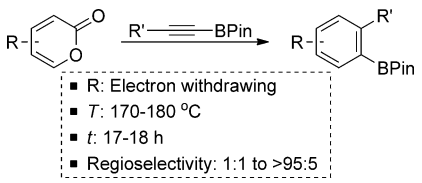
Cycloaddition

DOI: 10.1002/anie.201200917

A Mild Benzannulation through Directed Cycloaddition Reactions**

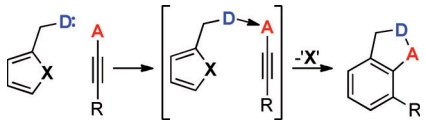
*James D. Kirkham, Roger J. Butlin, and Joseph P. A. Harrity**

The synthesis and study of aromatic compounds is a fundamental endeavor in organic chemistry. With regard to benzene, classical synthesis methods have been dominated by electrophilic and nucleophilic aromatic substitution processes, whereas ring synthesis has largely been the domain of heteroaromatic chemistry. However, ring synthesis has the advantage that it is not limited to specific substitution patterns dictated by pre-existing directing groups. For this reason, the use of cycloaddition strategies for the assembly of aromatic rings is of significance.[1] Studies conducted in our group in this area have placed a particular emphasis on incorporating boronic ester functionality.[2] Whilst some catalytic variants have emerged recently,[3] a significant drawback of this chemistry to date has been the requirement of high temperatures and long reaction times. For example, as outlined in Scheme 1, the cycloaddition of 2-pyrones and alkynylboronates requires harsh reaction conditions, is restricted to electron-deficient substrates, and provides products with variable levels of regiocontrol.[4]



Scheme 1. Alkynylboronate cycloadditions of 2-pyrones. Pin = pinacol.

In an effort to uncover milder methods of benzannulation, we have recently become interested in the use of directed cycloadditions for the mild and regiocontrolled synthesis of aromatic compounds. Central to our design was the use of an alkyne bearing a Lewis acid acceptor which would promote pre-association with a diene bearing a complementary Lewis base (Scheme 2). The resulting complex would provide a platform for rate enhancements in the ensuing cycloaddition.[5] Our preliminary studies indicated that this could be successful for highly activated dienes such as tetrazines,[6]

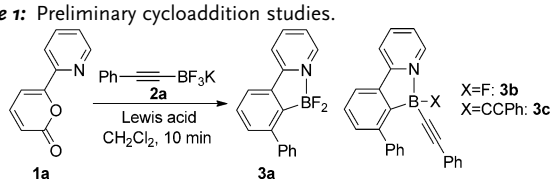


Scheme 2. Concept of directed cycloaddition.

although this chemistry was limited with respect to the scope of products that could be prepared. 2-Pyrones represented a more challenging class of substrates as their cycloadditions with alkynes generally require very high reaction temperatures (typically $>140\,^{\circ}C$) and long reaction times.[7] Moreover, such processes are often poorly regioselective and are relatively low yielding.[8] We report herein the successful implementation of this concept for the mild and regiospecific formation of 1,2,3-trisubstituted benzenes.[9,10]

We began our studies by investigating the cycloaddition of 2-pyrone **1a** with in situ generated phenylethynyldifluoroborane,[11] and our initial results were very encouraging. Significant conversion of **1a** was observed within 10 minutes at room temperature when reacted with the difluoroborane derived from the combination of trifluoroborate **2a** and TMSCl (Table 1, entry 1). Analysis of the reaction mixture confirmed

Table 1: Preliminary cycloaddition studies.



