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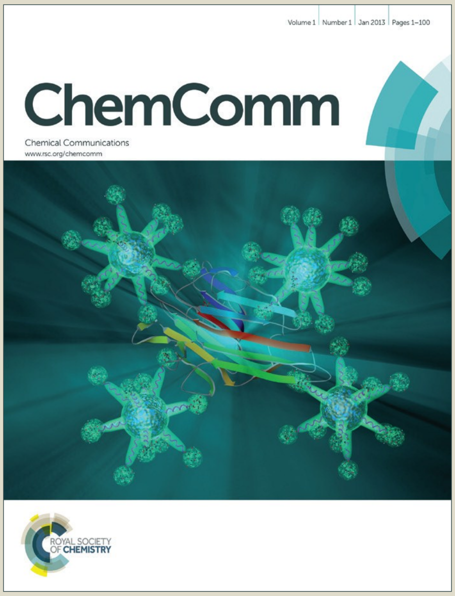

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Transition-metal Free reactions of boronic acids: Cascade addition – ring-opening of furans towards functionalized γ-Ketoaldehydes†

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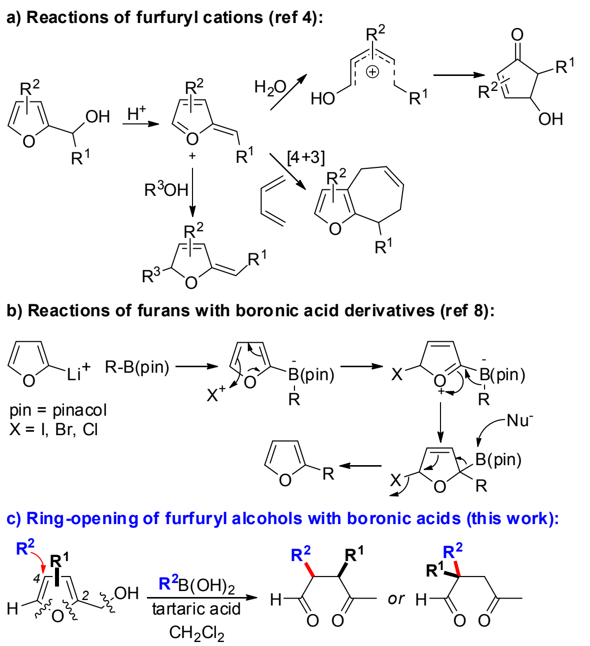
S. Roscales and A. G. Csákÿ*

We describe the first ring-opening of furfuryl alcohols with boronic acids to afford functionalized γ-ketoaldehydes. The transformation builds a new C-C bond at the original C-4 of the starting furan, and tolerates ring-substitution at C-3 and C-4 positions. The reaction takes place under metal-free conditions by promotion with tartaric acid.

Furans constitute a useful bridge between the chemistry of aromatic heterocycles and the chemistry of aliphatic or alicyclic compounds. Due to their relatively low aromaticity,[1] they participate in reactions typical of aromatics and also in reactions which are characteristic of alkenes or dienes, such as cycloadditions or ring-opening reactions. These processes constitute smart transformations from the standpoint of synthetic strategy: The carbon backbone of a furan can be decorated making use of classical aromatic reactions, and then transformed into an aliphatic or alicyclic compound which may be difficult to prepare otherwise.

Furfuryl alcohols constitute a special class of furans which have shown particular relevance in the context of ring-opening reactions.[2] The ability of their hydroxyl to act as leaving group furnishes stabilized furfuryl cations (Scheme 1a) which may act as intermediates in the formation of valuable targets such as 2-cyclopentenones (the Piancatelli reaction),[3] furan ring-fused cycloheptenes, or dihydrofuran-based exo enol ether / cyclic ketal natural products.[4]

On the other hand, boronic acids and their derivatives are bench-stable reagents useful in C-C bond-forming processes.[5] Under suitable activation, generally under transition-metal catalysis, they are able to transfer their carbon moiety to electrophilic centres under mild conditions. However, due to the low intrinsic reactivity of boronic acids,[6] transformations in which they act as carbon nucleophiles under metal-free conditions remain relatively scarce.[7,8]



Scheme 1 Reactions of furfuryl cations, reactions of furans with boronic acid derivatives, and ring-opening of furfuryl alcohols with boronic acids.

