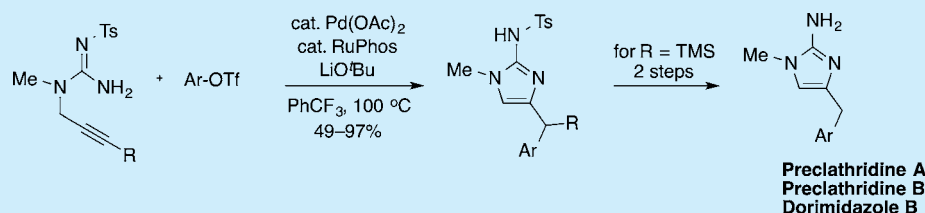# Synthesis of Substituted 2-Aminoimidazoles via Pd-Catalyzed Alkyne Carboamination Reactions. Application to the Synthesis of Preclathridine Natural Products

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Ⓢ *Supporting Information*

ABSTRACT: A new method for the synthesis of 2-aminoimidazole products is described. The heterocyclic products are generated in good yields via Pd-catalyzed carboamination reactions of *N*-propargyl guanidines and aryl triflates. This methodology generates both a C−N and C−C bond during the annulation step and facilitates the rapid construction of 2-aminoimidazole products with different aryl groups. The utility of this methodology was demonstrated in the total synthesis of preclathridine A, preclathridine B, and dorimidazole B from a single intermediate.

Cyclic guanidine natural products have garnered widespread attention due to their wide-ranging biological properties.[1] One interesting subclass of cyclic guanidines are substituted 2-aminoimidazole derivatives (1−5) (Figure 1).
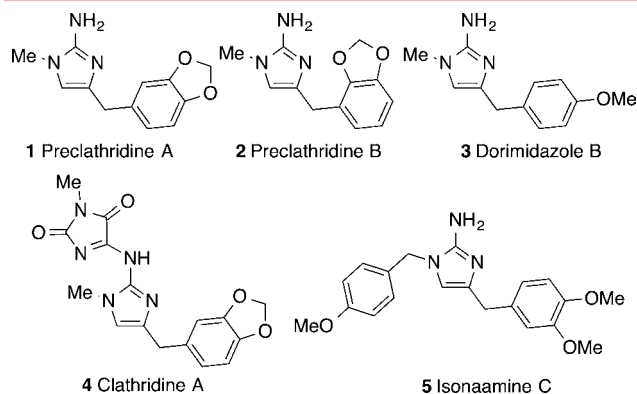

Figure 1. 2-Aminoimidazole natural products.

These compounds display a myriad of potentially useful biological activities. Members of this family of alkaloids have been shown to be human β-secretase (BACE1) inhibitors,[2] tubulin-binding agents,[3] and epidermal growth factor receptor inhibitors,[4] and also exhibit interesting antimicrobial[5] and antibiotic activity.[6] Classical methods for the construction of 2-aminoimidazoles generally involve either condensation reactions of α-amino- or α-haloketones or functionalization of imidazole derivatives.[7] More recently, the metal-catalyzed hydroamination of acyclic terminally substituted *N*-propargyl guanidines was reported as a useful means for generating substituted 2-aminoimidazoles.[8]

Although these strategies have proven to be highly valuable for the construction of 2-aminoimidazole-containing alkaloids, none involve C−C bond formation during the ring-closing step, and as a result, the synthesis of closely related alkaloids such as 1−3 cannot currently be accomplished from a single intermediate. Rather, different substrates are required to access compounds that differ in the nature of the 4-(arylmethyl) group. A more attractive synthetic approach to these compounds would be one that facilitates the conversion of a single, simple, starting material to any of these derivatives via installation of an appropriate aryl group, which could be obtained from a readily available compound such as an aryl halide or triflate.

We recently reported a method for the construction of saturated cyclic guanidines via Pd-catalyzed carboamination reactions between *N*-allyl guanidines 6 and aryl or alkenyl halides (Scheme 1a).[9] These cross-coupling reactions led to the formation of both a C−N bond and a C−C bond and afforded the products 7 in good yields.[10,11] We envisioned that this methodology could be employed for the synthesis of 2-aminoimidazole-containing products by simply using *N*-propargyl guanidine substrates 8 in place of the *N*-allyl substrates 6 (Scheme 1b). These transformations should generate products 9 bearing an exocyclic alkene, which would then isomerize either under the reaction conditions or during a workup step to afford the desired 2-aminoimidazole products

