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2*H*-Chromenes from Salicylaldehydes by a Catalytic Petasis Reaction

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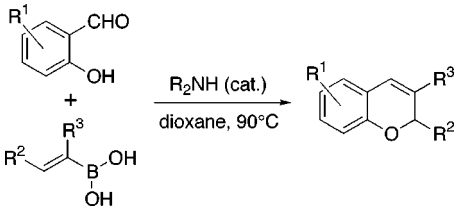
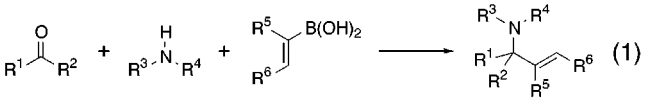
ABSTRACT



The Petasis condensation of vinylic or aromatic boronic acids, aromatic aldehydes, and amines is assisted by a hydroxy group adjacent to the aldehyde moiety. The products derived from salicylaldehydes and vinylboronic acids undergo cyclization to 2*H*-chromene compounds with ejection of amine upon heating. A catalytic preparation of 2*H*-chromenes using resin-bound amine is reported, allowing the convenient incorporation of a variety of components.

The in situ assembly of amine, carbonyl compound, and vinyl- or arylboronic acid (eq 1) has been developed by N. Petasis and co-workers[1] as a modern variation of the Mannich reaction.[2] Mannich-type processes lend themselves to mul-



(1)

ticomponent condensations.[3] What makes the Petasis process remarkable is the reactivity of the boronic acid component, which is inert to the carbonyl group but efficiently traps the C═N double bond of its derived iminium ions. Petasis has made the insightful connection between the propensity of a vinylboronic acid to take on a donor group to form an electron-rich "ate" complex and its utility as a selective nucleophile.[4] The Petasis reaction is thus an example of the remarkable chemistry that is enabled by the ready access to intermediates of expanded coordination number provided by certain main group elements (primarily B, Si, and Sn).

A perusal of the literature reveals that the overwhelming majority of non-glyoxylate electrophiles in the Petasis reaction bear a hydroxyl group α to the carbonyl unit. It has been noted that a vinylboronic acid is unreactive with an isolated iminium salt, suggesting that the formation of a vinylboronate adduct with a pendant heteroatom on the electrophile is important.[1a] Such a hypothesis has been made in a related reaction involving *N*-acyliminium ions,[5] and α-heterocyclic aldehydes have recently been shown to participate in the boronic acid Mannich process, presumably for the same reason.[6]

In the course of designing a system that uses the Petasis

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(3) Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*, Volume 4; Pergamon: London, 1999; pp 1083−1109.

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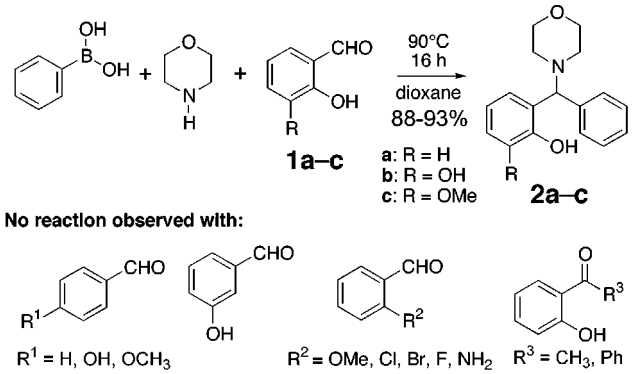
reaction as the covalent bond-forming event in reactive immunization,[7] we sought to explicitly test the proposition that, by coordinating to the boron center, a pendant hydroxyl could both activate the nucleophile and make the capture event intramolecular. Salicyladehyde derivatives were employed as shown in Scheme 1.

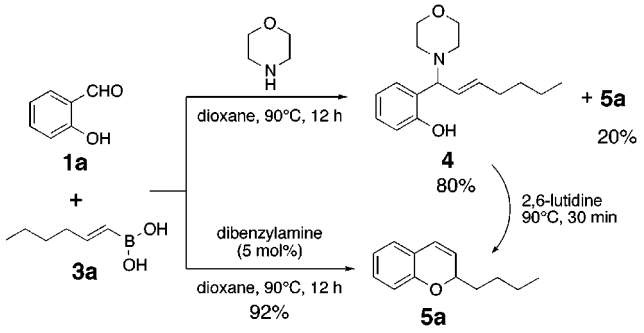
Scheme 1



Phenylboronic acid condenses with morpholine and aldehydes **1a**−**c** under standard conditions to give amines **2a**−**c** in good yields.[8] The Petasis group has independently reported related chemistry.[9] No reaction is observed when the hydroxyl group is omitted, moved to the *meta* or *para* positions, replaced by a halogen substituent, or capped as the methyl ether, strongly supporting the proposed role of the *o*-hydroxyl group. While a pendant amino group has been thought to be an effective activating unit,[1a] 2-aminobenzaldehyde is an unreactive substrate. An *o*-hydroxy group is unable to overcome the sluggish reactivity of ketones; thus, 2-hydroxyacetophenone and 2-hydroxybenzophenone are unreactive.

