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Boronic acid-promoted site-selective Fischer esterifications of sugar alcohols†

Sanjay Manhas, Yu Chen Lin, Grace Wang, Luke T. Kyne and Mark S. Taylor *

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A protocol for selective monoesterification of glycerol and pentose alcohols with fatty acids is described, using phenylboronic acid as a phase-transfer reagent. Formation of arylboronic ester intermediates serves both to increase the solubility of the alcohol substrate in nonpolar organic solvent and to selectively protect diol groups, allowing for efficient and selective condensation with the aliphatic carboxylic acid. A phase-switching workup with basic aqueous sorbitol solution is used to cleave the boronic ester groups and to separate the boronic acid from the monoester product. The method provides an operationally simple means of access to a class of bio-derived products that have been broadly applied as food additives, components of cosmetic products and pharmaceutical formations, plasticizers, and non-ionic surfactants.

Introduction

Carbohydrates and their derivatives (*e.g.*, sugar alcohols, sugar acids) show great promise as sustainable feedstocks for the production of organic molecules and polymers.[1–3] Their highly functionalized nature represents an obstacle for these types of applications, and has motivated the development of new methods for the site-selective chemical modification of sugar-derived compounds.[4–11]

Long-chain, aliphatic monoesters of sugar alcohols are a class of bio-derived products of particular importance. They are applied broadly as food additives, components of cosmetic products and pharmaceutical formulations, plasticizers, and as non-ionic surfactants in commercial and research settings.[12–15] The glycerolysis of fats, catalyzed by inorganic bases or by lipases,[16] is an important process for the manufacture of such compounds.[17] Due to the heterogeneity of the starting materials as well as selectivity issues, glycerolysis results in mixtures of products that must be separated, for example, by fractional distillation. To address this issue, methods based on condensation of aliphatic carboxylic acids with sugar alcohols have been developed. Although the use of well-defined starting materials is an advantage of the latter approach, the formation of mixtures remains a problem: it is not straightforward to achieve high levels of site-selectivity and to suppress over-functionalization (formation of di- and triester products) in such condensations.[18] Accordingly, chemists often resort to additional synthetic steps and protective group manipulations. For example, condensation of 1,2-*O*-isopropylidene-protected glycerol with a carboxylic acid or acyl chloride is a typical approach to the controlled synthesis of monoacylglycerols.[19,20] Regioselective ring-opening of glycidol by carboxylic acids is an alternative synthetic route.[21–23] In general, the amount of protective group-derived waste produced increases when these approaches are extended to acylations of higher sugar alcohols.[24] Catalysis by lipase enzymes provides another way to address the issue of selectivity in condensations of carboxylic acids with sugar alcohols.[16,25–30] Challenges associated with this approach include the low solubility of glycerol and other sugar alcohols in organic media, modest levels of selectivity for monoacylation, and the limited thermal stability of the enzyme catalysts.

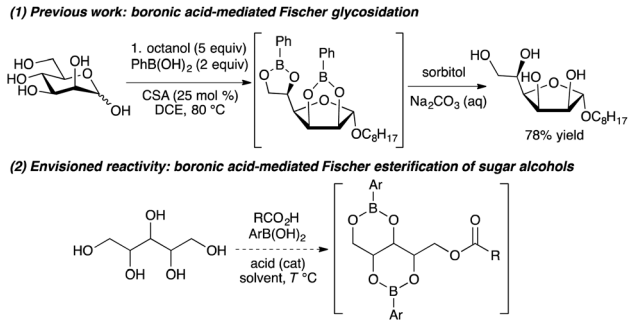
Here, we report a method for the direct, site-selective coupling of carboxylic acids with sugar alcohols by Fischer esterification in the presence of phenylboronic acid. Under the optimized conditions, arylboronic ester formation serves to transiently protect a diol motif[31] while enhancing the solubility of the sugar alcohol substrate in the organic solvent. The protocol provides efficient and selective access to monoesters of long-chain aliphatic carboxylic acids with glycerol, xylitol, ribitol and L-arabitol.

