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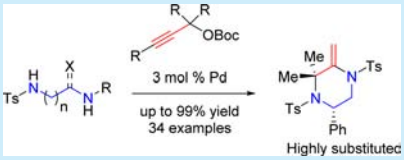
Palladium-Catalyzed Modular Synthesis of Substituted Piperazines and Related Nitrogen Heterocycles

Thomas D. Montgomery and Viresh H. Rawal*

Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States

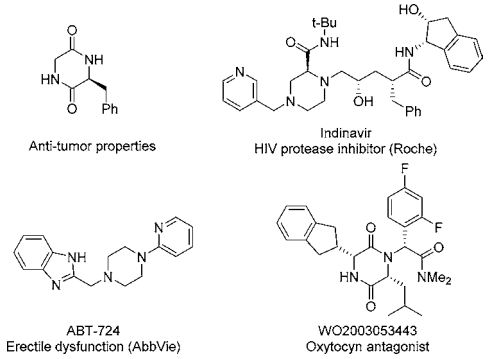
Supporting Information

ABSTRACT: We report here a novel method for the modular synthesis of highly substituted piperazines and related bis-nitrogen heterocycles via a palladium-catalyzed cyclization reaction. The process couples two of the carbons of a propargyl unit with various diamine components to provide nitrogen heterocycles in generally good to excellent yields and high regio- and stereochemical control.



A central goal of chemical synthesis is to develop efficient and reliable methods for making complex molecules. Of particular interest to organic and medicinal chemists are nitrogen-containing heterocycles, which are frequently found in natural products,[1] pharmaceutical drugs,[2] and drug-like compounds.[3] Among nitrogen heterocycles, the piperazine motif has attracted considerable attention, as it is present in many bioactive and pharmacologically interesting structures, examples of which are shown in Scheme 1.[4]

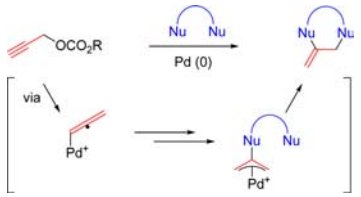
Scheme 1. Selection of Bioactive Piperazines



Given the importance of this scaffold, much effort has been directed toward the development of methods for its synthesis and/or functionalization.[5] The available routes to these heterocycles, whether through conventional, polar reactions[6] or by metal catalysis,[7] have certain limitations, such as the need for high temperatures or multiple steps. We present here a general method for the synthesis of diverse, highly substituted piperazines and related nitrogen heterocycles, starting from readily available building blocks. The reactions are promoted by palladium catalysts and proceed under mild reaction conditions to afford the cyclization products in good to excellent yields.

Among the different transition metals used for chemical synthesis, palladium has proven to be singularly versatile in its ability to generate electrophilic species in situ from stable pre-electrophiles. Over the years, we have reported several methods that take advantage of this capability, particularly for the C-3 functionalization of indoles and oxindoles.[8] More recently, we reported the use of propargyl carbonates as masked sources of bis-electrophiles for palladium-catalyzed reactions with indole- and oxindole-based bis-nucleophiles.[8,9] The reactions forge two carbon−carbon and/or carbon−nitrogen bonds and provide ready access to intricate spirocyclic products in good yields. The mechanistic underpinnings of these reactions—namely, that the first nucleophile reacts with an allenic-palladium electrophile, and the resulting product, after protonation, reacts with a second nucleophile—allows for the conception of numerous additional methods of value in synthesis (Scheme 2).[10,11] This report provides the first demonstration of the use

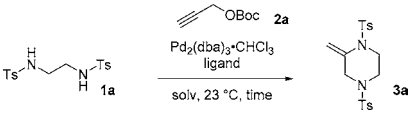
Scheme 2. Palladium-Catalyzed Reactions of Propargylates with Tethered Bis-nucleophiles



of diamine derivatives as bis-nucleophiles for such reactions, thereby offering a unique and general route to piperazine derivatives and other bis-nitrogen heterocycles.

