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Stereoselective Synthesis of Cyclic Guanidines by Directed Diamination of Unactivated Alkenes

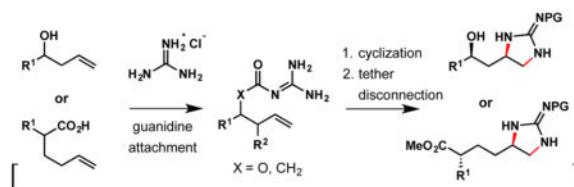
Artur K. Mailyan, Kyle Young, Joanna L. Chen, Bradley T. Reid, and Armen Zakarian*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93110, United States

Abstract

A method for a directed stereoselective guanidinylation of alkenes is described. The guanidine unit can be delivered as an intact fragment by a hydroxy or carboxy group, usually with a high level of stereocontrol. After the guanidine delivery, the directing group can be cleaved under exceptionally mild conditions, typically by alcoholysis in the presence of acetic acid. Broad functional group tolerance and mild reaction conditions for the cycloguanidilation suggest applications in medicinal chemistry and natural products synthesis.

Graphical Abstract



Guanidines are challenging targets for synthesis even by the standards of other nitrogen-containing compounds.¹ General methods for the introduction of the guanidyl group into complex structures, let alone stereoselective methods, are limited and typically involve guanidylation of a preinstalled amino group. These classic transformations include a coupling of primary amines with cyanamide,² pyrazolylcarboxamides,³ *S*-alkylisothiourea reagents,⁴ or trifluoromethane-sulfonyl guanidine reagents (Goodman reagent).⁵ Implementation of these strategies in the synthesis of complex guanidine-containing compounds and natural products thus can require extended synthetic routes, in some cases reducing the overall efficiency of the synthesis.

The recently emerging methods for vicinal diamination of alkenes provide an intriguing alternative for the synthesis of functionalized guanidines.⁶ Several inter- and intramolecular

*Corresponding Author: zakarian@chem.ucsb.edu.

Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02778. Experimental procedures, characterization of new compounds, and spectral data (PDF)

diaminations of unactivated alkenes with ureas, sulfamides, and guanidines catalyzed by palladium,⁷ nickel,⁸ copper,⁹ and gold complexes¹⁰ as well as halogenating reagents¹¹ have been reported. These promising approaches are yet to demonstrate a broad scope and applicability for stereoselective synthesis of cyclic guanidines with desired functionalization. The requirement for tethering of guanidine or another dinitrogen source by a simple alkyl chain complicates further functionalization of products, and still generally requires guanidilation of a preinstalled amino group at an earlier stage. Our interest in developing efficient strategies for the synthesis of guanidine alkaloids shown in Scheme 1a brought these limitations to our attention and prompted us to develop a method for a stereoselective delivery of the entire intact guanidine group to an unactivated alkene directed by a hydroxy and carboxy group. The method is operationally simple and readily allows for further functionalization of the installed guanidine.

As depicted in Scheme 1b, our reaction design requires attachment of guanidine to a hydroxy group by a carbamate linker followed by electrophilic cyclization onto the alkene. The initial goal was to develop a simple method for the attachment of guanidine to homoallylic alcohols using readily available guanidine hydrochloride. Although different prospective tethers were considered, including silyl, sulfonyl, and methylene, the majority of attempted transformations were unfruitful due to the low stability of intermediates and products. In contrast, we found that carbamates **3** could be prepared in two simple steps from alcohols **1** via an initial conversion to chloroformates with triphosgene or (1-imidazolyl)formates with 1,1'-carbonyl-diimidazole (CDI), followed by treatment with guanidine (Scheme 2). Both methods delivered the material of similar purity and in comparable yields (see Supporting Information); however, CDI was a more benign and user-friendly reagent due to considerably lower toxicity and volatility compared to triphosgene. In addition, when R¹ = Ar, CDI enabled a cleaner conversion to **3** without formation of carbonate side products observed with triphosgene. Therefore, for subsequent studies, 1,1'-carbonyldiimidazole had been used to access a set of substrates for intramolecular electrophilic delivery of guanidine to the double bond.

With an effective protocol for the preparation of substrates **3** established, the next goal was to identify optimal conditions for cycloguanidilation. Despite previous success in diamination and cycloguanidylation of alkenyl guanidines mediated by metal catalysis, only low conversions were observed under varying conditions with catalysts such as Pd(OAc)₂, NiCl₂, or CuI (Table 1, entries 1–5).

