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Aryl Boronic Acid-Catalysed Dehydrative Substitution of Benzylic Alcohols for C-O Bond Formation

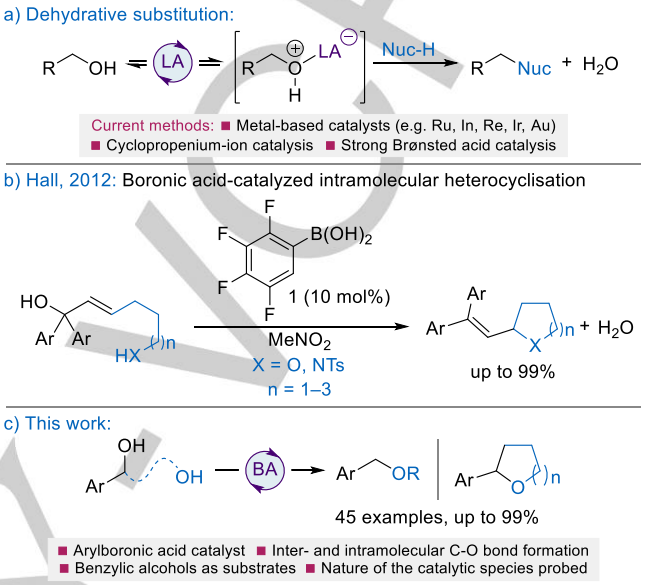
Susana Estopiñá-Durán,[a] Liam J. Donnelly,[a] Euan B. Mclean,[a] Bryony M. Hockin,[a] Alexandra M. Z. Slawin,[a] and James E. Taylor*[a],[b]

Abstract: A combination of pentafluorophenylboronic acid and oxalic acid catalyses the dehydrative substitution of benzylic alcohols with a second alcohol to form new C-O bonds. This method has been applied to the intermolecular substitution of benzylic alcohols to form symmetrical ethers, intramolecular cyclisations of diols to form aryl-substituted tetrahydrofuran and tetrahydropyran derivatives, and intermolecular crossed-etherification reactions between two different alcohols. Mechanistic control experiments have identified a potential catalytic intermediate formed between the arylboronic acid and oxalic acid.

Introduction

The alkylation of heteroatoms is one of the most widely used reactions in both academia and industry.[1] Alkylations are traditionally performed using substitution reactions of alkyl halides or stoichiometrically-activated alcohols with suitable nucleophiles. These processes typically require the use of super-stoichiometric amounts of activating agents and/or produce potentially hazardous by-products. While a number of catalytic variants of both the Mitsunobu and Appel reactions has also been reported,[2] these often use stoichiometric reagents to regenerate the active azodicarboxylates or phosphine catalysts, respectively.

The development of completely catalytic, redox neutral methods of using alcohols directly as electrophiles in alkylation reactions is attractive due to the wide availability of tractable alcohol substrates and the fact that water is the only by-product.[2c,3,4] Conceptually, one method of activating alcohols is through coordination of the hydroxyl group to a Lewis acid catalyst to enhance its leaving group ability (Scheme 1a). Nucleophilic substitution can then occur via an S_N1 or S_N2-type mechanism, releasing water as the by-product. Various metal-based catalytic systems have been reported for such dehydrative substitution reactions using heteroatom nucleophiles.[3b] For example, the nucleophilic substitution of allylic, propargylic,[5,6] and benzylic alcohols[7] has been explored using a variety of metal-based Lewis acids. Dehydrative substitution can also be performed using strong Brønsted acid catalysts, typically via an S_N1 mechanism.[8]



Scheme 1. Catalytic dehydrative substitution of alcohols.

Recently, aryl boronic acids have emerged as promising mild Lewis acid catalysts for the activation of alcohols towards dehydrative substitution reactions. Aryl boronic acids and/or boronate esters are attractive catalysts given that many are commercially available or are readily prepared, and they are generally stable and easy to handle.[9,10] Aryl boronic acids and boronate esters are also known to reversibly interact with both alcohols and water,[9] enabling suitable equilibria to be established that allows for both substrate activation and catalyst turnover, without recourse to the addition of stoichiometric additives.