Exploratory studies to assess the feasibility of the above-mentioned concept were carried out with bis-tosylated ethylenediamine (Scheme 3).[12] The reaction of **1a** and BOC-

Scheme 3. Optimization of Prototype Reaction



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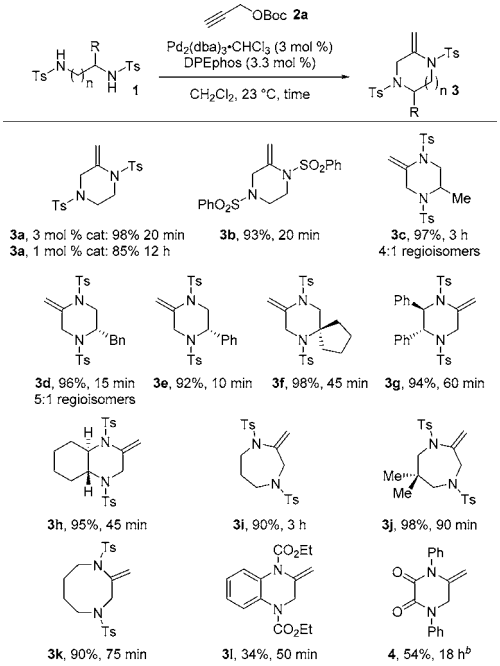
propargyl alcohol (**2a**) catalyzed by 5 mol % Pd(0) and DPEphos in acetone at room temperature gave the desired compound, piperazine **3a**, in 71% yield after only 30 min. The reaction rate and yield improved significantly in dichloromethane, with the product being formed in near-quantitative yield after just 10 min. Several different phosphine ligands were screened, and many gave similarly excellent results. Reduction of the catalyst loading to 3 mol % increased the reaction time slightly, but still gave the product in excellent yield. The scope of the new reaction was examined using the optimized conditions.

A broad range of bisamino-nucleophiles were evaluated to determine the capability of the cyclization reaction (Scheme 4).

Scheme 4. Substrate Scope[a]

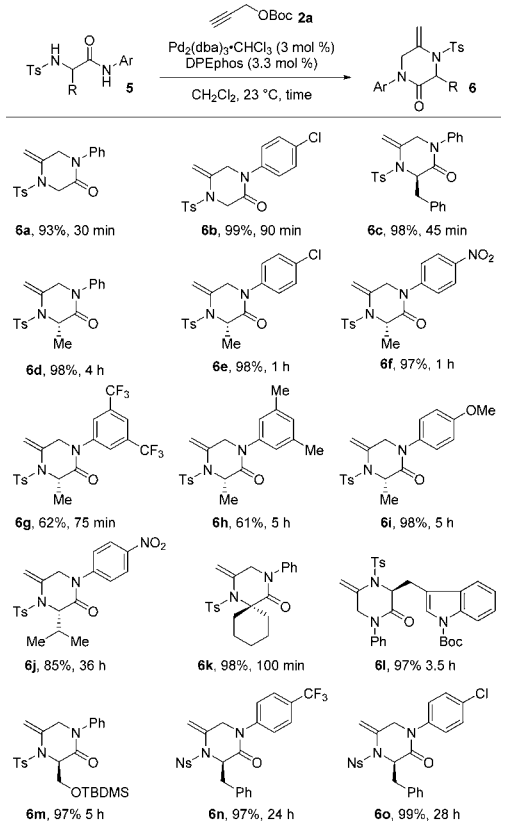


[a]Reaction conditions: substrate **1** (1 equiv), **2a** (1.3 equiv), $Pd_2(dba)_3$·$CHCl_3$ (0.015 equiv), DPEphos (0.033 equiv), CH_2Cl_2 (0.1 M). [b]$ClCH_2CH_2Cl$ used as solvent, with heating to 80 °C.