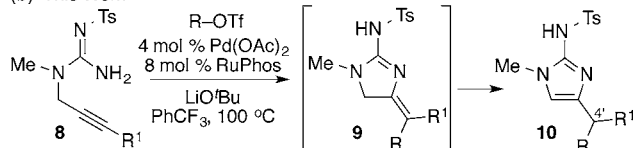**Scheme 1. Synthesis of Cyclic Guanidines via Pd-Catalyzed Carboamination Reactions**


(a) *Previous Work*
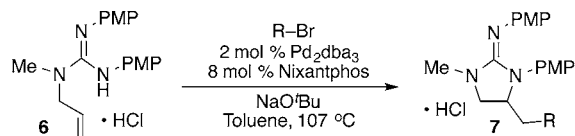
(b) *This Work*

10.[8a,c] Importantly, these transformations would effect installation of a C4′ aryl group during the ring-closing step. This would allow for straightforward introduction of different groups at the C4′ position, which cannot currently be accomplished using other existing methods. Herein we describe our initial findings on this new approach to the construction of 2-aminoimidazoles and the application of this method to the synthesis of three different alkaloid natural products (**1**−**3**) from a single intermediate.

In our original studies on the synthesis of saturated guanidines, we utilized substrates **6** bearing two PMP protecting groups. Despite the utility of these transformations, we were not able to develop conditions to remove both PMP aryl groups from the carboamination products. As such, in the present studies we elected to examine substrates bearing *N*-sulfonyl protecting groups, as these compounds can be prepared in a straightforward manner, and cleavage of *N*-sulfonyl groups from 2-aminoimidazoles has previously been demonstrated.[12]

At the outset of this project we decided to explore the reactivity of *N*-tosyl-*N*-propargyl guanidine substrate **8a**, which was prepared in four steps (63% overall yield) from commercially available materials (*N*-methylallylamine, trimethylsilylacetylene, and formaldehyde). Unfortunately efforts to couple **8a** with aryl bromide 3-bromophenyl-1,3-dioxolane using conditions previously employed for reactions of **6** were unsuccessful (eq 1). The desired 2-aminoimidazole was not obtained, and instead a mixture of hydroamination products **11a**−**b** was generated.

(1)

11a 44% R = TMS
11b 46% R = H
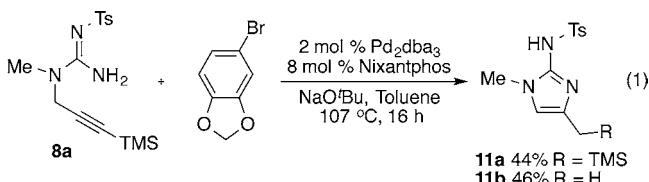
It seemed likely that the failure of **8a** to undergo successful carboamination was due to the decreased nucleophilicity of the *N*-tosyl guanidine as compared to the bis-PMP-protected guanidine present in **6**. This decreased nucleophilicity likely disfavors the key *syn*-aminopalladation step in the catalytic cycle;[13] previously reported cases of reactions that proceed via alkyne *syn*-aminopalladation involve relatively nucleophilic amines.[14] Our group has recently discovered that Pd-catalyzed carboamination reactions of relatively weak nitrogen nucleophiles (*N*-allylsulfamides) can be induced to proceed via *anti*-

aminopalladation pathways under appropriate conditions, which leads to significantly improved chemical yields for transformations of these types of substrates.[15,16] Thus, we reasoned that altering the reaction conditions to favor an *anti*-aminopalladation mechanistic pathway might promote the desired transformations of **8a** to 2-aminoimidazoles **10**.

To probe the hypothesis outlined above, *N*-propargyl guanidine substrate **8a** was subjected to the reaction conditions that had provided optimal results for Pd-catalyzed carboamination reactions of *N*-allyl sulfamides.[15a] As shown in Table 1,
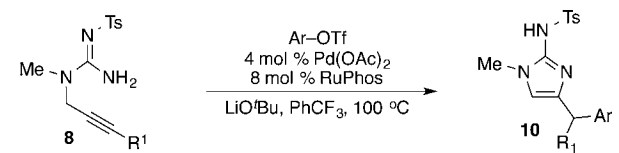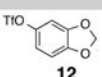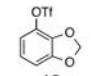
Table 1. Ligand Optimization[a]
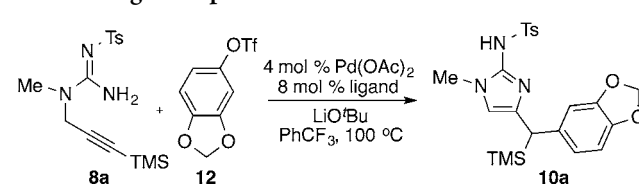
entry	ligand	NMR yield (isolated yield)
1	Nixantphos	70
2	Brettphos	45
3	*t*BuDavephos	41
4	CPhos	80
5	RuPhos	81 (80)