As shown in Scheme 2, vinylboronic acid **3a**[10] also reacts with salicylaldehyde, providing **4** in 80% yield along with a

Scheme 2



highly chromophoric compound, which was isolated and characterized as 2-butyl-2*H*-chromene, **5a**, presumably aris-

(8) Imine formation from salicylaldehydes is particularly facile: Green, R. W.; Sleet, R. J. *Aust. J. Chem.* **1969**, *22*, 917−919.

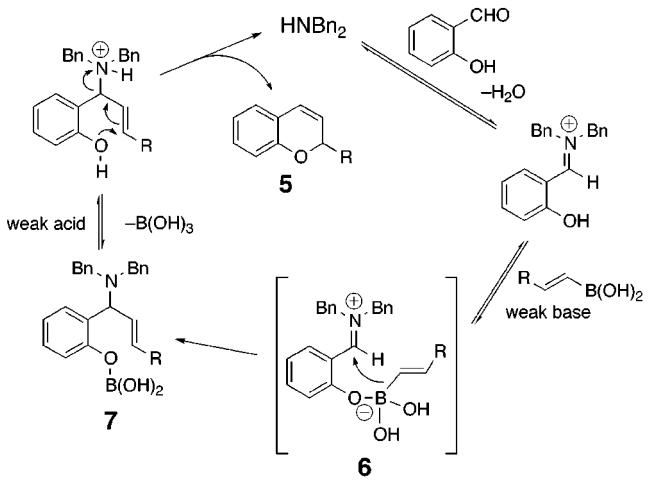
Table 1. Synthesis of 2*H*-Chromenes (**5**) from Alkenylboronic Acids (**3**) and *o*-Hydoxyaromatic Aldehydes (**1**) Using Resin-Supported Base **8** as Catalyst[a]

Alkenylboronic Acid	Aldehyde	Product (yield) [b]
3a	**1a**	**5a** (99%)
3a	**1b**	**5b** (88%)
3a	**1c**	**5c** (91%)
3a	**1d**	**5d** (90%)
3a	**1e**	**5e** (91%)
3a	**1f**	**5f** (85%)
3a	**1g**	**5g** (93%)
3b	**1a**	**5h** (96%)
3c	**1a**	**5i** (96%)
3d	**1a**	**5j** (75%)
3e	**1a**	**5k** (95%)
3f	**1a**	**5i** (91%)

[a] All reactions were performed using 40 mol % of **8** at 90 °C for 24 h. [b] Products isolated as pure compounds by filtration in the indicated yields.

ing by cyclization of the pendant hydroxyl group. Incubation of the mixture of **4** and **5a** with 2,6-lutidine afforded **5a** as the exclusive product. The 2*H*-chromene could likewise be prepared from salicylaldehyde and **3a** using catalytic (5 mol %) dibenzylamine in high yield. The proposed catalytic cycle is shown in Scheme 3. The key intermediate **6** is assembled

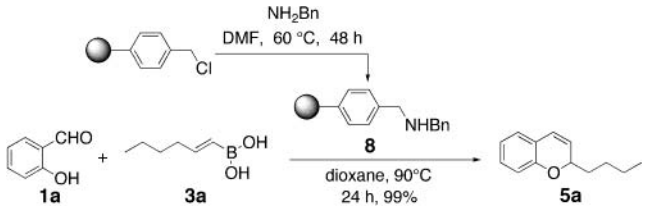
Scheme 3



by iminium ion formation and coordination of the phenolate oxygen to the boronic acid. Intramolecular vinyl group transfer provides **7**, the immediate precursor to allylic amines such as **4**. Cylclization to **5** is likely promoted by protonation of the amine as shown, regenerating the catalyst.

Primary amines are poor catalysts for the process, and commercially available aminomethyl polystyrene does not promote the assembly/cyclization sequence very well (after 24 h at 90 °C, approximately 25% of the starting aldehyde and boronic acid remain). However, the corresponding *N*-benzyl material **8**[11] is effective (Scheme 4). While high

Scheme 4



loadings (40−50 mol % of amine relative to aldehyde) are required to achieve good yields,[12] the resin is easy to prepare and pure products are obtained simply by filtration of the reaction mixtures. As shown in Table 1, a selection of alkenyl boronic acids and *o*-hydoxyaromatic aldehydes are converted to the corresponding 2*H*-chromenes in high yields by this procedure.

The 2*H*-chromene (benzopyran) moiety is found in a wide variety of natural products and dye compounds.[13] The convenient method described here complements existing synthetic procedures[12,14] and highlights the importance of a neighboring hydroxy group to organize electrophilic and nucleophilic components for the C−C bond-forming event.

Acknowledgment. We thank The Skaggs Institute for Chemical Biology for support of this work.

Supporting Information Available: Detailed descriptions of experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Equivalents of **8** vs yields of **5a**, obtained after 12 h reaction: 0.05, 20%; 0.10, 68%; 0.20, 75%; 0.30, 87%; 0.40, 95%.

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