Results and discussion

We have shown that arylboronic acids serve as phase-transfer reagents for Fischer glycosidations in low-polarity organic sol-

Department of Chemistry, University of Toronto, 80 St. George St., Toronto, ON M5S 3H6, Canada. E-mail: mtaylor@chem.utoronto.ca

†Electronic supplementary information (ESI) available: Experimental and computational details, characterization data, copies of NMR spectra for products **2a–f**, **3a–b** (PDF), X-ray crystal structure data for **2e** (.cif). CCDC 1903546. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9gc00901a



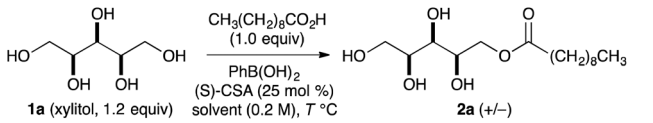
Scheme 1 Boronic acid-mediated Fischer glycosidation and Fischer esterification.

vents (Scheme 1, eqn (1)).[32] In these transformations, the boronic acid influences both the rate (due to solubility enhancement[33]) and the selectivity (due to differences in the stability of furanose- *versus* pyranose-derived boronic esters). For example, in the case of mannose, the furanoside product was generated selectively due to the favourable formation of the 2,3,5,6-bis-boronic ester. A 'phase-switching' workup with aqueous, basic sorbitol solution was used to cleave the product-derived boronic ester by transesterification while also facilitating the separation and recovery of the boronic acid reagent.[34,35] We reasoned that a similar principle could be applied to achieve selective Fischer esterifications of sugar alcohols (eqn (2)). In the case of a pentose alcohol, the formation of a bis-boronic ester would increase the solubility of the polar substrate in organic solvent[36] while leaving a single free OH group available for acid-mediated condensation with the aliphatic carboxylic acid. Although boronic esters have been employed as protective groups for acylations, silylations and alkylations of glycerol,[37] xylitol[38] and mannitol,[39,40] and for lipase-catalyzed esterifications,[27] we anticipated that the ability to conduct direct condensations of sugar alcohols with carboxylic acids in the presence of a boronic acid could form the basis of a particularly efficient and operationally simple protocol.

The coupling of xylitol (**1a**) with decanoic acid was studied to evaluate the effect of phenylboronic acid on the Fischer esterification of a sugar alcohol (Table 1). In the presence of $PhB(OH)_2$ (two equivalents relative to xylitol) and (*S*)-camphorsulfonic acid as catalyst ((*S*)-CSA, 25 mol%), condensation in 1,2-dichloroethane (DCE) solvent at 85 °C was accomplished in 55% yield after cleavage of the intermediate arylboronic ester by workup with aqueous base. A similar yield was obtained in toluene (oil bath temperature of 120 °C), whereas no product was obtained in 1,4-dioxane, perhaps due to the relatively high solubility of water in this solvent. Control reactions in toluene conducted in the absence of the arylboronic acid or (*S*)-camphorsulfonic acid showed no formation of the ester product. Without the boronic acid, the xylitol substrate remained largely insoluble under these reaction conditions.[36]

Product **2a** would be expected to arise from a bis-boronic ester having a free primary OH group. Two possible structures

Table 1 Evaluation of reaction conditions for the condensation of xylitol with decanoic acid[a]



Entry	Solvent, *T*	Equiv. $PhB(OH)_2$	Yield of **2a**[b]
1	DCE, 85 °C	2.4	55%
2	Dioxane, 110 °C	2.4	<5%
3	Toluene, 120 °C	2.4	60%
4	Toluene, 120 °C	0	<5%
5[c]	Toluene, 120 °C	2.4	<5%