[a]Reaction conditions: 1.0 equiv of **8a**, 1.2 equiv of **12**, 2.4 equiv of LiO*t*Bu, 4 mol % Pd(OAc)₂, 8 mol % ligand, PhCF₃ (0.1 M), 100 °C, 16 h.

the coupling of **8a** with aryl triflate **12** to afford 2-aminoimidazole **10a** was successfully achieved when Pd(OAc)₂ was employed as the palladium source along with the base LiO*t*Bu and the solvent PhCF₃. Significant amounts of desired product were obtained with several different phosphine ligands, including Nixantphos[17] and a variety of different Buchwald-type biarylphosphines (entries 1−5).[18] The primary side products generated in these reactions resulted from competing hydroamination of the alkyne (**11a** and **11b**), but this side reaction was less problematic than with the conditions shown in eq 1. Ultimately the RuPhos ligand was found to provide the best results (entry 5), affording the desired product **10a** in 80% isolated yield while only trace amounts of hydroamination side products were generated.

With optimized conditions in hand, the scope of these transformations was examined by coupling **8a** with a variety of aryl triflates (Table 2). Gratifyingly, aryl triflates bearing electron-donating, electron-neutral, and electron-withdrawing groups (entries 1−5) afforded the corresponding 2-amino-
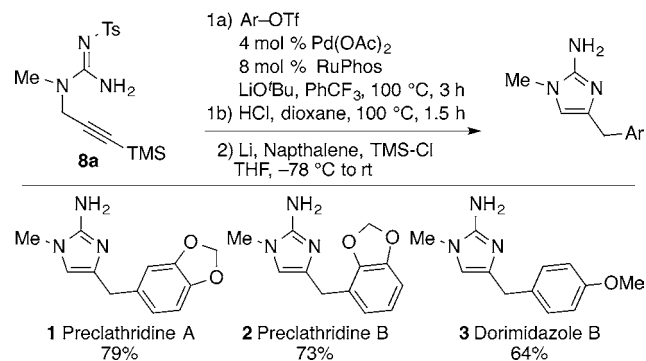
Table 2. Scope of Carboamination Reactions[a]

entry	R[1]	substrate	ArOTf	product	yield (%)[b]
1[c]	TMS	8a	**12**	10a	81
2	TMS	8a	**13**	10b	97
3	TMS	8a	p-MeO-C$_6$H$_4$OTf **14**	10c	92
4	TMS	8a	p-Me-C$_6$H$_4$OTf	10d	90
5	TMS	8a	p-PhC(O)C$_6$H$_4$OTf	10e	97
6	TMS	8a	o-Me-C$_6$H$_4$OTf	10f	89
7	Ph	8b	p-PhC(O)C$_6$H$_4$OTf	10g	49
8[d]	Ph	8b	p-MeO-C$_6$H$_4$OTf	10h	62

[a]Reaction conditions: 1.0 equiv of **8a** or **8b**, 2.0 equiv of Ar−OTf, 2.4 equiv of LiOtBu, 4 mol % Pd(OAc)$_2$, 8 mol % RuPhos, PhCF$_3$ (0.1 M), 100 °C, 3 h. [b]Isolated yield. [c]The reaction was conducted using 1.2 equiv of Ar−OTf. [d]The reaction was conducted using 5 equiv of Ar−OTf.

imidazole derivatives in good yields. Moreover, an *ortho*-methyl substituted aryl triflate also underwent smooth coupling with **8a** to generate product **10f** in high yield (entry 4). However, it was necessary to employ 2 equiv of most aryl triflates due to competing base-mediated cleavage of the triflate to the corresponding phenol. In most instances products bearing TMS-groups were stable under these conditions, and it was not necessary to rigorously monitor reactions to determine the exact time of completion; reactions could be conducted for up to 16 h with no product degradation (although efforts to optimize reaction times indicated most were complete in ca. 3 h). However, a relatively short reaction time (3 h) and somewhat careful monitoring of reaction progress were required for the coupling of substrate **8a** with 4-benzoylphenyl trifluoromethanesulfonate in order to prevent conversion of product **10e** to the corresponding desilylated compound (entry 5). Related transformations of substrate **8b**, which contains a phenyl-substituted alkyne, also provided the desired 2-amino-imidazole products. However, yields were lower than those in analogous transformations of **8a** due to competing hydro-amination of the substrate.

