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Metal-free allylation of electron-rich heteroaryl boronic acids with allylic alcohols

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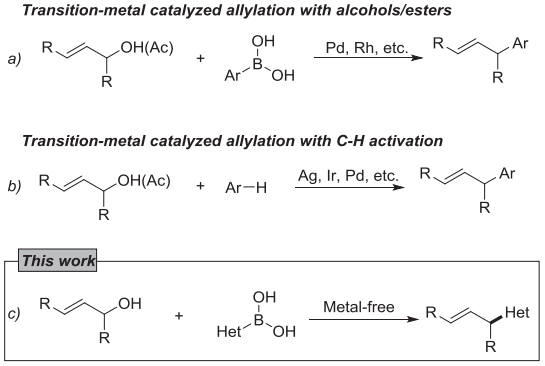
ABSTRACT

A convenient and regioselective cross-coupling of heteroaryl boronic acids with allylic alcohols under catalyst-free reaction conditions is described. The developed procedure is simple, works under external oxidant- and metal-free conditions, and proves to be very general with an unprecedented *ortho*-selectivity. This approach represents one of the very few examples of *ortho*-functionalization of boronic acids.

1. Introduction

Carbon–carbon bond formation is the essence of organic synthesis and provides the foundation for generating more complicated organic compounds from the simpler ones.[1] The transformations of allylic compounds are of paramount importance in C–C bond formations. The double bond can participate in a number of synthetically useful transformations, which provide resourceful access to highly diverse molecules. A well-established pathway for the generation of allylic products in current organic synthesis heavily relies on the transition-metal (Pd, Rh, Ag, Ir, etc.) catalyzed cross-coupling reactions.[2] In addition, previously developed reactions typically involve the use of allylic halides or allylic carboxylates, which usually produce stoichiometric quantities of hazardous byproducts (Scheme 1a,b). With this in mind, it has been recognized that it is highly desirable to develop new strategies for the generation of allylic intermediates that utilize inexpensive substrates, proceed under mild conditions, and are environmentally benign.

One such strategy is the utilization of allylic alcohol. If allylic alcohols can be used directly as alkylation agents, preparation of the corresponding halides or carboxylates would no longer be required, thus the overall process would become highly efficient and atom-economical. Despite their simple and efficient operation, alcohols are rarely used as substrates in allylation because of the low tendency for hydroxide to act as a leaving group.[3] In our previous work, we have recently reported Lewis/Brønsted acids catalyzed alkylation of indole and its derivatives with allylic alcohols.[4] Nevertheless, it remains a great challenge to synthesize the allylic products with a rational design at the molecular level using cheap and simple processes.



Scheme 1. Cross-coupling of allylic alcohols/esters with boronic acids.

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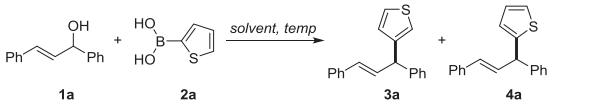
In very recent times, catalyst-free processes that do not require a metal or small molecules catalyst are of great importance because such procedures obviate the need for disposing the catalysts from the reaction residues and eliminating traces of metals (if any) from final compounds.[5] On the basis of previous work, we initiated a research program with the aim of exploring catalyst-free transformations of allylic alcohols with boronic acids in cross-coupling reactions. Use of boronic acids as the coupling partner was our first choice, owing to the advantages of these reagents regarding stability, commercial availability and relatively low toxicity when compared with other organometallics.[6] Herein, we describe our preliminary investigations toward an unprecedented regioselective and catalyst-free cross-coupling reactions of allylic alcohols with a series of electron-rich heteroaryl boronic acids and related reactants[5b,7] (Scheme 1c).

2. Results and discussion

The reaction of allylic alcohol **1a** with 2-thienylboronic acid **2a** was selected as a prototype reaction.[8,9] To our delight the reaction proceeded smoothly with 12 h in 39% yield (Table 1, entry 1). Surprisingly the allylic products were formed in a regioselective manner, predominantly with an unprecedented *ortho*-allylation product 2-thienyl substituted **3a** as the major component, not the ordinary *ipso*-product **4a** (**3a**:**4a** 3:1), although the first attempt of cross-coupling suffered from an incomplete conversion and partial dimerization of alcohol.

Table 1
Screening of reaction Conditions[a]