Under the optimized conditions, with 3 mol % palladium, the reaction of **1a** and **2a** proceeded rapidly to give piperazine **3a** in 98% isolated yield. Even with 1% loading, the reaction gave the desired product in high yield, albeit requiring 12 h for completion. Substituted ethylenediamine derivatives were also effective as bis-nucleophiles. The tosyl derivative of 1,2-diaminopropane gave piperazine **3c** in excellent yield and good regioselectivity (4:1). The related benzyl- and phenyl-substituted bis-sulfonamides, both in enantioenriched forms, afforded the corresponding piperazines (**3d** and **3e**, respectively) in high yields, and, in the case of **3e**, with complete regioselectivity. Geminal substitution is nicely tolerated in the substrate, as demonstrated by the formation of spirocyclized piperazine **3f** as the sole regioisomer, in near-quantitative yield. The reaction of the bis-tosylate of (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine and **2a** under the standard conditions provided diphenylpiperazine derivative **3g** in excellent yield. Likewise, *trans*-decahydroquinoxaline derivative **3h** was easily prepared using the general method. Notably, the cyclization procedure also provides easy access to larger ring-sized heterocycles. Thus, the reaction of the bis-tosylate of 1,3-diaminopropane and 2,2-dimethyl-1,3-diaminopropane with **2a** gave homopiperazines **3i** and **3j** in 90% and 98% yields, respectively. The corresponding reaction of the 1,4-diaminobutane bis-tosylate gave the eight-membered ring heterocycle **3k** in excellent yield. Finally, we have found that the cyclization reactions are not limited to sulfonamides of diaminoalkanes. Subjecting the bis-ethylcarbamate of 1,2-diaminobenzene (**1l**) to the standard reaction conditions gave benzopiperazine **3l** in modest yield. *N*,*N*′-Diphenyloxalamide was slow to react under the standard reaction conditions, but with heating gave the expected diketopiperazine **4** in good yield. These preliminary results showed that nitrogen nucleophiles possessing groups other than sulphonamides would be suitable for this palladium cyclization chemistry.

The encouraging oxalamide result motivated us to examine reactants possessing both aryl amide and sulfonamide groups. Such substrates were expected to be readily prepared from amino acids and to generate diverse 2-piperazinones. Two glycine-derived substrates (**5a**, R = H, Ar = C_6H_5; **5b**, R = H, Ar = 4-Cl-C_6H_4) were prepared and subjected to the standard reaction conditions, affording the respective piperazinone products **6a** and **6b** in excellent yields and as single regioisomers (Scheme 5). Both phenylalanine- and alanine-based substrates performed well, giving rise to highly substituted piperazinones **6c** and **6d**, respectively. A range of aryl groups can be incorporated into such structures, with electron-deficient aryls (**6e**–**6g**) generally reacting faster than their electron-rich counterparts (**6h**, **6i**). The hindered, valine-

Scheme 5. Piperazinone Substrate Scope[a]



[a]Reaction conditions: substrate **5** (1 equiv), **2a** (1.3 equiv), Pd_2dba_3·$CHCl_3$ (0.015 equiv), DPEphos (0.033 equiv), CH_2Cl_2 (0.1 M).

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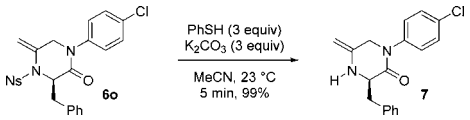
derived product can also be accessed, though a long reaction time and an electron-deficient aryl were required to achieve the desired product in good yield (**6j**). Surprisingly, a spirocyclized compound (**6k**) was easily prepared, with the starting material transformed to the product in less than 2 h. To further investigate the capability of this method, we prepared the more challenging and synthetically interesting tryptophan- and serine-derived substrates. While the free tryptophan substrate was unreactive, upon protection of the indole nitrogen the compound reacted smoothly to afford **6l** in near-quantitative yield. Similarly, the silyl-protected serine substrate reacted cleanly, providing **6m** in equally high yield. Finally, we have found that nosyl-group-protected substrates react just as well as the tosyl substrates and give the corresponding piperazinone products in quantitative yields (**6n**, **6o**).

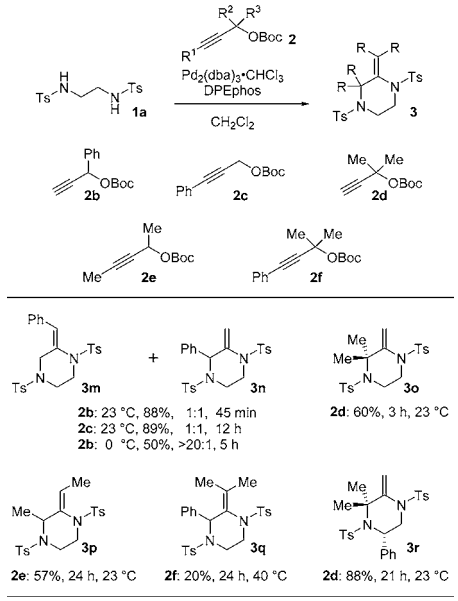
The advantage of the nosyl group over the tosyl is its ease of removal under mild conditions.[13] Indeed, treatment of **6o** to thiophenol and K_2CO_3 for just 5 min effected complete removal of the nosyl group to afford piperazinone **7** in quantitative yield. Remarkably, the product was isolated in its enamine form, with the exocyclic double bond intact, rather than as the imine or the endocyclic enamine tautomer (Scheme 6).

