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Palladium-Catalyzed Cross-Coupling of *N*-Sulfonylaziridines with Boronic Acids

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Supporting Information

ABSTRACT: A mild palladium-catalyzed cross-coupling of unsubstituted and 2-alkyl-substituted aziridines with arylboronic acid nucleophiles is presented. The reaction is highly regioselective and compatible with diverse functionality. A catalytic amount of base, a sterically demanding triarylphosphine ligand, and a phenol additive are critical to the success of the reaction. Coupling of a deuterium-labeled substrate established that ring opening of the aziridine occurs with inversion of stereochemistry.

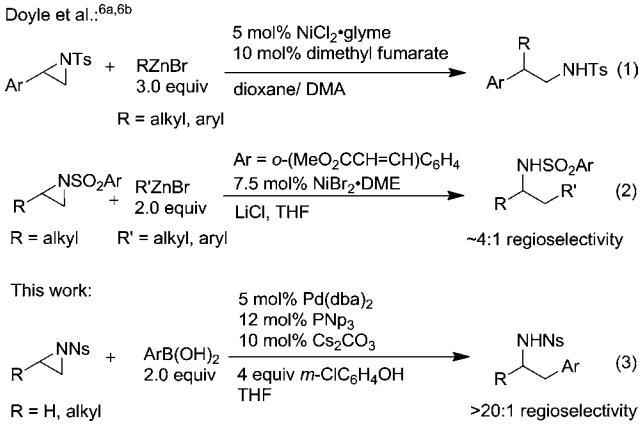
The β-phenethylamine motif is the structural basis for a large number of small molecules with distinctive and often desirable biological properties. This privileged structure is present in many important neurotransmitters and is used extensively in syntheses of drug targets for the treatment of depression and anxiety disorders, as well as Parkinson's and Alzheimer's diseases.[1] A high value is therefore placed on the development of efficient methods for the synthesis of substituted phenethylamine analogues.

One method for the synthesis of such compounds is the ring opening of aziridines with organometallic nucleophiles.[2] Generally, this requires the use of lithium diorganocuprates, often in the presence of a strong Lewis acid. This reaction, however, is inherently limited by the functional group compatibility of the cuprates and Lewis acids. As has been demonstrated amply with other reactions,[3] by using an appropriate catalyst it should be possible to replace the reactive organocuprates with boronic acid nucleophiles, which are much milder and generally more functional-group-compatible reagents.

Hillhouse[4] and Wolfe[5] have previously demonstrated that Ni(0) and Pd(0) complexes readily oxidatively add the C–N bond of aziridines. The resulting azametallacycles are isolable, and Wolfe was able to develop this finding into a catalytic isomerization of *N*-tosylaziridines to *N*-tosylimines, presumably via β-hydride elimination of the key metallacycle intermediate.[5a] Until recently, the potential cross-coupling ability of these alkylmetal complexes had not been exploited.

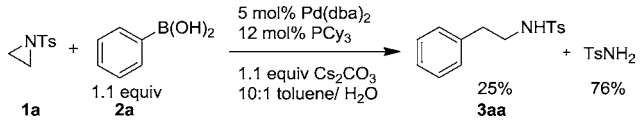
Within the last year, Doyle has reported a key advance in this field in the form of two sets of conditions for Ni-catalyzed coupling of aziridines with a variety of organozinc nucleophiles (Scheme 1). The first conditions work well for 2-arylaziridines but not for 2-alkylaziridines,[6a] while the second are successful for 2-alkylaziridines but require a custom sulfonamide protecting group. This second procedure also suffers from moderate regioselectivity (~4:1 linear:branched).[6b] Herein, we report the first cross-coupling of unsubstituted and 2-alkyl-substituted aziridines in which the nucleophilic components are boronic acids.[7]

Scheme 1. Previously Reported Aziridine Couplings



We began our investigation using *N*-tosylaziridine and phenylboronic acid as model coupling partners and conditions broadly resembling those in ref 5a, but found none of the desired product. Addition of water to the reaction mixture, however, gave a 25% yield of phenethylamine product **3aa** (Scheme 2). Notably, the remainder of the starting material had been converted to *p*-toluenesulfonamide. We suspected this byproduct was the result of β-hydride elimination and hydrolysis of the consequent imine.

