl guanidine substrates.
- xiii. In our prior studies on Pd-catalyzed carboamination reactions of PMP-protected guanidines with aryl bromides (reference 1) we observed the stereochemistry of a product closely related to **8n** resulted from *syn*-addition to a *Z*-alkene. This assignment was originally based on analogy to the outcome of reactions of related ureas, and has since been confirmed via nOe studies.
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Scheme 1. Diastereoselectivity Studies^a

^a**Conditions A (P = CN):** 1.0 equiv substrate **6**, 1.5 equiv R¹-Br, 2.0 equiv NaO^tBu, 1 mol % Pd₂(dba)₃, 4 mol % XPhos, toluene (0.1 M), 90 °C, 1 h. Reactions were conducted on a 0.15–0.2 mmol scale. ^b**Conditions B (P = Ts):** 1.0 equiv substrate **7**, 1.5 equiv Ar-OTf, 2.0 equiv LiO^tBu, 2 mol % Pd(OAc)₂, 4 mol % CPhos, PhCF₃ (0.2 M), 100 °C, 2 h. Reactions were conducted on a 0.3 mmol scale. All yields are isolated yields. ^cThe reaction was conducted using CPhos as ligand.

Scheme 2.
Mechanism

Scheme 3.
Synthesis/Deprotection of *N*-Mtr Guanidine 20.

Scheme 4.
Synthesis/Deprotection of *N*-Ts Guanidine 24.

Table 1Optimization Studies^a

entry	substrate	ligand	yield (%) ^b
1	6a	Xantphos	73
2	6a	Dpe-Phos	89
3	6a	CPhos	92
4	6a	XPhos	>99
5	7a	XPhos	25
6	7a	CPhos	33
7	7a	CPhos ^c	92

^aConditions: 1.0 equiv substrate **6a** or **7a**, 1.5 equiv PhBr, 2.0 equiv NaO^tBu, 1 mol % Pd₂(dba)₃, 4 mol % XPhos, toluene (0.1 M), 90 °C, 1 h. Reactions were conducted on a 0.2 mmol scale.

^bNMR yield using phenanthrene as internal standard.

^cThe reaction was conducted using PhOTf in place of PhBr, LiO^tBu in place of NaO^tBu, Pd(OAc)₂ in place of Pd₂(dba)₃, and PhCF₃ (0.2 M) in place of toluene, and a reaction temperature of 100 °C.

Table 2

Carboamination of *N*-Protected guanidines^a

6a-c: P = CN; 7a-c: P = Ts 8a-j: P = CN; 9a-g: P = Ts				
entry	substrate	R ¹ -X	product	yield (%) ^b
1	6a: R = H, n = 1	PhBr	8a	86
2	7a: R = H, n = 1	PhOTf	9a	92
3	6a	<i>p</i> -Cl-C ₆ H ₄ Br	8b	82
4	7a	<i>p</i> -Cl-C ₆ H ₄ OTf	9b	70
5	6a	<i>p</i> -MeO-C ₆ H ₄ Br	8c	85
6	7a	2-naphthylOTf	9c	80
7	7a	<i>o</i> -Me-C ₆ H ₄ OTf	9d	78 ^c
8	6b: R = Me, n = 1	PhBr	8d	88
9	7b: R = Me, n = 1	PhOTf	9e	86 ^d
10	6b	<i>p</i> - ^t BuC ₆ H ₄ Br	8e	86
11	6c: R = H, n = 2	PhBr	8f	98 ^e
12	7c: R = H, n = 2	PhOTf	9f	85
13	6c	<i>p</i> -MeO-C ₆ H ₄ Br	8g	94 ^e
14	6c	<i>p</i> -MeO-C ₆ H ₄ Br	8g	84 ^{e,f}
15	6c	<i>p</i> -PhC(O)C ₆ H ₄ Br	8h	81 ^e
16	7c	<i>p</i> -PhC(O)C ₆ H ₄ OTf	9g	96
17	6c		8i	97 ^e
18	6c		8j	95 ^g

^aConditions A (P = CN): 1.0 equiv **6**, 1.5 equiv R¹-Br, 2.0 equiv NaO^tBu, 1 mol % Pd₂(dba)₃, 4 mol % XPhos, toluene (0.1 M), 90 °C, 1 h.Conditions B (P = Ts): 1.0 equiv **7**, 1.5 equiv Ar-OTf, 2.0 equiv LiO^tBu, 2 mol % Pd(OAc)₂, 4 mol % CPhos, PhCF₃ (0.2 M), 100 °C, 2 h.

Reactions were conducted on a 0.2–0.3 mmol scale.

^b Isolated yield.^c This material contained ca 10% of an inseparable side product resulting from Heck arylation of the alkene.^d The reaction was conducted at 0.1 M concentration.^e The reaction was conducted using CPhos as ligand.^f The reaction was conducted on a 1 mmol scale.

^gThe reaction was conducted for 2 h at 90 °C.

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