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A novel and highly regioselective Cr-mediated route to functionalised quinone boronic ester derivatives

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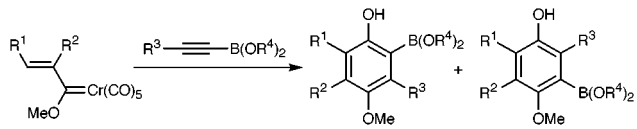
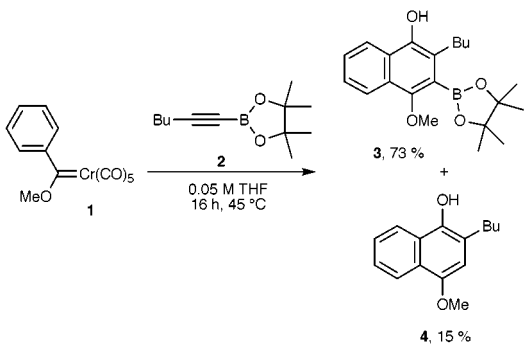
A novel and highly regioselective route to quinone boronic ester derivatives has been developed using a Fischer carbene mediated benzannulation process.

Arylboronic acids and esters represent one of the most heavily utilised classes of synthetic intermediates of recent times.[1] These compounds are typically prepared using alkyllithium or Grignard reagents and a suitable boronic ester or halide. More recently, palladium catalysed coupling of aryl halides with alkoxydiboron[2] or alkoxyborane[3] reagents has provided a mild alternative for conducting this transformation. In an effort to develop an efficient method for the preparation of complex aryl boronic esters, we envisaged a conceptually novel approach to these compounds by the employment of a Dötz annulation reaction[4] of Fischer carbene complexes[5] with alkynylboronates.[6] As illustrated in Scheme 1, this approach would provide a direct technique for the assembly of highly functionalised boronic ester derivatives from simple starting materials. We were mindful that disubstituted alkynes generally undergo insertion with low levels of regioselectivity[7] and therefore our initial goal was to investigate whether arylboronic esters could be prepared in this manner with useful levels of regiocontrol.

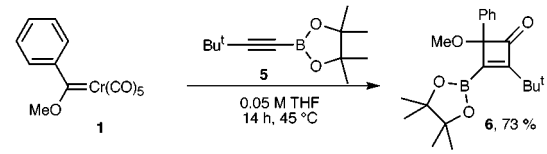


Scheme 1

As shown in Scheme 2, we were pleased to find that complex **1** reacted smoothly with pinacol ester **2** to provide arylboronate **3** in excellent yield, and remarkably, as a single regioisomer. Notably, a minor quantity of deboronated cyclisation product **4** was also produced but was easily separated from **3** by chromatography. The origin of the generation of **4** has not been unambiguously established although it likely arises from protodeboronation of **2** followed by annulation of the terminal alkyne.[8] The regiochemistry of boronate ester **3** was elucidated by X-ray crystallography and shows that the boronate unit is inserted adjacent to the methoxy unit.[9] We also examined the



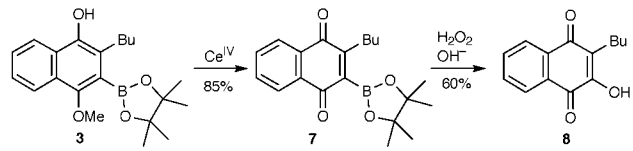
Scheme 2



Scheme 3

scope of the cyclisation process with respect to sterically hindered alkynylboronates (Scheme 3). The employment of *tert*-butyl substituted boronate **5** led only to the formation of cyclobutenone **6**. This result is in accord with Yamashita's observations that bulky electron deficient alkynes provide cyclobutenone products at the expense of benzannulated compounds.[10] Nonetheless, again a single regioisomer was observed and the product displayed an analogous insertion pattern to that outlined in Scheme 2.[9]

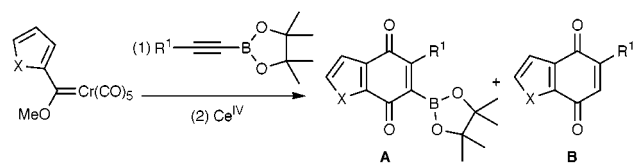
Having developed the technique to access hydroquinone boronic esters we turned our attention to conversion of these compounds to the corresponding quinones. As outlined in Scheme 4, hydroquinone **3** was oxidised smoothly to **7** in good yield with cerium ammonium nitrate in only 30 min at room temperature. *Significantly, these quinones represent a novel class of boronic esters and are a potentially valuable source of a range of quinone containing medicinally important agents.*[11] Whilst a thorough investigation of the functionalisation of the carbon–boron bond must await future studies, we have found that **7** is readily further oxidised to hydroxyquinone **8** through treatment with basic H_2O_2 for 20–30 min.



