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Ambient Temperature Nitrogen-Directed Difluoroalkynylborane Carboni−Lindsey Cycloaddition Reactions

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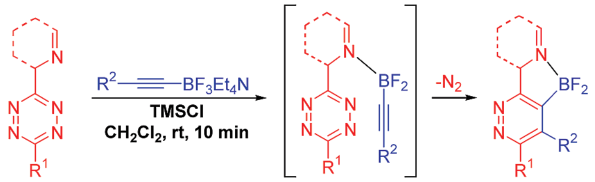
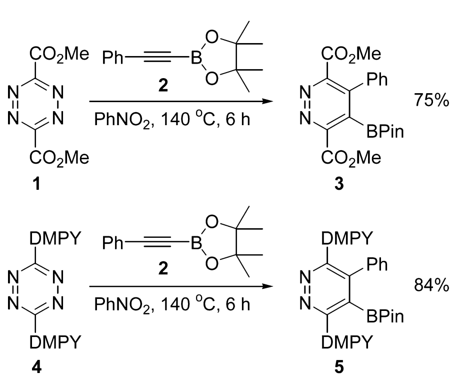
ABSTRACT



The in situ generation of alkynyldifluoroboranes in the presence of *N*-heterocycle substituted tetrazines provides a convenient and direct method for the synthesis of pyridazine difluoroboranes. The reactions proceed in 10 min under ambient conditions and provide the opportunity to assemble unsymmetrical products with complete regiocontrol.

The inverse electron demand Diels−Alder reactions of 3,6-disubstituted 1,2,4,5-tetrazines (Carboni−Lindsey reaction) provides an effective method for the synthesis of highly substituted pyridazines.[1] When alkynes are employed as substrates, the reactions typically require extensive heating and/or suffer from long reaction times unless highly reactive ynamines or ynol ethers or strained alkynes are employed.[2] In connection with our interest in the cycloaddition reactions of alkynylboronates, we demonstrated that the Carboni−Lindsey reaction can be employed to rapidly generate pyridazine boronic esters.[3] In line with the aforementioned alkyne reactivity profile, these cycloadditions require elevated temperatures but provide the corresponding products in high yield (Scheme 1).

Scheme 1



We were intrigued by the potential of alkynyltrifluoroborates to perform as dienophiles in the [4 + 2] cycloaddition to generate pyridazine trifluoroborates. In addition to potential synthetic utility, we were particularly interested in the relative ease of cycloaddition of these alkynes by comparison with

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(1) (a) Carboni, R. A.; Lindsey, R. V. *J. Am. Chem. Soc.* **1959**, *81*, 4342. (b) Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415. (c) Hamasaki, A.; Ducray, R.; Boger, D. L. *J. Org. Chem.* **2006**, *71*, 185. (d) Hamasaki, A.; Zimpleman, J. M.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 10767. (e) Rusinov, G. L.; Ishmetova, R. I.; Latosh, N. I.; Ganebnych, I. N.; Chupakhin, O. N.; Potemkin, V. A. *Russ. Chem. Bull.* **2000**, *49*, 355.

(2) (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2885.

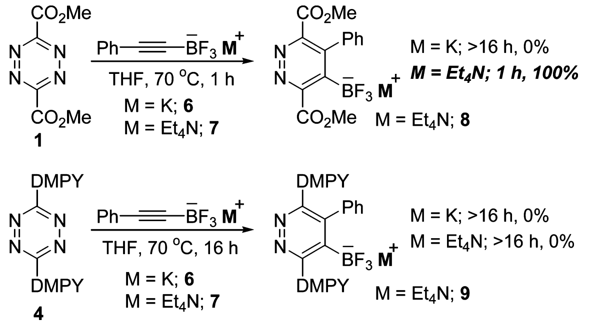
(3) (a) Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3889. (b) Gomez-Bengoa, E.; Helm, M. D.; Plant, A.; Harrity, J. P. A. *J. Am. Chem. Soc.* **2007**, *129*, 2691. (c) Helm, M. D.; Plant, A.; Harrity, J. P. A. *Org. Biomol. Chem.* **2006**, *4*, 4278.