Halogen-based reagents were examined next. Although conversion with iodine was still low (entry 8), it was substantially improved with *tert*-butylhypochlorite and dipyridineiodonium tetrafluoroborate (entries 6, 7). *tert*-Butyl hypochlorite effected *N*-chlorination only, affording a fairly unreactive dichloroguanidine product. The optimal reagent has been determined to be *N*-iodosuccinimide (NIS), which under optimal conditions (NaHCO₃, CH₃CN, 0 °C) enabled 100% conversion and delivered the product in 84% isolated yield (entry 10). Importantly, *complete diastereoselectivity* was observed, meeting our goal of stereocontrolled delivery of guanidine to the unactivated double bond directed by a preinstalled hydroxy group.

With the optimized set of reagents, the reaction scope was examined with a variety of aryl and alkyl substituted substrates derived from homoallylic alcohols (Figure 1). The substrate scope was designed to test compatibility with a range of reactive functional groups suitable for applications in medicinal chemistry and natural products synthesis. All products were isolated after guanidine sulfonylation to ease purification. We first established that *N*-nosylation, *N*-tosylation, and *N*-(4-methoxyphenyl)sulfonylation afford comparable isolated yields with **4a** (products **5a–c**) and proceeded with tosylation for the remainder of the substrate scope studies. Compounds comprising different linear and branched alkyl substituents readily undergo cyclization, producing expected guanidines **5d–f** in high yields as single diastereomers. The introduction of benzyl or silyl ethers as well as ester groups in the substrate side chain does not hamper the overall efficiency of guanidylation, affording compounds **5g–j** after tosylation.

In order to further explore the chemoselectivity of the cycloguanidylation method, substrates comprising the distant terminal alkyne and olefin moiety were examined. In both cases, application of standard conditions initially resulted in reduced yields of cyclic guanidine products; however, decreasing the reaction time to 2 h allowed the isolation of compounds **5k** and **5l** in substantially improved yields (70% and 50% respectively). Substrates derived from substituted benzyl alcohols were found to be unexpectedly less reactive compared to their aliphatic counterparts and require extended reaction times to reach full conversion. Nevertheless, phenyl (**5m**), naphthyl (**5n**), 4-bromophenyl (**5o**), 2-fluorophenyl (**5p**), and 4-cyanophenyl (**5q**) substrates were isolated after tosylation in practical yields and excellent stereoselectivity. At the same time, cyclization of the guanidine bearing a 4-methoxyphenyl group produced compound **5r** in only 12% yield, accompanied by significant amounts of decomposition products, presumably arising via a carbocationic pathway. The cyclization of substrates derived from both *syn*- and *anti*-3-methyl-1-alkene-4-ols was also investigated. The reaction of the latter with NIS produced cyclic product **5s** in 64% yield as a 2:1 mixture of diastereomers. Notably, the reaction of the *syn*-isomer gave rise to **5t** in 70% yield as a single diastereomer.

Substrates incorporating acylated primary amines were shown to undergo the cyclization under standard conditions; however, their separation from succinimide was troublesome. On the other hand, clean products were obtained in good yields after subsequent methanolysis (see below) as corresponding methyl carbonates **5u** and **5v**.

Next, two strategies to modify the carbonyl tether were explored. The rapid hydrolysis of compound **5a** mediated by aqueous lithium hydroxide readily furnished alcohol **6** in 95% yield (Scheme 3a). In addition, we discovered unprecedented and unexpected reactivity, whereby cyclic guanidine-derived carbamates reacted under exceptionally mild conditions with different alcohols resulting in regioselective ring opening of the carbamate to furnish corresponding carbonates **7** (Scheme 3b). The reaction requires no extra additives, but can be accelerated by addition of acetic acid. A range of simple aliphatic and aromatic alcohols can be utilized for this transformation providing orthogonally protected compounds **7a–f** in excellent yields. *t*-BuOH was found to be the only unreactive alcohol, presumably due to steric hindrance.

Encouraged by these results, we then envisioned that carboxylic acids might also serve as a directing group for the cycloguanidilation reaction. 2-Phenyl- and 3-phenylhexenoic acids were converted to acylguanidine substrates **8a** and **8b** by treatment with carbonyldiimidazole and guanidine (Scheme 4). Subsequent exposure to NIS under the standard conditions resulted in a clean cyclization; however, an attempt to isolate the product prior to tosylation led to a rapid polymerization of the material. A successful isolation was realized by treatment of the reaction mixture with *p*-toluenesulfonyl chloride, which allowed isolation of the cyclic guanidines **9a** and **9b** in 50% and 51% yield, respectively. These cyclic products were subjected to methanolysis, furnishing guanidyl esters **10a** and **10b** in good yields.