[a] Reaction conditions: **1a** (0.24 mmol, 1.2 equiv.), decanoic acid (0.2 mmol, 1.0 equiv.), $PhB(OH)_2$ (0.48 mmol, 2.4 equiv.), (*S*)-(+)-camphorsulfonic acid ((*S*)-CSA, 0.05 mmol, 25 mol%), solvent (1.0 mL), *T* °C, 24 h. [b] Yields of **2a** were determined by ^{1}H NMR spectroscopy of unpurified reaction mixtures after workup with aqueous base, using 1,2,3-trimethoxybenzene as a quantitative internal standard. [c] Reaction conducted without the addition of (*S*)-CSA.

for such an intermediate (**A** and **B**, arising from condensations with 1,3- and 1,2-diol groups, respectively) are depicted in Fig. 1. To assess the relative stabilities of these two isomers, gas-phase computational modelling was conducted with density functional theory, using the M06-2X functional[41] and the 6-311+G(d,p) basis set.[42] Isomer **A** was calculated to be the more stable, consistent with the more favourable formation of six-membered *versus* five-membered (trivalent) boronic esters,[43] and with previous observations related to threitol- and mannitol-derived bis-boronates.[40,44] It should be noted, however, that Dahlhoff and co-workers obtained a mixture of isomeric boronates upon condensation of xylitol with triethylboroxine.[38] At this stage, it is not fully clear whether the series of condensations that generates **2a** is under kinetic or thermodynamic control, considering the reversible nature of both the Fischer esterification and boronic ester formation; we note that evidence for reversible glycoside formation was obtained in our previous study of phenylboronic acid-mediated Fischer glycosidation of mannose.[32] Attempts to prepare the 3-*O*-acylated isomer of **2a** *via* the 1,2:4,5-bis-*O*-isopropylidene ketal (to probe whether isomerization to **2a** could take place under the conditions of Table 1, entry 4) were thwarted by acyl group migration under the acidic conditions used for hydrolysis of the ketal groups. Subjecting a mixture of two monoacylated

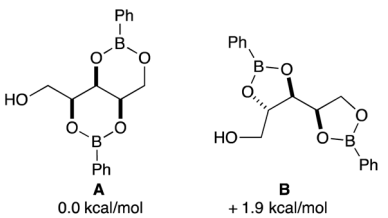
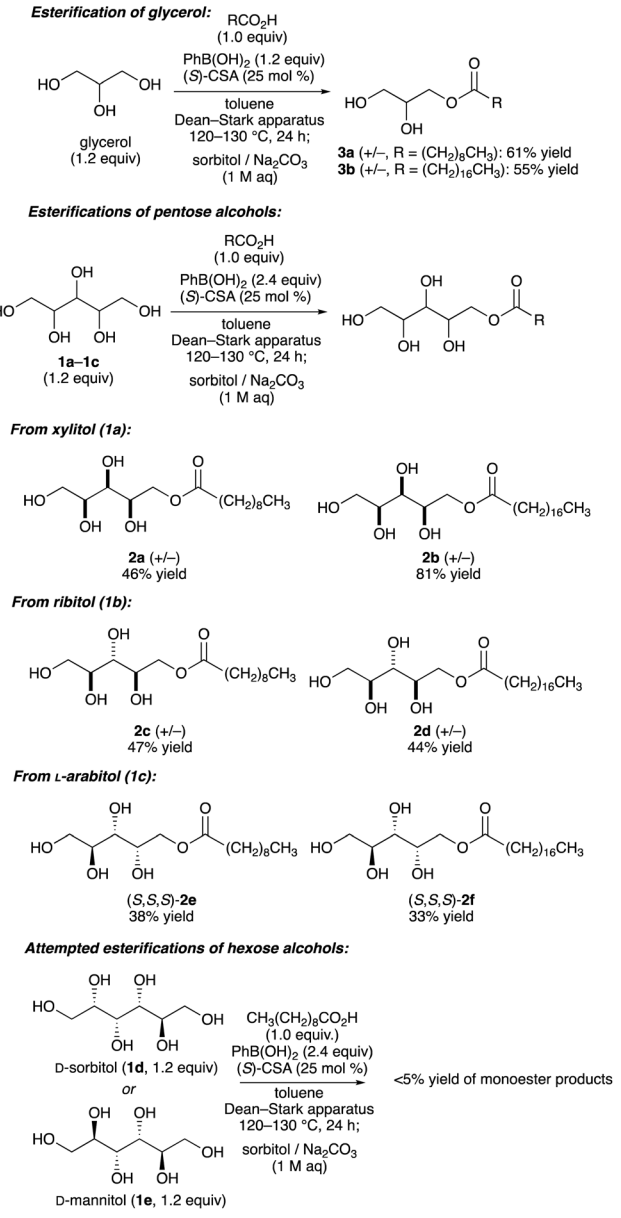