10.1021/ol902573x

the corresponding boronic esters.[4] Aromatic trifluoroborates have recently emerged as practical alternatives to boronic acid derivatives for cross-coupling and functionalization reactions.[5] These compounds are typically air- and moisture-stable crystalline solids and usually are generated from the corresponding boronic acid derivatives after treatment by KHF_2. While many of the reactions of organoboronic acid derivatives have been found to be compatible with the corresponding trifluoroborates, cycloaddition processes are significantly under-represented. Indeed, only recently has it been shown that 1,3-dienyl 2-trifluoroborates undergo Diels−Alder reactions with activated dienophiles, albeit at elevated temperatures.[6] Accordingly, we decided to investigate the potential of alkynyltrifluoroborates in [4 + 2] cycloaddition reactions with tetrazines, and our preliminary observations are reported herein.

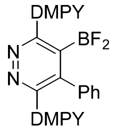
We began our studies by investigating the cycloaddition of alkynyltrifluoroborates bearing potassium and tetraethylammonium counterions with tetrazine **1**; our results are depicted in Scheme 2. Our initial observations were rather surprising; heating a mixture of potassium salt **6** and **1** in various solvents at reflux resulted in consumption of the tetrazine, but the corresponding pyridazine could not be identified from the resulting crude mixture. In marked contrast, however, the corresponding tetraethylammonium salt **7** underwent a remarkably smooth cycloaddition with **1** to provide the corresponding pyridazine **8** in quantititative yield. This observation suggested that tetraethylammonium alkynyltrifluoroborates are more reactive toward the Carboni−Lindsey reaction than the corresponding pinacol boronic esters as these dienophiles required significantly higher reaction temperatures and longer reaction times (cf. Schemes 1 and 2). We then extended our studies to the corresponding bis(3,5-dimethylpyrazol-1-yl) (DMPY) substituted tetrazine **4**. To our surprise, alkynyltrifluoroborates were found to be significantly less reactive in this case toward cycloaddition, independent of the counterion.

Scheme 2



In an effort to further explore this dichotomy, we attempted to prepare **9** (Scheme 2) from the corresponding pinacol boronate **5** to aid characterization in any subsequent cycloaddition optimization studies.[7]

Accordingly, treatment of **5** with KHF_2 followed by addition of Et_4NOH provided a new compound. To our surprise, however, the ^1H NMR spectrum indicated the absence of the expected tetraethylammonium counterion while HRMS suggested the product to be the pyridazine difluoroborane **10**.



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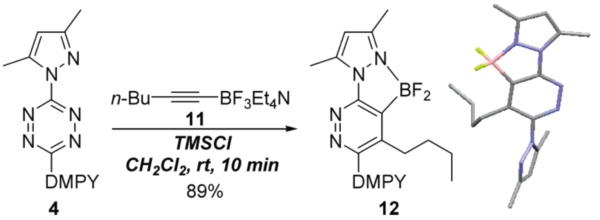
Aromatic difluoroboranes with adjacent amines have been reported and are known to exist as Lewis acid−base complexes.[8] We therefore suspected that the surprising formation of the difluoroborane over the expected trifluoroborate was due to complexation from the adjacent pyrazole moiety. This led us to speculate that the tetrazine cycloaddition could well be promoted by these Lewis basic substituents if the corresponding alkynyldifluoroboranes were employed.[9] The difluoroboranes can be generated in situ by addition of mild Lewis acids such as TMSCl.[10] Indeed, exposing a solution of alkyne **11** and tetrazine **4** in CH_2Cl_2 to TMSCl resulted in rapid consumption of both starting materials at room temperature within 10 min. Chromatographic purification provided the corresponding pyridazine **12** in excellent yield. The product was characterized by X-ray crystallography and allowed the proposed pyrazole−borane complex to be confirmed (Scheme 3).[11]

Scheme 3



We next wished to explore the scope of the nitrogen-directed cycloaddition, and our results are highlighted in Table 1. Pleasingly, the remarkable rate enhancements

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(4) For recent overviews, see: (a) Hilt, G.; Bolze, P. *Synthesis* **2005**, 2091. (b) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209.

