Iodine assisted modified Suzuki type reaction of bicyclic hydrazines: stereoselective synthesis of functionalized cyclopentenes†

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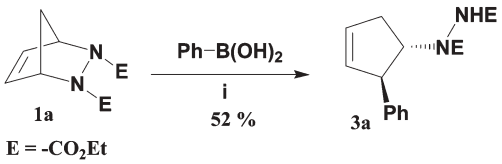
Bicyclic hydrazines undergo a facile palladium/iodine mediated stereoselective ring opening on reaction with organoboronic acids affording *trans*-3,4-disubstituted hydrazino cyclopentenes in good to excellent yield.

In recent years, the Suzuki reaction[1] has led to numerous spectacular results in synthetic organic chemistry. There are several examples in the literature where the classical Suzuki reaction has been applied in the synthesis of natural products and drug molecules.[2] The chemistry of boronic acids has been well utilized by Schopfer *et al.*[3] for the synthesis of selective estrogen receptor agonists for central nervous system disorders. The widely used Suzuki reactions are homocoupling of boronic acids and cross-coupling with organic halides. Aryl, alkenyl and alkynyl halides along with triflates and thioethers are considered as suitable substrates for the cross-coupling reactions.[4] This reaction has been used as an efficient method for the arylation of various N-containing aryls including pyrimidines and quinazolines.[5]

Modifications of the classical Suzuki reaction have always elicited great interest, especially when it is used for the cross-coupling with alkenes. Both palladium and rhodium catalyzed methods are known for the cross-coupling of organoboron compounds with alkenes. Kosugi and Mori observed a Pd(II) pathway for the Mizoroki–Heck type reaction of organoboron compounds with alkenes and alkynes. They extended the reaction to norbornene and norbornadiene to get the double arylated products.[6] Andrus *et al.* reported palladium–imidazolium carbene catalyzed Mizoroki–Heck coupling with aryl diazonium tetrafluoroborates.[7] However, the reaction was limited to substrates such as styrenes and acrylates. Lautens *et al.* independently reported a rhodium catalyzed coupling reaction of aryl boronic acids to olefins in aqueous media.[8,9]

Apart from the above mentioned reports, there are no detailed investigations on the reactivity of organoboron compounds with alkenes. Due to our sustained interest in the chemistry of bicyclic hydrazines[10] derived from cyclopentadiene and azadienophiles, we undertook an investigation of the palladium catalyzed reaction of aryl boronic acids with these substrates.

Our experiments started with the reaction of phenyl boronic acid with the bicyclic olefin[11] **1a** in the presence of $Pd(OAc)_2$/PPh_3/I_2 catalyst system in a 1 : 1 mixture of THF and H_2O. The reaction afforded 3-phenyl-4-hydrazinocyclopentene **3a** in 52% yield (Scheme 1). The structure of the product was assigned based on spectroscopic data and was further confirmed by HOMO-COSY analysis and by comparison to the literature data.[10,12]



Scheme 1 *Reagents and conditions*: i, boronic acid (1 equiv.), olefin (1 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), I_2 (5 mol%), K_2CO_3 (2.4 equiv.), THF–H_2O (1 : 1).

Detailed optimization studies were carried out to find out the best conditions for this transformation. Our first attempt was to find out the best catalyst system. Among the different catalysts (see Table 1) tried, $Pd(OAc)_2$/Ph_3P was found to be the best catalyst system.

To check the feasibility of using a Lewis acid instead of iodine, various Lewis acids (see Table 2) were tested for their performance. Since AgOTf and iodine gave comparable yield; we selected the readily available and cheap iodine as the promoter for our transformations. After the optimization studies, the best conditions for the reaction was found to be a 1 : 2 mixture of boronic acid and olefin with 10 mol% $Pd(OAc)_2$, 20 mol% Ph_3P and 5 mol% iodine with 2.4 equiv. K_2CO_3 in 1 : 1 THF–H_2O as solvent. Under these conditions, the reaction shown in Scheme 1 afforded the product **3a** in 93% yield.

