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A Nickel-Catalyzed Benzannulation Approach to Aromatic Boronic Esters**

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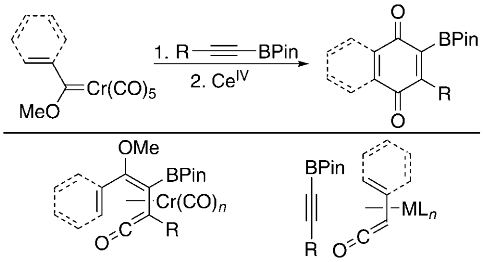
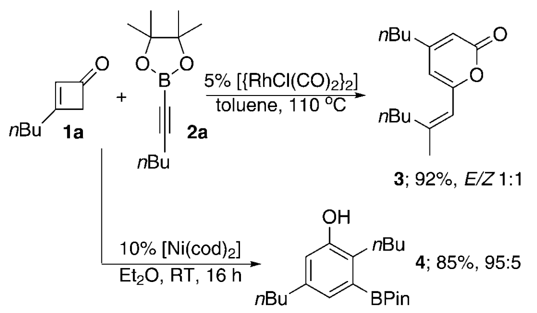
Benzannulation reactions are one of the most efficient and direct methods for assembling highly substituted aromatic compounds.[1] Nonetheless, this strategy provides a number of considerable challenges that relate to chemoselectivity and regioselectivity. With regard to exploiting such reactions for the production of synthetically useful organic compounds, aromatic boronic acids represent an important target as they are widely acknowledged as being amongst the most useful and versatile intermediates in synthetic chemistry.[2] Indeed, such compounds have been accessed by benzannulation techniques involving transition metal catalysis[3] and pericyclic[4] processes.

Our preliminary work in this area showed that the Dötz benzannulation reaction could be exploited to access quinone boronic esters in good yield and with excellent levels of regiocontrol.[5] As quinone boronic acids can serve as precursors to bioactive quinones,[6] and have recently emerged as useful substrates for regio- and stereocontrolled Diels–Alder reactions,[7] this technique held some significant synthetic potential. However, drawbacks associated with the requirement for a stoichiometric organochromium reagent in the Dötz benzannulation reaction prompted us to search for a transition metal catalyzed approach.

As outlined in Scheme 1, the Cr-mediated benzannulation reaction can be envisaged to be a Cr-templated ketene electrocyclization. We considered a metal-templated vinylketene [4+2] cycloaddition to be an alternative strategy to oxygenated aromatic boronic ester systems. Indeed, such processes are known and exploit readily available cyclobutenones as the vinylketene precursors. Specifically, Liebeskind et al. have carried out detailed studies into metal-mediated vinylketene formation and reactivity.[8] Moreover, the same group showed that Ni catalysis can mediate the reaction of cyclobutenones with alkynes to provide phenols.[9] In addition, Kondo, Mitsudo et al. have employed Rh and Ru catalysts to promote the cycloaddition of cyclobutenones with strained alkenes.[10] Danheiser has employed a tandem [2+2] cycloaddition–electrocyclic ring closure as a transition metal-free approach to highly substituted phenols.[11] Given that alkynylboronates are known to undergo transmetalation reactions with group 7 and 8 transition metal complexes,[12] we began our studies by investigating the potential for chemoselective cycloaddition of these substrates using Rh and Ni catalysts. As outlined in Scheme 2, while the Rh-mediated reaction of **1a** and **2a** delivered only the 2-pyrone **3** derived from cyclobutenone dimerization, $[Ni(cod)_2]$ (cod = cyclooctadiene) promoted a smooth benzannulation reaction at room temperature to provide the phenol **4** in high yield, and with excellent regioselectivity. This remarkable selectivity was unexpected as unsymmetrical alkynes typically undergo cycloaddition with only modest levels of regiocontrol (< 3:1).[9] With this exciting preliminary observation in hand, we decided to explore the scope of this Ni-catalyzed process and our results are depicted in Table 1.



Scheme 1. Metal-templated benzannulation. Pin = pinacol.



Scheme 2. Preliminary catalyst screening.