Scheme 2. Initial Conditions



After switching to the more reactive *N*-nosylaziridine **1c**, we conducted an extensive optimization of ligand, solvent, base, and ROH additive and found that the conditions in Table 1 gave the highest yield of the desired product (entry 1). The lower reactivity of the tosylaziridine is evident from the low yield in entry 2. In contrast to the nickel-catalyzed reaction,[6b] only the regioisomer derived from opening at the unsubstituted carbon atom was observed (>20:1 linear:branched). The effects

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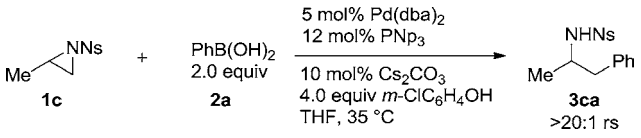
Table 1. Effects of Variation from Optimal Conditions



entry	variation from the above conditions	yield, %[a]
1	none	82
2	Ts protecting group on aziridine	32
3	PCy_3 instead of PNp_3	0
4	P(*t*-Bu)$_3$ instead of PNp_3	0
5	P(*o*-tol)$_3$ instead of PNp_3	44
6	P(2,4-$Me_2C_6H_3$)$_3$ instead of PNp_3	63
7	1 equiv of Cs_2CO_3	0
8	no Cs_2CO_3	75
9	K_2CO_3 instead of Cs_2CO_3	24
10	no *m*-ClC_6H_4OH	19
11	H_2O instead of *m*-ClC_6H_4OH	53
12	phenol instead of *m*-ClC_6H_4OH	61

[a]NMR yields using 1,3-dinitrobenzene as internal standard.

of variation of key reaction components are illustrated in Table 1.

Tri-1-naphthylphosphine was determined to be the optimal ligand. The steric demand of this ligand likely plays an important role in inhibiting β-hydride elimination.[8] Other sterically hindered triarylphosphines also afforded the desired product, but in reduced yield (Table 1, entries 5 and 6). Surprisingly, only unreacted aziridine was observed when sterically bulky trialkylphosphine ligands were used with the new optimized conditions (entries 3 and 4).

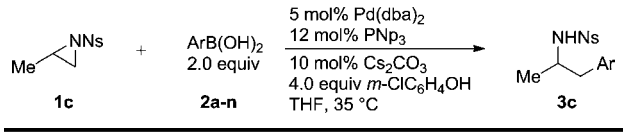
Catalytic amounts of cesium carbonate were necessary for the highest yield. Replacing Cs_2CO_3 with K_2CO_3 resulted in a large drop in yield (entry 9), as did increasing the amount of base to 1 equiv (entry 7). Omission of the base gave a minor reduction in yield (entry 8). Unlike most traditional cross-couplings, the present reaction does not necessarily require stoichiometric base, due to the basicity of the sulfonamide leaving group, but it appears that catalytic quantities do improve the yield, possibly by assisting transmetalation.