Table 1 Optimization studies for the best catalyst system

Catalyst	Ligand	Yield (%)
$Pd(OAc)_2$	Ph_3P	52
$PdCl_2$	Ph_3P	26
$Pd_2(dba)_3{\cdot}CHCl_3$	Ph_3P	38

Reagents and conditions: boronic acid (1 equiv.), olefin (1 equiv.), Pd catalyst (10 mol%), PPh_3 (20 mol%), I_2 (5 mol%), K_2CO_3 (2.4 equiv.), THF–H_2O (1 : 1)

Table 2 Lewis acid performance

Lewis acid	Yield (%)
I_2	52
$Sc(OTf)_3$	42
$Yb(OTf)_3$	35
AgOTf	55
$Cu(OTf)_2$	30

Reagents and conditions: boronic acid (1 equiv.), olefin (1 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Lewis acid (5 mol%), K_2CO_3 (2.4 equiv.), THF/H_2O (1 : 1)

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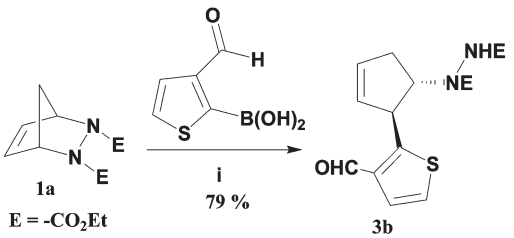


Scheme 2 *Reagents and conditions*: i, boronic acid (1 equiv.), olefin (2 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), I_2 (5 mol%), K_2CO_3 (2.4 equiv.), THF–H_2O (1 : 1).

It was of great interest to study the reactivity of heteroaryl boronic acids in the Pd catalyzed ring opening reactions. We selected 3-formyl-2-thiophene boronic acid for our studies and its reaction with bicyclic alkene **1a** afforded the ring opened product **3b** in 79% yield (Scheme 2).

Similar reactivity was observed with other bicyclic alkenes and the results obtained are summarized in Table 3. Then we turned our attention towards the tricyclic olefins derived from triazoline dione and cyclopentadiene.[13] These substrates also reacted in the same manner affording the aryl and heteroaryl substituted hydrazinocyclopentenes in good yields. The results are summarized in Table 4.

The mechanism of the reaction was found to be similar to that proposed for the C–N bond cleavage of bicyclic hydrazines in the palladium catalyzed reaction with organostannanes.[10] The catalytic cycle involves transmetallation of arylboronic acid to PdX_2 giving ArPdX, addition of ArPdX to the C–C double bond and elimination of X–Pd–Nu along with C–N bond cleavage. Though the catalytic cycle is not the same as that of classical Suzuki coupling, the present reaction can be viewed as a modified Suzuki type reaction of the bicyclic hydrazines.

The products of the reaction discussed above, *trans* vicinal disubstituted hydrazinocyclopentenes, are important intermediates

Table 3 Palladium-catalyzed reaction of azabicylic olefins with boronic acids

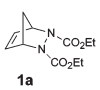
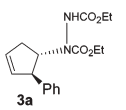
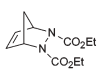
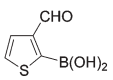
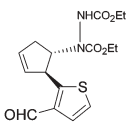
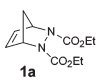
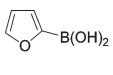
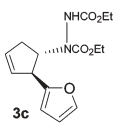
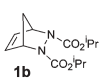
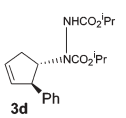
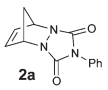
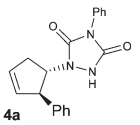
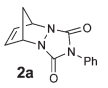
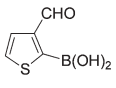
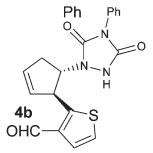
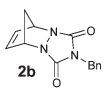
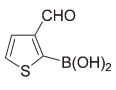
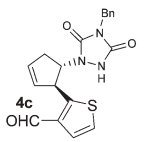
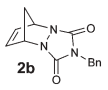
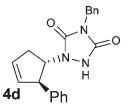
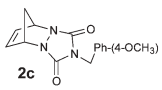
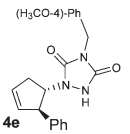
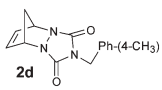
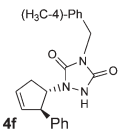
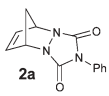
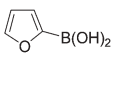
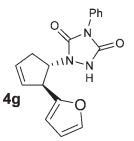
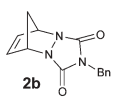
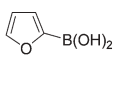
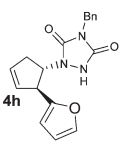
Entry	Substrate	Boronic acid	Time/h	Yield (%)	Product
1	 1a	$Ph–B(OH)_2$	24	93	 3a
2	 1a		36	79	 3b
3	 1a		36	72	 3c
4	 1b	$Ph–B(OH)_2$	24	63	 3d