Scheme 6. Nosyl Deprotection to Free Enamine



To expand further the scope of this piperazine synthesis, we examined the cyclization reaction of **1a** with several substituted propargyl carbonates (Scheme 7). Both phenyl-substituted propargyl carbonates, **2b** or **2c**, reacted at room temperature with **1a** to give a 1:1 mixture of piperazines **3m** and **3n**, the former as a 10:1 mixture of olefin isomers, the major one shown.[14] Interestingly, when the reaction of **2b** was carried out at 0 °C, the selectivity increased significantly, to >20:1, favoring compound **3m**, favoring the isomer shown by >20:1.

Scheme 7. Substituted Propargyl Carbonates[a]

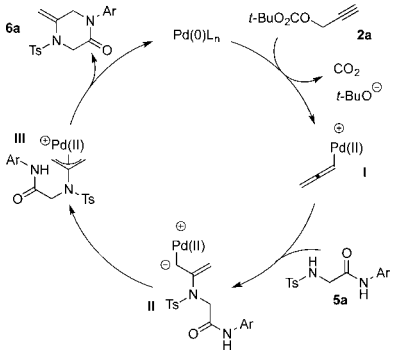


[a]Reaction conditions: bis-nucleophile substrate **1** (1 equiv), **2** (1.3 equiv), $Pd_2(dba)_3$·$CHCl_3$ (0.015 equiv), DPEphos (0.033 equiv), CH_2Cl_2 (0.1 M).

Gem-dimethyl-substituted propargylic carbonate **2d** gave the expected piperazine **3o**. The isomeric dimethyl-substituted propargyl carbonate (**2e**) reacted more slowly and gave piperazine **3p** as a single regio- and stereoisomer, the latter assigned as *Z*, based on NOESY data. The fully substituted propargyl carbonate **2f** reacted sluggishly at room temperature, and even under refluxing conditions gave the cyclization product **3q** in low yield, although as the sole regioisomer. Dimethyl propargyl carbonate **2e** could be combined with enantioenriched phenyl substituted substrate **1g** to provide piperazine **3r** in excellent yield and regioselectivity.

The observed products can be rationalized through the mechanism outlined in Scheme 8, illustrated for the

Scheme 8. Plausible Catalytic Cycle



regioselective reactions of amino acid derived substrates.[10,14] Oxidative addition of Pd(0) to propargyl *tert*-butyl carbonate **2a** should give cationic palladium allene species **I** and a *tert*-butoxide anion.[15] Nucleophilic attack at the central carbon of **I** by the more acidic sulfonamide nitrogen would then generate the Pd-carbenoid intermediate **II**, shown in its zwitterionic form.[16] Protonation of **II**, either intra- or intermolecularly, is expected to give Pd(II)-π-allyl species **III**. At this point, intramolecular attack by the aryl amide and reductive elimination would afford the desired product (**6a**) and regenerate the Pd(0) catalyst.[17]

In summary, we have developed a fundamentally new method for the synthesis of highly substituted piperazine- and piperazinone-type compounds via the palladium-catalyzed decarboxylative cyclization of propargyl carbonates with bis-nitrogen nucleophiles. The reactions proceed under mild conditions and give a wide range of products, tolerating significant modification of both the bis-nucleophile and the propargyl carbonate. The products are synthesized in generally excellent yields at low catalyst loadings, with a high degree of stereo- and regiochemical control. The examination of other bis-nucleophiles is expected to lead to the development of many additional annulation methods.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Experimental procedures and NMR spectra for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: vrawal@uchicago.edu.

Notes

The authors declare no competing financial interest.

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(12) Please see Supporting Information for a table of conditions showing some of the many parameters that were examined.

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