Seminal work by the groups of McCubbin[11] and Hall[12] has shown that electron-deficient aryl boronic acids catalyse Friedel-Crafts alkylation reactions of various arenes and heteroarenes using simple allylic or benzylic alcohols as the electrophile. Moran and co-workers further optimised the reaction conditions for the Friedel-Crafts alkylation process using a rapid screening technique,[13] which identified a combination of pentafluorophenylboronic acid (1 mol%) and oxalic acid (2 mol%) in nitromethane as the most effective. Hall and co-workers have reported that tetrafluorophenylboronic acid **1** is an effective catalyst for intramolecular heterocyclisation reactions of pendent oxygen and nitrogen nucleophiles onto tertiary allylic alcohols (Scheme 1b),[14] with two examples of intramolecular cyclisations onto benzylic alcohols. The same catalytic system has also been applied to the transposition of allylic alcohols[15] and the intermolecular alkylation of sulfonamide nucleophiles using benzylic alcohols.[16,17]

To date, arylboronic acid-catalysed intermolecular

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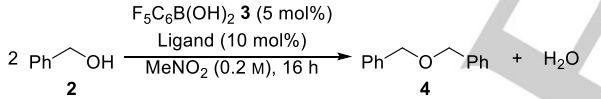
dehydrative substitution using readily available benzylic alcohols as the electrophilic component in combination with a second alcohol as the nucleophile has yet to be reported. Herein, we report that commercially available pentafluorophenylboronic acid is an efficient catalyst for such intermolecular dehydrative substitutions of benzylic alcohols, allowing formation of both symmetrical and unsymmetrical ether products.[18] The method has also been applied to the intramolecular dehydrative cyclisation of diols to form aryl-substituted tetrahydrofuran (THF) and tetrahydropyran (THP) derivatives. Preliminary investigations into the reaction mechanism and the nature of the active catalytic species are also reported.

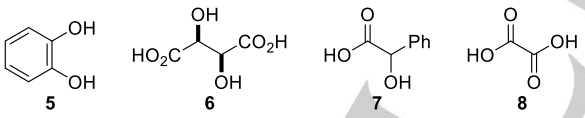
Results and Discussion

Investigations began using a single benzylic alcohol substrate as both the electrophile and nucleophile in a catalytic dehydrative substitution reaction. The intermolecular etherification of benzyl alcohol **2** into dibenzyl ether **4** was chosen as a model reaction, however an initial screen using various electron deficient aryl boronic acids as catalysts in nitromethane at 70 °C returned starting material in all cases (Table 1, entry 1).[19] Next, several ligands (10 mol%) were screened in combination with commercially-available pentafluorophenylboronic acid **3** (5 mol%). The use of catechol **5** gave no reactivity (Table 1, entry 2), but the use of either tartaric acid **6** or mandelic acid **7** gave modest amounts of the desired dibenzyl ether **4** after 16 h (Table 1, entries 3 and 4). Oxalic acid **8** significantly enhanced the reactivity, with 67% **4** isolated after 16 h at 70 °C (Table 1, entry 5). Reducing the ligand loading to 5 mol% resulted in a lower yield (Table 1, entry 6), however increasing the temperature to 90 °C using 10 mol% **8** gave ether **4** in 67% yield after only 3 h (Table 1, entry 7). A control experiment in the absence of boronic acid **3** under the otherwise optimal reaction conditions resulted in no product formation (Table 1, entry 8). Similarly, the use of other solvents, including various mixtures with nitromethane, led to no reactivity.[19]

The scope of the aryl boronic acid-catalysed intermolecular dehydrative etherification process was then investigated using substituted benzylic alcohols (Table 2). Benzhydrol was highly reactive and gave ether **9** in excellent 99% yield at rt. The use of 4-methylbenzyl alcohol under the previously optimised conditions at 90 °C gave several undesired side products, including those arising from Friedel-Crafts alkylation. However, reducing the reaction temperature to 40 °C allowed **10** to be obtained in 53% yield. In contrast, the reaction with 3-methylbenzyl alcohol required heating at 90 °C for an extended time (48 h) to form ether **11** in 62% yield. Halogen-substituted benzyl alcohols were particularly well tolerated, with 4-fluoro, 4-chloro- and 4-bromobenzyl alcohols giving the corresponding ethers **12–14** in excellent yields. However, the use of more sterically demanding 2-chloro- and 2-bromobenzyl alcohol led to reduced reactivity, with increased reaction times required to obtain ethers **15** and **16** in low 35% and 28% yield, respectively. Limitations of this methodology include the presence of highly

Table 1. Reaction optimisation.