While the precise mechanistic underpinnings related to the first C–N bond forming event are presently unclear, we hypothesize that the stereochemical outcome is governed by transannular interactions in the developing six-membered ring, maximizing the number of equatorial substituents.

In closing, we developed a method for directed stereo-selective guanidylation of alkenes. Guanidine can be delivered as an intact unit by a hydroxy or carboxy group, usually with a high level of stereocontrol. We demonstrated that, after guanidine delivery, the directing group can be cleaved under exceptionally mild conditions, typically by alcoholysis in the presence of acetic acid. Broad functional group tolerance and mild reaction conditions for the cycloguanidylation and subsequent tether removal or modification suggest applications in medicinal chemistry and natural products synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

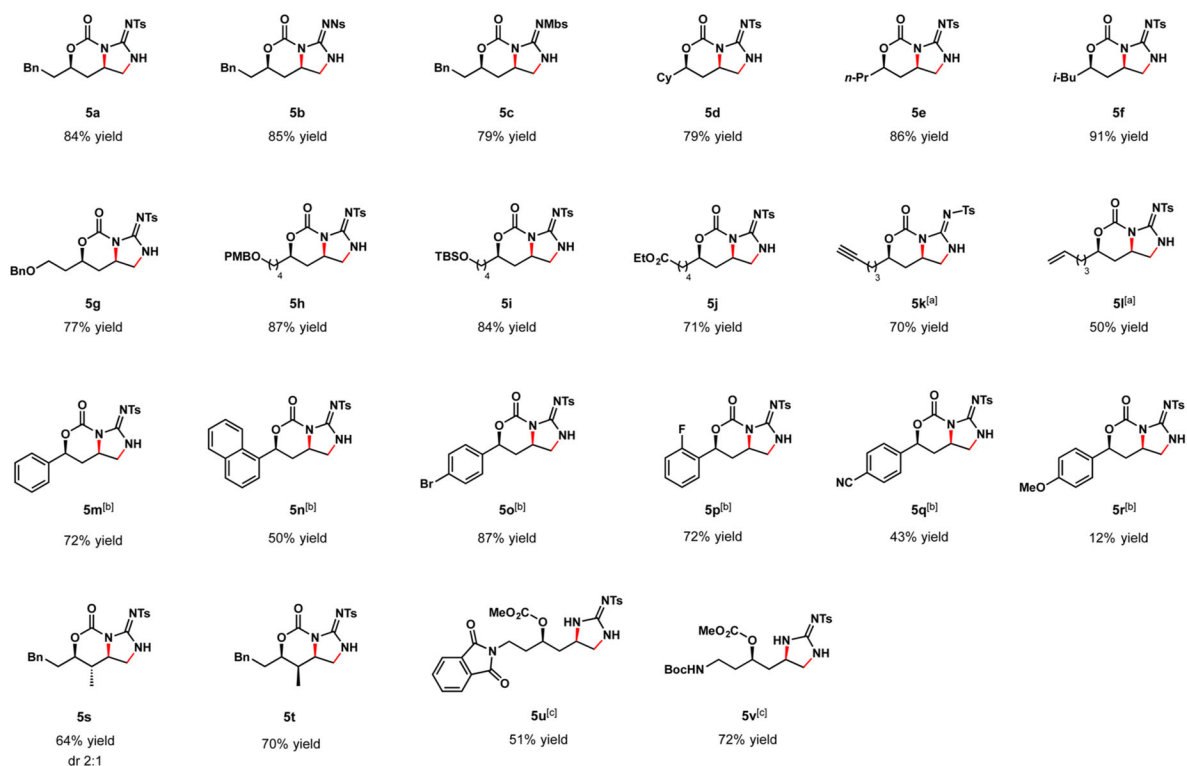
Acknowledgments

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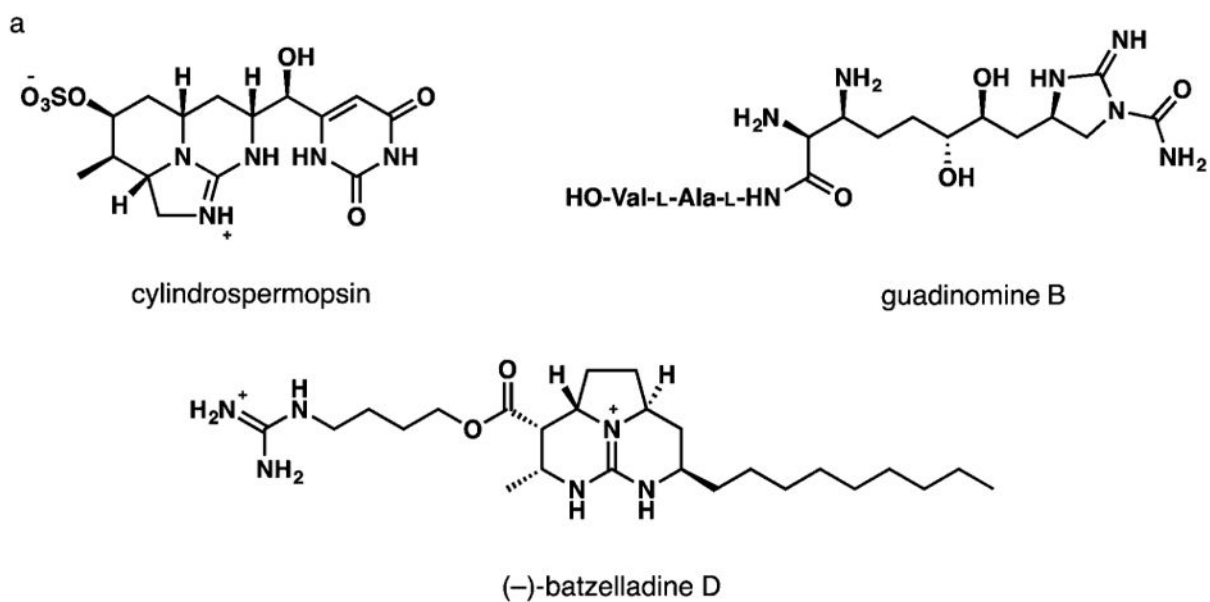
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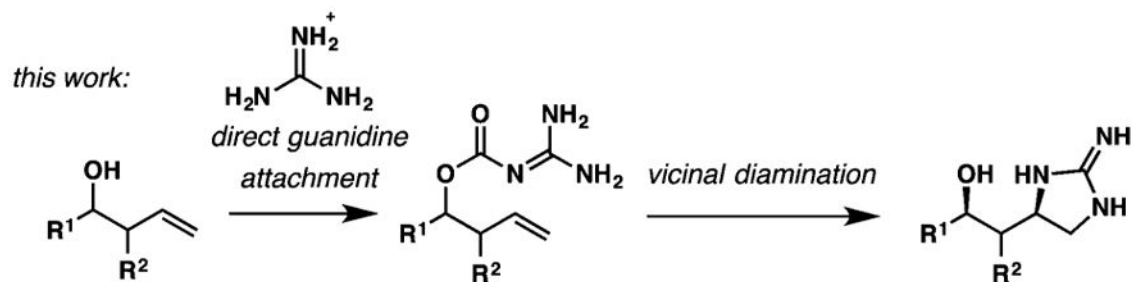
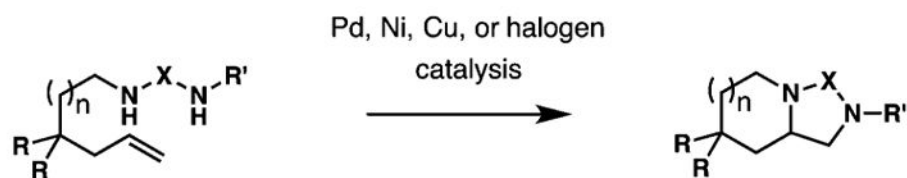
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**Figure 1.**