Entry[a]	Lewis acid	T [°C]	**3a** Yield [%][b]	**3b** Yield [%][b]	**3c** Yield [%][b]
1	TMSCl	25	12	8	50
2	$BF_3{\cdot}OEt_2$	25	75	10	10
3	$BF_3{\cdot}OEt_2$	0	40	21	20
4	$BF_3{\cdot}OEt_2$	40	82	5	5
5[c]	$BF_3{\cdot}OEt_2$	40	62	–	–

[a] Used 3 equiv of alkyne and Lewis acid. [b] Yield of isolated product. [c] Used 1 equiv of alkyne and Lewis acid. TMS = trimethylsilyl.

that cycloaddition had indeed taken place under these remarkably mild reaction conditions, however, disappointingly a mixture of alkynylated and fluorinated borane products, **3a–c**, was observed. Interestingly, switching the Lewis acid provided a better selectivity for the difluoroborane, and provided an excellent overall conversion (entry 2). Reducing the reaction temperature again provided a mixture, but warming the reaction to 40 °C provided good selectivity for the difluoroborane (entries 3 and 4). Finally, we found that the reaction could be conducted under similarly mild reaction

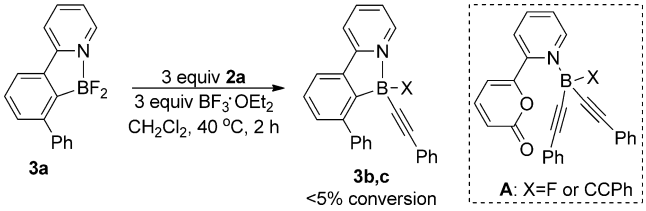
[*] J. D. Kirkham, Prof. J. P. A. Harrity
Department of Chemistry, University of Sheffield
Sheffield, S3 7HF (UK)
E-mail: j.harrity@sheffield.ac.uk
Dr. R. J. Butlin
Research and Development, AstraZeneca
Alderley Park, Macclesfield, SK10 4TG (UK)

[**] The authors are grateful to the EPSRC and AstraZeneca for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201200917.

conditions with stoichiometric quantities of alkyne, but a lower conversion was obtained (entry 5).

The formation of alkynylated by-products **3b,c** was unexpected and intriguing, and our preliminary rationale was envisaged on the basis of disproportionation of **3a** with the alkynyldifluoroborane present in solution. However, exposing a pure sample of **3a** to in situ generated alkynyldifluoroborane resulted in less than 5% conversion (as judged by 400 MHz ^{1}H NMR spectroscopy), thus suggesting that **3b**,**c** do not originate from the aryl difluoroborane **3a** itself (Scheme 3). Alternatively, disproportionation of alkynyldifluoroboranes to trialkynylboranes may be promoted by pyridine.[12,13] We therefore postulate that alkynylated products **3b**,**c** are formed from cycloaddition of intermediates such as **A**. This process would be competitive when cycloaddition is slow, and may well explain the reaction temperature/product distribution trends highlighted in Table 1.

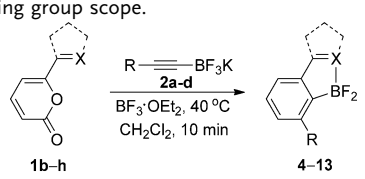


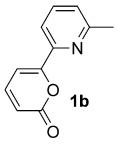
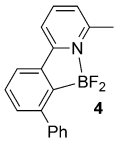
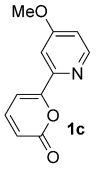
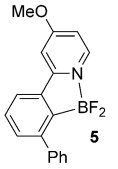
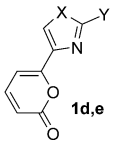
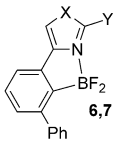
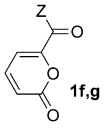
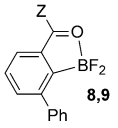
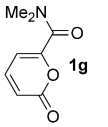
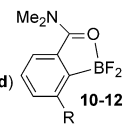
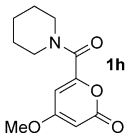
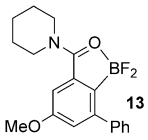
Scheme 3. Probing alkynylborane formation.