Scheme 4

In general, direct oxidation of the crude reaction mixture after benzannulation provided a simple and routine method for the isolation of quinone boronic ester compounds (Scheme 5). We briefly investigated the scope of this technique with respect to alkynylboronates and Fischer carbene complexes, as shown in Table 1.

Initial screening showed the reaction to be efficient in both polar and non-polar solvents. However, THF gave consistently higher yields of boronate esters. We attempted to promote the reaction by the employment of dry state conditions (Table 1, entry 3).[12] Unfortunately, adsorption onto silica gel served only

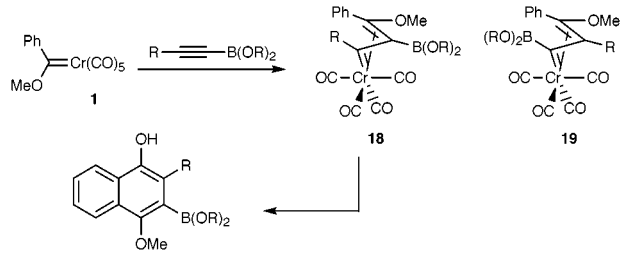


Scheme 5

Table 1 Benzannulation reaction of alkynylboronates and Fischer carbene complexes (see Scheme 5)

Entry	X	R^1	Conditions[a]	Product **A**	Yield (%)	Product **B**	Yield (%)
1	CH=CH **1**	Bu **2**	THF, 45 °C	**7**	66	**9**	6
2	CH=CH **1**	Bu **2**	Hexane, 45 °C	**7**	62	**9**	35
3	CH=CH **1**	Bu **2**	SiO_2, 45 °C	**7**	0	**9**	84
4	O **10**	Bu **2**	THF, 65 °C	**11**	47	**12**	30
5	CH=CH **1**	Ph **13**	THF, 45 °C	**14**	57	**15**	12
6	O **10**	Ph **13**	THF, 65 °C	16	35	**17**	42

[a] Reaction conditions: (1) 0.05 M solution of complex and 3 equiv. of alkyne heated for 14–16 h under inert atmosphere. (2) Crude reaction mixture dissolved in Et_2O and stirred for 0.5 h with 0.5 M Ce^{IV} in 0.1 M aq. HNO_3.



Scheme 6

to provide quinone **9**, albeit in high yield. The reaction was found to be readily extended to furan complex **10**, although higher temperatures and longer reaction times were generally required for complete conversion and resulted in the recovery of larger quantities of deboronated products (entries 4 and 6, Table 1). Nonetheless, these quinones were again isolated as single regioisomers.[13]

The origin of the high preference of insertion of the boronate group in the more hindered position adjacent to the MeO group is not clear at this time, however we are currently investigating three possible rationales. The insertion may simply be sterically controlled and therefore follows traditional insertion patterns where the boronate unit acts as the sterically less demanding group.[14] Alternatively, Hofmann has proposed that η^3-vinylcarbene complex intermediates are responsible for controlling regiochemical insertion patterns.[15] Therefore, **19** may be energetically disfavoured due to the positioning of the electron withdrawing boronate unit adjacent to the electrophilic carbene carbon atom (Scheme 6). Finally, a model proposed by Wulff to explain the contrasteric insertion of alkynylstannanes in the benzannulation process may be invoked whereby the regiochemistry is controlled by a Lewis acid/base interaction [CO→B(OR)$_2$] in the metallohexatriene intermediate **18**, thus directing regiochemical insertion.[16]

In conclusion, this study provides a rapid and efficient approach to a novel class of hydroquinone and quinone boronate esters.[17] Additionally, the boron unit is incorporated into these structures in a reliable and predictable fashion, and with excellent selectivity. Studies on the origin of regioselectivity are currently underway as are the employment of these intermediates in transition metal catalysed C–C coupling reactions.