In this paper we report a new reaction of furfuryl alcohols with boronic acids promoted by tartaric acid. The reaction builds a new C-C bond at the original C-4 of the starting furan simultaneously with the ring-opening process (Scheme 1).

Based on our previous results on metal-free additions of boronic acids to various kinds of substrates using different types of promoters, we began our studies by exploring the reaction between 2-furylcarbinol (**1a**) and (*E*)-2-phenylvinylboronic acid (**2a**) or potassium (*E*)-2-phenylvinyltrifluoroborate (**3a**). These optimization results are gathered in Table 1.

Only rapid degradation of the starting materials was observed (TCL-monitoring) under promotion with trifluoroacetic anhydride (TFAA) either when using **2a** or **3a**

Instituto Pluridisciplinar, Universidad Complutense, Campus de Excelencia Internacional Moncloa, 28040-Madrid, Spain. Tel: 34 913943280; E-mail: csaky@ucm.es

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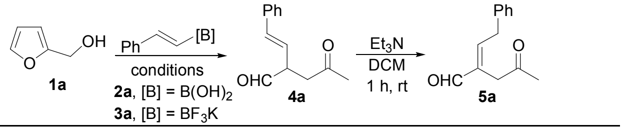
(Table 1, entries 1, 2). On the other hand, we were pleased to observe the formation of the γ-ketoaldehyde **4a** upon treatment of **1a** with **2a** when tartaric acid was used as the promoter (Table 1, entry 3). However, all attempts to isolate this compound completely pure were unsuccessful. Partial isomerization to **5a** was experienced upon chromatography on silica-gel or alumina stationary phases. Thus, we isomerized crude **4a** directly to **5a** with Et_3N prior to product isolation. Compound **5a** was obtained as a single *E* isomer, as confirmed by NOE measurements. Further improvement of the reaction conditions led to an increase in the molar ratio of tartaric acid (Table 1, entries 4 - 6) in DCM as solvent. We found that the addition of water was beneficial for the process (Table 1, entries 7 - 9). The reaction also worked using the trifluroborate **3a** instead of the boronic acid **2a** (Table 1, entry 10). The process could also be promoted with lactic acid (Table 1, entry 11), but not with diethyl tartrate (Table 1, entry 12). Under optimum conditions (Table 1, entry 8) the cascade ring-opening reaction / C-C bond formation was best performed with 1.0 equiv of tartaric acid and 3 equiv of H_2O in DCM for 18 h at rt.

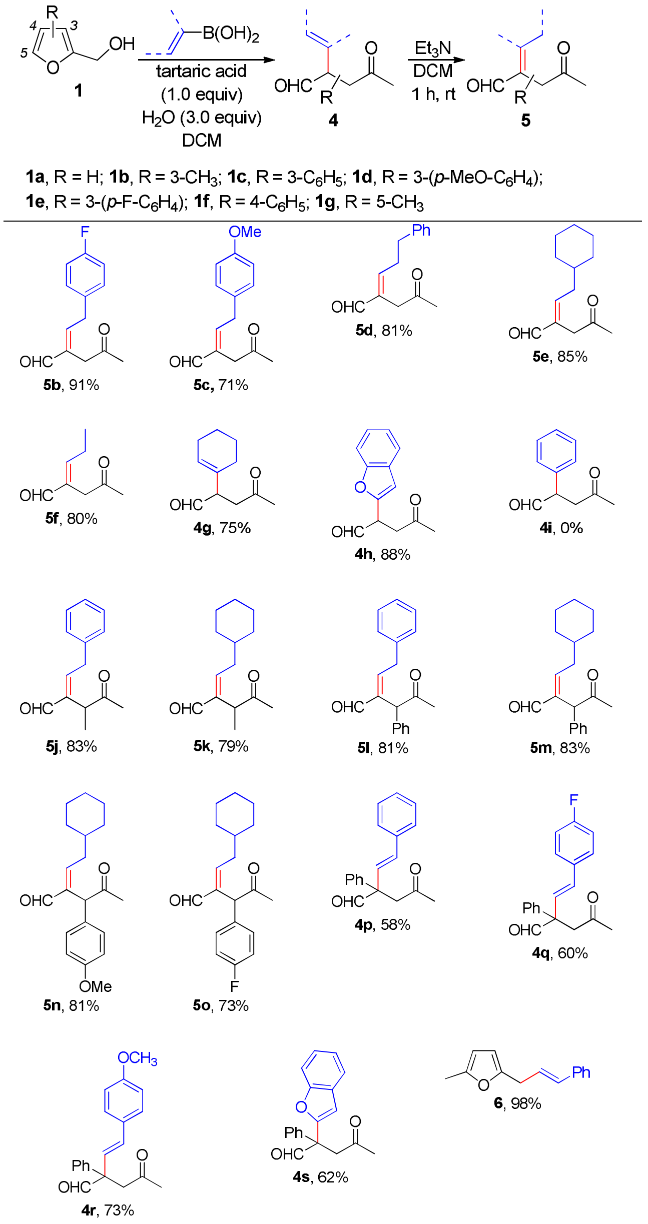
Table 1 Selected optimization conditions[a]