Having optimized the cycloaddition for the formation of difluoroborane complexes,[14] we turned our attention to exploring the scope of the reaction with regard to alternative directing groups; our results are shown in Table 2. We were pleased to discover that the chemistry could be extended to other pyridine-substituted pyrones (entries 1 and 2) as well as azole heterocycles (entries 3 and 4). In an effort to employ more synthetically versatile functionality, we employed the ester-substituted pyrone **1f**, but were disappointed to find that the cycloaddition failed in this case (entry 5). The low reactivity of **1f** provides additional evidence for a directing group promoted reaction, as this very electron-deficient pyrone would be expected to be more reactive than the dienes **1a–e** in inverse electron demand cycloadditions. In contrast to **1f**, the corresponding amide in **1g** was found to be a very effective directing group, thus providing the aromatic borane **9** in high yield (entry 6). The amide directing group is generally very effective and we highlighted the scope of this specific substrate in the rapid cycloaddition of a small series of alkynes (entries 7–9). Moreover, the amide-directed reaction can be extended to include pyrone substrates bearing electron-donating substituents which would be expected to retard the cycloaddition process (entry 10).

The potential of these complexes to undergo additional organic synthesis was next explored and we subjected compound **9** to a selection of representative organoboron transformations. Specifically, as highlighted in Scheme 4, oxidation to the corresponding phenol **14**, cross-coupling to biaryl product **15**, and conversion into the azido product **16** all proceeded smoothly under standard reaction conditions to give the appropriate products in good yield.

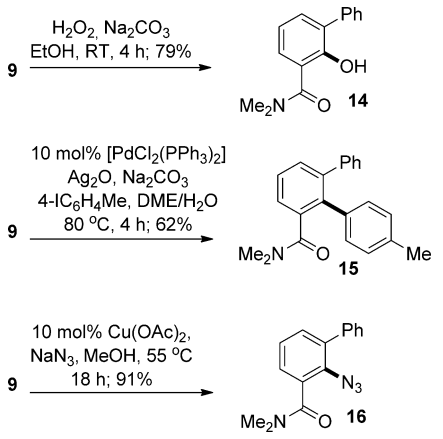
Table 2: Directing group scope.



Entry[a]	Pyrone	R	Product	Yield[b]
1	 **1b**	Ph (**2a**)	 **4**	82%
2	 **1c**	Ph (**2a**)	 **5**	70%
3	 **1d,e**	Ph (**2a**)	 **6,7**	X=S, Y=H; 74% (**6**)
4		Ph (**2a**)		X=O, Y=Me; 67% (**7**)
5	 **1f,g**	Ph (**2a**)	 **8,9**	Z=OMe; 0% (**8**)
6		Ph (**2a**)		Z=NMe$_2$; 92% (**9**)
7	 **1g**	Bu (**2b**)	 **10-12**	R=Bu; 65% (**10**)
8		SiMe$_3$ (**2c**)		R=SiMe$_3$; 70% (**11**)
9		1-cyclohexenyl (**2d**)		R=1-cyclohexenyl; 93% (**12**)
10	 **1h**	Ph (**2a**)	 **13**	54%

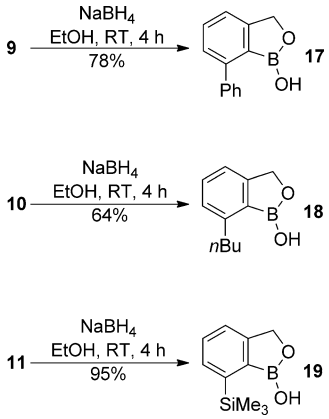
[a] The reactions were conducted using 3 equiv of alkyne and 3 equiv of $BF_3.OEt_2$ at 40°C over a period of 10 min. [b] Yield of isolated product.

The products highlighted in Table 2 that are generated by this methodology can be considered to be stable Lewis acid activated electrophiles. This classification suggests the intriguing possibility that different reactivity profiles might be uncovered at these positions. In the context of the present study, we were particularly interested in the amides present in compounds **9**–**12**. Specifically, amides are typically unreactive towards reduction by mild hydride sources unless activated by external Lewis acids,[15] so this transformation appeared to be ideal for establishing the activating effects of the $ArBF_2$ moiety. Indeed, treatment of **9** with sodium borohydride did result in reduction of the carbonyl group (**17**; Scheme 5). To



Scheme 4. Representative reactions of compound **9**. DME = 1,2-dimethoxyethane.

our delight, this transformation provided direct formation of the corresponding benzoxaboroles. Benzoxaboroles are an exciting class of organoboron compounds which have recently emerged as potential therapeutic targets because of their



Scheme 5. Synthesis of benzoxaboroles.

excellent physiochemical and biological properties.[16] As shown in Scheme 5, this present method represents a new approach to these compounds that facilitates the introduction of substituents adjacent to boron on the benzene ring (**17**–**19**).