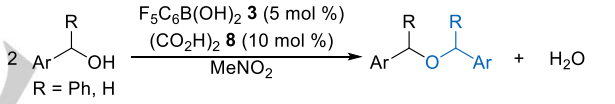


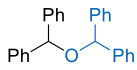


Entry	Ligand (mol%)	T (°C)	t (h)	Yield (%)[a]
1	–	70	16	0
2	**5** (10)	70	16	0
3	**6** (10)	70	16	38
4	**7** (10)	70	16	23
5	**8** (10)	70	16	67
6	**8** (5)	70	16	55
7	**8** (10)	90	3	67
8[b]	**8** (10)	90	3	0

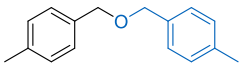
[a] Isolated yields after purification by column chromatography. [b] Reaction performed without $F_5C_6B(OH)_2$ **3**.

Table 2. Intermolecular dehydrative etherification of benzylic alcohols.

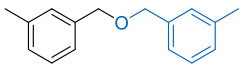




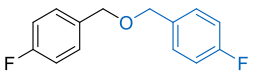
9, rt, 16 h
99%



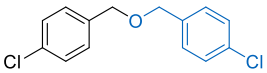
10, 40 °C, 3 h
53%



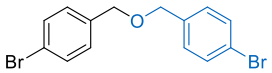
11, 90 °C, 48 h
62%



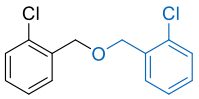
12, 90 °C, 3 h
76%



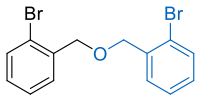
13, 90 °C, 3 h
97%



14, 90 °C, 3 h
98%

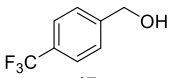


15, 90 °C, 144 h
35%

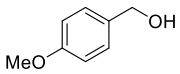


16, 90 °C, 144 h
28%

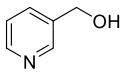
Unsuccessful Substrates



17
no reaction



18
complex mixture



19
complex mixture

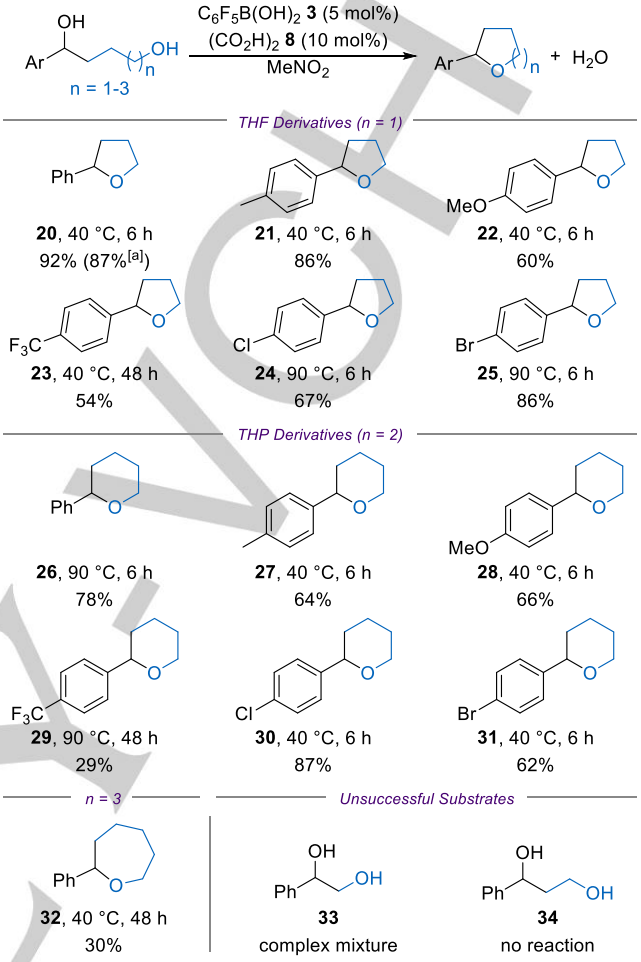
electron-withdrawing aryl substituents, for example 4-trifluoromethylbenzyl alcohol **17** returned only starting material even after extended reaction times. Conversely, electron-rich 4-methoxybenzyl alcohol **18** was highly reactive, resulting in a complex mixture of products including those from undesired Friedel-Crafts alkylation processes.[20] Lowering the temperature to either rt or –10 °C did not improve the selectivity of the reaction with **18**, with only minimal amounts of ether formation observed.[19] The use of heterocyclic alcohols, such as 3-pyridylcarbinol **19**, also resulted in a complex mixture under the standard reaction conditions.