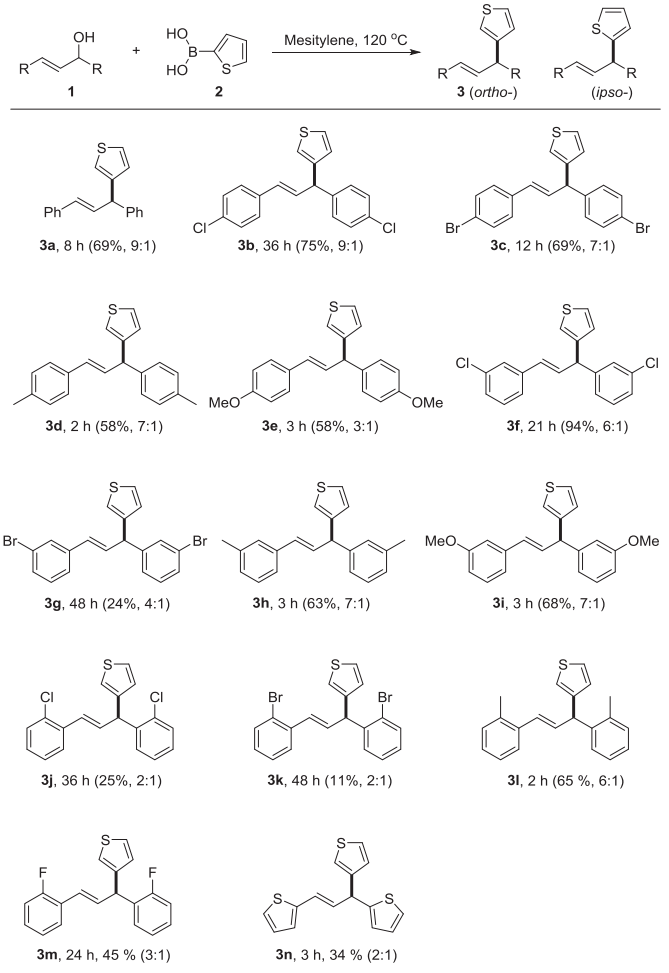
1a **2a** **3a** **4a**

Entry	Solvent	Time (h)	Yield (%)[b]	Ratio (**3a**:**4a**)[c]
1	CH_2Cl_2	12	39	3:1
2	Et_2O	18	16	3:1
3	THF	29	20	2:1
4	Dioxane	24	Trace	NA
5[d]	MeOH	24	Trace	NA
6	H_2O	24	Trace	NA
7	CH_3CN	6	32	5:1
8[e]	DMSO	24	30	1:2
9[e]	DMF	24	15	3:1
10[e]	Toluene	4	75	6:1
11[f]	Xylene	3	59	4:1
12[f]	**Mesitylene**	**8**	**69**	**9:1**
13[f]	Dichlorobenzene	1	62	4:1
14[f]	Anisole	3	55	6:1
15[g]	Mesitylene	8	49	2:1
16[h]	Mesitylene	8	66	8:1

The most successful entry is highlighted in bold.
[a] Reaction conditions: allylic alcohol **1a** (0.15 mmol, 1.0 equiv), 2-thienylbornic acid **2a** (0.22 mmol, 1.5 equiv), solvent (0.15 M), reflux.
[b] Combined yields are given for isolated products after column chromatography.
[c] Regioisomeric ratios determined by ^{1}H NMR of the final products.
[d] Methyl ester of **1a** was isolated as the major product.
[e] Reaction temperature: 110 °C.
[f] Reaction temperature: 120 °C.
[g] 3 Å molecular sieve (MS, 20 mg) was used as the additive.
[h] 4 Å MS (20 mg) was used as the additive.

We observed that the formation of unusual product **3a** occurred in the presence of a variety of solvents (Table 1, entries 2–14). The use of dioxane, methanol or water significantly decreased the reactivity, leading to trace products (Table 1, entries 4–6). When methanol was used as the solvent, only methyl ester of **1a** was isolated as the major product (Table 1, entry 5). In most cases, the 3-thienyl product **3a** was identified as the major isomer. In contrast, the use of DMSO afforded a slight preference for the *ipso*-substituted product **4a** (**3a**:**4a** 1:2, Table 1, entry 8). After a screening of reaction conditions, the optimum condition for the C–C bond formation reaction were identified as mesitylene at 120 °C, leading to the most significant increase of product formation with 69% yield and 9:1 selectivity (**3a**:**4a**, Table 1, entry 12). In an attempt to improve the yield and selectivity further, molecular sieve additives were tested. Unfortunately, all those efforts led to a dramatic decrease of product formation and distribution (Table 1, entries 15–16).

Afterward, the scope of the novel catalyst-free cross-coupling was explored between a set of allylic alcohols **1** and 2-thienylboronic acid **2a**. As shown in Scheme 2, both electron-donating and electron-withdrawing substituents were well tolerated, and moderate to good yields and regioselectivities of the corresponding *ortho*-substituted products were obtained. A broad range of functional groups, such as chloro (**3b**, **3f** and **3j**), bromo (**3c**, **3g** and **3k**), methyl (**3d**, **3h** and **3l**), methoxy (**3e** and **3i**) and fluoro (**3m**), were compatible with this protocol. Notably, *para*- and *meta*-substituents led to the desired products with high yields and good *ortho*-selectivities (Scheme 2, products **3b**–**i**). However, substituents in the *ortho*-position on the allylic alcohols (except the one with methyl group) generally provided products in poor yields



Scheme 2. Substrate scope. Reaction conditions: allylic alcohol **1** (1.5 equiv), 2-thienylboronic acid **2a** (1.0 equiv), mesitylene (0.15–0.30 M), under a nitrogen atmosphere, 120 °C. Combined yields are given for isolated products after column chromatography. The regioisomeric ratios in the parentheses (*ortho*:*ipso*) are determined by ^{1}H NMR.