In conclusion, we report a substrate-directed alkyne/2-pyrone [4+2] process that exhibits significant rate enhancements over traditional thermal techniques (typically > 140 °C, > 16 h to 40 °C, 10 min). Moreover, the directing groups can be synthetically useful motifs such as pyridines, azoles, or amides. As well as providing a mild method for benzene ring synthesis, the products have been shown to be amenable to additional functionalization through C–O, C–C, and C–N bond-forming reactions, and represent new precursors to benzoxaboroles, a class of organic boron compounds receiving significant attention as new small-molecule therapeutics.

Experimental Section

Typical cycloaddition procedure, as exemplified by the formation of **3a**: $BF_3.OEt_2$ (0.22 mL, 1.71 mmol) was added dropwise to pyran-2-one **1a** (98 mg, 0.57 mmol), and potassium alkynyltrifluoroborate **2a** (356 mg, 1.71 mmol) in dichloromethane (5 mL) at 40 °C over a period of 5 min under nitrogen. The resulting solution was stirred at 40 °C for 10 min. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL), and washed with saturated aqueous sodium bicarbonate (20 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the crude product was purified by flash silica chromatography (elution gradient 10 to 100 % ethyl acetate in petrol) to provide **3a** as a colorless solid: (128 mg, 82 %). Mp 196–198 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.33$–7.57 (5 H, m), 7.63 (1 H, dd, $J = 1.0$, 7.5 Hz), 7.74 (1 H, dd, $J = 0.5$, 7.0 Hz), 7.85 (2 H, m), 7.95 (1 H, d, $J = 8.0$ Hz), 8.14 (1 H, dt, $J = 1.5$, 8.0 Hz), 8.54 ppm (1 H, d, $J = 5.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 118.0$, 120.5, 123.5, 127.5, 128.5 (×2), 129.5, 132.5, 137.0, 141.5, 142.0, 143.5, 146.0, 156.0 ppm; ^{19}F NMR (235 MHz, $CDCl_3$): $\delta = -155.7$ ppm; FTIR: $\tilde{\nu} = 2922$ (w), 1623 (m), 1076 (s), 766 cm^{-1} (s). HRMS calculated for $C_{17}H_{12}BF_2N$ (ES +): m/z 280.1109, found: 280.1097.

Received: February 2, 2012
Published online: May 16, 2012

Keywords: boron · cross-coupling · cycloaddition · heterocycles · synthetic methods

[1] For recent reviews, see: a) S. Saito, Y. Yao, *Chem. Rev.* **2000**, *100*, 2901; b) M. Rubin, A. W. Sromek, V. Gevorgyan, *Synlett* **2003**, 2265; c) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095.

[2] a) J. E. Moore, M. W. Davies, K. M. Goodenough, R. A. J. Wybrow, M. York, C. N. Johnson, J. P. A. Harrity, *Tetrahedron* **2005**, *61*, 6707; b) M. D. Helm, J. E. Moore, A. Plant, J. P. A. Harrity, *Angew. Chem.* **2005**, *117*, 3957; *Angew. Chem. Int. Ed.* **2005**, *44*, 3889; c) J. E. Moore, M. York, J. P. A. Harrity, *Synlett* **2005**, 860; d) P. M. Delaney, J. E. Moore, J. P. A. Harrity, *Chem. Commun.* **2006**, 3323; e) D. L. Browne, J. F. Vivat, A. Plant, E. Gomez-Bengoa, J. P. A. Harrity, *J. Am. Chem. Soc.* **2009**, *131*, 7762; f) J. Huang, S. J. F. Macdonald, J. P. A. Harrity, *Chem. Commun.* **2009**, 436.