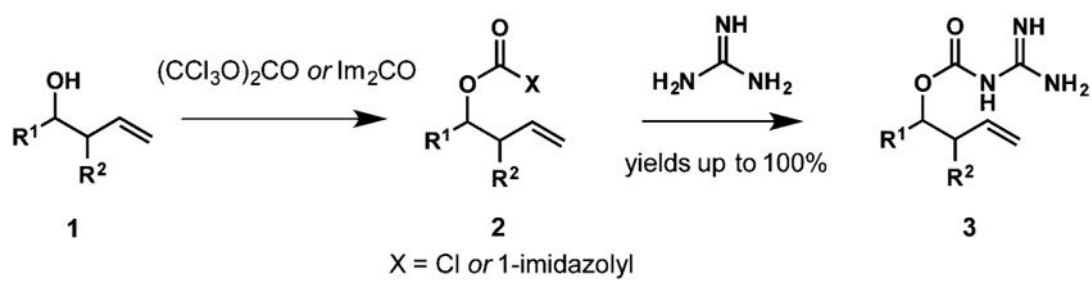
Substrate scope for the cycloguanidylation reaction. ^a The reaction was performed at 0 °C for 2 h. ^b The reaction was performed at 0 °C for 5 h and then at 23 °C for another 5 h. ^c Products were isolated after methanolysis.



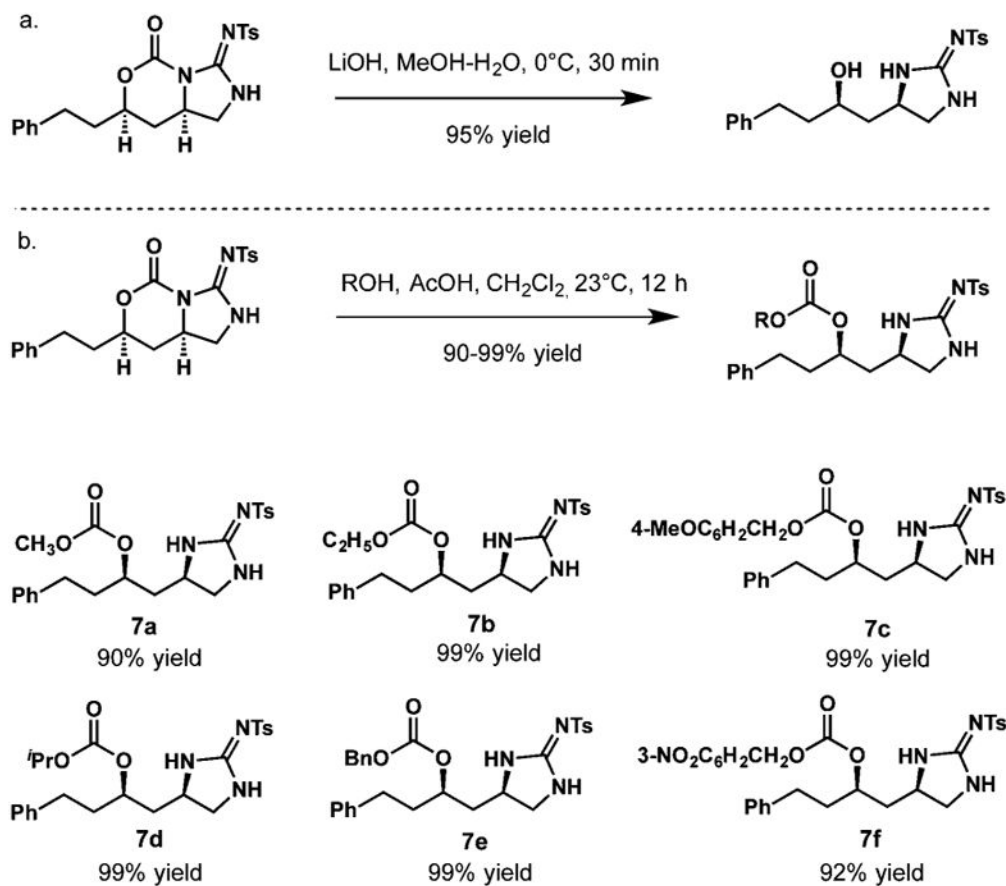
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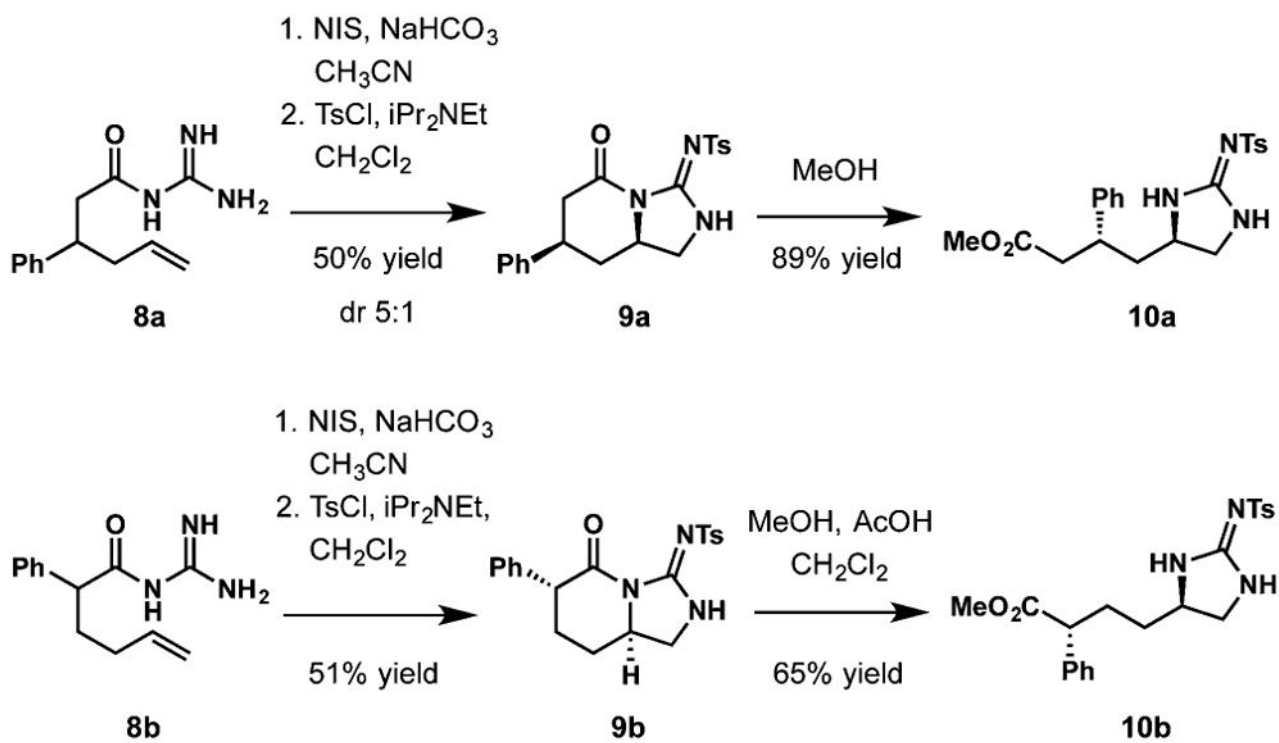
Scheme 1.