To demonstrate the utility of this methodology we undertook the total synthesis of 2-aminoimidazole alkaloids **1−3**. As shown in Scheme 2, *N*-tosyl protected substrate **8a** was coupled with three different aryl triflates using the optimized reaction conditions from above. However, in the synthesis of **1−3** the TMS-substituted products of these reactions were not isolated but, instead, were treated with 4 M HCl in dioxane to effect protodesilylation.[19] The *N*-tosyl groups were then cleaved from the resulting intermediates using Li/naphthalene, thereby providing alkaloids preclathridine A, preclathridine B, and dorimidazole B.[20,21] Overall, the three 2-aminoimidizole natural products **1−3** were synthesized in just six steps and good overall yields (40−48%) from commercially available materials. Importantly, this work highlights the power of Pd-catalyzed

Scheme 2. Synthesis of 2-Aminoimidazole Natural Products

carboamination reactions as a synthetic strategy for the construction of 2-aminoimidazole products and illustrates the potential to generate several different alkaloid derivatives from one intermediate (**8a**).

The rapid isomerization of putative intermediate **9** prevents us from making definitive statements about the mechanism of these reactions, as the stereochemistry of addition to the alkyne cannot be unambiguously established. However, given our prior observations that reaction conditions such as those employed in these transformations tend to favor *anti*-aminopalladation pathways, we suggest the mechanism illustrated in Scheme 3

Scheme 3. Catalytic Cycle
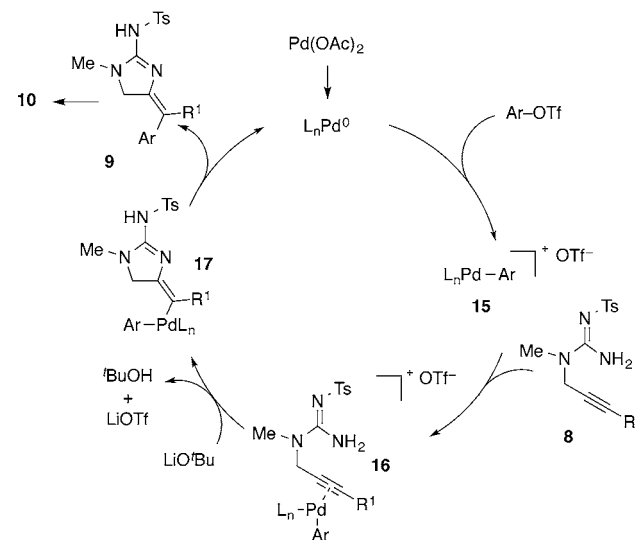
may be in operation.[15] Oxidative addition of the aryl triflate to palladium(0) generates cationic palladium complex **15**.[22] Coordination of the Pd-catalyst to the alkyne produces **16** and facilitates outer-sphere attack of the guanidine nucleophile onto the alkyne (*anti*-aminopalladation). Reductive elimination from Pd-alkenyl intermediate **17** affords the exocyclic product **9**, which then undergoes double-bond isomerization to give the desired 2-aminoimidazole product **10**.

In summary, we have developed a new strategy for the construction of 2-aminoimidazoles via the Pd-catalyzed alkyne carboamination of tosyl-protected *N*-propargyl guanidines and aryl triflates. The *N*-tosyl-2-aminoimidazole products are generated in good yields, and the *N*-tosyl group can be reductively cleaved in a single step. Notably, this strategy generates a C−C bond during the annulation event, thus

facilitating late-stage derivitization as illustrated through the total synthesis of preclathridine A, preclathridine B, and dorimidazole B in just two steps from a common intermediate. Continued studies on the use of Pd-catalyzed carboamination reactions of alkynes and alkenes in the synthesis of guanidine alkaloids are currently underway.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental procedures, characterization data for all new compounds, descriptions of stereochemical assignments, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) Steps 1a and 1b (overall) proceeded in 93%, 80%, and 94% yields in the synthesis of **1**, **2**, and **3**, respectively. See the Supporting Information for full experimental details.

(20) The reductive detosylations (step 2) proceeded in 85%, 91%, and 68% yields in the synthesis of **1**, **2**, and **3**, respectively.

(21) In prior syntheses of **1** and **3** reductive detosylation was accomplished using SmI$_2$ rather than Li/naphthalene. See ref 12.

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