We carried out the cycloaddition of cyclobutenone **1a** with alkynes bearing a selection of substituents. Specifically, we found that the trimethylsilyl alkynylboronate **2b** underwent cycloaddition to give the corresponding phenol **5a** in excellent yield, and once again as a single regioisomer (Table 1, entry 1). Surprisingly, the corresponding phenylalkyne **2c** showed a drastic reduction in regioselectivity, moreover, the isomer bearing the boronate in the *ortho*-position to the phenol **6b** was now favored (entry 2).

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[*] A.-L. Auvinet, Prof. J. P. A. Harrity
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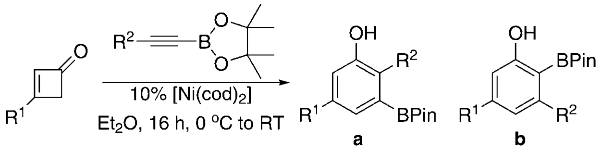
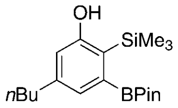
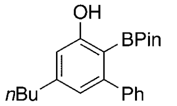
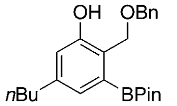
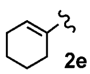
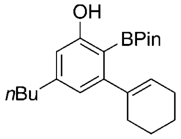
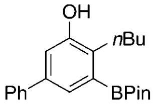
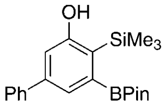
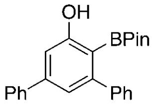
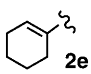
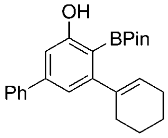
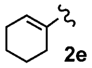
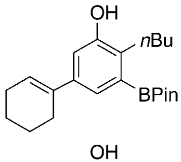
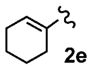
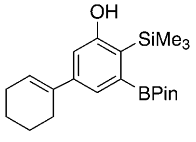
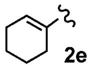
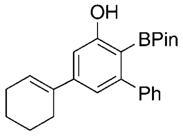
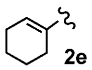
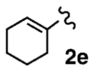
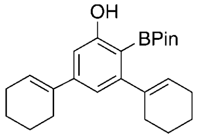
Table 1: Nickel-catalyzed aromatic boronic ester synthesis.

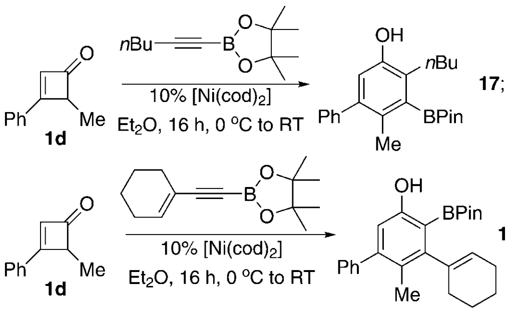


No.	R^1	R^2	Phenol[a]		Yield (**a**/**b**)
1	*n*Bu, **1a**	Me_3Si, **2b**		**5**	81% (>98:2)
2	*n*Bu, **1a**	Ph, **2c**		**6**	76% (33:67)
3	*n*Bu, **1a**	CH_2OBn, **2d**		**7**	48% (93:7)
4	*n*Bu, **1a**	 **2e**		**8**	79% (15:85)
5	Ph, **1b**	*n*Bu, **2a**		**9**	54% (85:15)
6	Ph, **1b**	Me_3Si, **2b**		**10**	75% (>98:2)
7	Ph, **1b**	Ph, **2c**		**11**	67% (44:56)
8	Ph, **1b**	 **2e**		**12**	67% (33:67)
9	 **2e**	*n*Bu, **2a**		**13**	92% (>98:2)
10	 **2e**	Me_3Si, **2b**		**14**	59% (>98:2)
11	 **2e**	Ph, **2c**		**15**	63% (44:56)
12	 **2e**	 **2e**		**16**	61% (31:69)

[a] Major isomer shown. Bn = benzyl.