Having demonstrated the desired reactivity using a single benzylic alcohol, the use of two different alcohols was next investigated. It was envisioned that selective activation of a benzylic alcohol would allow dehydrative substitution with a second, non-benzylic alcohol. First, the intramolecular dehydrative substitution of secondary benzylic alcohols bearing a pendant primary alcohol substituent to form THF derivatives was studied (Table 3). Under the previously optimised conditions, the intramolecular cyclisation of 1-phenylbutane-1,4-diol proceeded smoothly at 40 °C, forming THF **20** in 92% yield with no products from competing intermolecular processes observed. This reaction was also performed on a preparative 11 mmol scale, giving 1.4 g of THF **20** in 87% yield. The presence of a mildly electron-donating 4-methyl substituent was well tolerated, affording THF **21** in 86% yield. Notably, in contrast with the intermolecular substitution, incorporation of a strongly electron-donating 4-methoxy aryl substituent was tolerated in the intramolecular substitution to give **22** in good yield. In addition, cyclisation in the presence of an electron-withdrawing 4-trifluoromethyl substituent was also possible, with THF **23** isolated in 54% yield after an extended 48 h reaction time. Halogen substituents were again well tolerated, with products **24** and **25** obtained in good yield after reaction at 90 °C.

Next, the synthesis of 2-aryl substituted THP derivatives from 1,5-diols was investigated under the standard reaction conditions. The same trends in reactivity were observed, with neutral and electron-rich aryl substituents reacting to give products **26**-**28** in good yield. In this case, incorporation of an electron-withdrawing 4-trifluoromethyl substituent resulted in lower reactivity, with THF **29** obtained in only 29% yield after 48 h at 90 °C. As before, 4-chloro and 4-bromo-aryl substitution was well tolerated, with THP products **30** and **31** isolated in 87% and 62% yield, respectively. The formation of larger 2-phenyloxepane **32** from the corresponding 1,6-diol was only moderately successful, giving 30% yield after 48 h at 40 °C. Attempts to apply this methodology to the formation of smaller ring sizes was unsuccessful, with 1,2-diol substrate **33** giving a complex mixture under the standard reaction conditions while efforts to form oxetanes from 1,3-diol **34** returned only starting materials.

The use of two different alcohols in an intermolecular crossed etherification process via selective catalytic dehydrative substitution was then investigated. Initially, the reaction of benzhydrol **35** as the electrophile in combination with an excess of methanol as the nucleophilic component was studied using

Table 3. Intramolecular dehydrative etherification.

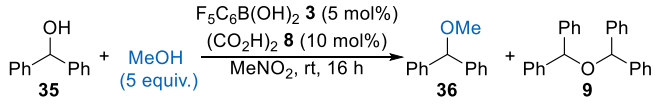


[a] Reaction performed on an 11 mmol scale.

pentafluorophenylboronic acid **3** (5 mol%) and oxalic acid **8** (10 mol%) in $MeNO_2$ at room temperature (Table 4). Complete conversion of benzhydrol was observed, with a 70:30 mixture of the desired crossed ether product **36** and the benzhydrol derived symmetrical ether **9** obtained as determined by ^1H NMR spectroscopic analysis. The ratio of product **36** to **9** could be improved by lowering the reaction concentration (Table 4, entries 2 and 3), with the reaction starting with 0.05 M benzhydrol **35** giving 90:10 **36**/**9** after 16 h. However, further lowering the concentration gave no additional improvement (Table 4, entry 4), and similarly using 10 equiv. MeOH led to no further increase in product ratio (Table 4, entry 5).

The scope of the intermolecular crossed etherification process was investigated through variation of the alkyl alcohol component in combination with benzhydrol **35** (Table 5). Various alkyl-substituted alcohols were applicable under the previously optimised conditions, with complete conversion of benzhydrol **35** observed in all cases. Crossed ethers **37**-**41** were all obtained as the major product as a mixture with a minor amount of symmetric ether **9** derived from benzhydrol **35**. The use of

Table 4. Optimisation of intermolecular dehydrative crossed etherification.