Table 4 Palladium-catalyzed reaction of azatricycllc olefins with boronic acids

Entry	Substrate	Boronic acid	Time/h	Yield (%)	Product
1	 2a	$Ph–B(OH)_2$	24	86	 4a
2	 2a		36	61	 4b
3	 2b		36	60	 4c
4	 2b	$Ph–B(OH)_2$	24	52	 4d
5	 2c	$Ph–B(OH)_2$	24	56	 4e
6	 2d	$Ph–B(OH)_2$	24	40	 4f
7	 2a		36	84	 4g
8	 2b		36	89	 4h

in the synthesis of pharmaceutically important cyclopentane derivatives. For example, Carbovir[14] has been known to act as a potential anti-HIV agent. 1,2-Disubstituted cyclopentanes are well known for their activity as small potent potentiators of AMPA receptors[15] and COX-2 inhibitors.[16] Nucleoside type antibodies such as nikkomycins and polyoxins,[17] glycosidase inhibitors like mannostatins and trehazolins[18] and polyhydroxycyclopentitol containing natural products[19] are some of the biologically active disubstituted cyclopentanes. Some hydrazinocyclopentitols[20] themselves are shown to be active as mannosidase inhibitors. Some of the pharmaceutically important disubstituted cyclopentanes are shown in Fig. 1

In conclusion, we have unravelled a novel reactivity of organoboronic acids with bicyclic hydrazines leading to the stereoselective formation of *trans* vicinal disubstituted cyclopentenes in good to

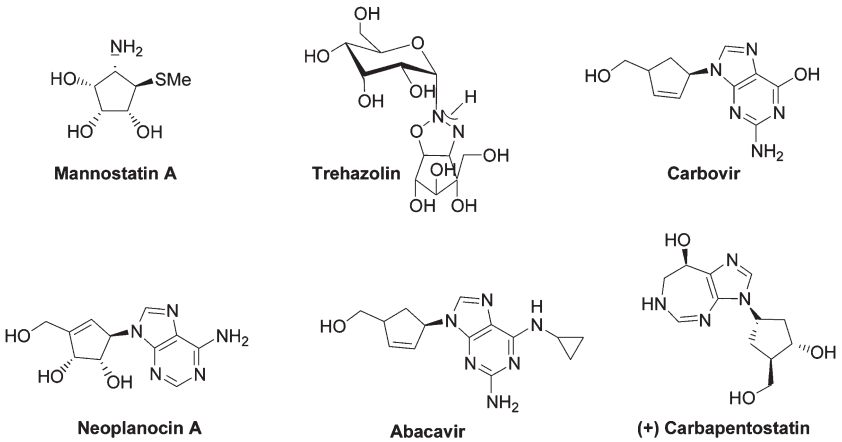


Fig. 1 Some pharmaceutically important disubstituted cyclopentanes.

excellent yield. This is the first report on the use of the modified Suzuki reaction for the synthesis of functionalized cyclopentenes. The synthesized molecules are potentially amenable to a number of synthetic transformations and can be efficiently utilized in the synthesis of a number of pharmaceutically important molecules. Further work to utilize the developed method towards the synthesis of carbocyclic nucleosides is in progress and will be reported in due course.

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