[3] a) V. Gandon, D. Leboeuf, S. Amslinger, K. P. C. Vollhardt, M. Malacria, C. Aubert, *Angew. Chem.* **2005**, *117*, 7276; *Angew. Chem. Int. Ed.* **2005**, *44*, 7114; b) G. Hilt, K. I. Smolko, *Angew. Chem.* **2003**, *115*, 2901; *Angew. Chem. Int. Ed.* **2003**, *42*, 2795; c) Y. Yamamoto, J.-i. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2004**, *126*, 3712; d) A.-L. Auvinet, J. P. A. Harrity, G. Hilt, *J. Org. Chem.* **2010**, *75*, 3893; e) A.-L. Auvinet, J. P. A. Harrity, *Angew. Chem.* **2011**, *123*, 2821; *Angew. Chem. Int. Ed.* **2011**, *50*, 2769.

[4] P. M. Delaney, D. L. Browne, H. Adams, A. Plant, J. P. A. Harrity, *Tetrahedron* **2008**, *64*, 866.

[5] For a review of substrate directed reactions, see: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307.

[6] J. F. Vivat, H. Adams, J. P. A. Harrity, *Org. Lett.* **2010**, *12*, 160.

[7] K. Afarinkia, T. D. Nelson, M. V. Vinader, G. H. Posner, *Tetrahedron* **1992**, *48*, 9111.

[8] A. Reed, C. Schilling, R. Tarvin, T. Rettig, J. Stille, *J. Org. Chem.* **1969**, *34*, 2188.

[9] For early studies on boron-tethered intramolecular Diels–Alder cycloadditions of 2-pyrones, see: K. Narasaka, S. Shimada, K. Osoda, N. Iwasawa, *Synthesis* **1991**, 1171.

[10] For Lewis base directed arene borylation, see: a) S. Kawamorita, H. Ohmiya, K. Hara, A. Fukuoka, M. Sawamura, *J. Am. Chem. Soc.* **2009**, *131*, 5058; b) K. Yamazaki, S. Kawamorita, H.

Ohmiya, M. Sawamura, *Org. Lett.* **2010**, *12*, 3978; c) S. Kawamorita, T. Miyazaki, H. Ohmiya, T. Iwai, M. Sawamura, *J. Am. Chem. Soc.* **2011**, *133*, 19310; d) A. Ros, B. Estepa, R. López-Rodríguez, E. Álvarez, R. Fernández, J. M. Lassaletta, *Angew. Chem.* **2011**, *123*, 11928; *Angew. Chem. Int. Ed.* **2011**, *50*, 11724.

[11] For the Lewis acid assisted formation of difluoroboranes from trifluoroborate salts, see: E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, *60*, 3020.

[12] E. C. Ashby, W. E. Foster, *J. Org. Chem.* **1964**, *29*, 3225; M. J. Bayer, H. Pritzkow, W. Siebert, *Eur. J. Inorg. Chem.* **2002**, 2069.

[13] Addition of pyridine to in situ generated alkynyldifluoroborane followed by **1a** provides an approximately 1:1:1 ratio of **3a**,**b**,**c**, together with an additional product which is consistent with a pyridine triphenylethynyl/borane complex. See the Supporting Information for details.

[14] For recent reports of amine-complexed difluoroboranes, see: a) R. L. Giles, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, G. E. Smith, A. Whiting, *J. Organomet. Chem.* **2003**, *680*, 257; b) S. W. Coghlan, R. L. Giles, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, G. E. Smith, A. Whiting, *J. Organomet. Chem.* **2005**, *690*, 4784; c) R. Luisi, A. Giovine, S. Florio, *Chem. Eur. J.* **2010**, *16*, 2683.

[15] For recent studies and leading reference, see: a) S. H. Xiang, J. Xu, H.-Q. Yuan, P.-Q. Huang, *Synlett* **2010**, 1829; b) G. Barbe, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 18.

[16] F. L. Rock, W. Mao, A. Yaremchuk, M. Tukalo, T. Crepin, H. Zhou, Y.-K. Zhang, V. Hernandez, T. Akame, S. J. Baker, J. J. Plattner, L. Shapiro, S. A. Martinis, S. J. Benkovic, S. Cusack, M. R. K. Alley, *Science* **2007**, *316*, 1759.