Fig. 1 Structures and calculated Gibbs free energies (gas phase, M06-2X/6-311+G(d,p) of xylitol-derived bis-boronic esters **A** and **B**.

sugar alcohol products to $PhB(OH)_2$ and (*S*)-CSA under the conditions of Table 1, entry 3 resulted in only 5% yield of the intermolecular transesterification product, with recovery of the starting esters and decomposition products accounting for the remainder of the mass balance (see the ESI†). This observation suggests that the arylboronic acid-promoted monoesterification reaction may not be under thermodynamic control, although further experiments should be undertaken to address this issue.

Preparative esterifications of glycerol, xylitol, ribitol and L-arabitol with decanoic acid and octadecanoic acid were conducted in toluene on 2.0 mmol scale, using a Dean–Stark azeotropic distillation apparatus to drive the condensations to completion (Scheme 2). Liquid–liquid extraction with 1 M aqueous sorbitol/Na_2CO_3 solution was then used to accomplish cleavage of the boronic ester groups by transesterification. The partitioning of the organoboron compound into the aqueous phase facilitated purification of the sugar alcohol-derived monoester, while also allowing for recovery of $PhB(OH)_2$ after acidification and extraction of the aqueous sorbitol solution. After the phase-switching workup, the monoester products were isolated by recrystallization. Using this protocol, with 1.2 equivalents of $PhB(OH)_2$, glycerol monocaprate and monostearate (**3a** and **3b**) were synthesized in 61% and 55% yield, respectively. For the pentose-derived sugar alcohols, 2.4 equivalents of $PhB(OH)_2$ were used to ensure complexation of two diol moieties. The yields of esterification of these substrates were more variable, with the formation of emulsions during the phase-switching workup being an issue in certain instances. The syntheses of **2a**, **2c** and **3a** could be conducted on 10.0 mmol scale with only minimal decreases in yield (3–6%) from those obtained on 2.0 mmol scale (see the ESI†).



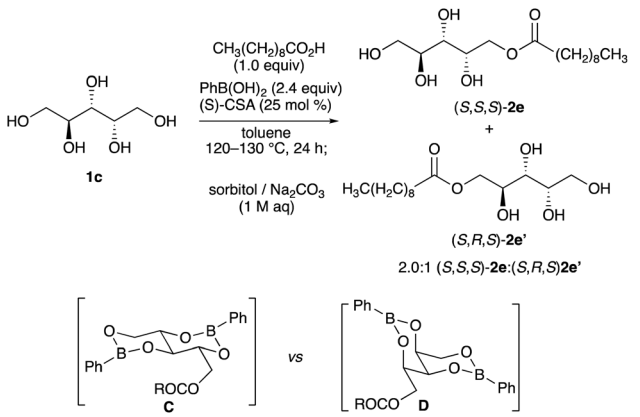
Scheme 2 Phenylboronic acid-mediated Fischer glycosidations.