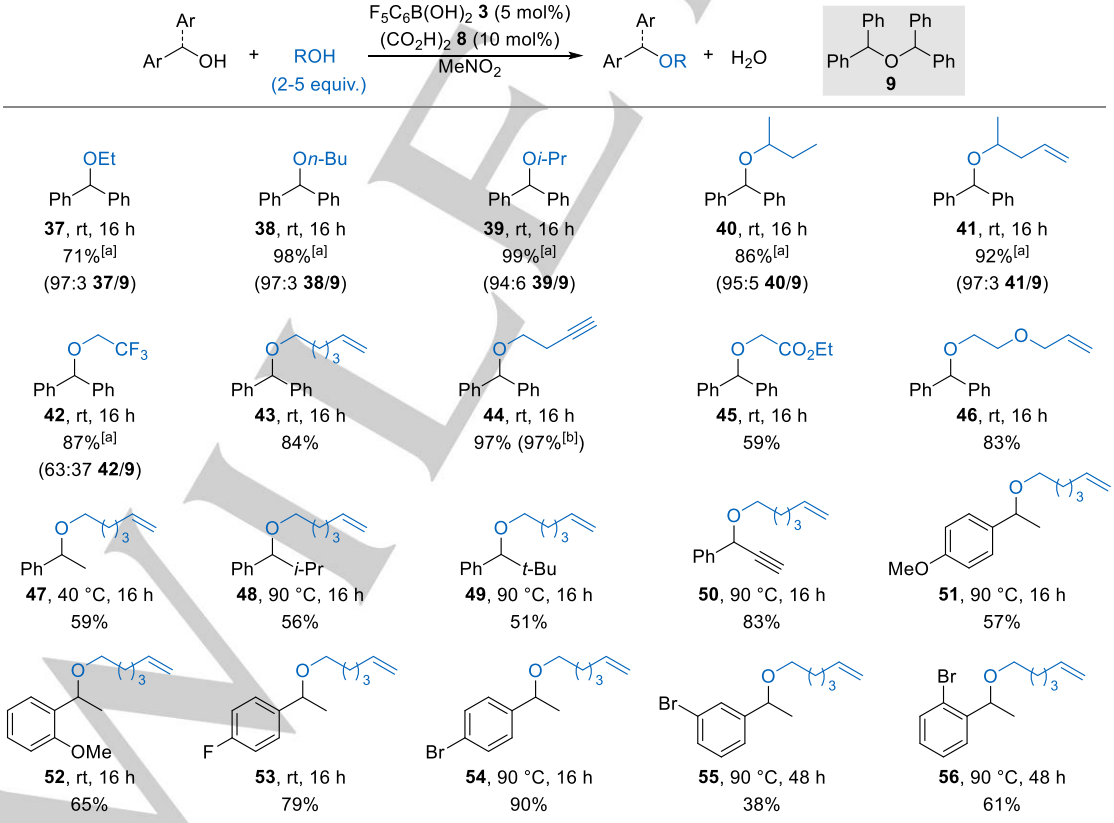


Entry	[**35**] / M	Conv. (%)[a]	**36**:**9**[a]
1[b]	0.2	97	70:30
2	0.1	>98	75:25
3	0.05	>98 (71[c])	90:10
4	0.03	>98	88:12
5[d]	0.05	>98	90:10

[a] Determined by ^{1}H NMR analysis. [b] Reaction using 5 mol% oxalic acid. [c] Isolated yield of 90:10 mixture. [d] Reaction using 10 equiv. MeOH.