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Notes and references

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8 Alkynylboronates are readily hydrolysed to the parent alkyne in the presence of protic reagents, (ref. 6), it is therefore plausible that the phenolic benzannulated product mediates alkyne protodeboronation. Indeed, hex-1-yne was recovered in the volatile material isolated from the reaction mixture in Table1, entry 1.
9 *Crystal data* for **3**: $C_{21}H_{29}BO_4$, M = 356.25, triclinic, a = 9.4916(6), b = 11.1685(8), c = 18.9638(13) Å, α = 90.1890(10), β = 91.2770(10), γ = 92.5080(10)°, U = 2007.9(2) Å^3, Z = 4, D_c = 1.179 g cm^{-3}, space group $P\bar{1}$ (no. 2), T = 150 K, Mo-Kα radiation (λ = 0.71073 Å), μ(Mo-Kα) = 0.079 mm^{-1}, F(000) = 768. Data were collected in the range 1.83 < θ < 28.36°, 5420 independent reflections (R_{int} = 0.0549), final R = 0.0778, with allowance for the thermal anisotropy of all non-hydrogen atoms. For **6**: $C_{21}H_{29}BO_4$, M = 356.25, monoclinic, a = 8.845(2), b = 19.493(5), c = 12.055(3) Å, β = 103.804(6)°, U = 2018.5(10) Å^3, Z = 4, D_c = 1.172 g cm^{-3}, space group $P2_1/n$ (a non-standard setting of $P2_1/c$, no. 14), T = 150 K, Mo-Kα radiation (λ = 0.71073 Å), μ(Mo-Kα) = 0.079 mm^{-1}, F(000) = 768. Data were collected in the range 2.03 < θ < 28.31°, 1895 independent reflections (R_{in} = 0.0932), final R = 0.0618, with allowance for the thermal anisotropy of all non-hydrogen atoms. CCDC 182/1418.
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13 The rigorous establishment of compounds **11** and **16** is ongoing but at present is assumed to follow the same insertion patterns as outlined in Scheme 4.
14 The *A* value of the alkynyl substituent can often serve as a useful guide to predicting regioselectivity (ref. 10). In this context, studies are underway to determine the *A* value of a range of boronic ester moieties and will be the subject of a future disclosure.
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17 Typical experimental procedure as exemplified by benzannulation of complex **1** and alkyne **2** (Scheme 2): to a solution of **1** (102 mg, 0.327 mmol) in THF (6.4 ml) was added alkyne **2** (204 mg, 0.980 mmol) *via* syringe under nitrogen. The reaction mixture was stirred at 45 °C for 14 h and concentrated by rotary evaporation. Purification of the resulting residue by silica gel chromatography provided hydroquinone **4** (ref. 18) (11 mg, 15%) and boronate ester **3** (85 mg, 73%) which could be crystallised from hexanes to provide an amber solid, mp 116–116.5 °C.; δ_H (250 MHz, $CDCl_3$)0.96 (3H, t, J 7.3, CH_3CH$_2$), 1.42 (12H, s, CH_3), 1.47–1.72 (4H, m, CH$_2$CH_2CH$_3$), 2.73 (2H, app t, J 7.9, C=CCH_2), 3.91 (3H, s, CH_3O), 4.93 (1H, br s, O*H*), 7.39–7.53 (2H, m, Ar-*H*) 7.95–8.03 (1H, m, Ar-*H*), 8.05–8.13 (1H, m, Ar-*H*); δ_C (62.9 MHz, $CDCl_3$) 14.1, 24.7, 24.9, 30.2, 33.0, 63.5, 84.0, 121.6, 122.0, 124.3, 125.2, 125.9, 126.6, 144.4, 153.9; ν_{max}/cm^{-1} 3445 (br), 2991 (m), 2977 (m), 1662 (m), 1142 (s) (calc. for $C_{21}H_{29}BO_4$: C, 70.80; H, 8.20. Found: C, 70.67; H, 8.36%).
18 ^{13}C and ^{1}H spectra of **4** were identical to an authentic sample prepared from hex-1-yne: A. Yamashita, S. Ayako, R. G. Schaub, M. K. Bach, G. J. White and A. Toy, *J. Med. Chem.*, 1990, **33**, 775.

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