Entry	Conditions	**5a** Yield (%)[b]
1	**2a**, TFAA (0.5 equiv), DCM, rt, 1 h	---
2	**3a**, TFAA (0.5 equiv), DCM, rt, 1 h	---
3	**2a**, tartaric acid (0.3 equiv), DCM, rt, 18 h	36
4	**2a**, tartaric acid (0.5 equiv), DCM, rt, 18 h	53
5	**2a**, tartaric acid (1.0 equiv), DCM, rt, 18 h	62
6	**2a**, tartaric acid (1.0 equiv), Tol, rt, 18 h	51
7	**2a**, tartaric acid (1.0 equiv), DCM, H_2O (1.0 equiv), rt, 18 h	70
8	**2a**, tartaric acid (1.0 equiv), DCM, H_2O (3.0 equiv), rt, 18 h	89
9	**2a**, tartaric acid (1.0 equiv), DCM, H_2O (5.0 equiv), rt, 18 h	88
10	**3a**, tartaric acid (1.0 equiv), DCM, H_2O (3.0 equiv), rt, 18 h	83
11	**2a**, lactic acid (1.0 equiv), DCM, H_2O (3.0 equiv), rt, 18 h	78
12	**2a**, diethyl tartrate (1.0 equiv), DCM, H_2O (3.0 equiv), rt, 18 h	---

[a] Reaction scale: 1.2 equiv of **2a** or **3a**. [b] Yield of product isolated after flash column chromatography.

Under the optimized conditions, firstly we extended the reaction of **1a** to other boronic acids towards the synthesis of a variety of γ-ketopentanals.[9] The results are gathered in Scheme 2. We began by considering other (*E*)-2-arylvinylboronic acids endowed with electron-accepting and electron-donating groups at the aryl ring (**5b**, **5c**). In addition, we were satisfied to see that the reaction could also be extended to non-styryl alkenylboronic acids (**5d**-**f**). When a 1-substituted alkenylboronic acid was used, we were pleased to find that the primary reaction product (racemic) was stable enough to chromatographic purification (**4g**). This was also the case with a heteroarylboronic acid (**4h**). However, no reaction occurred with phenylboronic acid (**4i**).



Scheme 2 Ring-opening reactions of furans with boronic acids: scope and limitations.

Next, we investigated the scope and limitations of the reaction with regard to the substitution of the furan ring. Substitution at 3-position led to attack of the boronic acid at C-4 of the furan ring, affording 2,3-disubstituted-γ-ketopentanals (**5j**-**o**). When 4-substituted furfuryl alcohols where used, the formation of the new C-C bond again took place at C-4 of the furan ring, giving rise to 2,2-disubstituted-γ-ketopentanals (**4p**-