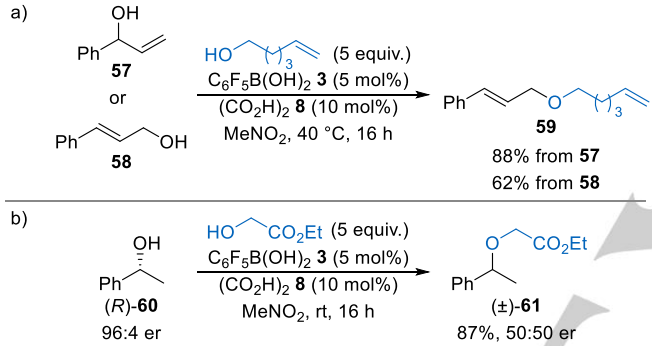
trifluoroethanol as a nucleophile was less well tolerated, forming a 63:37 mixture of ether **42** to **9**. Pleasingly, the use of hex-5-en-1-ol resulted in selective crossed dehydrative substitution, with ether **43** isolated as the sole product in 84% yield. Alkynyl substitution was also well tolerated, with ether **44** obtained in an excellent 97% yield. The synthetic utility of this procedure was further demonstrated by performing this reaction on an 11 mmol scale, allowing the isolation of 2.52 g of ether **44**. Substrates bearing pendant functional groups including esters and allyl ethers were also tolerated, forming ethers **45** and **46** in good yields. Next, the benzylic alcohol component was varied using hex-5-en-1-ol as the standard nucleophile. Alkyl-substituted secondary benzylic alcohols reacted to give ethers **47**-**49** in good yields. Importantly, the reaction was completely selective for the crossed-intermolecular substitution process, with no symmetrical ether formation or unwanted elimination to form styrene derivatives observed. The presence of an alkynyl substituent on the secondary carbinol centre did not affect the reactivity, with ether **50** isolated in 83% yield after reaction at 90 °C. Substitution on the aryl ring was also possible, with electron-donating or halogen-substituted 4-methoxy-, 2-methoxy- 4-fluoro- and 4-bromophenyl ethanol well tolerated to form ethers **51**-**54** in high yields. The use of both 3-bromo- and 2-bromophenyl ethanol as electrophiles gave ethers **55** and **56** in 38% and 61% yield, respectively after 48 h at 90 °C. However, the presence of an electron-withdrawing 4-trifluoromethyl substituent gave no reactivity and returned only starting materials. The reaction of primary benzyl alcohol **2** with alkyl alcohols such as methanol or hex-5-en-1-ol under the standard conditions were also unsuccessful, returning only unreacted starting materials.

Table 5. Intermolecular dehydrative crossed etherification.



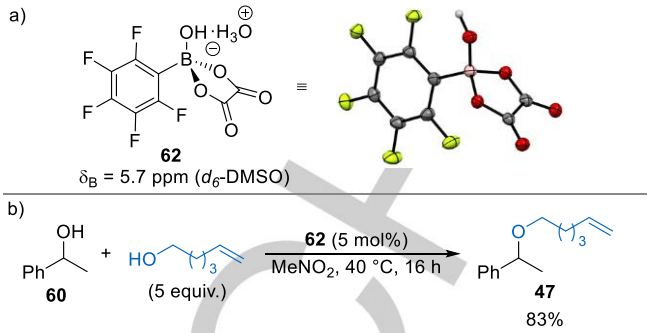
[a] Combined yield. [b] Reaction performed on an 11 mmol scale.

A series of control experiments was performed to investigate the mechanistic pathway and to probe the nature of any catalytic species formed between pentafluorophenylboronic acid **3** and oxalic acid **8**. First, the intermolecular crossed-dehydrative substitution using hex-5-en-1-ol was performed under the standard reaction conditions using both α-vinylbenzyl alcohol **57** and isomeric cinnamyl alcohol **58** (Scheme 2a). In both cases, linear ether product **59** was obtained as a single regioisomer in good yield, consistent with the formation of a common intermediate. Next, the dehydrative substitution protocol was performed using enantiomerically pure (*R*)-1-phenylethan-1-ol **60** and ethyl glycolate (Scheme 2b). Ether product **61** was formed in 87% yield, but with complete erosion of enantiopurity.[21] These experiments are therefore consistent with a catalytic S_N1-type substitution pathway proceeding via a planar carbocation intermediate, and is in line with the proposed mechanisms for aryl boronic acid-catalysed Friedel-Crafts alkylation processes.[11,12]



Scheme 2. Control experiments.