Propargyl ether **2d** underwent insertion to favor **7a**, albeit in modest yield (entry 3) whereas the 1-cyclohexenyl-substituted alkyne **2e** exhibited a similar regiochemical preference as the Ph-substituted alkyne **2c** (entry 4). Extending the study to include other 3-substituted cyclobutenones provided a more complete picture of the regiochemical trends; alkynylboronates bearing sp^3-based substituents showed high selectivities (5:1 to >98:2) for regioisomer **a**, whereas those bearing sp^2-based substituents generally showed more modest levels of regiocontrol, largely favoring isomer **b**.[13]

We next explored the cycloaddition of more heavily substituted cyclobutenones in an effort to access more heavily substituted aromatic products. In addition, we were interested in how incorporating susbtituents adjacent to the carbonyl would modulate the selectivities in comparison with the 3-substituted cyclobutentones depicted in Table 1. In the event, incorporating a methyl group at C4 resulted in the formation of highly substituted phenols **17** and **18** in good yield, with improved regioselectivities (in comparison to the reaction of **1b**) being observed in both cases (Scheme 3).



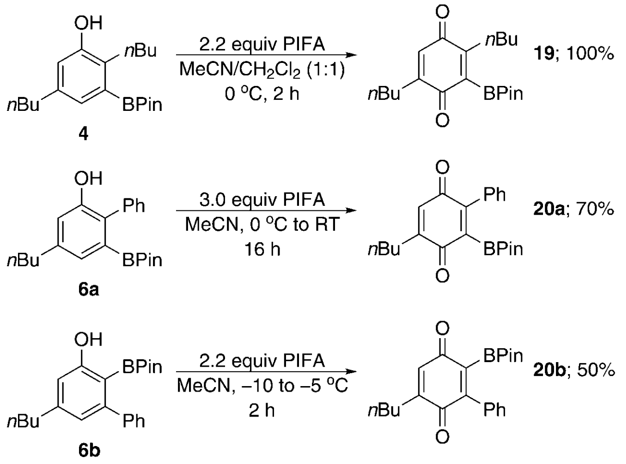
17; 68%, >98:2

18; 57%, 80:20

Scheme 3. Cycloaddition of C4-substituted cyclobutenone **1d**.

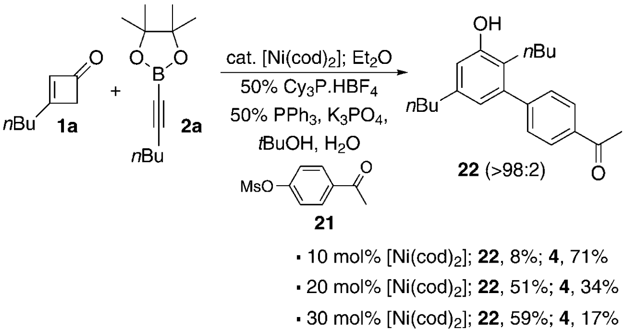
With regard to functionalization of the aromatic boronic ester cycloadducts, we were cognizant of the fact that we began this study to address some limitations in our Cr-mediated approach to quinone boronic esters, where a stoichiometric quantity of Fischer carbene complex is required. Moreover, employing the Dötz reaction for the synthesis of monocyclic quinones is challenging because of the relative instabilities of substrate vinylcarbene complexes. We therefore set out to explore whether the Ni-catalyzed cycloaddition could be appropriate for the synthesis of quinone boronic acids and our results are summarized in Scheme 4. To our delight, phenol **4** was smoothly oxidized by PIFA[14] within 2 h to provide the corresponding quinone **19** in quantitative yield. The chemistry was further employed on regioisomers **6a** and **6b**; the former compound also underwent oxidation in high yield whereas the latter phenol gave a lower yielding reaction due to the surprising instability of quinone **20b**.[15]

The Ni-catalyzed alkyne cycloaddition outlined above critically depends on obviating organoboron to organonickel transmetalation during the benzannulation process (either at the alkyne or phenol stage). We speculated, however, that upon addition of base to this reaction mixture, the products would be activated towards Ni-catalyzed cross-coupling



Scheme 4. PIFA: phenyliodine bis(trifluoroacetate).