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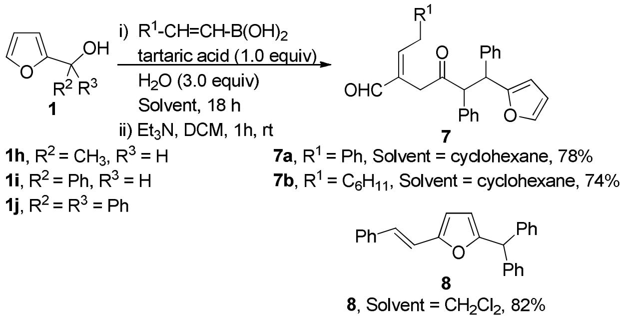
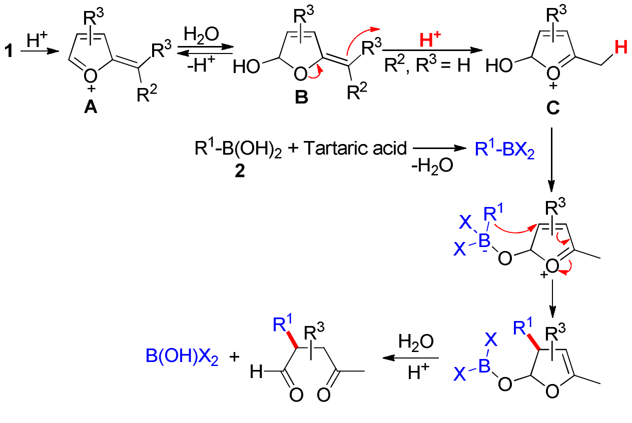
s). However, no reaction was observed between 5-methyl-2-furylmethanol (**1g**) and (*E*)-2-phenylvinylboronic acid (**2a**). Instead, treatment of **1g** with potassium (*E*)-2-phenylvinyltrifluoroborate (**3a**) led to benzylic substitution without ring-opening (**6**). Also, no reaction was observed when starting from 3-furylmethanol.

Last, we considered the possibility of using secondary furfuryl alcohols (Scheme 3). No reaction was observed between **1h** and (*E*)-2-phenylvinylboronic acid (**2a**) under standard reaction conditions. On the other hand, the reaction of the 1-aryl-1-(2-furyl)methanol **1i** with **2a** or **2e** led to γ-ketoaldehydes **7a**,**b**. In the case of the diphenylfurylcarbinol **1j**, the product of attack to position C-5 (**8**) was obtained instead.



Scheme 3 Reactions of secondary and tertiary furfuryl alcohols.

A plausible reaction course that can explain the ring-opening reaction of furans with boronic acids is proposed in Scheme 4. We have observed that furfuryl alcohol **1a** does not suffer transformation when treated with tartaric acid and H_2O in DCM alone in the absence of a boronic acid, and we have also checked that 4-oxopent-2-enal does not react with (*E*)-2-phenylvinylboronic acid (**2a**) under these reaction conditions. These observations rule out the possibility of the formation of compounds **4** via direct ring-opening (H_2O, H^+) of the furan ring of the starting furfuryl alcohols **1** followed by conjugate addition.[10] The reaction course gathered in Scheme 4 is based on the well-known intermediates of the ring-opening reaction of furfuryl alcohols in the Piancatelli[3,4] reaction. Thus, addition of H_2O to the 5-position of the furanoxonium cation **A** will give rise to the key intermediate **B**. Protonation would render a γ-oxo-α,β-unsaturated oxonium cation (intermediate **C**), which after coordination to an *in situ* generated electron-deficient trivalent boron species[11] (RBX_2) will transfer intramolecularly the carbon backbone of the original boronic acid. The latter step is similar to a conjugate Petasis reaction.[12] Final hydrolysis furnishes the γ-ketoaldehydes **4**. The proposed reaction course also explains the failure of the reaction with **2a** when the 5-position of intermediate **A** is blocked by a substituent, due to slow conversion to **B**. However, under these circumstances, intermediate **A** can be attacked by a potassium trifluoroborate[13] (**3a**) to give benzylic substitution (compound **6**). The formation of compounds **7** (R^2 = Ph, R^3 = H) can be understood following a similar pathway, by reaction of the key enol intermediate **B** with a second equivalent of the furanoxium cation **A** at the benzylic position instead of protonation, and the formation of compound **8** (R^2, R^3 = Ph) by rapid direct attack to the corresponding intermediate **A** at C-5 position.



Scheme 4 Plausible reaction course for the ring-opening reactions.