Although the use of pentafluorophenylboronic acid **3** in combination with oxalic acid **8** has been reported for dehydrative Friedel-Crafts reactions,[13,16] the exact nature of the intermediate catalytic species has not previously been studied. A preparative experiment reacting pentafluorophenylboronic acid **3** with oxalic acid **8** (2 equiv.) in $MeNO_2$ at 90 °C followed by removal of the solvent yielded a white powder, from which small crystals could be obtained. X-Ray crystallographic analysis showed the formation of hydrated boronate ester **62** (Scheme 3a),[22,23] with ^{11}B, ^{19}F and $^{13}C\{^1H,^{19}F\}$ NMR spectroscopic analysis in d_6-DMSO consistent with this structure.[19,24] Boronate ester complex **62** is a competent pre-catalyst for the crossed-etherification, forming product **47** in comparable yields to in situ catalyst formation (Scheme 3b). However, boronate ester **62** cannot be unambiguously identified as the active catalytic species in solution, as NMR analysis in d_3-$MeNO_2$ shows the formation of a dynamic equilibrium between at least three species.[19] The same equilibrium is established between a mixture of pentafluorophenylboronic acid **3** and oxalic

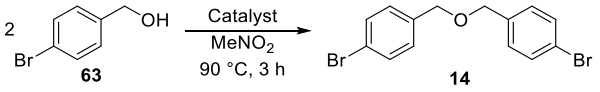


Scheme 3. Nature of the catalytic species.

acid **8** (1:2 **3**/**8**) in d_3-$MeNO_2$, which includes the non-coordinated arylboronic acid **3** (δ_B = 26.8 ppm) and two tetrahedral sp^3-hybridised boron species (δ_B = 7.4 and 5.4 ppm).[25,26] These signals are analogous to the signal observed for **62** in d_6-DMSO (δ_B = 5.7 ppm) and may be the result of different hydrated forms of **62** in solution.[27,28] This is consistent with the increased Lewis acidity of the boron atom upon complexation with oxalic acid resulting in a greater affinity for the both water and the solvent.[29]

Further control experiments were performed to probe whether the active boron species in solution acts as either a Lewis acid or Brønsted acid catalyst. Isolated complex **62** was a competent pre-catalyst for the intermolecular etherification of benzylic alcohol **63**, forming ether **14** is 95% yield after 3 h (Table 6, entry 1). The use of alternative strong Brønsted acids as catalysts resulted in minimal product formation. For example, trifluoroacetic acid (TFA) gave a complex mixture of products after 3 h (Table 6, entry 2), while (+)-camphorsulfonic acid ((+)-CSA) gave no reactivity (Table 6, entry 3). However, the use of 4-toluenesulfonic acid (*p*-TsOH·H_2O) did show some reactivity, giving 36% conversion into ether **14** (Table 6, entry 4). Therefore, while alternative Brønsted acid catalysts show some reactivity,

Table 6. Brønsted acid catalysis control experiments.

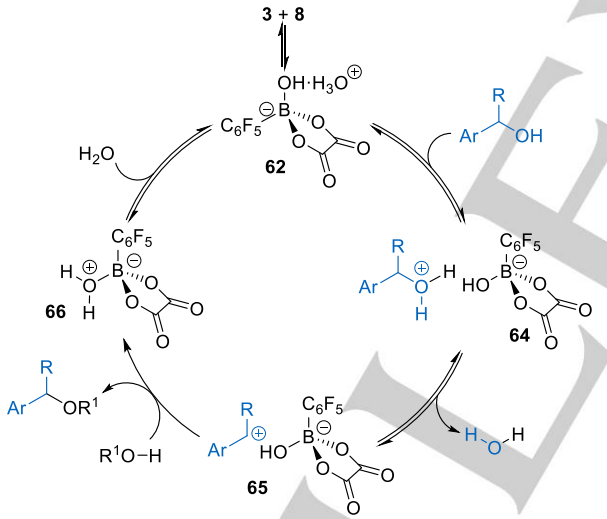


Entry	Catalyst (mol%)	Additive (mol%)	Conv. (%)[a]
1	**62** (5)	–	>98 (95[b])
2	TFA (5)	–	Complex mixture
3	(+)-CSA (5)	–	0
4	*p*-TsOH·H_2O (5)	–	36
5	$C_6F_5B(OH)_2$ **3** (5) $(CO_2H)_2$ **8** (10)	2,6-(*t*-Bu)$_2C_5H_3N$ (5%)	0

[a] Determined by ^1H NMR analysis. [b] Isolated yield

the arylboronic acid catalyst system provides both increased reactivity and selectivity. Performing the reaction under the standard conditions in the presence of sterically demanding 2,6-di-*tert*-butyl pyridine (5 mol%) results in complete inhibition, with no ether product formed within 3 h (Table 6, entry 5). This result suggests that the active aryl boron species formed in solution acts as a Brønsted acid catalyst.