The yield of product **2b** compares favorably to that obtained for the coupling of xylitol and oleic acid catalysed by Novozym 435 (2-methyl-2-butanol solvent, 60 °C, reduced pressure: 98.2% conversion of oleic acid, 66.6% selectivity for monoacylation).[28] Compound **2a** has been synthesized in three steps (formation of the bis-acetonide, esterification and hydrolysis of the ketal groups) in 18% overall yield.[24] A higher yield of **2a** (88% over three steps) has been obtained by protection of the diol groups as ethylboronic esters.[38] Relatively few methods for the synthesis of monoesters derived from ribitol or arabitol (products **2c**–**2f**) have been reported; monoacylation of these sugar alcohols with lauric acid was achieved in roughly 40% yield using immobilized *Candida antarctica* lipase in acetone at 50 °C.[29] This protocol was also conducted in flow using a packed bed reactor.[29]

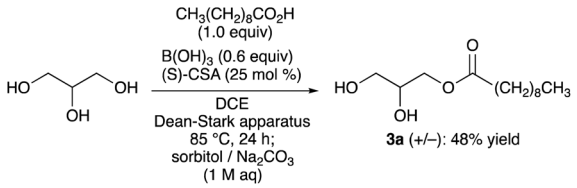
For monoesterifications of L-arabitol (**1c**), mixtures of diastereomers were generated using the phenylboronic acid-mediated protocol: a 2.0 : 1 ratio of (*S*,*S*,*S*)-**2e** to (*S*,*R*,*S*)-**2e′** was obtained after phase-switching workup and prior to purification. After recrystallization from ethanol, the (*S*,*S*,*S*)-isomer was isolated in 38% yield, and its relative configuration was established by single crystal X-ray diffraction analysis. It is conceivable that the observed diastereoselectivity arises from a (modest) thermodynamic preference for the formation of *trans*-fused bis-boronate **C** over *cis*-fused **D** (Scheme 3). In any case, the ability to access **2e** and **2f** in enantio- and diastereomerically enriched form is noteworthy. Opportunities may exist to employ these compounds as chiral surfactants or liquid crystals.[24,38]

As anticipated based on the proposal shown in Scheme 1, six-carbon sugar alcohols (*e.g.*, D-sorbitol **1d**, D-mannitol **1e**) did not undergo selective esterification under the optimized conditions. Partial boronate formation from such substrates is known to be challenging: for example, treatment of D-mannitol with two equivalents of $PhB(OH)_2$ has been shown to result in the exclusive formation of the tris-boronic ester.[31]

The phase-switching transesterification enables the straightforward separation and recovery of the arylboronic acid



Scheme 3 Diastereoselectivity in the esterification of **1c**, and structures of the proposed bis-boronic ester intermediates **C** and **D**.



Scheme 4 Boric acid-promoted monoacylation of glycerol.

promoter:[32,34] after preparation of monoester **2a**, $PhB(OH)_2$ was recovered in 78% yield by acidification of the aqueous sorbitol fractions and extraction with ethyl acetate (see the ESI†). Attempts were also made to develop a more cost-effective monoesterification protocol using boric acid in place of $PhB(OH)_2$. Since the reaction of boric acid with diols can generate spiro-borates *via* 2 : 1 complexation, a 0.5 : 1 $B(OH)_3$: diol ratio (rather than 1 : 1, as was employed for the $PhB(OH)_2$-mediated reactions) was used. Under these conditions, monoacylation of glycerol with decanoic acid was achieved in only slightly lower (unoptimized) yield relative to that obtained using $PhB(OH)_2$ (48% *versus* 61%: Scheme 4). Attempts to apply the boric acid-mediated protocol to pentose alcohols were unsuccessful, perhaps due to the potential for formation of several isomeric spiro-borates from such substrates.

Conclusions

In summary, the use of phenylboronic acid as a phase-transfer reagent has enabled an operationally simple and robust method for selective monoesterification of glycerol and pentose alcohols by direct condensation with fatty acids. The formation of arylboronic esters that are soluble in nonpolar organic media allows for efficient Fischer esterification with the aliphatic carboxylic acids, with azeotropic removal of water being employed to drive the condensations to completion. Phase-switching deprotection of the boronic ester ester products facilitates the isolation of the sugar alcohol monoesters and the recovery of the phenylboronic acid promoter. New diastereomerically and enantiomerically enriched monoesters of L-arabitol have been synthesized using this method. The results further illustrate the utility of organoboron compounds as phase-transfer reagents for selective transformations of polyhydroxylated compounds in organic solvents.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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