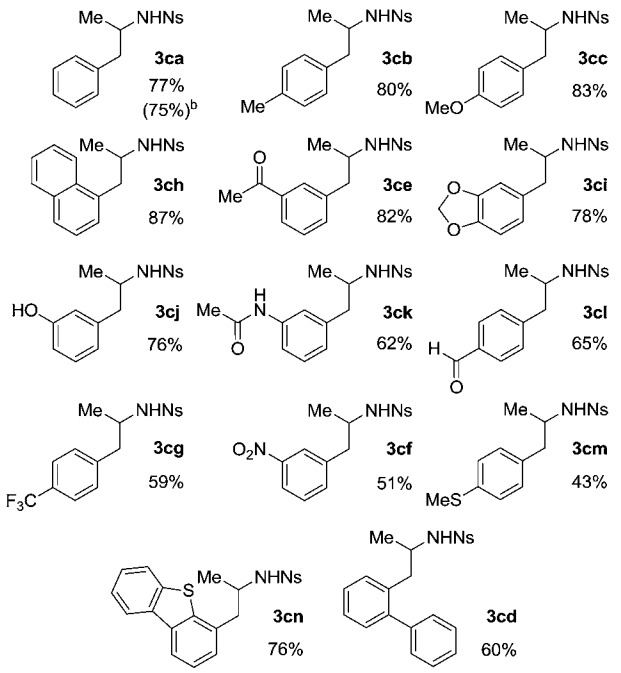
We found *m*-chlorophenol to be a crucial additive in this reaction. In its absence, little desired product is formed (entry 10). Using other acidic proton donors such as water and phenol gave somewhat lower yields (entries 11 and 12).

The optimized conditions were applied to the coupling of aziridine **1c** with an array of substituted arylboronic acids (Table 2). Though the differences were minor, electron-rich arylboronic acids gave generally higher yields of product, while electron-poor arylboronic acids were sometimes accompanied by slightly lower yields (**3cl**,**cg**,**cf**). The reaction is highly tolerant of diverse functional groups such as ketone, amide, aldehyde, acetal, ether, thioether, and nitro functionalities. It is also tolerant of boronic acids with functional groups bearing acidic hydrogens, such as phenol (**3cj**) and amide (**3ck**). The reaction of **1c** and **2a** was performed on a 2 mmol scale and gave **3ca** in nearly identical yield (75% vs 77%). The attempted coupling of alkylboronic acids under these conditions did not give the desired product.

The scope of the reaction with regard to the aziridine component was also investigated (Table 3). The reaction can be applied to the unsubstituted aziridine **1d** and several 2-alkyl-substituted aziridines (**1e**–**g**). Good to excellent yields are

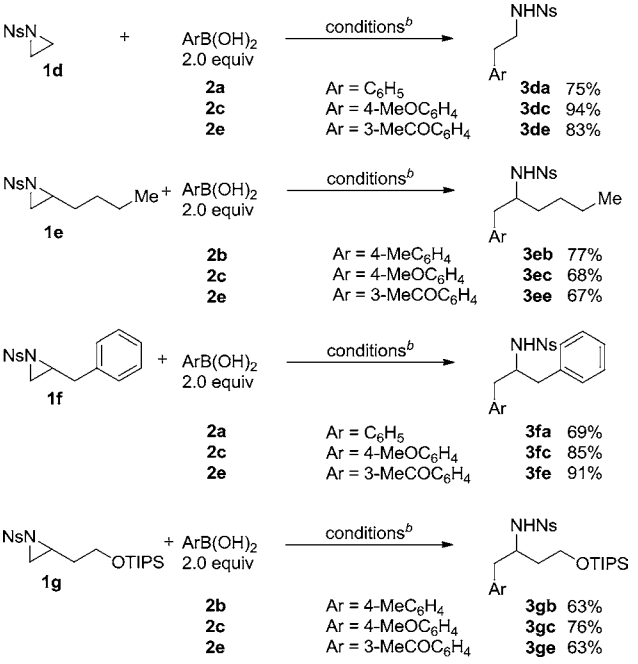
Table 2. Boronic Acid Scope[a]





[a]Isolated yields. [b]2 mmol scale.