Based upon the above evidence, a possible reaction mechanism for dehydrative nucleophilic substitution using arylboronic acid catalysis is outlined in Scheme 4. A dynamic equilibrium between pentafluorophenylboronic acid **3** and oxalic acid **8** in solution forms complex **62**, which is likely to act as a strong Brønsted acid catalyst. Protonation of a benzylic alcohol forms ion pair **64**, which is sufficiently activated to dissociate into ion pair **65**. Reaction of carbocation **65** with a suitable alcohol nucleophile gives the substitution product, with the released boronate species **66** is likely to be in equilibrium with other hydrated forms in the presence of water.[27] Reversible protonation of the different alcohols rationalise the selectivity in the crossed-etherification processes, with only benzylic alcohols capable of forming a stabilised carbocation for onwards reaction. Although the proposed mechanism is consistent with the observed reaction scope and control experiments, alternative mechanisms involving different boronate intermediates and/or Lewis acid catalysis cannot be unequivocally ruled-out at this stage.



Scheme 4. Plausible reaction mechanism.

Conclusions

Catalytic inter- and intramolecular dehydrative substitution of benzylic alcohols with a second alcohol to form C-O bonds can be achieved using commercially available pentafluorophenylboronic acid **3** (5 mol%) and oxalic acid **8** (10 mol%). The method is applicable to the synthesis of various symmetrical and non-symmetrical ethers, as well as aryl substituted THF and THP derivatives, with the products generally formed in good yields and water formed as the only by-product. Preliminary mechanistic investigations suggest a catalytic S_N1 substitution process is likely to occur. Boronate ester **62**, formed from the reaction of **3** and **8** under the reaction conditions, has been fully characterised and is a competent precatalyst for the reaction. Ongoing studies within our laboratory are aimed at further investigating the scope and mechanism of arylboronic acid-catalysed dehydrative substitution processes.

Experimental Section

General: For general experimental details, characterisation data, and ^{1}H and $^{13}C\{^{1}H\}$ NMR traces for novel compounds, see the Supporting Information.[30]

Representative procedure for intermolecular dehydrative crossed etherification: The required nucleophilic alcohol (5.0 equiv.) was added to a solution of pentafluorophenylboronic acid **3** (5 mol%) and oxalic acid **8** (10 mol%) in $MeNO_2$ (0.05 M) and was stirred at rt for 5 mins. The required benzylic alcohol (1.0 equiv.) was added and the reaction stirred at the stated temperature until complete by TLC analysis. The reaction was cooled to rt, diluted with toluene and concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography.

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Keywords: alcohols • homogeneous catalysis • boronic acids • etherification • substitution

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[24] It is likely that in solution, boronate ester **62** is coordinated with d_6-DMSO in place of H_2O.

[25] In d_3-$MeNO_2$ the three boron-containing species are present in an approximate 7:7:1 ratio at equilibrium, as determined by $^{19}F\{^1H\}$ NMR spectroscopic analysis. The addition of water, which is formed during the etherification process, does not affect the position of equilibrium.

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[29] Attempts to characterise the trigonal complex formed between pentafluorophenyl boronic acid **3** and oxalic acid **8** in non-coordinating solvents such as $CHCl_3$ or CD_2Cl_2 were unsuccessful due poor solubility.

[30] The data underpinning this research can be found at DOI: https://doi.org/10.15125/BATH-00561.

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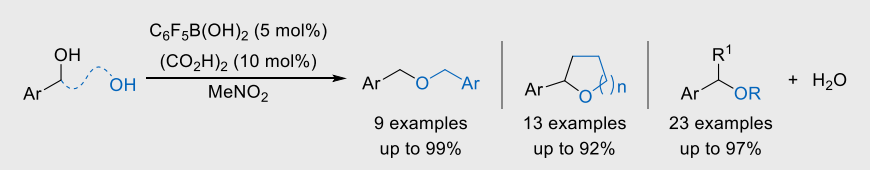

Take some water: Pentafluorophenylboronic acid catalyses the inter- and intramolecular dehydrative substitution of benzylic alcohols with a second alcohol as the nucleophile to form ether products.

*S. Estopiñá-Durán, L. J. Donnelly, E. B. Mclean, B. M. Hockin, A. M. Z. Slawin, J. E. Taylor**

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Aryl Boronic Acid-Catalysed Dehydrative Substitution of Benzylic Alcohols for C-O Bond Formation