(5) (a) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

(6) (a) De, S.; Welker, M. E. *Org. Lett.* **2005**, *7*, 2481. (b) De, S.; Day, C.; Welker, M. E. *Tetrahedron* **2007**, *63*, 10939.

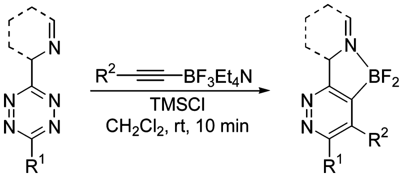
(7) Perrin and co-workers have recently used the alkynylboronate cycloaddition chemistry followed by KHF_2 to generate pyridazine trifluoroborates: Li, Y.; Asadi, A.; Perrin, D. M. *J. Fluorine Chem.* **2009**, *130*, 377.

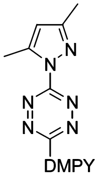
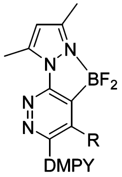
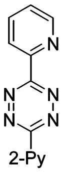
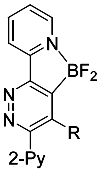
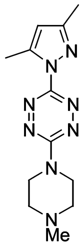
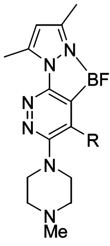
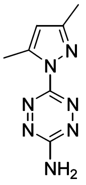
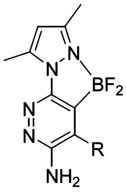
(8) (a) Vedejs, E.; Nguyen, T.; Powell, D. R.; Schrimpf, M. R. *Chem. Commun.* **1996**, 2721. For a recent overview of these compounds and related boronic acid derivatives, see: (b) Georgiou, I.; Ilyashenko, G.; Whiting, A. *Acc. Chem. Res.* **2009**, *42*, 756.

(9) For a review of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(10) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.

Table 1. Nitrogen-Directed Cycloaddition Reactions[a]



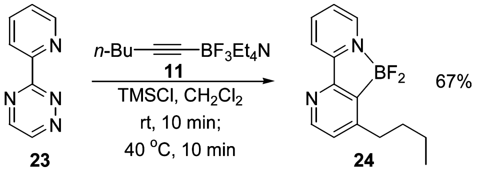
entry	tetrazine	pyridazine	yield[b]
1	 **4**		R = Ph, **13;** 99%
2			R = H, **14;** 75%
3	 **15**		R = Ph, **16;** 85%
4			R = *n*-Bu, **17;** 84%
5	 **18**		R = Ph, **19;** 91%
6			R = *n*-Bu, **20;** 80%
7	 **21**		R = Ph, **22;** 69%

[a] Reaction conditions: a CH_2Cl_2 solution of tetrazine (1 equiv) and tetraethylammonium alkynyltrifluoroborate (1.5 equiv) was treated with TMSCl (1.5 equiv), and the reaction was stirred at room temperature until the red color of the tetrazine had faded (∼10 min). [b] Isolated yields. 2-Py: 2-pyridyl.

observed in these processes are maintained over a series of alkyne substrates, and the corresponding products were obtained in high yield (entries 1 and 2). Moreover, we were able to extend these studies to the bis-2-pyridyl substituted tetrazine **15** (entries 3 and 4); notably, this substrate is not reactive enough to undergo cycloaddition with alkynylboronates. Further evidence for the role of a basic N-atom in promoting the cycloaddition was obtained by performing the reaction with unsymmetrical tetrazine **18**; pleasingly, the reaction was completely regioselective and the expected products **19** and **20** were obtained in excellent yield (entries 5 and 6). Finally, free aminotetrazine **21** was also found to undergo cycloaddition to provide **22** as a single regioisomer, albeit in a more modest yield (entry 7).[12]