thereby offering an intriguing opportunity to develop a one-pot cycloaddition–coupling protocol, whereby a single transition metal catalyst would perform two different C−C bond-forming transformations. Our studies towards this end are summarized in Scheme 5. Optimization of the Ni-catalyzed cross-coupling of boronic ester **4** using the detailed studies of Percec et al.[16] as a basis highlighted PCy_3/PPh_3 as a suitable ligand combination, and so we decided to employ these conditions in the one-pot reaction. Accordingly, carrying out the cycloaddition with 10 mol% Ni catalyst followed by addition of P ligands, base, and mesylate **21** to the reaction mixture resulted in formation of **22** in poor yield. We noted, however, that the reaction mixture contained a significant amount of boronate cycloadduct **4**, suggesting that the Ni catalyst had decomposed during the benzannulation reaction. Indeed, increasing the initial loading of the Ni catalyst resulted in improved conversion to the biaryl product. These results demonstrate that a single Ni catalyst can perform sequential catalytic processes in a single vessel, and studies are underway to identify a more efficient catalyst system.[17]



Scheme 5. One-pot Ni-catalyzed cycloaddition and cross-coupling.

In conclusion, we have found that alkynylboronates participate in remarkably regioselective benzannulation reactions with cyclobutenones at room temperature in the presence of a Ni catalyst. This chemistry offers a versatile and catalytic route to quinone boronic esters, as well as the opportunity to carry out benzannulations and cross-coupling reactions in one-pot with a single Ni pre-catalyst.

Experimental Section

Typical cycloaddition procedure, as exemplified by the formation of **4**: A flame-dried Schlenk tube was charged with 3-*n*-butylcyclobutenone **1a** (50.0 mg, 0.40 mmol) and *n*-butylalkynylboronate **2a** (167.6 mg, 0.80 mmol) in anhydrous diethyl ether (1 mL) under an argon atmosphere. The mixture was cooled to 0 °C before addition of $[Ni(cod)_2]$ (5 mg, 0.02 mmol, 5 mol%). The mixture was stirred at 0 °C for 1.5 h and another portion of $[Ni(cod)_2]$ (5 mg, 0.02 mmol, 5 mol%) was added before being allowed to reach room temperature and stirred overnight. The reaction mixture was filtered through a pad of silica gel and the volatiles were removed in vacuo. The crude mixture was purified by flash chromatography over silica gel, eluting with pentane/EtOAc (95:5) to provide the desired compound as an oil. Recrystallization from petrol provided the product as a colorless crystalline solid (113.7 mg, 85%, 95:5). M.p. 81–83 °C; 1H NMR (400 MHz, $CDCl_3$): $\delta = 0.91–0.98$ (6H, m), 1.34–1.64 (20H, m), 2.52–2.56 (2H, m), 2.87–2.91 (2H, m), 4.68 (1H, br), 6.73 (1H, d, $J = 1.5$ Hz), 7.19 ppm (1H, d, $J = 1.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 14.0, 22.5, 23.1, 24.8, 27.9, 33.6, 33.7, 35.1, 83.4, 118.0, 128.5, 132.0, 141.1, 153.1 ppm; FTIR: 3412 (br), 2957 (s), 2930 (s), 2859 (m), 1608 (w), 1580 (w), 1424 (m), 1369 (s), 1144 cm^{-1} (s); HRMS calcd for $C_{20}H_{34}BO_3$: m/z 333.2601, found 333.2595.

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Keywords: alkynylboronates · boronic esters · cycloadditions · cyclobutenones · quinones

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[13] The product regiochemistry can be directly assigned by inspection of the phenolic OH resonance by ^{1}H NMR spectroscopy. Regioisomer **a** shows a broad signal at 5 ppm whereas the signal is shifted to 8 ppm in regioisomer **b** due to hydrogen-bonding to the adjacent boronate. The regiochemistry of compound **4** was also confirmed by X-ray crystallography. See Supporting Information for details.

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[15] It was not possible to rule out the assignment of compounds **19** and **20** as *ortho*-quinones, hence the *para*-quinone assignment is tentative. Nonetheless, this assignment is based on the propensity of sterically hindered I^{III} oxidants to generate the *para*-isomers: R. M. Moriarty, O. Prakash, *Org. React.* **2001**, *57*, 327.

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[17] The cross-coupling of boronate **4** with **21** using 20% [Ni(cod)$_2$] and 40% PCy$_3$ resulted in a 76% yield of **22**.