Table 3. Aziridine Scope[a]



[a]Isolated yields. [b]Conditions: 5 mol % of $Pd(dba)_2$, 12 mol % of PNp_3, 10 mol % of Cs_2CO_3, 4 equiv of *m*-ClC_6H_4OH, THF, 35 °C.

obtained with arylboronic acids possessing both electron-donating and electron-withdrawing functionalities. In all cases excellent regioselectivity (>20:1) was observed. Unfortunately,

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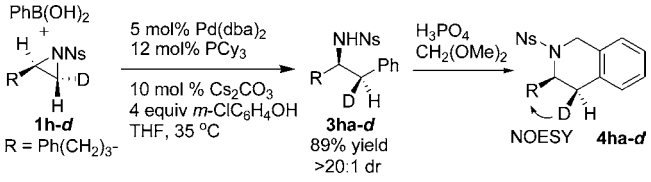
the present conditions do not appear to be applicable to 2,2-disubstituted and 2,3-disubstituted aziridines.

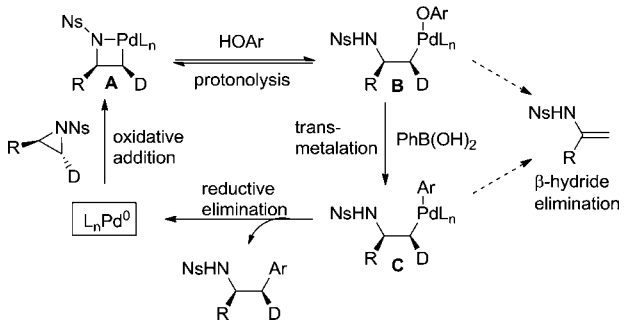
To probe the mechanism of this reaction, deuterium-labeled aziridine **1h-*d*** was prepared and subjected to the standard reaction conditions (Scheme 3). The coupled product, **3ha-*d***, was formed as a single diastereomer in 89% yield. Pictet–Spengler cyclization established that ring opening had occurred with 100% inversion of stereochemistry. This is consistent with the stoichiometric studies of Hillhouse and Wolfe establishing that oxidative addition occurs by an S_N2 mechanism and is in contrast to the stereochemical scrambling observed by Doyle.

Scheme 3. Deuterium-Labeled Substrate Coupling



A plausible catalytic cycle for this coupling reaction is depicted in Scheme 4. Oxidative addition of the aziridine to Pd(0) gives the azametallacycle **A**. The high selectivity for addition of the unsubstituted C–N bond and clean inversion of stereochemistry are consistent with previous stoichiometric studies by Wolfe. After oxidative addition, transmetalation of the boronic acid and reductive elimination of the product must take place. However, since the coupling largely fails in the absence of ROH additive, direct transmetalation of the boronic acid with the metallacycle does not appear to be viable. Instead, we posit that protonolysis of the metallacycle with the alcohol gives the Pd alkoxide **B**, which can then undergo transmetalation and reductive elimination to give the product.

Scheme 4. Proposed Catalytic Cycle



One key to the success of this reaction is preventing β-hydride elimination of the alkyl–Pd intermediate. The metallacycle itself is stereoelectronically resistant to β-hydride elimination but does not undergo direct transmetalation. After protonolysis, however, the ring-opened intermediates **B** and **C** are susceptible to β-hydride elimination. The key role of the *m*-chlorophenol additive is presumably to minimize the lifetime of these two species by careful control of the protonolytic equilibrium and the rate of transmetalation. Interestingly, the pK_a of *m*-chlorophenol (pK_a(DMSO) = 15.8)[9a] is close to that of the sulfonamide product (pK_a(DMSO) = 13.9 for $NsNH_2$),[9b] which suggests that roughly matching the acidity of the phenol and the sulfonamide may be important.

In summary, we have developed a new palladium-catalyzed procedure for coupling 2-alkyl-substituted *N*-nosylaziridines with arylboronic acid nucleophiles. The reaction is promoted by the use of sterically demanding triarylphosphine ligands, the presence of catalytic base, and addition of a suitable protic additive which presumably plays a role in transmetalation. Furthermore, the reaction is highly regioselective and tolerant of a wide range of functionalities, allowing for quick and efficient synthesis of highly desirable substituted β-phenethylamine products.

■ ASSOCIATED CONTENT

Supporting Information

Text and figures giving experimental procedures, spectral characterizations, and additional data. 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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