Due to the dense functionalization present in the γ-ketoaldehydes **4** and **5** which resulted from the ring-opening reaction of furans with boronic acids, a variety of synthetically useful transformations can be envisioned for this type of compounds. This makes them them attractive as intermediates in diversity oriented synthesis.[14] For instance (Scheme 5), we have considered the transformation of selected examples of crude compounds **4** into the polysubstituted furans[15] **9** by a cascade cyclization / Friedel-Crafts acylation (Scheme 4a), compounds **5a**,**e** have been converted into the α-alkylidene-γ-butyrolactones[16] **11** by a reduction / oxidation sequence (Scheme 4b), and compounds **4p**-**s** have been cyclized to the cyclopentenone **12** (Scheme 4c) or subjected to base-induced deformylation to the β,γ-unsaturated ketones[17] **13** (Scheme 4d), which have been thus synthesized under transition-metal-free conditions, or to ketone **14**.

In conclusion, we have developed a new ring-opening reaction of furans using boronic acids as reagents under metal-free conditions. The transformation allows the generation of a new C-C bond at the original C-4 of the starting furfuryl alcohol. This gives rise to γ-ketoaldehydes functionalized at carbon C-2 or at carbons C-2 and C-3: Monofunctionalization at C-2 has been achieved when starting from 2-furylmethanol, difunctionalization at C-2 and C-3 has been achieved when starting from 3-substituted-2-furylmethanols, and double functionalization at C-2 has been achieved when starting from 4-substituted-2-furylmethanols. The potential usefulness of these compounds in diversity oriented synthesis has been highlighted by selected examples of their transformations into polysubstituted furans, α-alkylidene-γ-butyrolactones, cyclopentenones or β,γ-unsaturated ketones.

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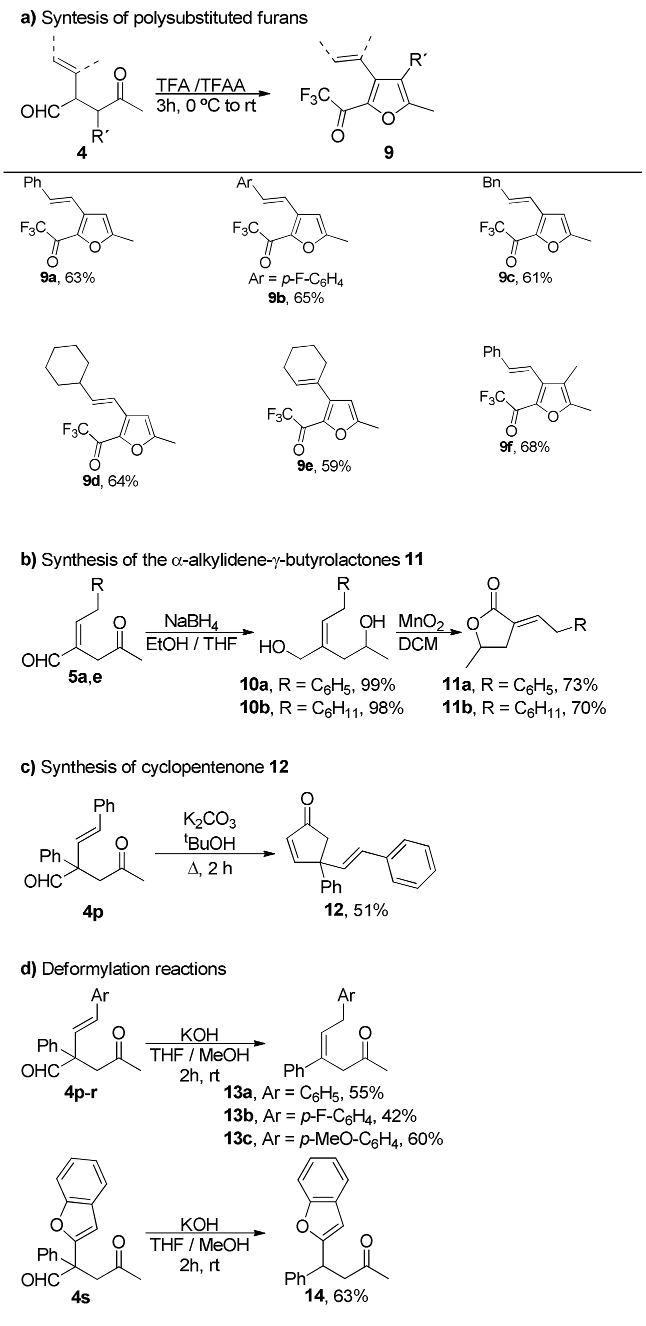

Scheme 5 Transformations of the γ-ketoaldehydes **4** and **5**.

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