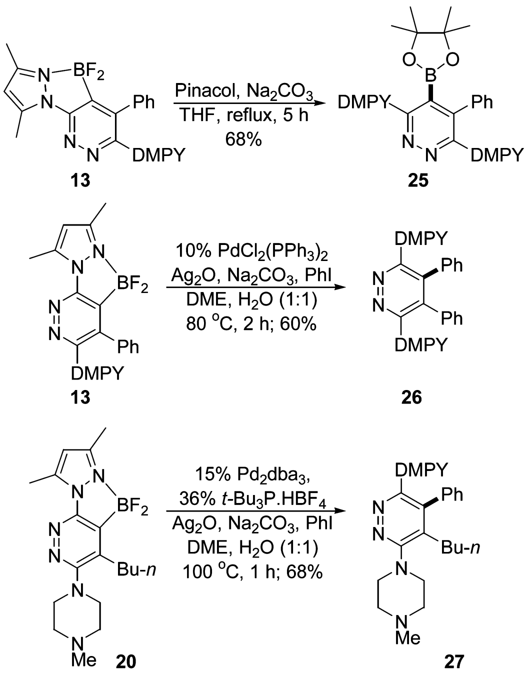
The remarkable rate enhancements afforded by this N-directed Carboni−Lindsey reaction suggested that this paradigm could be employed to promote cycloadditions of significantly less reactive dienes. Specifically, 1,2,4-triazines typically require strongly electron-withdrawing substituents to facilitate a reaction with simple alkynes and alkenes.[13] Indeed, we have found these heterocycles to be unreactive toward alkynylboronates. These substrates therefore provided an ideal opportunity to exploit this technique in this challenging cycloaddition process. In the event, 3-(2-pyridyl)-1,2,4-triazine **23** required moderate heating to promote a reaction with **11**; however, complete conversion was observed within 20 min to provide bipyridine **24** in good yield. Again, a single product regioisomer was obtained (Scheme 4).[14]

Scheme 4



With a series of novel pyridazine difluoroboranes in hand, our final goal was to confirm the potential of the cycloadducts in further functionalization reactions. We first wanted to demonstrate that these products could be converted to the corresponding pinacol esters, as we have shown that these compounds can undergo various C−C and C−O bond-forming reactions.[3a,c] Pleasingly, heating a THF solution of pinacol and **13** in the presence of base provided pinacol ester **25** in good yield. We next wanted to demonstrate that the difluoroboranes could undergo cross-coupling reactions directly. Indeed, after examining a series of trifluoroborate

Scheme 5



cross-coupling conditions,[5,15] we found Ag_2O to be particularly effective[15a] and were able to successfully prepare compounds **26** and **27** after some Pd-catalyst screening (Scheme 5).[16]

In conclusion, we report a novel N-directed cycloaddition reaction of difluoroalkynylboranes for the mild and regioselective synthesis of heteroaromatic borane derivatives. Studies are underway to establish the scope and generality of this strategy.

Acknowledgment. The authors are grateful to the EPSRC for financial support (EP/D03213X/1).

Supporting Information Available: Full experimental details and characterizaton data, copies of ^1H and ^{13}C NMR spectra for all products, and a crystallographic information file (CIF) for compounds **12** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) CCDC-750154 contains the supplementary crystallographic data for compound **12**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) Despite the higher reactivity of diester tetrazine **1** in alkyne cycloadditions (see ref 1e), this diene fails to react under the conditions shown in Table 1. This observation suggests that the enhanced reaction rates are not simply due to an inherently more reactive alkynyldifluoroborane dienophile.

(13) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, p 507.

(14) The regiochemistry of compounds **19** and **24** were assigned by NOE spectroscopy, and the regiochemistry of compound **22** was assigned by X-ray crystallography (see Supporting Information). The regiochemistry of compound **20** has been assigned by inference.

(15) (a) Adonin, N. Y.; Babushkin, D. E.; Parmon, V. N.; Bardin, V. V.; Kostin, G. A.; Mashukov, V. I.; Frohn, H.-J. *Tetrahedron* **2008**, *64*, 5924. (b) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973. (c) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875.

(16) Reducing the catalyst loading in the coupling of **20** to 7.5% Pd_2dba_3, 18% $t\text{-}Bu_3P{\cdot}HBF_4$ results in a 48% yield of **27**.