Scheme 2.

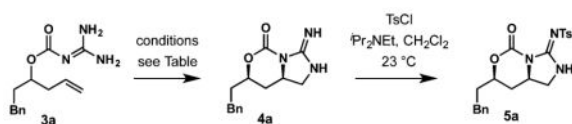


Scheme 3.



Scheme 4.

Table 1

Identification of Optimal Reagent for Cycloguanidylation^a

entry	reaction conditions	conversion (%)	yield (%)
1	10 mol % Pd(OAc) ₂ , CuI, K ₂ CO ₃ , DMF, 23 °C, 24 h	0	0
2	25 mol % Pd(OAc) ₂ , PhI(OAc) ₂ , CH ₂ Cl ₂ , 23 °C, 24 h	15	0
3	5 mol % Pd(OAc) ₂ , PhI(OAc) ₂ , NMe ₄ Cl, NaOAc, CH ₂ Cl ₂ , 23 °C, 24 h	30	0
4	10 mol % NiCl ₂ , PhI(OAc) ₂ , NaOAc, DMF, 23 °C, 24 h	0	0
5	10 mol % CuI, K ₂ CO ₃ , 10 mol % 2,2'-bipyridine, O ₂ , DMF, 60 °C, 24 h	0	0
6	3 equiv of <i>t</i> -BuOCl, CH ₂ Cl ₂ , 0 °C, 20 min	100 ^b	0
7	Py ₂ IBF ₄ , toluene, 23 °C or reflux, 24 h	65	0
8	2.1 equiv of I ₂ , NaHCO ₃ , CH ₂ Cl ₂ , 23 °C, 6 h	15	0
9	2.1 equiv of NIS, NaHCO ₃ , CH ₂ Cl ₂ , 23 °C, 1 h	100	62
10	2.1 equiv of NIS, NaHCO₃, CH₃CN, 0 °C, 5 h	100	84

^aSee Supporting Information for additional details; isolated yields of **5a** after tosylation are reported. Conversion measured by ¹H NMR analysis of a crude mixture of products.

^bDichloroguanidine is isolated.